Patent Trial and Appeal Board

A, petition has been filed in Patent Number 9,593,066, Application Number 14/849,981 on March 30, 2020.

The AIA Review Number is IPR2020-00769.

To view the documents filed in this petition, go to https://ptab.uspto.gov and Search for the AIA Review Number.

- Enter your search criteria on the "Search PTAB" page
- Type in the AIA Review Number or Patent Number
- You will need to answer the CAPTCHA to prove that you are not a robot.
- Click on the "Search" button
- The search results will appear identifying the AIA Review Number
- Click on the "View Documents" button
- A pop up window will appear with a list of documents
- Click on the "Download" button to download the document.

Questions regarding this notice should be directed to the Patent Trial and Appeal Board at 571-272-7822.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	REQUEST ID
14/849,981	9593066	1672	102656

PAIR Correspondence Address/Fee Address Change

The following fields have been changed to Customer Number 166905 on 01/03/2020 via Private PAIR in view of the certification copied below that authorized the change.

- Correspondence Address

The address for Customer Number 166905 is:
166905
Foley & Lardner LLP
3000 K Street N.W.
Suite 600
Washington, DC 20007-5109

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

An attorney or Agent of Record registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature:	/Stephen B. Maebius/
Name:	Stephen B. Maebius
Registration Number:	35264

To: ipdocketing@foley.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 22428

Feb 23, 2017 03:34:48 AM

Dear PAIR Customer:

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 22428 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
14849981	ISSUE.NTF	02/22/2017	080618-1581

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/849,981	03/14/2017	9593066	080618-1581	6653

22428 7590 02/22/2017

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Hitesh BATRA, Herndon, VA;
United Therapeutics Corporation, Silver Spring, MD;
Sudersan M. TULADHAR, Silver Spring, MD;
Raju PENMASTA, Herndon, VA;
David A. WALSH, Palmyra, VA;

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 01/30/2017

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER
VALENROD, YEVGENY

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 01/30/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/849,981	09/10/2015	Hitesh BATRA	080618-1581	6653

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	05/01/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 01/30/2017
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/849,981	09/10/2015	Hitesh BATRA	080618-1581	6653

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	05/01/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1672	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/849,981	09/10/2015	Hitesh BATRA	080618-1581	6653

22428 7590 01/30/2017

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	**PAPER NUMBER**
1672	

DATE MAILED: 01/30/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/849,981	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *RCE filed on 12/29/16*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,2 and 4-11*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 1/10/17; 12/29/16
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☒ Other *Continued Examination*.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

The present application is being examined under the pre-AIA first to invent provisions.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/29/16 has been entered.

Withdrawn rejections

Rejection of claims 1-2 and 4-11 over US patent 8,242,305 and application 14/754,932 is withdrawn in view of the terminal disclaimer filed on 12/29/16.

Conclusion

Claims 1-2 and 4-11 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YEVGENY VALENROD whose telephone number is (571)272-9049. The examiner can normally be reached on mon-fri 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun G. Sajjadi can be reached on 571-572-3311. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/849,981
Date Submitted: DEC 29 2016				**Filing Date**	9/10/2015
(use as many sheets as necessary)				**First Named Inventor**	Hitesh BATRA
Sheet	1	of	3	Art Unit	1672
				Examiner Name	Yevgeny Valenrod
				Attorney Docket Number	080618-1581

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D1	Redacted Petitioner's Reply to Patent Owner's Response to Petition filed on September 27, 2016 in *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, with Exhibits 1022-1028.	
	D2	Petitioner's Demonstratives filed November 28, 2016, in *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393	
	D3	Patent Owner Response to Petition filed November 23, 2016, in *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, with Redacted Exhibits 2006, 2020, 2022, 2058 and 2059 filed November 23, 2016, 1151 pages.	
	D4	Patent Owner Demonstratives filed November 23, 2016, in *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, 62 pages.	
	D5	Decision Redacted Institute of *Inter Partes* Review dated November 23, 2016, in *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, 53 pages.	
	D6	Service copy of Third Party Submission dated October 16, 2016, filed but not entered in US 14/849,981 on October 16, 2016, with 6 indicated attachments, 822 pages.	
	D7	Redacted Defendant Sandoz Inc.'s Invalidity Contentions dated February 5, 2015, *United Therapeutics Corporation (Plaintiff) v. Sandoz Inc. (Defendant),* In The United States District Court for the District of New Jersey, Civil Action No. 3:14-cv-5499(PGH)(LHG), 90 pages.	
	D8	Defendant Sandoz Inc.'s Invalidity Contention Chartss dated February 5, 2015, *United Therapeutics Corporation (Plaintiff) v. Sandoz Inc. (Defendant),* In The United States District Court for the District of New Jersey, Civil Action No. 3:14-cv-5499(PGH)(LHG), 189 pages.	

Examiner Signature		Date Considered	

4823-8067-7182.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Y.V/

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/849,981
Date Submitted: DEC 29 2016				**Filing Date**	9/10/2015
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1672
				Examiner Name	Yevgeny Valenrod
Sheet	2	of	3	Attorney Docket Number	080618-1581

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D9	Defendant Actavis Laboratories FL, Inc. Preliminary Invalidity Contentions, dated August 30, 2016, *United Therapeutics Corporation, and Supernus Pharmaceuticals, Inc., (Plaintiff) v. Actavis Laboratories FL, Inc., (Defendant)*, In The United States District Court for the Distritc of New Jersey, Civil Action No. 3:16-cv-01816-PGS-LHG, Civil Action No. 3:16-cv-03642-PGS-LHG, 330 pages, (see particularly pages 18-20, 42-62 and 269-280).	
	D10	Exhibit G, Invalidity Claim Chart for the '393 patent, January 12, 2015, 66 pages.	
	D11	Defendant Teva Pharmaceuticals USA, Inc.'s Amended Non-Infringement and Invalidity Contentions, dated April 24, 2015, *United Therapeutics Corporation (Plaintiff) v. Teva Pharmaceuticals USA, Inc. (Defendant)*, In The United States District Court for the District of New Jersey, Civil Action No. 3:14-cv-05498(PGS)(LHG), 94 pages, (see particularly pages 22-54).	
	D12	Arumugan et al., "A New Purification Process for Pharmaceutical and Chemical Industries," Organic Process Research & Development, 2005, 9:319-320.	
	D13	Burk et al., "An Enantioselective Synthesis of (S)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation," J. Org. Chem., 2003, 68:5731-5734.	
	D14	Eliel et al., Stereochemistry of Organic Compounds, 1994, 322-325.	
	D15	Harwood et al., Experimental organic chemistry: Principles and Practice, 1989, 127-134.	
	D16	Jones, Maitland Jr., Organic Chemistry, 2nd Ed., 2000, 153-155.	
	D17	Lin et al., "Benzindene Prostaglandins. Synthesis of Optically Pure 15-Deoxy-U-68,215 and Its Enantiomer via a Modified Intramolecular Wadsworth-Emmons-Wittig Reaction," J. Org. Chem., 1987, 52:5594-5601.	
	D18	McManus et al., "Tetrazole Analogs of Plant Auxins," J. Org. Chem., 1959, 24:1464-1467.	
	D19	Monson, Richard S., Advanced Organic Synthesis, Methods and Techniques, 1971, 178-188.	
	D20	Ohno et al., "Development of Dual-Acting Benzofurans for Thromboxane A2 Receptor Antagonist and Prostacyclin Receptor Agonist: Synthesis, Structure-Activity Relationship, and Evaluation of Benzofuran Derivatives," J. Med. Chem., 2005, 48:5279-5294.	
	D21	Olmsted III et al., Chemistry, The Molecular Science, Mosby-Year Book, Inc., Chapter 10 "Effects of Intermolecular Forces," 1994, 428-486.	
	D22	Pavia et al., Introduction to Organic Laboratory Techniques, First Edition, 1998, 648.	
	D23	Physicians' Desk Reference, 59 Edition, 2005, for Bicillin® L-A (penicillin G benzathine suspension), 5 pages.	
	D24	Priscinzano et al., "Piperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909): High Affinity Ligands for the Dopamine Transporter," J. Med. Chem., 2002, 45:4371-4374.	

Examiner Signature		Date Considered	

4823-8067-7182.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Y.V/

PTO/SB/08 (modified)

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** Date Submitted: DEC 29 2016 *(use as many sheets as necessary)* Sheet 3 of 3	*Complete if Known*	
	Application Number	14/849,981
	Filing Date	9/10/2015
	First Named Inventor	Hitesh BATRA
	Art Unit	1672
	Examiner Name	Yevgeny Valenrod
	Attorney Docket Number	080618-1581

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D25	REMODULIN® label, 2014, 17 pages.	
	D26	Schoffstall, et al., Microscale and Miniscale Organic Chemistry Laboratory Experiments, 2004, 2nd Ed., 200-202.	
	D27	Sorrell, Thomas N., Organic Chemistry, 1999, 755-758.	
	D28	Wiberg, Laboratory Technique in Organic Chemistry, 1960, 112.	
	D29	Yu et al., "Novel Synthetic Route of a Pivotal Intermediate for the Synthesis of 1β-Methyl Carbapenem Antibiotics," Organic Process Research & Development, 2006,10:829-832.	

Examiner Signature	/YEVGENY VALENROD/	Date Considered	01/25/2017

4823-8067-7182.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Y.V/

PTO/SB/08 (modified)

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/849,981
Date Submitted: JAN 10 2017				**Filing Date**	9/10/2015
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1672
				Examiner Name	Yevgeny Valenrod
Sheet	1	of	1	Attorney Docket Number	080618-1581

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	E1	Redacted Defendant Watson Laboratories, Inc.'s Invalidity Contentions dated December 11, 2015, *United Therapeutics Corporation (Plaintiff) v. Watson Laboratories, Inc. (Defendant)*, In The United States District Court for the District of New Jersey, Civil Action No. 3:15-cv-05723-PGS-LHG, 35 pages.	

Examiner Signature	/YEVGENY VALENROD/	Date Considered	01/25/2017

4831-5029-0752.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Y.V/

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14849981	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

CPC- SEARCHED		
Symbol	Date	Examiner
C07C 59/72; 51/08; 51/41; 51/412; 213/08; 405/0075	1/25/2017	YV

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
562/466		1/25/2017	YV

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	1/25/2017	YV
Inventor	1/25/2017	YV
C07C 59/72; 51/08; 51/41; 51/412; 213/08; 405/0075	1/25/2017	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14849981	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/22/2016	11/23/2016	01/25/2017						
1	1	✓	✓	=						
2	2	✓	✓	=						
	3	✓	-	-						
3	4	✓	✓	=						
4	5	✓	✓	=						
5	6	✓	✓	=						
6	7	✓	✓	=						
7	8	✓	✓	=						
8	9	✓	✓	=						
9	10	✓	✓	=						
10	11		✓	=						

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("8497393").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/01/25 16:15
L2	1	("8242305").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/01/25 16:15
L3	1	("4683330").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/01/25 16:15
L4	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/01/25 16:15
L5	32	((Hitesh) near2 (Batra)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L6	24	((Sudersan) near2 (Tuladhar)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L7	30	((Raju) near2 (Penmasta)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L8	248	((David) near2 (Walsh)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L9	276	L5 or L6 or L7 or L8	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L10	24	L9 and treprostinil	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L11	539	c07c59/72.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L12	870	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/01/25 16:15
L13	1282	L11 or L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/01/25 16:15
L14	47	L13 and treprostinil	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15

EAST Search History (Prior Art)

L15	42	L14 and purity	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L16	38	L15 and HPLC	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:15
L17	1	("6765117").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/01/25 16:15
L18	2	wo "2005007081"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2017/01/25 16:15
L19	4	"9242350"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2017/01/25 16:15
L20	1	("8242305").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/01/25 16:15
L21	1	("9156786").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/01/25 16:15
L22	633	C07C51/08.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/01/25 16:15
L23	565	C07C51/41.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/01/25 16:15
L24	2312	C07C51/412.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/01/25 16:16
L25	1034	C07C213/08.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/01/25 16:16

EAST Search History (Prior Art)

L26	26	C07C405/0075.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/01/25 16:16
L27	5582	l11 or l12 or l22 or l23 or l24 or l25 or l26	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/01/25 16:16
L28	75	L27 and treprostinil	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:17
L29	576	L27 and alkylation	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:17
L30	29	L28 and alkylation	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:17
L31	52	L28 and hydrolysis	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:17
L32	21	l31 and l30	US-PGPUB; USPAT; USOCR	OR	ON	2017/01/25 16:17

EAST Search History (Interference)

		<This search history is empty>				

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14849981	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

CPC							
Symbol						**Type**	**Version**
C07C		59	/	72		F	2013-01-01
C07C		51	/	08		I	2013-01-01
C07C		51	/	412		I	2013-01-01
C07C		213	/	08		I	2013-01-01
C07C		51	/	41		I	2013-01-01
A01N		37	/	10		A	2013-01-01
C07C		39	/	12		A	2013-01-01
C07C		39	/	17		A	2013-01-01
C07C		59	/	60		A	2013-01-01
C07C		405	/	0075		I	2013-01-01
			/				
			/				
			/				
			/				
			/				

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
C07C		51	/	08	I	1	1	2013-01-01
C07C		59	/	72	I	1	2	2013-01-01
C07C		51	/	412	I	2	1	2013-01-01
C07C		59	/	72	I	2	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	01/25/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14849981	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION		
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED	
562	466	C 0 7 C 59 / 72 (2006.01.01)		
CROSS REFERENCE(S)		C 0 7 C 51 / 08 (2006.01.01)		
		C 0 7 C 51 / 41 (2006.01.01)		
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)	C 0 7 C 213 / 08 (2006.01.01)		

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 10
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672 (Primary Examiner)	01/25/2017 (Date)	O.G. Print Claim(s) 1 O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14849981	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1														
2	2														
3	4														
4	5														
5	6														
6	7														
7	8														
8	9														
9	10														
10	11														

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	01/25/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 01/30/2017
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/849,981	09/10/2015	Hitesh BATRA	080618-1581	6653

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	05/01/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1672	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Foley & Lardner LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: United Therapeutics Corporation

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Silver Spring, MD

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☒ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0741 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Stephen B. Maebius/ Date Jan. 30, 2017

Typed or printed name Stephen B. Maebius Registration No. 35,264

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal	
Application Number:	14849981
Filing Date:	10-Sep-2015
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh BATRA
Filer:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1581
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt	
EFS ID:	28203111
Application Number:	14849981
International Application Number:	
Confirmation Number:	6653
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh BATRA
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Strawderman
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1581
Receipt Date:	30-JAN-2017
Filing Date:	10-SEP-2015
Time Stamp:	14:05:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$960
RAM confirmation Number	013117INTEFSW14100600
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IFTM.pdf	125969 8d65cf5dfc60dd7011205a73a3ecbc3c9247c876	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30801 f24145bd6d01284ed1a611e588c15be98ff800e9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	156770		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

To: ipdocketing@foley.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 22428

Jan 30, 2017 03:41:39 AM

Dear PAIR Customer:

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 22428 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
14849981	NOA	01/30/2017	080618-1581
	1449	01/30/2017	080618-1581
	1449	01/30/2017	080618-1581

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/849,981	BATRA ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 12/29/16	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:
Lawana Hixon

U.S. Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	14/849,981
Filing Date:	9/10/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6653

NOTIFICATION OF RELATED PROCEEDINGS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant hereby provides UTC's Responses to Invalidity Contentions against US Patent 8,497,393 ("the '393 patent"), which is the issued parent of the above-captioned patent application, from the following proceedings:

United Therapeutics Corp. (Plaintiff and Counterclaim-Defendant) v. Sandoz, Inc. (Defendant and Counterclaim-Plaintiff), Civil Action No. 3:14-cv-05499-PGS-LHG;

United Therapeutics Corp. (Plaintiff and Counterclaim-Defendant) v. Teva Pharmaceuticals USA, Inc. (Defendant and Counterclaim-Plaintiff), Civil Action No. 3:14-cv-05498-PGS-LHG;

United Therapeutics Corp. (Plaintiff and Counterclaim-Defendant) v. Watson Laboratories, Inc. (Defendant and Counterclaim-Plaintiff), Civil Action No. 3:15-cv-05723-PGS-LHG; and

United Therapeutics Corporation and Supernus Pharmaceuticals, Inc. (Plaintiffs) v. Actavis Laboratories FL, Inc. (Defendant), C.A. No. 16-cv-01816 (PGS)(LHG), C.A. No. 16-cv-03642 (PGS)(LHG).

The purpose of this notice is to provide plaintiff UTC's responses to the invalidity contentions submitted with the recently filed Information Disclosure Statements. Certain confidential information has been redacted, as well as information not related to the '393 patent.

Respectfully submitted,

Date Jan. 10, 2017

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, New Jersey 07102-5426
(973) 286-6700
clizza@saul.com

OF COUNSEL:
Douglas Carsten
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real, Suite 200
San Diego, CA 92130

Veronica S. Ascarrunz
WILSON SONSINI GOODRICH & ROSATI
1700 K Street, NW, Suite 500
Washington, DC 20006

William C. Jackson
BOIES, SCHILLER & FLEXNER LLP
5301 Wisconsin Avenue, NW
Washington, DC 20015

Attorneys for Plaintiffs
United Therapeutics Corporation
and Supernus Pharmaceuticals, Inc.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION, and SUPERNUS PHARMACEUTICALS, INC., Plaintiffs, v. ACTAVIS LABORATORIES FL, INC., Defendant.	C.A. No.: 16-cv-01816 (PGS)(LHG) C.A. No.: 16-cv-03642 (PGS)(LHG) **HIGHLY CONFIDENTIAL-ATTORNEYS EYES ONLY**

PLAINTIFFS' RESPONSES TO ACTAVIS LABORATORIES, FL, INC.'S INVALIDITY CONTENTIONS FOR U.S. PATENT NOS. 8,497,393; 9,050,311; 8,747,897; 8,349,892; 7,417,070; 7,544,713; 8,252,839; 8,410,169; AND 9,278,901

Plaintiffs United Therapeutics Corporation ("United Therapeutics) and Supernus Pharmaceuticals, Inc. ("Supernus") (together, "Plaintiffs") hereby provide their Responses to Actavis Laboratories FL, Inc.'s ("Actavis" or "Defendant") Invalidity Contentions ("Contentions") for U.S. Patent Nos. 8,497,393 (the "'393 patent"); 9,050,311 (the "'311 patent"); 8,747,897 (the "'897 patent"); 8,349,892 (the "'892 patent"); 7,417,070 (the "'070 patent"); 7,544,713 (the "'713 patent"); 8,252,839 (the "'839 patent"); 8,410,169 (the "'169 patent"); and 9,278,901 (the "'901 patent) (collectively, "the Asserted Patents") pursuant to Local Patent Rules 3.1, 3.4 and 3.6(g) and the Amended Scheduling Order (D.I. 29). The Responses include the following:

Scheduling Order Paragraph 7(a): For each item of asserted prior art, the identification of each limitation of each asserted claim that Plaintiffs believe is absent from the prior art with an explanation why the prior art does not anticipate the claim;

Paragraph 7(b): Where obviousness is alleged, an explanation of why the prior art does not render the asserted claim obvious;

Paragraph 7(c): Plaintiffs' responses follow the order of the invalidity chart required by Paragraph 2(c) of the Scheduling Order, and set forth Plaintiffs' agreement or disagreement with each allegation therein and the written basis thereof; and

Paragraph 7(d): The production or the making available for inspection and copying of any document or thing that Plaintiffs intend to rely on in support of their Responses. Plaintiffs intend to rely upon all of the documents and things referred to herein in support of its Responses. Any document or thing referred to herein that was not already produced by Actavis or Plaintiffs will be made available for inspection and copying.

As a preliminary matter, Actavis, who bears the burden to prove invalidity by clear and convincing evidence, has failed to provide "a chart identifying where specifically in each alleged item of prior art each limitation of each asserted claim is found." L. Pat. R. 3.3(c). Actavis's Local Patent Rule 3.3(c) charts ("Invalidity Charts") erroneously label each claim a "Claim Term" and simply characterize lists of references that purport to disclose "Invalidity Contentions" with no corresponding reference to which limitation within the claim Actavis purports to address. Accordingly, Actavis has not identified with specificity where every single limitation of every claim is found in the prior art in contravention to the Court's Scheduling Order and this Court's Local Patent Rules. Accordingly, Actavis has waived any argument that any limitation of any claim of the Asserted Patents is found in the prior art. Due to Actavis's failure to abide by its obligations, Plaintiffs' responses cannot properly "follow the order of the invalidity chart . . . and set forth [Plaintiffs'] agreement or disagreement with each allegation therein" and therefore no response is required. *Id.* at 3.4A(c). L. Pat. R. 3.4A(d) and Actavis's contentions should be stricken. Actavis is now precluded from arguing any invalidity of the Asserted Patents. *See Merck Sharp & Dohme Corp. v. Sandoz, Inc.*, C.A. No. 12-3289 (PGS)(LHG), 2014 WL 997532 (D.N.J. Jan. 6, 2014) (Goodman, Mag.) (finding arguments not made in original invalidity contentions were waived); *Anascape, Ltd. v. Microsoft Corp.*, C.A. No. 9:06-CV-158, 2008 WL 7180756, at *1-4 (E.D. Tex. May 1, 2008) (Clark, J.) (granting patentee's motion to strike certain invalidity contentions that merely generally referenced a prior art item without specifically mapping aspects of the prior art reference to each element of the claim; denying motion of accused infringer to amend its invalidity contentions to correct the deficiencies) ("Defendants' invalidity contentions simply assume that Anascape can guess what controllers correspond to which disclosed prior art reference. Allowing such a 'mix-and-match' [invalidity] contention

disclosure game to stand would encourage violation of the rules and discourage the voluntary exchange of information."). Rather than abide by its obligations under the Local Patent Rules and Scheduling Order, Actavis purports to "reserve" many "rights" such as to rely on prior art it has failed to identify in its contentions. *See, e.g.,* AIC at 18. It has waived any "right" to do so and cannot rely on arguments or prior art not set forth in its contentions. Similarly, by failing to satisfy the requirement of L. Pat. R. 3.3(b) to "expla[in] why the prior art renders the asserted claim obvious, including identification of [specific] combinations of prior art,", and instead listing only dozens to hundreds of potential prior art combinations, Actavis has waived any argument regarding specific combinations of prior art not explicitly disclosed and explained.

The Scheduling Order and Local Patent Rules do not require Plaintiffs to respond to the 265-page narrative document entitled "Defendant Actavis Laboratories Fl, Inc.'s Preliminary Invalidity Contentions" ("AIC" or "Actavis Invalidity Contentions") that accompanied the claim charts served by Actavis. Nonetheless, Plaintiffs address below certain misleading or incorrect statements in the Actavis Invalidity Contentions and provide context for the accompanying validity claim charts. By not addressing any assertion made in the Actavis Invalidity Contentions, Plaintiffs do not hereby waive any rights or arguments with respect to such assertion.[1]

---

[1] Additionally, Actavis cites a multitude of alleged prior art references within the narrative document as anticipating and/or rendering obvious the claims of specific asserted patents without any further discussion of the alleged invalidating disclosures of these references either within the relevant section of the narrative document or within the relevant claim chart. *See, e.g.*, AIC at 20-22 (listing Ansel, Gould, Grant, EP 04776104, App. No. 12/078,955, Orenitram® – Highlights of Prescribing Information, and Tyvaso® and Tyvaso® Label as invalidating the '070 patent without any further explanation of their alleged invalidating disclosures within the '070 patent narrative or claim chart); *see also id.* at 71-72 (listing Vizza as prior art to the '070 patent and summarizing its disclosures without any explanation of how these disclosures allegedly invalidate the '070 patent); *id.* at 64, n.5 (citing U.S. Patent No. 6,054,486 in a single footnote without any indication of whether Actavis contends this reference is prior art). Accordingly, Actavis has waived its ability to rely on such references to invalidate the relevant asserted patents.

Moreover, in its Invalidity Contentions, Actavis included lengthy statements and stances regarding the purported legal standards. Those statements and stances were not required by the rules. Accordingly, Plaintiffs need not respond to Actavis's characterizations of the relevant law, which are inaccurate and misleading in any event. Plaintiffs do not hereby waive any rights or arguments with respect to Actavis's purported legal standards and related arguments and will respond to such matters as necessary in accordance with the Scheduling Order.

I. THE ASSERTED CLAIMS OF U.S. PATENT NO. 8,497,393 ARE VALID[2]

A. The Scope and Content of the Alleged Actavis Prior Art

Actavis cites a number of references in its Invalidity Chart, without reference or explanation as to what limitation is purportedly met by such references. The discussion below highlights certain representative sections of these and related references to show that their actual teachings do not support Actavis's anticipation and/or obviousness arguments. Plaintiffs reserve their rights to rely upon other sections of these references and/or additional references to support Plaintiffs' contentions that none of these references, whether considered alone or in combination anticipate and/or render obvious the asserted '393 patent claims, and to more fully expand its contentions during the course of factual and expert discovery in this case. Plaintiffs do not admit that any of Actavis's references actually constitute relevant or enabling prior art and also reserve

---

Nonetheless, Plaintiffs have addressed certain misleading or incorrect statements in the Actavis Invalidity Contentions regarding such references. By not addressing references not discussed in the Actavis Invalidity Contentions, Plaintiffs do not hereby waive any rights or arguments with respect to such references should Actavis later be permitted to rely on them.

[2] In addition to the analysis provided in this section and the appended claim chart (*i.e.*, Exhibit A) discussing the validity of the '393 patent and rebutting Actavis's Invalidity Contentions and Invalidity Chart, Plaintiffs further incorporate by reference their arguments and analysis in favor of patentability of the '393 patent presented in IPR206-00006. In particular, Plaintiffs incorporate by reference the following from *Steadymed Ltd. v. United Therapeutics Corp.*, IPR2016-00006 (P.T.A.B.): 1) Patent Owner Preliminary Response; 2) Patent Owner Response; 3) Declaration of Robert M. Williams, Ph.D.; and 4) Declaration of Robert R. Ruffolo, Jr., PhD.

the right to antedate or otherwise remove any of Actavis's alleged prior art. Plaintiffs' response to Actavis's anticipation and obviousness arguments regarding the '393 patent can be found herein and in the accompanying claim chart, attached as Exhibit A hereto. In addition, Plaintiffs provide below additional background information and explanation as to why (a) the prior art identified by Actavis neither anticipates nor renders obvious the claims of the '393 patent; and (b) why the Asserted Claims are not invalid based upon Actavis's other invalidity arguments.

B. Prosecution History of the '393 Patent

During prosecution of the '393 patent, the USPTO considered and rejected many of the same arguments and prior art as those in Actavis's Invalidity Contentions. As discussed further below, the USPTO already considered and found that the '393 patent was patentable over the same arguments Actavis now makes. The prior art Actavis cites, even if enabling and not cumulative to the art of record, does not refute the USPTO's reasons for allowance.

C. The Asserted Claims of the '393 Patent Are Not Anticipated

The Asserted Claims are not anticipated because no single, enabling reference identified by Actavis discloses each and every element of the claimed invention. Actavis's Invalidity Chart does not specify which references allegedly anticipate the '393 patent, but Actavis's narrative identifies the '117 Patent[3], Moriarty et al., the *Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)*, J. Org. Chemistry., 69(6), 1890-1902 (2004) ("Moriarty 2004"), United Therapeutics' own Remodulin® drug product, and U.S. Patent Publication No. 2005/0085540 (April 2005) ("Phares 2005") in its anticipation section. Actavis's contentions

[3] For the purposes of these Responses, Plaintiffs adopt the shortened prior art reference labels outlined in Actavis's Invalidity Contentions.

provide very limited detail as to why such references anticipate the claims other than the allegation that treprostinil was disclosed in each. The fact that each reference discloses treprostinil or salts of treprostinil does not mean that the claims of the asserted patents are anticipated. Indeed, the USPTO reviewed many references that disclosed treprostinil (including each of the published documents Actavis cites) and allowed the claims. The mere disclosure of treprostinil cannot anticipate the claims. Specifically, the '393 patent discloses a different and more pure treprostinil product with less impurities than the prior art. Indeed, during prosecution, the '393 patent was initially rejected by the examiner in view of the Moriarty 2004 reference (which discloses the same synthesis as the '117 patent) and the examiner subsequently allowed the claims over the reference because the products were different. '393 Patent File history, Office Action dated May 15, 2013 (UTC_WAT_00001593-1598); Office Action Response dated June 5, 2013 (UTC_WAT_00001603-1611); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001626-1631). Additionally, the specification of the '393 patent details many of the differences of the '117 patent and Moriarty 2004 (identified as "Former Process") as compared to the '393 patent in Example 6 which is incorporated herein. '393 patent, col. 15, l. 1- col. 17, l. 25.

As an initial matter, Plaintiffs note that the synthesis disclosed in the '117 patent and Moriarty 2004 are essentially the same (together "the Moriarty references"). *See* '117 patent, col. 7-10; Moriarty 2004 at 1894-96. Additionally, the Remodulin® treprostinil products, on sale prior to the priority date of the '393 patent, were also made by the '117 patent process. For example, in a document entitled "Treprostinil Drug Substance Impurities," all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by Moriarty references' process. *See* UTC-Sand-Rem00334054-057 and

UTC-Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty references' process. *See, e.g.*, UTC-Sand-Rem00001712-741; UTC-Sand-Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTCSand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTCSand-Rem01111355-357; UTC-Sand-Rem01117901-906; UTC-Sand-Rem01117910-912; UTCSand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Still other documents show that the batches made by the '393 patent process have a better average impurity profiles as well as less total impurities.[4] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the alleged prior art specifies the level of purity or minimal level of impurities that the '393 patent provides.

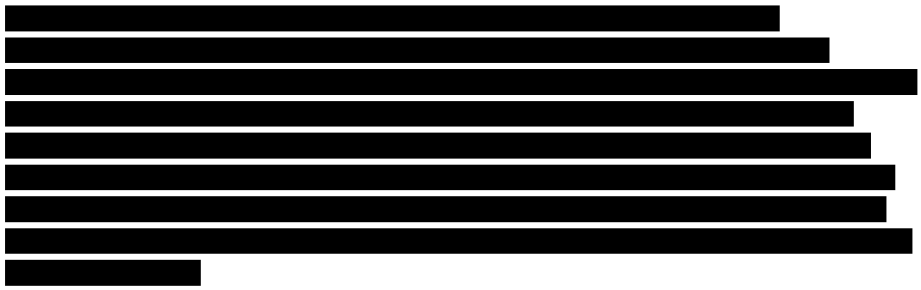
Additionally, the FDA accepted a new purity specification when United Therapeutics implemented the inventions of the '393 patent. For example, a process validation report

[4] The documents cited here for batches of treprostinil made by the Moriarty references process and by the '393 patent process are illustrative examples. Discovery in this case is in the early stages and expert discovery has not started. Thus, Plaintiffs reserve the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes are different.

(Protocol No. "VAL-00131") states that it applies to "production of treprostinil diethanolamine intermediate (UT-15C-I), a chemical intermediate used for the production of active pharmaceutical ingredients treprostinil (UT-15) and treprostinil diethanolamine (UT-15C)." Validation Report at 8 (UTC-Sand-Rem000092436-449). This validation report also shows that each of steps (a)-(c) of the claims of the '393 patent are carried out in this new process. *Id.* At 5-7.

A Process Optimization Report also provides results for batches resulting from step (d) of the claims of the '393 patent, which was performed on specific batches of the diethanolamine salt intermediate produced by steps (a)-(c) that are referenced in the Validation Report. Process Optimization at p. 2 (UTC-Sand-Rem01104769-779) (*compare* batch numbers of Validation Report at p. 4). The Process Optimization Report also states that "diethanolamine salt (UT-15C intermediate) of UT-15 is converted to UT-15 [treprostinil] by an acid-extraction removal of the diethanolamine to give UT-15 [treprostinil] . . . ." The percent yield and purity levels of the final treprostinil product are compared to the former process therein, further demonstrating the differences that result in the final treprostinil product when all of steps (a)-(d) of the '393 patent are performed. Process Optimization Report at 3.

Additionally, a letter from United Therapeutics to the FDA, which references the Validation Report, states as follows:



Validation Report at 2. The Validation Report further states:

> In all lots, the total unidentified impurity level (%AUC) decreased from triol to UT-15C intermediate. [redacted]

Id. at 3. Finally, this FDA Letter states that, when the new process was implemented, "it was observed that the purity of the treprostinil improved close to 100%," and the letter proposes that "the range of the specification for the HPLC assay for treprostinil be shifted from 97-101% to 98-102% so that it is centered at 100%." *Id.* at 3-4. The FDA subsequently approved United Therapeutics' proposed implementation of the '393 patent process and the increased purity standard. FDA Approval Letter, UTC-Sand-Rem00087652-53.

Because the product produced by the '393 patent is superior, *inter alia* in impurity profiles, purity, yields and other characteristics of the product, it is not anticipated or rendered obvious. *See, e.g., Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1308 (Fed. Cir. 2009) (Newman, J., *dissenting*) ("The facts of Thorpe did not concern the exception and expedient where process terms are invoked to describe a new product of complex structure. This exception is rarely invoked. The general rule requiring claims to have a process-free definition of the structure of a new product accommodates most inventions. Some recent exceptions are seen in emerging aspects of biotechnology."); *see also Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565 (Fed.Cir.1991) (process to obtain a "highly purified and concentrated" product that was "largely free of contaminants," was not anticipated by previous disclosure of the product), *overruled on other grounds by Abbott Labs v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009); *see also Steadymed Ltd. v. United Therapeutics Corp.*, IPR2016-00006, Paper 8, (Jan. 14, 2016

P.T.A.B.) (Patent Owner Preliminary Response) (providing further analysis and evidence that the product produced by the '393 patent is superior to the alleged prior art and thus not anticipated or obvious); *id.* at Paper 39 (Jul. 13, 2016 P.T.A.B) (Patent Owner Response) (same); *id.* at EX2020 (Jul. 13., 2016 P.T.A.B) (Declaration of Robert M. Williams, Ph.D.) (same); *id.* at EX2022 (July 13, 2016 P.T.A.B) (Declaration of Robert R. Ruffolo, Jr., PhD) (same). If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable); *United Therapeutics Corp. v. Sandoz, Inc.*, Civ. Nos. 12-1617, 13-316, 2014 U.S. Dist. LEXIS 121573, at *140-149 (D.N.J. Aug. 29, 2014) (finding that the '117 patent was not anticipated by prior art disclosures of treprostinil due to a differentiating structure implied by the claimed process). Actavis fails to provide any evidence that the alleged prior art products and the '393 patent's product are structurally and functionally the same. Additionally, early syntheses of treprostinil by the Moriarty references' process yielded less pure products in terms of impurities, yield, and other analytical data.

With respect to the Phares 2005 reference, it does not disclose what starting treprostinil material is used and therefore cannot anticipate (explicitly or inherently) the final treprostinil product of the '393 patent because each method of producing treprostinil would contain its own distinct impurity profile. In fact, the process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *United Therapeutics*, 2014 WL 4259153 at 53-55. Accordingly, Actavis cannot establish anticipation based on a

teaching of any treprostinil salt product that does not also identify the source of its starting treprostinil material. Indeed, Actavis fails to identify any specific purity in Phares 2005 that would anticipate any claim of the '393 patent.

Claim 2 requires that the product have a purity of no less than 99.5%. Moriarty 2004 is the only reference cited by Actavis that discloses a purity with at least 99.5%, but as previously described, the product of the Moriarty 2004 reference is different and the USPTO explicitly considered that claim in relation to the Moriarty 2004 reference and allowed the '393 patent. '393 Patent File history, Office Action dated May 15, 2013 (UTC_WAT_00001593-1598); Office Action Response dated June 5, 2013 (UTC_WAT_00001603-1611); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001626-1631). Actavis provides no additional citations or support for any other asserted claim. Therefore, the '117 patent, Phares 2005, United Therapeutics' Remodulin®, and Moriarty 2004 do not anticipate any claim of the '393 patent.

Further, dependent claims 2-8 and 10-22 are not anticipated by the cited references because they depend from a novel base claim, as well as because they recite additional limitations which further distinguish these claims over the prior art.

D. The Asserted Claims of the '393 Patent Are Not Rendered Obvious by Actavis's Alleged Prior Art

As noted above, Actavis, who bears the burden to prove invalidity by clear and convincing evidence, has failed to provide "a chart identifying where specifically in each alleged item of prior art each limitation of each asserted claim is found." L. Pat. R. 3.3(c). Accordingly, Actavis has waived any argument that any limitation of any claim of the '393 patent is found in the prior art.

Actavis provides no specific obviousness combination in its Invalidity Chart. Actavis's narrative identifies a laundry list of alleged obviousness combinations having hundreds of permutations, failing both to "expla[in] why the prior art renders the asserted claim obvious" and to provide "[a] chart identifying where specifically in each alleged item of prior art each limitation of each asserted claim is found." L. Pat. R. 3.3(b). Specifically, Actavis alleges the '393 patent's claims would be rendered obvious by various combinations of one or more of the Moriarty references in various combinations with one or more of Monson, *Advanced Organic Synthesis, Methods and Techniques*, (1971) ("Monson"), Eliel, *Stereochemistry of Organic Compounds*, (1994) ("Elliel"), Jones, Organic Chemistry, 2nd Ed. 2000 ("Jones"), Japanese Patent App. No. 56-1222328A, September 1981 ("Kawakami"), Ege, S., *Organic Chemistry Second Edition*, (1989) ("Ege"), and/or U.S. Patent Publication No. 2005/0165110 ("Wade"). AIC at 55-56. Nevertheless, despite using language that could suggest hundreds of potential combinations, Actavis provides no analysis as to why or how a person of ordinary skill in the art ("POSA") would make even one of these listed combinations. Actavis's narrative is merely a meandering recital of various disclosures in the prior art—including the reliance on references *not* listed in any proposed combinations—without any effort made to put forward a *prima facie* case of why or how a POSA would take these teachings to arrive at the process for making the highly pure treprostinil claimed by the '393 patent, or whether a POSA would even have a reasonable expectation of success in doing so. Accordingly, Actavis has waived its obviousness defenses because they have failed to recite even one *prima facie* case of obviousness. *See, e.g., Horizon Pharma AG v. Watson Labs. Inc.* C.A. No. 13- 5124, 2015 U.S. Dist. LEXIS 80853, at *14-18 (D.N.J. Feb. 24, 2015) (denying defendant's motion to amend its contentions, finding that the Defendant had not acted "diligently" and noting that the Local Rules "require parties to

crystallize their theories of the case early in the litigation and to adhere to these theories once they have been disclosed") (citing *Nova Measuring Instruments Ltd. v. Nanometrics, Inc.*, 417 F. Supp. 2d 1121, 1122-23 (N.D. Cal. 2006)). Regardless, none of the references cited by Actavis, alone or in combination, would render obvious any claim of the '393 patent.

First, Actavis's contentions regarding the alkylation and hydrolysis steps do not advance their obviousness allegations. For example, Actavis cites McManus for the contention that alkylation using chloroacetonitrile and subsequent hydrolysis to a carboxylic acid was known, but fails to indicate how this is relevant to the obviousness analysis because the '393 patent itself references disclosures that demonstrate those same steps—such as the '117 patent and Moriarty 2004—and the USPTO already considered and found that the '393 patent was distinguishable over those disclosures. *See* AIC at 46-48; '393 Patent at col. 1, ll. 22-28; '393 Patent File history, Office Action dated May 15, 2013 (UTC_WAT_00001593-1598); Office Action Response dated June 5, 2013 (UTC_WAT_00001603-1611); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001626-1631). Further, Actavis cites Lin and Aristoff, but these references fail to even disclose treprostinil and discuss other prostaglandins not related to the product of the '393 patent. Indeed, most the references identified in Actavis's Invalidity Chart do not disclose treprostinil.

Second, Actavis cites several references discussing "purification" steps, but Actavis fails to identify how or why any of these references would be used by a person of skill in the art to further purify and optimize the existing prior art treprostinil to arrive at the claims of the '393 patent, and fails to discuss whether a person of skill in the art would have a reasonable expectation of success in doing so. *See* AIC at 46-48.

Specifically, Actavis cites Monson, Arumugan et al., *A New Purification Process for Pharmaceutical and Chemical Industries*, Organic Process Research and Development 2005 ("Arumuguan") and Yu et al., *Novel Synthetic Route of a Pivotal Intermediate for the Synthesis of 1a-Methyl Carbapenem Antibiotics*, Organic Process Research & Development 2006 ("Yu") for the fact that "column chromatography is not favored for large-scale production," cites Monson and Harwood to support its allegations that the use of crystallization and recrystallization as a purification technique was well-known, and similarly cites Eliel and Jones to show that "carboxylate ammonium salts are formed from adding a carboxylic acid with an amine and that those salts can be purified by recrystallization." *See* AIC at 47. Actavis then asserts that "a POSA would have been motivated to [modify the prior art synthesis of treprostinil utilizing column chromatography] by applying an obvious form of purification, salt crystallization, to form known salt forms of treprostinil." Actavis's assertion fails for several reasons. As examples, Actavis fails to provide any evidence, or indeed argue, that the substitution would have been expected to result in the highly pure treprostinil claimed in the '393 patent, and Actavis fails to discuss whether crystallization/recrystallization would even address the issues as to why column chromatography is allegedly not favored in large-scale production. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (a claim is not proved obvious merely by demonstrating that something was possible or known in the prior art).

Additionally, Actavis has failed to show that step (c) of the '393 patent would necessarily lead to the same final product if made from different starting treprostinil materials than that made from steps (a) and (b). The process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *United Therapeutics*, 2014 WL 4259153 at 53-55. During prosecution, United Therapeutics demonstrated that the final

treprostinil product from the '393 patent is physically different than that of the Moriarty references. Thus, even if the Moriarty references' treprostinil products were used as a starting point, Actavis has failed to provide any evidence that, if step (c) was somehow obvious to apply, that the resulting treprostinil product would necessarily be the same as the products claimed in the '393 patent. For example, the declaration of Dr. Walsh submitted during original prosecution shows that certain impurities in representative examples are reduced below detectable amounts by step (c), while others are still present in detectable amounts, such as treprostinil stereoisomer 3AU90. '393 Patent File History at 346-350. Both the type of impurity, as well as the relative amount of that impurity in the starting treprostinil material, may impact the impurity profile of the final product after step (c), yet there is absolutely no disclosure of any specific impurities or total amount of impurities by Actavis on this point.

Actavis also cites Sorrell, Wiberg, Schoffstall, and Pavia, but each only provides a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. *See* AIC at 48, 49. In fact, most of Actavis's purification references do not disclose treprostinil, prostacyclin analogues, or preferred methods of purification for such substances. And instead of providing a specific method of purifying complex molecules such as prostacyclin analogues, Actavis's cited references largely provide a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. Moreover, Actavis fails to provide any detail on how or why a person of ordinary skill in the art would look to very basic and sometimes decades old references to determine how to make the highly pure product produced by the '393 patent or have any reasonable expectation of success in doing so.

Third, Actavis also cites the 2005 Physician's Desk Reference, Burk, Ohno, and Priscinzano for the contention that the diethanolamine salt was known and preferred. *See* AIC at 49. But the asserted claims of the '393 patent do not all require specifically that carboxylic ammonium salts are formed from carboxylic acids and amines and do not specifically require the diethanolamine salt. Contrary to Actavis's arguments, these references only show very general information that is not directed towards benzindene prostacyclin analogues, much less treprostinil. Indeed, a person of ordinary skill in the art would not have considered these additional basic references to improve the product of the existing prior art treprostinil products and would not have a reasonable expectation of success in combining these very basic references with known syntheses of treprostinil.

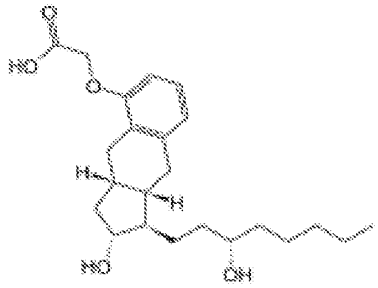
Fourth, Actavis cites Wade to show that physiologically acceptable salts of treprostinil include salts derived from bases such as ammonia, N-methyl-D-glucamine, magnesium, arginine, and lysine. AIC at 49. Once again, however, Actavis fails to provide any detail as to how this is relevant to the obviousness of the asserted claims.

Fifth, Actavis also cites Phares 2005, Kawakami, and Ege for the proposition that steps (c) and (d) of the '393 patent were obvious. None of these references, however, disclose steps (c) or (d) as claimed in the '393 patent. Specifically, Actavis alleges that it would have been obvious to a person of ordinary skill in the art to contact "a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt" and that this salt "can be further precipitated and purified" or dissolved into its fee-acid form. *See* AIC at 50. These references alone or in combination, however, do not establish that the '393 patent's claims were obvious.

Actavis apparently cites Phares 2005 at page 48 for teaching step (c); however, the cited portion merely describes an example of how to make treprostinil diethanolamine from a starting

material of treprostinil acid, but provides no detail whatsoever about how the starting treprostinil acid was made or where it comes from. Similarly, Actavis cites Phares 2005 at pages 85-93 (*see* AIC '393 Claim Chart at 2) as relevant, but these portions describe a clinical study of sustained release capsules and tablets of treprostinil diethanolamine and to a polymorph characterization study of treprostinil diethanolamine. Again, there is no indication in this portion of Phares 2005 what process was actually used to make the starting "treprostinil acid" for the treprostinil diethanolamine. And, as discussed above, Phares 2005 fails to disclose the synthetic route or purity of the claimed treprostinil product. However, the process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *See United Therapeutics*, 2014 WL 4259153 at *53-55. Accordingly, by failing to show that performing step (c) on a starting treprostinil material, which has a different impurity profile than a starting treprostinil material made by performing steps (a) and (b) of the asserted claims, would necessarily lead to an identical product, Actavis's arguments relating to obviousness over Phares 2005 necessarily fail.

Regarding Kawakami, Actavis has failed to establish that the '393 patent is obvious over any Kawakami combination. Simply put, Kawakami is directed to entirely different compounds with entirely different impurity profiles than the '393 patent. The alleged "prostacyclin compound" disclosed in Kawakami is a two ring structure, yet the core three ring structure of treprostinil is key to its pharmaceutical usefulness (*United Therapeutics*, 2014 WL 4259153 at *4-5) and is also present in every structure of every step of the '393 patent. *See, e.g.*, '393 patent claim 1.



Treprostinil

"prostacyclin compound" in Kawakami

Indeed, nothing in Kawakami comes close to even addressing the treprostinil product of the '393 patent much less how a skilled artisan would or would not go about synthesizing or purifying the product. Thus, a skilled artisan would have had no motivation to combine Kawakami with, for example, Phares or the Moriarty references, and would have had no reasonable expectation of success of obtaining the same high purity treprostinil product of the '393 patent. Additionally, to the extent Actavis is alleging that Kawakami could remedy the deficiencies of the prior art treprostinil compounds (*e.g.*, Moriarty references compounds) to disclose the impurity profile of the claimed treprostinil products, Actavis has failed to establish a motivation to combine or reasonable expectation of success of forming a salt of the prior art treprostinil compounds with a purity profile of the products in the claims.

Indeed, Actavis offers no basis from which to draw any conclusion about whether an impurity reduction step in Kawakami would possibly have any relevance to a process to synthesize and or purify a totally different structure such as treprostinil. To illustrate this point further, Kawakami is directed to purifying E- and Z-isomers of "prostacyclin compounds" from one another. In order for the E- and Z-isomers to exist, the "prostacyclin compound" must have

an alkene. Treprostinil, on the other hand, contains no mixture of E/Z isomers. In fact, it cannot because it does not contain an alkene capable of E/Z isomerization. Actavis has failed to provide a factual basis as to how or why the separation of E/Z isomers of an alkene would provide a motivation to combine or reasonable expectation of success in a compound not containing an alkene capable of E/Z isomerization, such as treprostinil. For these reasons, a skilled artisan would have no motivation to look at Kawakami in order to arrive at the claimed invention of the '393 patent.

Similarly, Ege provides no additional support for Actavis's obviousness contentions. Ege is merely an undergraduate chemistry textbook with only generalized descriptions of carboxylic acids and related synthetic procedures, and discloses nothing about any prostacyclin derivative, much less treprostinil free acid. Indeed, Ege fails to disclose anything about the synthesis of pharmaceuticals at all. Ege merely shows it was known to form a free acid from treatment of the corresponding carboxylate salt with a strong acid, but this fact alone provides no reason why a skilled artisan, based on any reference, would conduct a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step with a reasonable expectation of obtaining the claimed products of the '393 patent's claims. In fact, Ege actually suggests this "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would be relatively useless as a means for purifying treprostinil. *See* Ege at 8 (stating that the "properties of carboxylic acids are useful for separating them from reaction mixtures containing neutral and basic compounds," which is irrelevant to the claimed treprostinil process). Thus, Ege would not create an expectation of success for separating one carboxylic-acid compound (*e.g.,* treprostinil free acid) from other carboxylic-acid containing compounds (*e.g.,* different stereoisomers of treprostinil free acid).

In reviewing Actavis's invalidity contentions, it is evident that Actavis misunderstands the claims of the '393 patent. For example, the claimed invention is not the discovery that carboxylic acids react with bases, but rather that compounds of Formula (I), and in particular treprostinil or a salt thereof, can be obtained with a superior purity profile compared to the prior art. Specifically, performing step (c) on a product which resulted from steps (a) and (b) provided a product with reduced impurities—which was not disclosed in the Moriarty references and resulted in a significant improvement in the treprostinil product being made at the time of invention. In fact, during prosecution of the '393 patent established the impurity profile of the '393 patent claims is different from the impurity profiles of Moriarty 2004. *See* '393 Patent File History, Office Action Response dated June 5, 2013 (UTC_WAT_00001603-1611). Actavis appears to argue that the salt formation step would have been obvious to reduce or remove acidic or basic impurities, but each of these reduced or removed impurities are neither strongly acidic or basic as each are either diastereomers of treprostinil—which is very weakly acidic—or similarly neutral ester and triol impurities. The '393 patent therefore not only reduced the weakly acidic impurities present from the Moriarty process, but also unexpectedly reduced or eliminated nonacidic impurities as well. Thus, even under Actavis's erroneous understanding, it was unexpected that the salt formation step would remove these additional impurities.

Finally, Actavis fails to address the distinctive structural and functional characteristics of the product produced by the '393 patents claims. If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d at 279; *see also United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573 at *140-149 (finding claims directed to producing a

treprostinil product valid over prior art disclosures of treprostinil due to the structural and functional differences of the product produced by the claims). Because Actavis failed to provide any evidence that the alleged prior art products—alone or modified by the teachings of other references—and the '393 patent's product are structurally and functionally the same, Actavis's obviousness contentions fail.

In sum, Actavis fails to identify how or why a person of ordinary skill in the art would look to the twenty-seven references to make the very pure treprostinil product claimed in the '393 patent or have a reasonable expectation of success in doing so. Thus Actavis has failed to demonstrate essential pieces of a *prima facie* case of obviousness, and thus has failed to clearly and convincingly show that '393 patent is invalid. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 933, (U.S. 2013) (citing *Procter & Gamble*, 566 F.3d at 994) (To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so."). Instead, what Actavis has presented is a case of hindsight, by using the teachings of the patent as a blueprint to pick and choose from the prior art. *See Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into use of hindsight'"); *see also State Industries, Inc. v. A.O. Smith Corp.*, 221 U.S.P.Q. (BNA) 958, 973 (M.D. Tenn. 1983), *aff'd in part, rev'd in part*, 751 F.2d 1226 (Fed. Cir. 1985) (an infringer's need to cite a large number of prior art references can indicate to a court that the invention was novel and not obvious.). Moreover, there would have been no legitimate reason or motivation for a skilled artisan at the

time of invention to combine the cited references, and these references, alone or in combination, do not render the claims obvious.

1. The Dependent Claims Are Further Patentably Distinct Due to Their Additional Limitations

Claims 2-8 and 10-22 are nonobvious over the cited references because they depend from valid base claims as well as because they recite additional limitations which further distinguish these claims over the prior art.

For example, Claims 6, 10, 15, and 21-22 are to the free acid of Formula (I) or treprostinil. As mentioned above, all of Actavis's alleged combinations of prior art start with a Moriarty process reference. The free acid treprostinil in the Moriarty process was analyzed by United Therapeutics, and representative samples were found to contain a different impurity profile.

As explained previously, the claimed free-acid compounds, including treprostinil, produced by the processes of claims 6, 10, 15, and 21 provided a new product that induced FDA to adopt a new purity standard for treprostinil free acid due to the excellent purity of the final product. Furthermore, United Therapeutics demonstrated that treprostinil free acid made by the claimed methods provided a compound without many of the impurities included in the free acid treprostinil of the Moriarty references processes, including the two different stereoisomers of treprostinil.

The prior art does not provide a reason that a skilled artisan would include a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step. For example, Phares 2005 merely discloses forming a salt from treprostinil free acid of undisclosed origin. There is no

suggestion that this salt should then be converted back to the free acid (*e.g.*, there is no suggestion of using the salt formation as a purification method).

As discussed above, the impurities in representative examples of the Moriarty process include two different stereoisomers of treprostinil free acid. The prior art identified by Actavis, *i.e.*, Ege, however suggests that a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would not remove these compounds from the product. Thus, a skilled artisan looking to make the free acid product of claims 6, 10, 15, and 21-22, such as treprostinil free acid, would have understood the Moriarty references combined with the Actavis prior art (*e.g.*, Phares 2005 and Ege) to suggest simply making the treprostinil free acid product of the Moriarty references, and not undergoing the additional time and expense of a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step. In fact, at least one Actavis prior art reference, Ege, actually teaches away from the usefulness of this step.

In sum, even though Actavis cites prior art (*e.g.*, Phares 2005) that allegedly discloses forming a salt from treprostinil free acid, and prior art (*e.g.*, Ege) that generally discusses that carboxylate salt formation was known in the art, there would have been no motivation or expectation of success in using these teachings on the already-formed free acid disclosed in the Moriarty references, and Actavis has failed to establish that a skilled artisan would have carried out steps necessary to inherently obtain the claimed products. Thus, Actavis fails to establish *prima facie* case that claims 6, 10, 15 and 22 are invalid as obvious.

2. Secondary Considerations[5]

Actavis has not established a *prima facie* case of obviousness. Thus, Plaintiffs are not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness provide strong evidence that the claims of the '393 patent are not obvious and, in fact, represent a surprising solution to a serious problem of minimizing potentially hazardous impurities and providing a safer and purer treprostinil product.

a) Long-Felt Need

At the time of the invention, there was a long-felt need to have a shorter, more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner with fewer impurities. Treprostinil has five chiral centers resulting in 32 possible stereoisomers so the potential for stereoisomeric impurities is high and only the treprostinil stereoisomer has the desired pharmaceutical effect. *United Therapeutics*, 2014 WL 4259153 at *2-3. Treprostinil is also a very potent drug so any stereoisomeric impurities would also potentially be potent and could potentially have deleterious effects. *Id.* Thus, there was a need to reduce the amount of impurities as much as possible and the product of the '393 patent further reduces impurities over the previous treprostinil products made by the prior art.

b) Teaching Away

The prior art taught away from the invention claimed in the '393 patent as indicated above and the accompanying charts.

---

[5] A brief summary of Plaintiffs' contentions regarding these secondary considerations for each patent and citations to representative supporting documentations appears herein. Plaintiffs reserve their rights to further develop these contentions and expect to produce additional, non-privileged documents and information relevant to these issues during the course of fact and expert discovery consistent with the scheduling order and local rules.

c) Unexpected Results

The results of the claimed inventions in the '393 patent were unexpected. For example, the use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was unexpected. Moreover, it was unexpected that the salt purification step reduced not only diastereomeric impurities, but also non-acidic impurities as well. Thus, a person of skill in the art would not have expected the results of the '393 patent to be so successful.

d) Commercial Success

The '393 patent is used in the current production of Tyvaso®, Remodulin®, and Orenitram® which all contain treprostinil. The inventions claimed in the '393 patent have reduced the cost of making treprostinil and increased efficiency. Tyvaso®, Remodulin®, and Orenitram® are commercially successful products. Tyvaso®, Remodulin®, and Orenitram® compete well against potential alternative products; for example, Remodulin® competes well against alternatives such as Flolan. The commercial success of Tyvaso®, Remodulin®, and Orenitram® are reflected in both gross sales figures and relevant market share. Specifically, United Therapeutics made approximately $325.6million, $438.8 million and $463.1 million in Tyvaso® revenues, representing 36 percent, 39 percent and 36 percent of total net revenues for the years ended December 31, 2012, 2013 and 2014, respectively. United Therapeutics (2014), 10-K Report at p. 8, available at http://ir.unither.com/annuals-proxies.cfm. Also, United Therapeutics made approximately $458.0 million, $491.2 million and $553.7 million in Remodulin® revenues, representing 50 percent, 44 percent and 43 percent of its total net revenues for the years ended December 31, 2012, 2013 and 2014, respectively. *Id.* at 6. Orenitram® was launched in the US market in Q2 2014. It is expected that Orenitram® has the

potential to reach $1 billion in annual sales. As of Q2 of 2016, Orenitram® sales grew by nearly 46% compared to the second quarter of 2015 and 470% since the second quarter of 2014 when the product was first launched. For the first half of 2016 United Therapeutics' sales of Orenitram® exceeded $ 78 million. Upon approval by the FDA, United Therapeutics' share price went up by 14%. United Therapeutics will make available for inspection and copying documents demonstrating the commercial success of Tyvaso®, Remodulin®, and Orenitram®.

e) Acclaim and Acknowledgement of Success

The invention claimed in the '393 patent has been praised and acknowledged by researchers, clinicians, and patients as a breakthrough treatment for pulmonary hypertension. United Therapeutics will make available for discovery documents reflecting this acclaim and acknowledgement of success.

f) Copying

The non-obviousness of the '393 patent is evidenced by Actavis's own actions. Actavis seeks to copy the invention of the '393 patent by offering a copycat version of Orenitram®. The non-obviousness of the '393 patent is additionally evidenced by the actions of several other generic pharmaceutical companies who have attempted to copy Remodulin® and Tyvaso®. *See, e.g., United Therapeutics Corp. v. Sandoz, Inc.*, Civil Action No. 3:14-cv-05499-PGS-LHG (D.N.J. 2014); *United Therapeutics Corp. v. Teva Pharma*, Civil Action No. 3:14-cv-05498-PGS-LHG (D.N.J. 2014); *United Therapeutics Corp. v. Watson*, Civil Action No. 3:15-cv-05723-PGS-LHG (D.N.J. 2015). As stated, above, the '393 patent product and process is currently used in the production of Remodulin®, Tyvaso®, and Orenitram®.

E. The Asserted Claims of the '393 Patent Are Not Invalid for Obviousness-Type Double Patenting

Actavis's entire obviousness-type double-patenting argument can be summarized as: because the claims of the '117 patent, '311 patent, and the '393 patent are each directed to the same chemical compound, treprostinil (and its pharmacologically acceptable salt form), then that mere disclosure of treprostinil in the '117 and '311 patents necessarily renders obvious the claims of the '393 patent. *See* AIC at 56-57. Actavis is wrong. As previously discussed, the mere disclosure of treprostinil does not render obvious any claim of the '393 patent.

Moreover, Actavis does not correctly apply the law on obviousness-type double patenting. Inexplicably, Actavis recites the rule that obviousness-type double patenting requires that only the claims of the prior art are compared to the asserted claims, but then ignores the rule's application and relies upon each patent being "directed to the product treprostinil and its pharmacologically acceptable salt form". *See* AIC at 57; *see also Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385 (Fed. Cir. 2003) (reciting the law for obviousness-type double patenting). Nevertheless, the claims of the '393 patent are very different than the claims of the '117 patent. Specifically, the '393 patent's claims recite different process elements from the '117 patent's claims. *Compare* '117 patent cl. 1; *with* '393 patent cl. 1. For example, the '117 patent's claims require that treprostinil be stereoselectively produced using the source limitations of starting enyne and cyclized intermediate. Further, the '117 patent claims do not disclose steps (a), (b), (c), or (d) of the '393 patent claims. Also, the '117 patent claims do not disclose a product with at least 99.5% purity as required by claim 2 of the '393 patent. Actavis's contentions, however, gloss over the process elements of the claims, while providing no support

for its apparent assumption that these process elements are irrelevant to an obviousness-type double patenting analysis. This oversight alone is fatal to this invalidity defense.

Furthermore, not only are the claims of the '117 patent very different than the claims of the '393 patent, but also the patents' resulting products are structurally and functionally different from each other. For example, as described above, the '393 patent produces a treprostinil drug product having a higher level of average purity, lower number of individual impurities, and is a better product as compared to the drug product of the '117 patent. *See supra* discussion of Moriarty References. Also, the '117 patent does not specifically disclose treprostinil diethanolamine salt. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Because the '393 patent's treprostinil product is structurally and functionally different from the '117 patent's product, it is also patentably distinct. *See In re Garnero*, 412 F.2d at 279; *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573 at *140-149 (finding claims directed to producing a treprostinil product valid over prior art disclosures of treprostinil due to the structural and functional differences of the product produced by the claims).

Similarly inapposite are Actavis's arguments as to the '311 patent. First, the '311 patent is directed to a *method* of producing a *crystalline salt* of treprostinil. The '393 patent is directed to an improved pure treprostinil produced by a novel method. As noted above in connection with Phares 2005, which is a parent application to the asserted '311 patent, the starting treprostinil material used in the '311 patent is not disclosed and therefore cannot anticipate (explicitly or inherently) the final treprostinil product of the '393 patent because each method of

producing treprostinil would contain its own distinct impurity profile. No specific purity or method of synthesis is disclosed in the '311 patent that would render the claims of the '393 patent obvious.

Thus, the '117 patent does not render the claims of the '393 patent invalid for obviousness-type double patenting.

F. The Asserted Claims of the '393 Patent Are Not Invalid for Lack of Enablement or Lack of Written Description

Actavis claims that:

> [I]f plaintiff contends that it would have required undue experimentation for a POSA to apply the knowledge known to a POSA from the prior art to obtain the claimed methods (for example it would have required undue experimentation to find particular bases or a particular alkylating agent), the claims would then be invalid for lack of an enabling description. To the extent that plaintiff contends that certain bases or reaction conditions, for example, are unique and that undue experimentation would have been required to practice the claimed method, the claims of the '393 patent are not enabled or fail to meet the written description requirement.

AIC at 60-61. Actavis conflates the distinct concepts of enablement, written description and undue experimentation, and fails to sufficiently allege invalidity on these bases.

Enablement is met "when at the time of filing the application one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (citing *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988)). Therefore, the relevant inquiry as to whether "undue experimentation" is required for purposes of determining enablement is measured from the specification, not the "prior art procedures" as Actavis asserts. Further, whether undue experimentation is required "is not a single, simple factual determination, but rather a conclusion reached by weighing many factual considerations." *Id.* Actavis fails to even contend relevant factors related to (1) the quantity of experimentation necessary, (2) the amount of direction or

guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Accordingly, Actavis has failed to even allege facts sufficient to establish by clear and convincing evidence that the asserted claims of the '393 patent are not enabled. Moreover, one skilled in the art, having read the specification, could practice the invention of the '393 patent without undue experimentation given the clear teachings to make the more pure treprostinil product claimed.

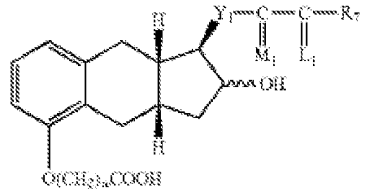
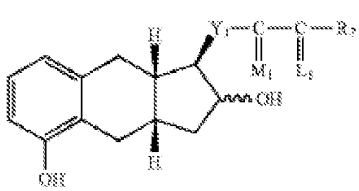
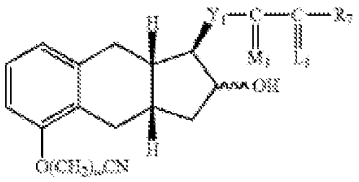
Additionally, the test for sufficiency of written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Actavis's contentions are insufficient as to written description because they fail to even allege that the disclosures of the '393 patent do not convey to a POSA that United Therapeutics had possession of the claimed subject matter. Each of the asserted claims of the '393 patent fulfill the requirements of written description by conveying that the inventors were in possession of the claimed subject matter as of the filing date.

[redacted]

EXHIBIT A

UNITED STATES PATENT NO. 8,497,393[15]

A. Response to Actavis's Invalidity Contentions – United States Patent No. 8,497,393

Claim	Representative Deficiencies in Prior Art Disclosure
Claim 1	
A product comprising a compound of formula I (I)  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III)  wherein w=1,2, or 3;	Actavis failed to provide a "chart identifying where specifically in each alleged item of prior art each limitation of each asserted claim is found." L.P. R. 3.3(c). Even though Actavis improperly lists claim 1 as a single limitation, Plaintiffs response "follow[s] the order of [Actavis's] chart."[16] The Asserted Claims are not anticipated because no single, enabling reference identified by Actavis discloses each and every element of the claimed invention. Actavis's Invalidity Chart does not specify which references allegedly anticipate the '393 patent, but Actavis's narrative identifies the '117 Patent, Moriarty et al., The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: synthesis of UT-15 (Treprostinil), J. Org. Chemistry., 69(6), 1890-1902 (2004) ("Moriarty 2004"), United Therapeutics' own Remodulin® drug product, and U.S. Patent Publication No. 2005/0085540 (April 2005), ("Phares 2005") in its anticipation section, but with very limited

[15] This case is only in the initial stages of discovery and Plaintiffs are still investigating its claims against Actavis. The responses to Actavis's invalidity contentions set forth herein are therefore based on information presently available to Plaintiffs. Plaintiffs reserve their rights to amend and/or supplement these contentions pursuant to the Local Patent Rules.

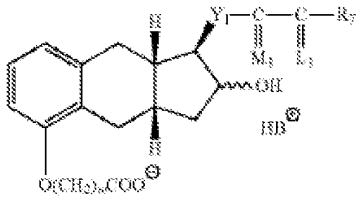
[16] Actavis provides claim 1 as a single limitation and thus does not identify which of the references it lists under claim 1 allegedly disclose each limitation. Actavis has therefore waived arguments regarding the absence of any particular limitation in its cited references including by failing to identify any specific combinations of references for obviousness in its claim chart.

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
Y_1 is trans-CH=CH–, cis-CH+CH–, –$CH_2(CH_2)_m$–, or –C=C–; m is 1, 2, or 3; R_7 is (1) –C_pH_{2p}–CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy, optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl (4) cis-CH=CH–CH_2–CH_3, (5) –$(CH_2)_2$–CH(OH) –CH_3, or (6) –$(CH_2)_3$–CH=$C(CH_3)_2$; –C(L_1)–R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl; (2) 2-(2-furyl)ethyl,	detail as to why such references anticipate the claims other than the allegation that treprostinil was disclosed in each of these references. The fact that each reference discloses treprostinil or salts of treprostinil does not mean that the claims are anticipated. Indeed, the Patent Office reviewed many references that disclosed treprostinil (including each of the published documents Actavis cites) and allowed the claims, as Actavis acknowledges. *See* AIC at 46 (citing to discussion of the development of treprostinil in the '393 patent, which cites Moriarty 2004, Phares 2005, and the '117 patent). Thus the mere disclosure of treprostinil cannot anticipate the claims. Specifically, the '393 patent discloses a different and more pure treprostinil product with fewer impurities than the prior art. Indeed, during prosecution, the '393 patent was rejected by the Examiner in view of the Moriarty 2004 reference (which discloses the same synthesis as the '117 patent) and the Examiner subsequently allowed the claims over the reference because the products were different. '393 Patent File history, Office Action dated May 15, 2013 (UTC_WAT_00001593-1598); Office Action Response dated June 5, 2013 (UTC_WAT_00001603-1611); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001626-1631). Additionally, the specification of the '393 patent details many of the differences of the '117 patent and Moriarty 2004 (identified as "Former Process") as compared to the '393 patent in Example 6 which is incorporated herein. '393 patent, Col. 15:1-17:25.[17]

[17] Plaintiffs further incorporate by reference their arguments and analysis in favor of patentability of the '393 patent presented in IPR206-00006. In particular, Plaintiffs incorporate by reference the following which demonstrate the

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
(3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro, (b) hydrolyzing the product of formula III of step (a) with a base, (c) contacting the product of step (h) with a base B to form a salt of formula I_s, (I_s)  and, (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	As an initial matter, United Therapeutics notes that the synthesis disclosed in the '117 patent and Moriarty 2004, are essentially the same. *See* '117 patent, Col. 7- 10; Moriarty 2004 at 1894-96. Additionally, the Remodulin treprostinil products, on sale prior to the priority date of the '393 patent, were also made by the '117 patent process. Since the synthetic method for treprostinil described in each of these references is essentially the same as that set forth in the '117 patent, they will be considered together ("the Moriarty references"). The Phares 2005 reference, however, does not disclose a synthesis for treprostinil, but only its enantiomer. Thus, it is unclear what process Actavis is alleging was used to make the treprostinil referenced in Phares 2005. Regardless, none of the allegedly anticipating references disclose, explicitly or inherently, the synthesis process recited in the '393 patent's claims. Indeed, Actavis does not even argue that they do. Moreover, the product of the '393 patent is structurally and functionally different than the products of the Moriarty references and Phares 2005 because the '393 patent has a higher level of average purity, lower number of individual impurities, and better product. For example, in a document entitled "Treprostinil Drug Substance Impurities", all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by Moriarty references' process. *See*

differences between the products of the Former Process and the claims of the '393 patent from *Steadymed Ltd. v. United Therapeutics Corp.*, IPR2016-00006 (P.T.A.B.): 1) Patent Owner Preliminary Response; 2) Patent Owner Response; 3) Declaration of Robert M. Williams, Ph.D.; and 4) Declaration of Robert R. Ruffolo, Jr., PhD.

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	UTC-Sand-Rem00334054-057 and UTC-Sand-Rem01156295-302; *see also*, UTCSand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty references' process. *See, e.g.*, UTCSand-Rem00001712-741; UTC-Sand-Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTC-Sand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTC-Sand-Rem01111355-357; UTC-Sand-Rem01117901-906; UTC-Sand- Rem01117910-912; UTC-Sand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Still other documents

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	show that the batches made by the '393 patent process have a better impurity profile on average as well as less total impurities.[18] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the alleged prior art specifies the level of purity or minimal level of impurities that the '393 patent provides. Additionally, the FDA accepted a new purity specification when United Therapeutics implemented the inventions of the '393 patent. For example, a process validation report (Protocol No. "VAL-00131") states that it applies to "production of treprostinil diethanolamine intermediate (UT-15C-I), a chemical intermediate used for the production of active pharmaceutical ingredients treprostinil (UT-15) and treprostinil diethanolamine (UT-15C)." Validation Report at 8 (UTC-Sand-Rem00092436-449). This validation report also shows that each of steps (a)-(c) of the claims of the '393 patent are carried out in this new process. *Id.* at 5-7. A Process Optimization Report also provides results for batches resulting from step (d) of the claims of the '393 patent, which was performed on specific batches of the diethanolamine salt intermediate produced by steps (a)- (c) that are referenced in the Validation Report. Process Optimization at 2 (UTC-Sand-Rem01104769-779) (*compare* batch numbers 03L6002, 03L6003, 03M6004,

[18] The documents cited herein for batches of treprostinil made by the Moriarty references' process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, Plaintiffs reserve the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different.

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	and 03M6006, which are the same UT-15C batch numbers of Validation Report at 4). The Process Optimization Report also states that "diethanolamine salt (UT-15C intermediate) of UT-15 is converted to UT-15 [treprostinil] by an acid-extraction removal of the diethanolamine to give UT-15 [treprostinil]…" The percent yield and purity levels of the final treprostinil product are compared to the former process therein, further demonstrating the differences that result in the final treprostinil product when all of steps (a)-(d) of the '393 patent are performed. Process Optimization Report at 3. Additionally, a letter from United Therapeutics to the FDA, which references the Validation Report, states as follows: [redacted] Validation Report at 2. The Validation Report further states: In all lots, the total unidentified impurity level (%AUC) decreased from triol to UT-15C intermediate. [redacted]

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	[redacted] *Id.* at 3. Finally, this FDA Letter states that, when the new process was implemented, "it was observed that the purity of the treprostinil improved close to 100%", and the letter proposes that "the range of the specification for the HPLC assay for treprostinil be shifted from 97- 101% to 98-102% so that it is centered at 100%." *Id.* at 3-4. The FDA subsequently approved United Therapeutics' proposed implementation of the '393 process and the increased purity standard. FDA Approval Letter, UTC-Sand-Rem00087652-53. Because the product produced by the '393 patent is superior, *inter alia* in impurity profiles, purity, yields and other characteristics of the product, it is not anticipated or rendered obvious. *See, e.g., Abbott Labs. v. Sandoz, Inc.*, 566 F.3d at 1308 (J. Newman, *dissenting*) ("The facts of Thorpe did not concern the exception and expedient where process terms are invoked to describe a new product of complex structure. This exception is rarely invoked. The general rule requiring claims to have a process-free definition of the structure of a new product accommodates most inventions. Some recent exceptions are seen in emerging aspects of biotechnology."); *see also Scripps Clinic,* 927 F.2d at 1565 (process to obtain a "highly purified and concentrated" product that was "largely free of contaminants," was not anticipated by previous

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	disclosure of the product). If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d at 279; *see also Amgen*, 580 F.3d at 1364, 1367, 1370 (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable); *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573 at *140-149 (finding that the '117 patent was not anticipated by prior art disclosures of treprostinil due to a differentiating structure implied by the claimed process). Actavis fails to provide any evidence that the alleged prior art products and the '393 patent's product are structurally and functionally the same. Additionally, early syntheses of treprostinil by the Moriarty references' process yielded less pure products in terms of impurities, yield, and other analytical data. The Phares reference does not disclose what starting treprostinil material is used and therefore cannot anticipate (explicitly or inherently) the final treprostinil product of the '393 patent because each method of producing treprostinil would contain its own distinct impurity profile. In fact, the process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *United Therapeutics*, 2014 WL 4259153 at 53- 55. Accordingly, Actavis cannot establish anticipation based on a teaching of any treprostinil salt product that does not also identify the source of its starting treprostinil material. Indeed, Petitioner fails to identify any specific purity in Phares 2005 that would

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	anticipate any claim of the '393 patent. Claim 2 requires that the product have purity of no less than 99.5%. Moriarty 2004 is the only reference cited by Actavis that discloses a purity with at least 99.5%, but as previously described, the product of the Moriarty 2004 reference is different and the Patent Office explicitly considered that claim in relation to the Moriarty 2004 reference and allowed the '393 patent. '393 Patent File history, Office Action dated May 15, 2013 (UTC_WAT_00001593-1598); Office Action Response dated June 5, 2013 (UTC_WAT_00001603-1611); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001626-1631). Actavis provides no additional citations or support for any other asserted claim. Therefore, the '117 patent, Phares, United Therapeutics' Remodulin®, and Moriarty 2004 do not anticipate any claim of the '393 patent. Further, dependent claims 2-8 and 10-22 are not anticipated by the cited references because they depend from a novel base claim, as well as because they recite additional limitations which further distinguish these claims over the prior art. **The Asserted Claims of the '393 Patent Are Not Rendered Obvious By Actavis's Alleged Prior Art** As previously discussed, Actavis provides no specific obviousness combinations in its Invalidity Chart. Instead, in its narrative, Actavis presents "numerous different combinations", having hundreds of permutations. AIC at 55-56. Specifically, Actavis alleges the '393 patent's claims would be rendered obvious by one or more of the

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	Moriarty references in various combination with one or more of Monson, Eliel, Jones, Kawakami, Ege, and/or Wade. *Id.* Nevertheless, despite proposing hundreds of combinations, Actavis provides *no analysis* as to why or how a skilled artisan would make *even one* of these listed combinations. Actavis's narrative is merely a meandering recital of various disclosures in the prior art—including the reliance on references *not* listed in any proposed combinations—without any effort made to put forward a *prima facie* case of why or how a skilled artisan would take these teachings to arrive at the process for making the highly pure treprostinil claimed by the '393 patent, or whether a skilled artisan would even have a reasonable expectation of success in doing so. Accordingly, Actavis has waived its obviousness defenses because they have failed to recite even one *prima facie* case of obviousness. *See, e.g., Horizon Pharma AG*, 2015 U.S. Dist. LEXIS 80853 at *14-18 (denying defendant's motion to amend its contentions, finding that the Defendant had not acted "diligently" and noting that the local rules "require parties to crystallize their theories of the case early in the litigation and to adhere to these theories once they have been disclosed") (citing *Nova Measuring*, 417 F. Supp. 2d at 1122-23). Regardless, none of the references cited by Actavis, alone or in combination, would render obvious any claim of the '393 patent.[19] First, Actavis's contentions regarding the alkylation and hydrolysis steps do not advance

[19] In addition to the nonobviousness contentions presented herein and in the accompanying chart, Plaintiffs incorporate by reference the novelty arguments presented above.

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	their obviousness allegations. For example, Actavis cites McManus for the contention that alkylation using chloroacetonitrile and subsequent hydrolysis to a carboxylic acid was known, but fails to indicate how this is relevant to the obviousness analysis because the '393 patent itself references disclosures that demonstrate those same steps—such as the '117 patent and Moriarty 2004—and the Patent Office already considered and found that the '393 patent was distinguishable over those disclosures. *See* AIC at 46-48; '393 Patent at 1:22-28; '393 Patent File History: Office Action dated May 15, 2013 (UTC_WAT_00001593-1598); Office Action Response dated June 5, 2013 (UTC_WAT_00001603-1611); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001626-1631). Further, Actavis cites Lin and Aristoff, but these references fail to even disclose treprostinil and discuss other prostaglandins not related to the product of the '393 patent. Indeed, most the references identified in Actavis's Invalidity Chart do not disclose treprostinil. Second, Actavis cites several references discussing "purification" steps, but Actavis fails to identify how or why any of these references would be used by a person of skill in the art to further purify and optimize the existing prior art treprostinil to arrive at the claims of the '393 patent, and fails to discuss whether a person of skill in the art would have a reasonable expectation of success in doing so. *See* AIC at 46-48. Specifically, Actavis cites Monson, Arumugan and Yu for the fact that "column chromatography is not favored for large-scale production", cites Monson and Harwood21 to

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	support its allegations that the use of crystallization and recrystallization as a purification technique was well-known, and similarly cites Eliel and Jones to show that "carboxylate ammonium salts are formed from adding a carboxylic acid with an amine and that those salts can be purified by recrystallization." *See* AIC at 46-48. Actavis then concludes "a POSA would have been motivated to [modify the prior art synthesis of treprostinil utilizing column chromatography] by applying an obvious form of purification, salt crystallization, to form known salt forms of treprostinil." Actavis's conclusion fails for several reasons. As examples, Actavis fails to provide any evidence, or indeed argue, that the substitution would have been expected to result in the highly pure treprostinil claimed in the '393 patent, and Actavis fails to discuss whether crystallization/recrystallization would even address the issues as to why column chromatography is allegedly not favored in large-scale production. *See KSR*, 550 U.S. at 418 (a claim is not proved obvious merely by demonstrating that something was possible or known in the prior art). Additionally, Actavis has failed to show that step (c) of the '393 patent would necessarily lead to the same final product if made from different starting treprostinil materials than that made from steps (a) and (b). The process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *United Therapeutics*, 2014 WL 4259153 at 53-55. During prosecution, United Therapeutics demonstrated that the final treprostinil product from the '393 patent is physically different than that of the Moriarty references. Thus, even if the Moriarty references' treprostinil

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	products were used as a starting point, Actavis has failed to provide any evidence that, if step (c) was somehow obvious to apply, that the resulting treprostinil product would necessarily be the same as the products claimed in the '393 patent. For example, the declaration of Dr. Walsh submitted during original prosecution shows that certain impurities in representative examples are reduced below detectable amounts by step (c), while others are still present in detectable amounts, such as treprostinil stereoisomer 3AU90. '393 Patent File History at p. 346-350. Both the type of impurity, as well as the relative amount of that impurity in the starting treprostinil material, may impact the impurity profile of the final product after step (c), yet there is absolutely no disclosure of any specific impurities or total amount of impurities by Actavis on this point. Actavis also cites Sorrell, Wiberg, Schoffstall, and Pavia, but each only provides a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. *See* AIC at 49-50. In fact, most of Actavis's purification references do not disclose treprostinil, prostacyclin analogues, or preferred methods of purification for such substances. And instead of providing a specific method of purifying complex molecules such as prostacyclin analogues, Actavis's cited references largely provide a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. Moreover, Actavis fails to provide any detail on how or why a person of ordinary skill in the art would look to very basic and sometimes decades old references to determine how to make the highly pure product produced by the '393

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	patent or have any reasonable expectation of success in doing so. Third, Actavis also cites the 2005 Physician's Desk Reference, Burk, Ohno, and Priscinzano for the contention that the diethanolamine salt was known and preferred. *See* AIC at 49. But the asserted claims of the '393 patent do not all require specifically that carboxylic ammonium salts are formed from carboxylic acids and amines and do not specifically require the diethanolamine salt. Contrary to Actavis's arguments, these references only show very general information that is not directed towards benzindene prostacyclin analogues, much less treprostinil. Indeed, a person of ordinary skill in the art would not have considered these additional basic references to improve the product of the existing prior art treprostinil products and would not have a reasonable expectation of success in combining these very basic references with known syntheses of treprostinil. Fourth, Actavis cites Wade to show that physiologically acceptable salts of treprostinil include salts derived from bases such as ammonia, N-methyl-D-glucamine, magnesium, arginine, and lysine. AIC at 49. Once again, however, Actavis fails to provide any detail as to how this is relevant to the obviousness of the asserted claims. Fifth, Actavis also cites Phares 2005, Kawakami, and Ege for the proposition that steps (c) and (d) of the '393 patent were obvious. None of these references, however, disclose steps (c) or (d) as claimed in the '393 patent. Specifically, Actavis alleges that it would have been obvious to a person of ordinary skill in the art to contact "a carboxylic

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt" and that this salt "can be further precipitated and purified" or dissolved into its fee-acid form. *See* AIC at 50. These references alone or on combination, however, do not establish that the '393 patent's claims were obvious. Actavis apparently cites Phares 2005 at page 24 for teaching step (c); however, the cited portion merely describes an example of how to make treprostinil diethanolamine from a starting material of treprostinil acid, but provides no detail whatsoever about how the starting treprostinil acid was made or where it comes from. Similarly, Actavis cites Phares 2005 at pages 85-93 as relevant to the teachings of step (c), but these portions describe a clinical study of sustained release capsules and tablets of treprostinil diethanolamine and to a polymorph characterization study of treprostinil diethanolamine. Again, there is no indication in this portion of Phares 2005 what process was actually used to make the starting "treprostinil acid" for the treprostinil diethanolamine. And, as discussed above, Phares 2005 fails to disclose the synthetic route or purity of the claimed treprostinil product. However, the process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *See United Therapeutics*, 2014 WL 4259153 at *53-55. Accordingly, by failing to show that performing step (c) on a starting treprostinil material, which has a different impurity profile than a starting treprostinil material made by performing steps (a) and (b) of the asserted claims, would necessarily lead to an identical product, Actavis's arguments relating to obviousness over Phares 2005

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	necessarily fail. Regarding Kawakami, Actavis has failed to establish that the '393 patent is obvious over any Kawakami combination. Simply put, Kawakami is directed to entirely different compounds with entirely different impurity profiles than the '393 patent. The alleged "prostacyclin compound" disclosed in Kawakami is a two ring structure, yet the core three ring structure of treprostinil is key to its pharmaceutical usefulness (*United Therapeutics*, 2014 WL 4259153 at *4-5) and is also present in every structure of every step of the '393 patent. *See, e.g.*, '393 patent claim 1. Indeed, nothing in Kawakami comes close to even addressing the treprostinil product of the '393 patent much less how a skilled artisan would or would not go about synthesizing or purifying the product. Thus, a skilled artisan would have had no motivation to combine Kawakami with, for example, Phares 2005 or the Moriarty references, and would have had no reasonable expectation of success of obtaining the same high purity treprostinil product of the '393 patent. Additionally, to the extent Actavis is alleging that Kawakami could remedy the deficiencies of the prior art treprostinil compounds (*e.g.*, Moriarty references compounds) to disclose the impurity profile of the claimed treprostinil products, Actavis has failed to establish a motivation to combine or reasonable expectation of success of forming a salt of the prior art treprostinil compounds with a purity profile of the products in the claims. Actavis offers no basis from which to draw any conclusion about whether an impurity reduction step in Kawakami would possibly have any relevance to a process to synthesize

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	and or purify a totally different structure such as treprostinil. To illustrate this point further, Kawakami is directed to purifying E- and Zisomers of "prostacyclin compounds" from one another. In order for the E- and Z-isomers to exist, the "prostacyclin compound" must have an alkene. Treprostinil, on the other hand, contains no mixture of E/Z isomers. In fact, it cannot because it does not contain an alkene capable of E/Z isomerization. Actavis has failed to provide a factual basis as to how or why the separation of E/Z isomers of an alkene would provide a motivation to combine or reasonable expectation of success in a compound not containing an alkene capable of E/Z isomerization, such as treprostinil. For these reasons, a skilled artisan would have no motivation to look at Kawakami in order to arrive at the claimed invention of the '393 patent. Similarly, Ege provides no additional support for Actavis's obviousness contentions. Ege is merely an undergraduate chemistry textbook with only generalized descriptions of carboxylic acids and related synthetic procedures, and discloses nothing about any prostacyclin derivative, much less treprostinil free acid. Indeed, Ege fails to disclose anything about the synthesis of pharmaceuticals at all. Ege merely shows it was known to form a free acid from treatment of the corresponding carboxylate salt with a strong acid, but this fact alone provides no reason why a skilled artisan, based on any reference, would conduct a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step with a reasonable expectation of obtaining the claimed products of the '393 patent's claims. In fact, Ege actually suggests this "carboxylate salt formation and regeneration of the neutral

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	carboxylic acid" step would be relatively useless as a means for purifying treprostinil. *See* Ege at 8 (stating that the "properties of carboxylic acids are useful for separating them from reaction mixtures containing neutral and basic compounds", which is irrelevant to the claimed treprostinil process). Thus, Ege would not create an expectation of success for separating one carboxylicacid compound (*e.g.*, treprostinil free acid) from other carboxylic-acid containing compounds (*e.g.*, different stereoisomers of treprostinil free acid). By its invalidity contentions, it is obvious that Actavis misunderstands the claims of the '393 patent. For example, the claimed invention is not the discovery that carboxylic acids react with bases, but rather that compounds of Formula (I), and in particular treprostinil or a salt thereof, can be obtained with a superior purity profile compared to the prior art. Specifically, performing step (c) on a product which resulted from steps (a) and (b) provided a product with reduced impurities—which was not disclosed in the Moriarty references and resulted in a significant improvement in the treprostinil product being made at the time of invention. In fact, during prosecution of the '393 patent established the impurity profile of the '393 patent claims is different from the impurity profiles of Moriarty 2004. *See* '393 Patent File History, Office Action Response dated June 5, 2013 (UTC_WAT_00001603-1611). Actavis appears to argue that the salt formation step would have been obvious to reduce or remove acidic or basic impurities, but each of these reduced or removed impurities are neither strongly acidic or basic as each are either diastereomers of treprostinil—which is very weakly acidic—or similarly neutral ester and triol impurities. The '393 patent therefore not only reduced the

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	weakly acidic impurities present from the Moriarty process, but also unexpectedly reduced or eliminated non-acidic impurities as well. Thus, even under Actavis's erroneous understanding, it was unexpected that the salt formation step would remove these additional impurities. Finally, Actavis fails to address the distinctive structural and functional characteristics of the product produced by the '393 patents claims. If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d at 279; *see also United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573 at *140-149 (finding claims directed to producing a treprostinil product valid over prior art disclosures of treprostinil due to the structural and functional differences of the product produced by the claims). Because Actavis failed to provide any evidence that the alleged prior art products—alone or modified by the teachings of other references—and the '393 patent's product are structurally and functionally the same, Actavis's obviousness contentions fail. In sum, Actavis fails to identify how or why a person of ordinary skill in the art would look to these twenty-five references to make the very pure treprostinil product claimed in the '393 patent or have a reasonable expectation of success in doing so. Thus Actavis has failed to demonstrate essential pieces of a *prima facie* case of obviousness, and thus has failed to clearly and convincingly show that '393 patent is invalid. *See In re Cyclobenzaprine*, 676 F.3d

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	at 1069 (citing *Procter & Gamble*, 566 F.3d at 994) (To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.") Instead, what Actavis has presented is a clear case of hindsight, by using the teachings of the patent as a blue print to pick and choose from the prior art. *See Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into use of hindsight'"); *see also State Industries,* 221 U.S.P.Q. (BNA) at 973 (an infringer's need to cite a large number of prior art references can indicate to a court that the invention was novel and not obvious.). Moreover, there would have been no legitimate reason or motivation for a skilled artisan at the time of invention to combine the cited references, and these references, alone or in combination, do not render the claims obvious. Neither Olmsted nor Sharp discuss treprostinil or a pharmaceutically acceptable salt of treprostinil, much less a method of producing it according to the present invention. Sharp and Olmsted does not mention treprostinil or any benzindene prostacyclin and provides only a general description of purification techniques. Olmsted discusses the idea of recrystallization of an already existing solid with impurities in a single solvent—it does not discuss the claimed method Olmsted at 476. Sharp at 64 discusses the utility of crystallization where solid compounds are more soluble in hot than cold

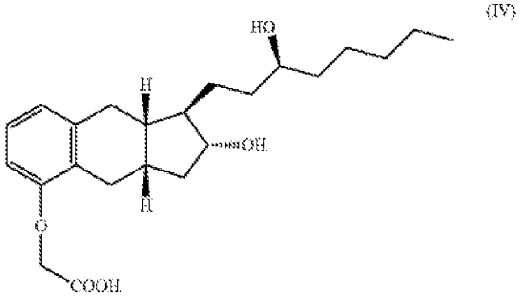
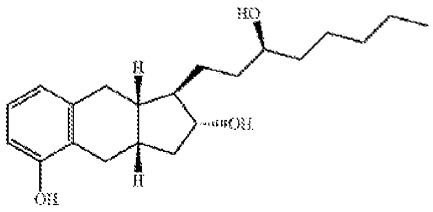
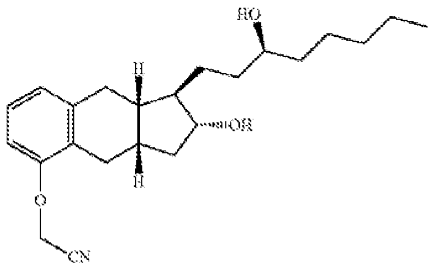
(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	solvents, not the use of different solvents or any direction toward the claimed method. Plaintiffs incorporate by reference herein its discussion above, including with respect to secondary consideration of nonobviousness.
Claim 2	
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	*See* Claim 1.
Claim 3	
The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	*See* Claim 1. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. While Actavis's narrative alleges that the '117 Patent & Moriarty 2004 disclose "the alkylating agent is ClCH2CN", as described above in connection with claim 1, these disclosures are unavailing as the claimed process steps are distinguishable from these references, which the PTO has already decided. Moreover, the vast majority of the prior art cited by Actavis provides no disclosure of these particular alkylating agents whatsoever.
Claim 4	
The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. While Actavis's narrative alleges that certain prior art (*i.e.*, '117 Patent and Moriarty 2004) disclose a KOH or NaOH base, similar to what has been described above in connection with claim 1, this disclosure does not advance Actavis's arguments because it does not teach or suggest that KOH or NaOH is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 5	
The product of claim 1, wherein the base B in	*See* Claim 1. Actavis does not present an

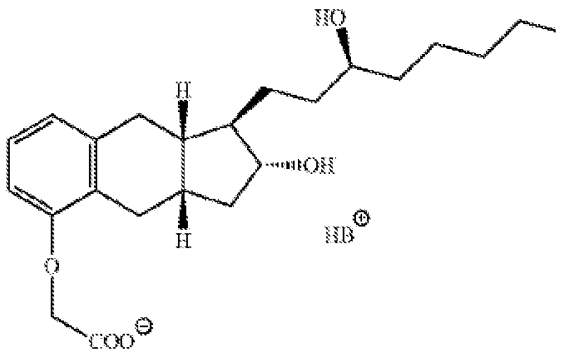
(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	independent reason for the obviousness of this claim so no response is needed. Actavis's narrative alleges that Phares 2005 discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred," and Wade discloses "physiologically acceptable salts of treprostinil include salts derived from these [claim 13's] bases." However, similar to what has been as described above in connection with claim 1, this disclosure does not advance Actavis's arguments because Wade and Phares 2005 does not teach or suggest that a base B as defined in this claim is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 6	
The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.	*See* Claim 1. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (*i.e.*, "reacting the salt formed in step (c) with an acid to form the compound of formula I") And while Actavis's narrative alleges that certain prior art (*i.e.*, '117 Patent & Moriarty 2004) discloses that salts of treprostinil could be reacted with diluted HCl to from treprostinil, similar to what has been described above in connection with claim 1, the prior art, alone or in combination, does not disclose or otherwise suggest that claimed step (d) is performed on the treprostinil compound formed by steps (a), (b), and (c), as this claim requires.
Claim 7	
The product of claim 1, wherein Y_1 is $–CH_2CH_2–$; M_1 is α-OH:β-H or α-H:β-OH; $–C(L_1)$-R_7 taken together is $–(CH_2)_4CH_3$; and w	*See* Claim 1. Actavis does not present an independent reason for the obviousness of this claim so no response is needed.

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
is 1.	
Claim 8	
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See* Claim 1. Actavis does not present an independent reason for the obviousness of this claim so no response is needed.
Claim 9	
A product comprising a compound having formula IV (IV)  Or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, (V)  (VI) 	The difference between claim 9 and claim 1 is that the structures displayed are limited to synthesis of treprostinil. Actavis provides no additional citations or information regarding this claim limitation over what was provided for claim 1. Plaintiffs incorporate by reference all arguments regarding Claim 1 above.

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
(b) hydrolyzing the product of formula VI of step (a) with a base, (c) contacting the product of step (h) with a base B to form a salt of formula IV_s, and .  (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	
Claim 10	
The product of claim 9, wherein the purity of product of step (d) is at least 99.5%.	*See* claim 9. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior art discloses step (d) (*i.e.*, "reacting the salt formed in step (c) with an acid to form the compound for formula I.")
Claim 11	
The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.	*See* Claim 9. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. While Actavis's narrative alleges that the '117 Patent & Moriarty 2004 disclose "the alkylating agent is ClCH2CN", as described above in connection with claim 1, these disclosures are unavailing as the claimed process steps are distinguishable from these

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	references, which the PTO has already decided.
Claim 12	
The product of claim 9, wherein the base in step (b) is KOH.	*See* Claim 9. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. While Actavis's narrative alleges that certain prior art (*i.e.*, '117 Patent and Moriarty 2004) disclose a KOH base, similar to what has been described above in connection with claim 1, this disclosure does not advance Actavis's arguments because it does not teach or suggest that KOH is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 13	
The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	*See* Claim 9. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. Actavis's narrative alleges that Phares 2005 discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred", and Wade discloses "physiologically acceptable salts of treprostinil include salts derived from these [claim 13's] bases." However, similar to what has been as described above in connection with claim 1, this disclosure does not advance Actavis's arguments because Wade and Phares 2005 does not teach or suggest that a base B as defined in this claim is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 14	
The product of claim 9, wherein the base B is diethanolamine.	*See* Claim 9. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. While Actavis's narrative alleges that Phares

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
	2005 discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred", similar to what has been described above in connection with claim 1, this disclosure does not advance Actavis's arguments because Phares 2005 does not teach or suggest that diethanolamine is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 15	
The product of claim 9, wherein the acid in step (d) is HCl.	*See* Claim 9. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (*i.e.*, "reacting the salt formed in step (c) with an acid to form the compound of formula I") And while Actavis's narrative alleges that certain prior art (*i.e.*, '117 Patent & Moriarty 2004) discloses that salts of treprostinil could be reacted with diluted HCL to from treprostinil, similar to what has been described above in connection with claim 1, the prior art, alone or in combination, does not disclose or otherwise suggest that claimed step (d) is performed on the treprostinil compound formed by steps (a), (b), and (c), as this claim requires.
Claim 16	
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See* Claim 9. Actavis does not present an independent reason for the obviousness of this claim so no response is needed.
Claim 17	
The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysinc, L-	*See* Claims 9 and 16. Actavis does not present an independent reason for the obviousness of this claim so no response is needed.

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
arginine, tricthanolamine, and diethanolamine.	While Actavis's narrative alleges that Phares 2005 discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred", similar to what has been as described above in connection with claim 1, this disclosure does not advance Actavis's arguments because Phares 2005 does not teach or suggest that a base B as defined in this claim is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 18	
The product of claim 17, wherein the base B is diethanolamine.	*See* Claims 9, 16, and 17. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. While Actavis's narrative alleges that Phares 2005 discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred", similar to what has been described above in connection with claim 1, this disclosure does not advance Actavis's arguments because Phares 2005 does not teach or suggest that diethanolamine is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 19	
The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	*See* Claim 1. Actavis does not present an independent reason for the obviousness of this claim so no response is needed.
Claim 20	
The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group	*See* Claim 9. Actavis does not present an independent reason for the obviousness of this claim so no response is needed.

(Exh. A Cont'd)

Claim	Representative Deficiencies in Prior Art Disclosure
consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	
Claim 21	
The product of claim 1, wherein step (d) is performed.	*See* Claim 1. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (*i.e.*, "reacting the salt formed in step (c) with an acid to form the compound of formula I")
Claim 22	
The product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).	*See* Claims 1 and 21. Actavis does not present an independent reason for the obviousness of this claim so no response is needed. The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (*i.e.*, "reacting the salt formed in step (c) with an acid to form the compound of formula I"). Actavis's narrative alleges that certain prior art (*i.e.*, Moriarty 2004, Remodulin, '117 Patent, & Phares2005) disclose treprostinil salts (*e.g.*, treprostinil sodium) being sold as an FDA approved treatment. However, as mentioned above, none of the prior art discloses that the pharmaceutically acceptable salt was "formed from the product of step (d)" as required by this claim.

BLANK ROME LLP
Stephen M. Orlofsky
David C. Kistler
New Jersey Resident Partners
301 Carnegie Center, 3d Floor
Princeton, NJ 08540
Telephone: (609) 750-7700

OF COUNSEL:
William C. Jackson
BOIES, SCHILLER & FLEXNER LLP
5301 Wisconsin Ave, NW
Washington, DC 20015

Douglas Carsten
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real
Suite 200
San Diego, CA 92130

Attorneys for Plaintiff/Counterclaim Defendant
United Therapeutics Corporation

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORP., Plaintiff and Counterclaim-Defendant, v. SANDOZ, INC., Defendant and Counterclaim-Plaintiff.	Civil Action No.: 3:14-cv-05499-PGS-LHG **HIGHLY CONFIDENTIAL-ATTORNEYS EYES ONLY**

UNITED THERAPEUTICS CORP.'S RESPONSES TO SANDOZ, INC.'S INVALIDITY CONTENTIONS

Plaintiff United Therapeutics Corporation ("UTC") hereby provides its Responses to Invalidity Contentions, including the Validity Claim Chart attached thereto as Exhibit A (collectively "Response"), under Local Patent Rule 3.4A, as modified by paragraph 6 of the Scheduling Order. (D.I. 22.) Discovery in this case is ongoing; UTC therefore reserves the right to move to amend its Infringement Contentions in light of the ongoing discovery in this case and any additional information uncovered as the case progresses. The Responses include the following:

Local Patent Rule 3.4A(a) For each item of asserted prior art, the identification of each limitation of each asserted claim that UTC believes is absent from the prior art;

Local Patent Rule 3.4A(b) If obviousness is alleged, an explanation of why the prior art does not render the asserted claim obvious;

Local Patent Rule 3.4A(c) The Responses follow the order of the invalidity chart required under Local Patent Rule 3.3(c), and set forth UTC's agreement or disagreement with each allegation therein and the written basis thereof; and

Local Patent Rule 3.4A(d) UTC will make available for inspection and copying any document or thing that it intends to rely on in support of its Responses herein.

I. THE ASSERTED CLAIMS OF U.S. PATENT NO. 8,497,393 ARE VALID

Sandoz, who bears the burden to prove invalidity by clear and convincing evidence, has failed to provide "a chart identifying where specifically in each alleged item of prior art each limitation of each asserted claim is found." L. Pat. R. 3.3(c). Sandoz provides a laundry list of references in its Invalidity Narrative for the '393 patent, but Sandoz provides no details whatsoever on many of the references or which references allegedly anticipate and/or render obvious any claim of the '393 patent. Sandoz has therefore waived any argument regarding any

alleged anticipation or obviousness based on any of these additional references listed that are not in Sandoz's Invalidity Chart by failing to identify any specific references for anticipation or any specific combination of references for obviousness in their claim chart. Moreover, Sandoz's entire Invalidity Contention Chart consists of many of the same citations repeated over and over for multiple claims. Accordingly, UTC's responses cannot properly "follow the order of the invalidity chart...and set forth [UTC's] agreement of disagreement with each allegation therein". L. Pat. R. 3.4A(d). Instead, UTC has combined and summarized many arguments in response to Sandoz's repeated arguments.

With regard to obviousness specifically, Sandoz has provided minimal "explanation of why the prior art renders the asserted claim obvious, including an identification of any combinations of prior art showing obviousness." L. Pat. R. 3.3(b). Sandoz has therefore also waived any further argument regarding these references beyond citations from each reference in it chart and similarly has waived any specific obviousness combination other than those identified in Sandoz's Invalidity Contention Chart. And Sandoz has failed to provide any reason that would have prompted a person of ordinary skill in the art to arrive at the invention or why they would have a reasonable expectation of success with anything other than hindsight.

1. The Scope and Content of the Alleged Sandoz Prior Art

A brief summary of the prior art below shows that many of the references Sandoz relies upon to support its invalidity contentions disclose the same information as many other references and the majority of which were disclosed to the Patent Office during prosecution of the '393 patent. The discussion below highlights certain representative sections of these and related references to show that their actual teachings do not support Sandoz's anticipation and/or obviousness arguments. UTC reserves its right to rely upon other sections of these references

and/or additional references to support UTC's contentions that none of these references, whether considered alone or in combination anticipate and/or render obvious the asserted '393 patent claims, and to more fully expand its contentions during the course of factual and expert discovery in this case. UTC does not admit that any of Sandoz's references actually constitute relevant or enabling prior art and also reserves its rights to antedate or otherwise remove any of Sandoz's alleged prior art.[1]

2. Prosecution History of the '393 Patent Application

It is worth noting that, during prosecution of the '393 patent, the U.S. Patent and Trademark Office considered and rejected many of the same arguments and prior art as those in Sandoz's Invalidity Contentions. The prior art Sandoz cites, even if enabling and not cumulative to the art of record, does not refute the PTO's reasons for allowance.

3. The Asserted Claims Of The '393 Patent Are Not Anticipated and/or Rendered Obvious

UTC's response to Sandoz's anticipation and obviousness arguments regarding the '393 patent can be found herein and in the accompanying claim chart, as required by the Scheduling Order and Local Patent Rules, attached as Exhibit A, respectively, hereto. In addition, UTC provides below additional background information and explanation as to: (a) why the prior art identified by Sandoz neither anticipates nor renders obvious the claims of the '393 patent; and (b) why the Asserted Claims are not invalid based upon Sandoz's other invalidity arguments. In brief, the Asserted Claims are not anticipated because no single, enabling reference identified by

[1] The Scheduling Order and Local Patent Rules do not require a response to the narrative portion of Sandoz's Invalidity Contentions. *See, e.g.*, Scheduling Order ¶ 6. By providing this response, United Therapeutics does not hereby waive any rights or arguments with respect to any of the assertions in that narrative.

Sandoz discloses each and every element of the claimed invention. They are not rendered obvious because none of the references identified by Sandoz, whether considered alone or in combination, teaches or suggests to one of ordinary skill in the art the inventions defined by the Asserted Claims.

Additionally, the products of the prior art are different from the products claimed in the '393 patent. If the process for producing a product according to a product-by-process claim imparts distinctive structural and functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable). Because the product produced by the '393 patent is superior, *inter alia* in impurity profiles, purity, yields and other characteristics of the product it is not anticipated or rendered obvious. *See, e.g., Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1308 (Fed. Cir. 2009) (J. Newman, *dissenting*) ("The facts of Thorpe did not concern the exception and expedient where process terms are invoked to describe a new product of complex structure. This exception is rarely invoked. The general rule requiring claims to have a process-free definition of the structure of a new product accommodates most inventions. Some recent exceptions are seen in emerging aspects of biotechnology."); *see also Scripps Clinic & Research Foundation v. Genentech, Inc.,* 927 F.2d 1565 (Fed.Cir.1991) (process to obtain a "highly purified and concentrated" product that was "largely free of contaminants," was not anticipated by previous disclosure of the product), *overruled on other grounds by Abbott Labs v. Sandoz, Inc*., 566 F.3d 1282 (Fed. Cir. 2009). If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the

product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable). Additionally, a source limitation present in the claim can impart structural and functional differences in the product. *Amgen*, 580 F.3d at 1367-68.

a) **U.S. Patent No. 4,306,075 ("the '075 patent")**

The product produced by the claimed process is vastly different from the product of the '075 patent. While the chemical structure of treprostinil may be the same, the respective impurity profiles are expected to be different, the synthetic method is different and the synthetic efficiency is different. Specifically, the '075 patent produces product in much lower yields and is unsuitable to produce pharmaceutical grade treprostinil because of overall synthetic efficiency. Thus, the '075 patent cannot anticipate claim 1.

Sandoz claims that the 0.096g of treprostinil product anticipates the claim, however, there is no evidence as to the purity of that sample and the synthesis itself was not reproducible. UTC-Sand-Rem01096057-059. Sandoz previously admitted that "early preparations [of treprostinil] resulted in complex mixtures of diastereomers requiring separation and low yields…Other early efforts by Upjohn in optimizing the preparation of treprostinil focused on closure strategies for the center ring, which also suffered from lack of sufficient stereocontrol and/or low yields due to lengthy synthetic sequences, such as those disclosed in Aristoff '075." Sandoz I Invalidity Contentions at 47. Sandoz's previous Invalidity Contentions operate as an admission of a party opponent, and confirm that even Sandoz itself recognizes the validity of the '393 patent, and the superiority of the product produced by the claimed process of the '393 patent.

Sandoz's admission is further supported by the disclosure of the '393 patent itself, which referenced the '075 patent on its face and incorporates it by reference. '393 patent at 1:23-24. Moreover, the Patent Office specifically considered the'075 patent and expressly allowed the '393 patent over the reference, confirming that the '075 patent does not anticipate the claims of the '393 patent.

Furthermore, as even Sandoz appears to acknowledge in its previous Invalidity Contentions, the synthetic disclosure in the '075 patent provides for a large number of steps and would result in low yields of impure product. Indeed, the treprostinil product formed by the '075 patent synthetic method would be expected to have a different impurity profile than the treprostinil produced by the claimed process of the '393 patent in lower yield.

Moreover, with regard to claim 2, the '075 patent does not disclose any product of formula I (including treprostinil) with a purity of at least 99.5% pure. In fact, the only reference Sandoz contends discloses treprostinil with at least 99.5 % purity is the Moriarty 2004 reference. During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Indeed, the Moriarty 2004 reference itself specifies how poor the '075 patent process was and identified multiple problems with the product of the '075 patent. UTC-Sand-Rem00069616. Thus, a person of ordinary skill in the art would not combine the teachings of the '075 patent and Moriarty 2004. For these reasons the '075 patent does not anticipate and/or render obvious any claim of the '393 patent.

b) **U.S. Patent No. 4,668,814 ("the '814 patent") and European Patent Publication No. 0159784A1 ("EP '784")**

The '814 patent and EP '784 essentially share the same disclosure of synthetic methods for the crude treprostinil product and other compounds. Indeed, Sandoz has nearly identical

contentions for each reference. SIC at 9-24. In addition, Aristoff '814 presents the same synthetic pathway for treprostinil as the EP '784. Since the synthetic method for treprostinil described in '814 patent is the same as that set forth in EP '784, both will be considered together ("the '814 patent references")

Claim 1 of the '393 patent is not anticipated by '814 patent references because the product produced by the claimed method is different from the product of the '814 patent references. While the chemical structure of treprostinil may be the same, the respective impurity profiles, the synthetic method and synthetic efficiency is different. Specifically, the '814 patent references produce products in lower yields and is not suitable to scale-up for large-scale pharmaceutical use because of overall synthetic efficiency.

Additionally, Sandoz fails to demonstrate that the product of the '814 patent references are structurally and functionally the same as the claimed product. Sandoz has already expressly admitted that "early preparations [of treprostinil] resulted in complex mixtures of diastereomers requiring separation and low yields" and "[o]ther early efforts by Upjohn in optimizing the preparation of treprostinil focused on closure strategies for the center ring, which also suffered from lack of sufficient stereocontrol and/or low yields due to lengthy synthetic sequences." Sandoz I Initial Invalidity Contentions at 47. Sandoz's admission is further supported by the disclosure of the '393 patent itself, which referenced the '814 patent, on its face. *See* '393 patent References Cited.

The products of the '393 patent are structurally and functionally different than the products of the '814 patent references. Upjohn's early syntheses yielded inadequate products in

terms of impurities, yield, and other analytical data.[2] For example, the SynQuest Process Optimization For the Manufacture of UT-15 report dated December 28, 2007, states that an early Aristoff synthesis of treprostinil (being an optimized version of the '814 patent synthesis) "yielded a diastereomeric mixture of [treprostinil intermediate]" and subsequent steps added additional chiral centers, thus the Aristoff synthesis "could not allow the production of large-scale quantities of [treprostinil] in an economical way because of extensive separation problems which resulted from the plethora of stereomers formed in this non-stereoselective process." UTC-Sand-Rem00000177. *See also* UTC-Sand-Rem0000177-180 (abandoning the attempt to improve Aristoff synthesis); 180-182; *see generally*, UTC-Sand-Rem-0000145-358.

The report also notes that the Upjohn chemists "obtained a crude product corresponding to a mixture of diastereomers [of treprostinil]. Five to ten recrystallizations were necessary…This prior work did not offer much guidance for our purification of the final product [treprostinil] because they had a mixture of stereomers at this stage." UTC-Sand-Rem-00000216. The '814 patent references do not disclose a pure treprostinil product, and while the '814 patent also does not disclose the need for five to ten recrystallizations or other extensive work-up procedures, the Synquest report makes clear that the product of the '814 patent was inadequate even with additional purification techniques not disclosed in the references themselves.

Additionally, the lots produced by the prior Upjohn optimized synthesis have a different impurity profile, different average optical rotation, and lower average yield (even after multiple recrystallizations) than lots produced using the '393 patent synthesis that were referenced by Sandoz. SIC at 57-60; *see, also*, UTC-Sand-Rem00061829-62075 at 62013-62015; *see also*

[2] UTC reserves the right to use the entire documents Sandoz cited in their narrative contention response.

UTC-Sand-Rem00022256-22299; UTC-Sand-Rem00025786-26109; and UTC-Sand-Rem00045530-45996. Additionally, a person of ordinary skill in the art would understand that the scale of a chemical reaction can greatly affect the yield and level of impurities. The scale of the reactions disclosed in the '814 patent reference is on the gram scale. Likewise, the lots made from the Upjohn synthesis were made on a smaller scale than several of the later development and commercial lots of treprostinil made using the '393 patent synthesis.[3] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. A person of ordinary skill in the art would therefore understand that any improvements in the commercial lots of treprostinil made using the '393 patent synthesis are further magnified over the Upjohn synthesis products given their small scale. Sandoz has therefore failed to show the '814 patent references disclose the same pure treprostinil products claimed in the '393 patent. Thus, the '814 patent references fail to anticipate claim 1 of the '393 patent.

Sandoz claims that the 1.2g sample of treprostinil in Example 3 of the '814 patent is 95% pure and anticipates the claim, however, there is no evidence within the '814 patent or EP '784 as to the purity of that sample. Sandoz previously admitted that "early preparations [of treprostinil] resulted in complex mixtures of diastereomers requiring separation and low yields…Other early efforts by Upjohn in optimizing the preparation of treprostinil focused on closure strategies for the center ring, which also suffered from lack of sufficient stereocontrol and/or low yields due to lengthy synthetic sequences." Sandoz I Invalidity Contentions at 47. In addition to the '075 patent, the '814 patent is the only other Upjohn route and therefore Sandoz

[3] The documents cited herein for batches of treprostinil made by the '117 patent process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different.

was referring to that route as well. Sandoz' previous Invalidity Contentions operate as an admission of a party opponent, and confirm that even Sandoz itself recognizes the validity of the '393 patent, and the superiority of the product produced by the claimed process of the '393 patent.

Moreover, with regard to claim 2, the '814 patent does not disclose any product of formula I (including treprostinil) with a purity of at least 99.5% pure. In fact, the only reference Sandoz contends discloses treprostinil with at least 99.5 % purity is the Moriarty 2004 reference. During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Indeed, the Moriarty 2004 reference itself specifies how poor the '814 patent references were and identified multiple problems with the products of the '814 patent references. UTC-Sand-Rem00069614-16. Moreover, as described above, even with multiple recrystallizations not described in the '814 patent, the product could not be improved to a higher purity for scale up. Thus, a person of ordinary skill in the art would not combine the teachings of the '814 patent references and Moriarty 2004. For these reasons, the '814 patent references do not anticipate and/or render obvious any claim of the '393 patent.

c) **2006 Remodulin Package Insert, Prior Sale of Remodulin, U.S. Patent No. 6,765,117 ("the '117 patent") and J. Org. Chem. 2004, 69, 1890-1902 (2004) ("Moriarty 2004") (collectively, "the Moriarty references")**

The '117 patent and Moriarty 2004 references disclose the same synthesis for treprostinil. Additionally, the treprostinil referenced in the 2006 Remodulin Package Insert and the Remodulin on sale prior to the priority date of the '393 patent were also made by the '117 patent

process.[4] Since the synthetic method for treprostinil described in each of these references is the same as that set forth in the '117 patent, they will be considered together ("the Moriarty references").

Claim 1 of the '393 patent is not anticipated by the Moriarty references because the product produced by the claimed method is different from the product of the Moriarty references. While the chemical structure of treprostinil may be the same, the respective impurity profiles, the synthetic method and synthetic efficiency is different. Specifically, the Moriarty references produce products in lower yields with more impurities.

During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference (and the '117 patent) because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Contrary to Sandoz's allegations, the Walsh declaration did not require that the '393 patent provide only a certain subset of impurities, but was used to show that there were less total impurities present and less overall impurities. Indeed, the batch record used by Walsh to show the differences was a representative example. On average, the batches of treprostinil made by the '393 patent have less number of impurities and less total impurities than an average of treprostinil made by the '117 patent.

The products of the '393 patent are structurally and functionally different than the products of the Moriarty references.[5] Indeed, Sandoz only looks at the first 5 Process

---

[4] Indeed, the 2006 Remodulin Package Insert does not disclose any synthesis and the "sale" of Remodulin similarly does not disclose any specific synthesis. In fact, Sandoz has admitted that the '393 patent process was not used to make Remodulin (and therefore not "on sale") until after the priority date of the '393 patent. *See*, SIC at 61 ("By mid-2008, UTC had modified its manufacturing process to include the process steps claimed in the '393 patent.").

[5] UTC reserves the right to use the entire documents Sandoz cited in their narrative contention response.

Optimization batches of the '393 patent treprostinil for comparison to prior batches made by the Moriarty process, but then also only looks at the last few years of the Moriarty process when it was fully optimized and run at scale. SIC at 55-61; *see also* UTC-Sand-Rem01096535-36. First, a comparison of the first few developmental batches made to years of optimized batches is an unfair comparison. Even under this comparison, however, the 5 '393 patent batches showed that only 1 batch had <0.05% [redacted] impurity, only 1 batch had <0.05% [redacted] impurity, none of the batches had any [redacted] impurity and all batches had <0.05% [redacted] impurity and <0.05% [redacted] impurity. UTC-Sand-Rem01096535-36. This is a very low amount for these impurities given that these were the first few batches made with the process. The last six years of Moriarty batches made, however, had more impurities on average per impurity of several impurities than these 5 initial '393 patent batches. *Id.*

A much better comparison, however, would look at the impurity profiles of the first 5 batches of the Moriarty batches (including LRX-97J01, LRX-98A01, LRX-98B01, UT15-98H01, UT15-98I01) as a comparison to these first 5 batches of the '393 patent that Sandoz cites. See, UTC-Sand-Rem00021934-39; UTC-Sand-Rem01156295-295; UTC-Sand-Rem01096536. Indeed, under that analysis, the average '393 patent batch had far less total impurities, and individual impurities as the Moriarty batches had an a much higher average amount of many impurities including [redacted] *Id.* Additionally, the average Moriarty batch had many times the total impurities of the average '393 patent batch. *Id.* Beyond the first 5 batches of treprostinil made by the '393 patent, other later batches also confirm that the average batch made by the '393 patent is superior to the batches made by the Moriarty references in terms of quality, impurities present, and total impurities, among other properties. Given the potency of treprostinil, any impurity is a potential

safety concern and a person of ordinary skill would want to minimize these impurities. The product of the '393 patent is structurally and functionally different than the products of the prior art that contained treprostinil because the '393 patent has a higher level of average purity, lower number of individual impurities, and better product. For example, in a document entitled Treprostinil Drug Substance Impurities, all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by the '117 patent and Moriarty 2004 process. *See* UTC-Sand-Rem00334054-00334057 and UTC-Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty process. See, e.g., UTC-Sand-Rem01096537, PTX-100a, UTC-Sand-Rem00001673-702; UTC-Sand-Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTC-Sand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTC-Sand-Rem01111355-357; UTC-Sand-Rem01117901-906; UTC-Sand-Rem01117910-912; UTC-Sand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Other documents show that the batches made by the '393 patent process have a better impurity profile on average as well as

less total impurities.[6] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the prior art specifies the average level of purity or minimal level of impurities that the '393 patent provides.

Additionally, a person of ordinary skill in the art would understand that the scale of a chemical reaction can greatly affect the yield and level of impurities. The scale of the reactions disclosed in the Moriarty references on average is smaller than the scale of batches made by the '393 patent. *See* UTC-Sand-Rem01096533 ("The following chart lists in detail the changes that occurred in the process between Chicago [using Moriarty process] and Silver Spring [using '393 process]. In Silver Spring, the diethanolamine salt was introduced as a purification step and the batch size was increased from [redacted] to [redacted]."). Despite this jump in batch size, the overall purity of the '393 patent process was reported as 99.9% compared to 99% for the Moriarty process. *Id.* A person of ordinary skill in the art would therefore understand that any improvements in the commercial lots of treprostinil made using the '393 patent synthesis is further magnified over the Moriarty synthesis products given the difference in scale. Sandoz has therefore failed to show the Moriarty references disclose the same pure treprostinil products claimed in the '393 patent.

Additionally, Sandoz claims that the Moriarty reference teaches the performance of step (c) because when the KOH reacts with the treprostinil in step (b), "some molecules of treprostinil acid necessarily and unavoidably react again with KOH to form treprostinil potassium, which is then converted back to treprostinil acid by subsequent addition of HCl." SIC at 75. Not so. As

[6] The documents cited herein for batches of treprostinil made by the '117 patent process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different and reserves the right to cite any document from Sandoz's Contentions.

described and claimed, the treprostinil is made in a separate step and not simply *in situ* with KOH. Indeed, step (c) specifies that it must "contact the product of step (b)" that is, the completed step, before proceeding on to the next step. Additionally, none of the Moriarty references (with the exception of Moriarty 2004) disclose a product with at least 99.5% purity as required in Claim 2. As previously discussed, the disclosure of the 99.7% amount in the Moriarty 2004 reference also did not anticipate and/or render obvious claim 2 and would not be combined with these other references. *See, e.g.*, Claim 2 for the '814 patent references above. Thus, Sandoz has failed to show that any of the Moriarty references disclose step (c) of claim 1. Thus, a person of ordinary skill in the art would not combine the teachings of the Moriarty references with Moriarty 2004. For these reasons the Moriarty references do not anticipate and/or render obvious any claim of the '393 patent.

d) **U.S. Patent Application Publication No. 2005/0085540A1 ("Phares") including obviousness based on Phares In Combination with Moriarty 2004, and Phares In Combination with Moriarty 2004 and Anderson, N. "Practical Process Research & Development: A Guide for Organic Chemists, p. 13, 223, 226 (2000) ("Anderson")**

Sandoz provides separate Invalidity Charts for 1) Phares (SIC at 61-71), 2) Phares again (SIC at 92-104), 3) Phares in combination with Moriarty 2004 (SIC at 104-125), and 4) Phares in combination with Moriarty 2004 and Anderson (SIC at 126-141). Sandoz repeats many of the same arguments in each of the above referenced charts and so many will be addressed together.

(1) Phares

The asserted claims of the '393 patent are not anticipated and/or rendered obvious by Phares because the product produced by the claimed method is different from the product of Phares. Although treprostinil and Remodulin are discussed in Phares, the mere disclosure of treprostinil does not anticipate any claim of the '393 patent. In fact, contrary to Sandoz's

allegations, Phares does not specifically teach the synthesis of treprostinil, but summarily teaches the synthesis of its enantiomer (-) -treprostinil and notes that (+)-treprostinil can be prepared in the same manner. [0143-0145]. All that Phares discloses is the synthesis of (-)-treprostinil without indicating how that would be altered to synthesize (+)-treprostinil and is therefore not enabled with regard to teaching a synthesis for (+)-treprostinil. *Id.* Additionally, there is no indication of the purity or potential impurities present in a batch of treprostinil (because no synthesis is disclosed).

The product of the Phares publication is structurally and functionally different from the product of Phares. First, as Sandoz admits, Phares does not indicate the purity of diethanolamine. SIC at 112. Instead, Phares only indicates that Form B polymorph of the treprostinil diethanolamine disclosed has a melting point of 107C. [0337] but the data shows a larger range of melting point from about 100-110.[7] The '393 patent, however, indicates that the melting point for Form B is more than 104C. '393 patent, col. 12, ll. 52-55. Thus, it is not clear that the treprostinil diethanolamine from Phares is the same as the treprostinil diethanolamine of the '393 patent. Moreover, Phares does not disclose any purity data for treprostinil diethanolamine. Additionally, Phares was considered by the Patent Office during prosecution and appears on the face of the '393 patent. While the chemical structure of treprostinil and/or treprostinil diethanolamine may be the same, the respective impurity profiles, the unknown synthetic method and resulting product are expected to be different.

[7] It is also not clear from Phares that 107C is the melting point of Form B of treprostinil diethanolamine. The DSC thermogram shows a single endotherm at 107C and Phares claims "that is consistent with a melting event" but this is not necessarily the correct melting point for treprostinil diethanolamine as the endotherm is much broader than 107C. *See* Phares, [0335, Figures 20 and 21].

Moreover, Sandoz claims that Phares discloses step (c) at [0105]. SIC at 131. The disclosure cited, however, only states that "Treprostinil acid acid [sic] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling." [0105]. This disclosure, however, does not indicate the source or purity of treprostinil used and as indicated above, there is no indication of the purity of the resulting salt form. Similarly, Phares does not disclose a product with a purity of at least 99.5%. None of the data cited by Sandoz in Phares describes a product that is 99.5% pure. Thus, Phares fails to anticipate and/or render obvious the asserted claims of the '393 patent.

(2) Phares in combination with Moriarty 2004

The combination of Moriarty 2004 and Phares do not render the claims of the '393 patent obvious. As detailed above, Phares alone does not disclose any specific treprostinil product (only its enantiomer) and the treprostinil diethanolamine disclosed is expected to be different than the treprostinil diethanolamine of the '393 patent. Similarly, there would be no reason to combine the teachings of Phares and Moriarty. Even if they were combined, however, as discussed above, Moriarty 2004 alone does not disclose the same treprostinil product as the treprostinil made by the '393 patent as it has, on average, a lower purity and more impurities present. *See*, Moriarty References above.

Both Phares and Moriarty 2004 were disclosed to the Patent Office during prosecution of the '393 patent. Moreover, the batches made by the Moriarty 2004 process are of a lower purity and have a different impurity profile than the treprostinil made by the '393 patent process so even if a person of ordinary skill in the art were to combine these references, Phares does not specify a synthesis for treprostinil so the Moriarty 2004 synthesis would presumably be used to

then further make the diethanolamine salt form from Phares. *See, e.g.*, Phares and Moriarty References, above. Even if this were the case, however, because both the Moriarty 2004 treprostinil and the Phares treprostinil diethanolamine are of lower and/or different purity, there is no evidence to suggest that the resulting product would be the same as the product of the '393 patent. Thus, Phares in combination with Moriarty 2004fails to render obvious the asserted claims of the '393 patent.

(3) Phares in combination with Moriarty 2004 and Anderson

The above response to Phares, Moriarty 2004, and Phares in combination with Moriarty are incorporated herein. Sandoz only cites Anderson for the allegation that "a person of ordinary skill in the art would have been motivated to avoid the 'drawbacks' of column chromatography, which is 'labor intensive; process that is used generally as a last resort and that diethanolamine salts were known and "the solubility of acid salts of the amines (Table 3.7) can provide some operating advantages on scale.". SIC at 127. This is inaccurate, however, as diethanolamine is NOT disclosed in Table 3.7 and is not listed as an "amine useful for scale-up." Anderson, Table 3.7. Instead, only diethylamine is listed, not diethanolamine. *Id.* Regardless of whether a POSA would have preferred to avoid column chromatography, however, is irrelevant. Column chromatography is commonly used for such complicated molecules as treprostinil, which has 5 chiral centers. Indeed, there is no discussion of using a diethanolamine salt in the Anderson citations provided by Sandoz. As previously described, the combination of Phares and Moriarty 2004 do not render the claims obvious and Anderson does not disclose any information about treprostinil or its synthesis nor even disclose that diethanolamine would have been useful for scale-up. Indeed, it was an unexpected result that the salt step disclosed in the '393 patent

worked to remove impurities. Thus, the addition of Anderson to the combination of Phares and Moriarty 2004 does not render the claims of the '393 patent obvious.

e) **"Synthetic Approaches to the 2002 New Drugs" Li, et. al., Mini-Reviews in Medicinal Chemistry, Vol. 4 at pp.207-233 (2004) ("Li") and Sorbera, et. al., "UT-15, Treatment of Pulmonary Hypertension, Treatment of Peripheral Vascular Disease," Drugs of the Future, Vol. 26(4), pp. 364-374 (2001) ("Sorbera")**

Both Li and Sorbera only disclose summaries of other known syntheses of treprostinil and disclose no new information on the product, synthesis, or purity/impurity profile of the treprostinil products disclosed in the prior references. Li cites U.S. Patent 6,441,245 ("the '245 patent") and WO 9921830 ("WO '830") for the summary of the treprostinil synthesis disclosed. SDZ5499 0005382-83. Both the '245 patent and WO '830 were disclosed to the Patent Office during prosecution of the '393 patent and listed on the face of the patent. In fact, the '245 patent is cited by the '393 patent "treprostinil, and other prostacyclin derivatives have been prepared as described in...U.S. Patent No. 6,441,245..." '393 patent, Col. 1, ll. 23-26. Although the Li article cites the last step involves titration of treprostinil with NaOH, neither WO '830 or the '245 patent disclose this step. Thus, this step is not supported by the reference and is therefore not enabled as there is no indication that Li actually synthesized anything and is simply reporting previously listed syntheses. Instead, WO '830 and '245 patent discloses the crude product (treprostinil) was purified by column chromatography and no further steps were taken. Sandoz-Trep0007792-93; '245 patent, col. 18, ll. 26-29. Thus, in addition to not disclosing the last salt step, these references use the same synthesis as the '117 patent and Moriarty 2004. Thus, UTC incorporates its arguments regarding the '117 patent and Moriarty 2004 herein. *See* Moriarty References, above.

Similarly, Sorbera cites the '075 patent, EP 784, and WO '830 for syntheses of treprostinil and provides no additional information beyond what is in each of these references regarding the purity, impurity profiles, synthesis or composition of the drug product. As previously discussed, none of these references anticipate and/or render obvious any claim of the '393 patent. *See*, '075 patent, '814 patent references, and Moriarty references charts above. Additionally Neither Li or Sorbera disclose the product of claim 1 with at least 99.5% purity as required by claim 2. Additionally, neither Li nor Sorbera render obvious this claim with Moriarty 2004 for the same reasons as the '117 patent and Moriarty 2004 do not render obvious the claim. *See* Moriarty References, above. For these reasons, Li and Sorbera do not anticipate and/or render obvious any of the asserted claims of the '393 patent.

4. Secondary Considerations

Sandoz has not established a *prima facie* case of obviousness. Thus, UTC is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirm that the Asserted Claims would not have been obvious and, in fact, represent a surprising solution to a serious problem of minimizing potentially hazardous impurities and providing a safer and purer treprostinil product.

a) **Long felt Unmet Need**

At the time of the invention, there was a long-felt need to have a shorter, more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner with less impurities. Treprostinil has five chiral centers resulting in 32 possible diastereomers so the potential for diastereomeric impurities is high and only the treprostinil stereoisomer has the desired pharmaceutical effect. Treprostinil is also a very potent drug so any diastereomeric impurities would also potentially be potent and could potentially have deleterious effects. Thus,

there was a need to reduce the amount of impurities as much as possible and the product of the '393 patent further reduces impurities over the previous treprostinil products made by the prior art.

b) **Unexpected Results**

The results of the claimed inventions in the '393 were unexpected. The use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was an unexpected. Thus, a person of skill in the art would not have expected the results of the '393 patent to be so successful.

c) **Commercial Success**

The '393 patent is used in the current production of Remodulin and has reduced the cost of making Remodulin® and increased efficiency. Remodulin is a commercially successful product that competes well against other alternatives such as Flolan. The commercial success of Remodulin® is reflected in both gross sales figures and relevant market share. UTC will make available for inspection and copying documents demonstrating the commercial success of Remodulin®.

d) **Copying**

The non-obviousness of the '393 patent is evidenced by Sandoz's own actions. Sandoz copied not only the active ingredient treprostinil sodium, but also the process claimed in the '393 patent.

5. Obviousness-Type Double Patenting based on U.S. Patent No. 7,417,070 ("the '070 patent") and U.S. Patent No. 6,765,117 ("the '117 patent")

Sandoz's entire obviousness-type double-patenting argument with regard to the '070 patent is that because claim 1 of the '070 patent claims a compound having the structure of

treprostinil diethanolamine, then that necessarily renders obvious the claims of the '393 patent by the mere disclosure of the structure. SIC at 77-79. Sandoz is wrong. As previously discussed with regard to Phares, the mere disclosure of treprostinil diethanolamine does not render obvious any claim of the '393 patent. Indeed, Sandoz ignores that obviousness-type double patenting requires that only the claims of the prior art must be compared to the asserted claims. The claims of the '393 patent are very different than claim 1 of the '070 patent. Indeed, Sandoz provides no citation for its assertion that process elements are irrelevant specifically when performing an obviousness-type double patenting analysis and no citation that the species/genus argument applies as well. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Moreover, the synthesis used to make the diethanolamine salt in the '070 patent would result in a structurally and functionally different product than the '393 patent for the same reasons as Phares as the '070 patent is the issued patent of the Phares patent publication. Thus, all arguments regarding Phares are incorporated herein. *See* Phares response.

Similarly, the claims of the '117 patent are very different than the claims of the '393 patent and would result in different product. Moreover, the '117 patent does not specifically disclose treprostinil diethanolamine. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Moreover, the products of the '117 patent and the '393 patent are structurally and functionally different. *See*

Moriarty References above. Other than structural and functional differences, the products of the '117 patent and the '393 patent are also different as the '117 patent product must be stereoselectively produced using the source limitations of starting enyne and cyclized intermediate. Indeed, neither the '070 patent claims or the '117 patent claims disclose steps (a), (b), (c), or (d) of the '393 patent claims. Similarly, neither the '070 patent claims nor the '117 patent claims disclose a product with at least 99.5% purity. Thus, neither the '070 patent nor the '117 patent render the claims of the '393 patent invalid for obviousness-type double patenting.

Stephen M. Orlofsky
David C. Kistler
New Jersey Resident Partners
BLANK ROME LLP
301 Carnegie Center, 3d Floor
Princeton, NJ 08540
Telephone: (609) 750-7700

Of Counsel

William C. Jackson
BOIES, SCHILLER & FLEXNER LLP
5301 Wisconsin Ave, NW
Washington, DC 20015

Veronica S. Ascarrunz
WILSON SONSINI GOODRICH & ROSATI
1700 K Street, NW
Suite 500
Washington, DC 20006

Robert A. Delafield II
WILSON SONSINI GOODRICH & ROSATI
900 S. Capital of Texas Hwy
Las Cimas IV, Fifth Floor
Austin, TX 78746

Dated: March 23, 2015

/s/ Douglas H. Carsten
Douglas H. Carsten
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real
Suite 200
San Diego, CA 92130

Attorneys for Plaintiff/Counterclaim Defendant United Therapeutics Corporation

CERTIFICATE OF SERVICE

I hereby certify that on March 23, 2015, a copy of the foregoing was served on principal counsel of record as set forth below via email.

Eric I. Abraham
Christina L. Saveriano
HILL & WALLACK LLP
200 Carnegie Center
Princeton, NJ 08540
609-924-0808
609-452-1888 (fax)
eabraham@hillwallack.com
csaveriano@hillwallack.com

Thomas P. Steindler
MCDERMOTT WILL & EMERY LLP
500 North Capitol Street, NW
Washington, DC 20001
202-756-8000
202-756-8087 (fax)
tsteindler@mwe.com
bjacobs@mwe.com
cmay@mwe.com

Lauren N. Martin
MCDERMOTT WILL & EMERY LLP
227 W. Monroe Street
Chicago, IL 60606
312-372-2000
312-984-7700 (fax)
kstolte@mwe.com
lmartin@mwe.com

Attorneys for Defendant and Counterclaim-Plaintiff Sandoz, Inc.

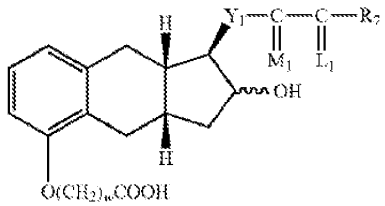
/s/ Douglas H. Carsten
Douglas H. Carsten

EXHIBIT A

UNITED THERAPEUTICS' RESPONSE TO SANDOZ'S INVALIDITY CONTENTIONS

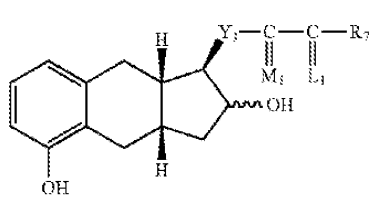
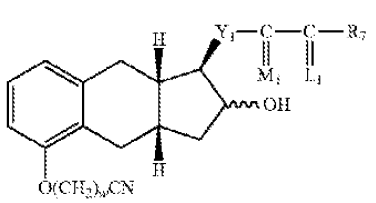
UNITED STATES PATENT NO. 8,497,393[1]

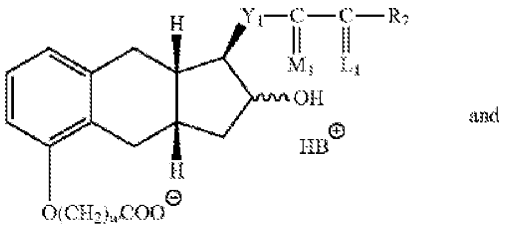
I. Disclosure of Validity Contentions – United States Patent No. 8,497,393

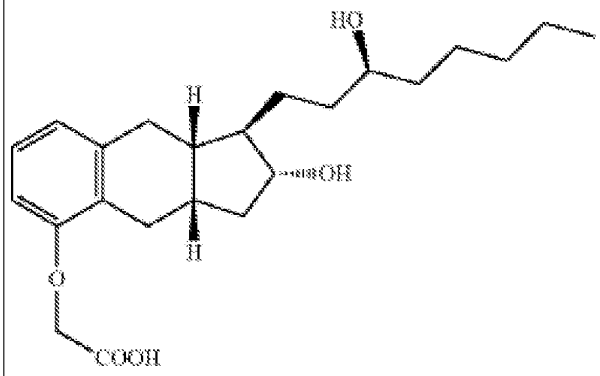
Anticipation and/or Obviousness based on U.S. Patent No. 4,306,075 ("the '075 patent")	
Claim	**Deficiencies in Prior Art**
Claim 1	
1. A product comprising a compound of formula I (I)  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	The product produced by the claimed process is vastly different from the product of the '075 patent. While the chemical structure of treprostinil may be the same, the respective impurity profiles are expected to be different, the synthetic method is different and the synthetic efficiency is different. Specifically, the '075 patent produces product in much lower yields and is unsuitable to produce pharmaceutical grade treprostinil because of overall synthetic efficiency. Thus, the '075 patent cannot anticipate claim 1. If the process for producing a product according to a product-by-process claim imparts distinctive structural and functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable). Because the product produced by the claimed process is superior, *inter alia* in yield and purity, to the product produced by the method disclosed in the '075 patent, it is not anticipated. *See, e.g., Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1308 (Fed. Cir. 2009) (J. Newman, *dissenting*) ("The facts of Thorpe did not concern the exception and expedient where process terms are invoked to describe a new product of complex

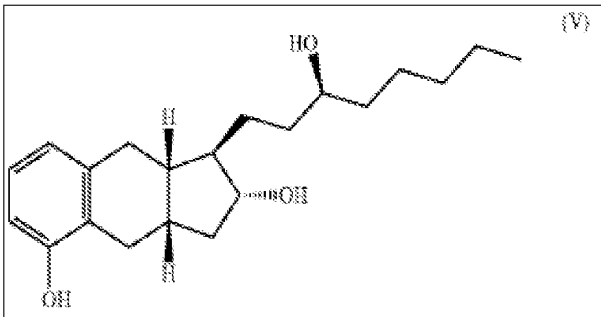
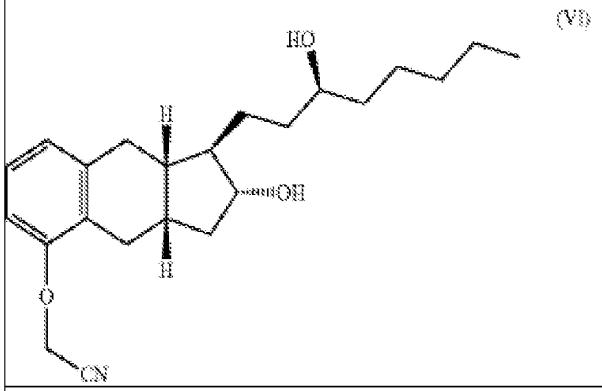
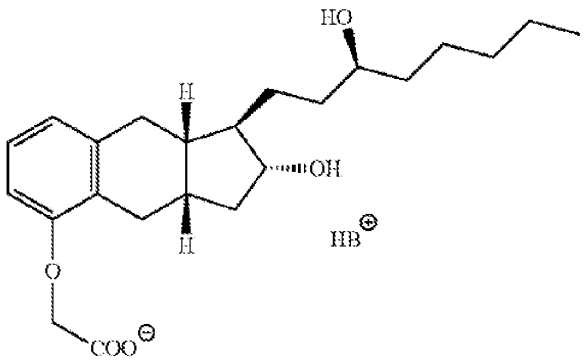
[1] In addition to the references specifically cited herein, United Therapeutics reserves the right to rely on other materials and information including, but not limited to, the references cited by Sandoz in its invalidity contentions, expert opinion, and any additional references uncovered during discovery.

	structure. This exception is rarely invoked. The general rule requiring claims to have a process-free definition of the structure of a new product accommodates most inventions. Some recent exceptions are seen in emerging aspects of biotechnology."); *see also Scripps Clinic & Research Foundation v. Genentech, Inc.,* 927 F.2d 1565 (Fed.Cir.1991) (process to obtain a "highly purified and concentrated" product that was "largely free of contaminants," was not anticipated by previous disclosure of the product), *overruled on other grounds by Abbott Labs v. Sandoz, Inc*., 566 F.3d 1282 (Fed. Cir. 2009). Sandoz claims that the 0.096g of treprostinil product anticipates the claim, however, there is no evidence as to the purity of that sample and they synthesis itself was not reproducible. UTC-Sand-Rem01096057-059. Sandoz previously admitted that "early preparations [of treprostinil] resulted in complex mixtures of diastereomers requiring separation and low yields…Other early efforts by Upjohn in optimizing the preparation of treprostinil focused on closure strategies for the center ring, which also suffered from lack of sufficient stereocontrol and/or low yields due to lengthy synthetic sequences, such as those disclosed in Aristoff '075." Sandoz I Invalidity Contentions at 47. Sandoz's previous Invalidity Contentions operate as an admission of a party opponent, and confirm that even Sandoz itself recognizes the validity of the '393 patent, and the superiority of the product produced by the claimed process of the '393 patent. Sandoz's admission is further supported by the disclosure of the '393 patent itself, which referenced the '075 patent on its face and incorporates it by reference. '393 patent at 1:23-24. Moreover, the Patent Office specifically considered the'075 patent and expressly allowed the '393 patent over the reference, confirming that the '075 patent does not anticipate the claims of the '393 patent. Furthermore, as even Sandoz appears to acknowledge in its previous Invalidity Contentions, the synthetic disclosure in the '075 patent provides for a large number of steps and would result in low yields of impure product. Indeed, the treprostinil product formed

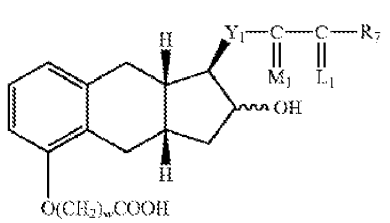
	by the '075 patent synthetic method would be expected to have a different impurity profile than the treprostinil produced by the claimed process of the '393 patent in lower yield.
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,  (II)  (III) wherein w=1, 2, or 3; Y_1 is trans-CH=CH----, cis-CH=CH----, ----$CH_2(CH_2)_m$----, or ----C≡C----; m is 1, 2, or 3; R_7 is (1) ----C_pH_{2p}----CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH----CH_2----CH_3, (5) ----$(CH_2)_2$----CH(OH)----CH_3, or (6) ----$(CH_2)_3$----CH=C$(CH_3)_2$; ----$C(L_1)$----R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl;	Sandoz fails to identify any disclosure of step (a) in the '075 patent and has therefore waived any argument that the '075 patent discloses step (a).

(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
(b) hydrolyzing the product of formula III of step (a) with a base,	Sandoz fails to identify any disclosure of step (b) in the '075 patent and has therefore waived any argument that the '075 patent discloses step (b).
(c) contacting the product of step (b) [sic] with a base B to form a salt of formula I_s (I_s)  and	Sandoz fails to identify any disclosure of step (c) in the '075 patent and has therefore waived any argument that the '075 patent discloses step (c).
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	Sandoz fails to identify any disclosure of step (d) in the '075 patent and has therefore waived any argument that the '075 patent discloses step (d).
Claim 2	
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	The '075 patent does not disclose any product of formula I (including treprostinil) with a purity of at least 99.5% pure. In fact, the only reference Sandoz contends discloses treprostinil with at least 99.5 % purity is the Moriarty 2004 reference. During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Indeed, the Moriarty 2004 reference itself specifies how poor the '075 patent process was and identified multiple problems with the product of the '075 patent. UTC-Sand-Rem00069616. Thus, a person of ordinary skill in the art would not combine the teachings of the '075 patent and Moriarty 2004.

Claim 4	
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	Sandoz fails to identify any disclosure of step (b) or use of NaOH or KOH in the '075 patent and has therefore waived any argument that the '075 patent discloses these claim limitations.
Claim 8	
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Sandoz fails to identify any disclosure of not purifying the compound of formula (III) and has therefore waived any argument that the '075 patent discloses these claim limitations.
Claim 9	
9. A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 is applicable to claim 9. *See*, claim 1.
wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,	

 	
(b) hydrolyzing the product of formula VI of step (a) with a base,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 is applicable to claim 9. *See*, claim 1.
(c) contacting the product of step (b) with a base B to form a salt of formula IV_s, and 	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 is applicable to claim 9. *See*, claim 1.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	

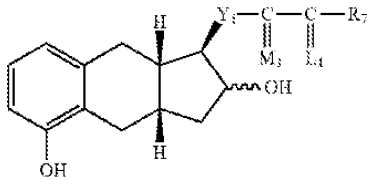
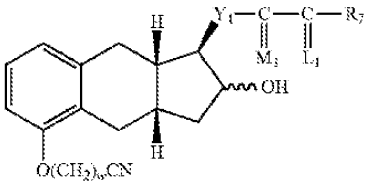
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	The only difference between claim 16 and claim 8 of the '393 patent is their dependence of claims 9 and 1, respectively. Thus, each of the arguments for claim 8 is applicable to claim 16. *See*, claim 8.

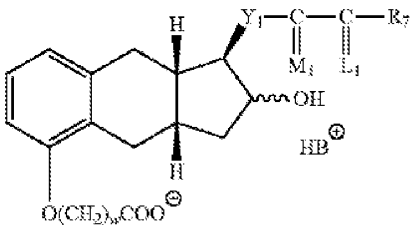
Anticipation and/or Obviousness based on U.S. Patent No. 4,668,814 ("the '814 patent") and European Patent Publication No. 0159784A1 ("EP '784")	
Claim	**Deficiencies in Prior Art**
Claim 1	
1. A product comprising a compound of formula I  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	The '814 patent and EP '784 essentially share the same disclosure of synthetic methods for the crude treprostinil product and other compounds. Indeed, Sandoz has nearly identical contentions for each reference. SIC at 9-24. In addition, Aristoff '814 presents the same synthetic pathway for treprostinil as the EP '784. Since the synthetic method for treprostinil described in Aristoff '814 is the same as that set forth in EP '784, both will be considered together ("the '814 patent references"). Claim 1 of the '393 patent is not anticipated by '814 patent references because the product produced by the claimed method is different from the product of the '814 patent references. While the chemical structure of treprostinil may be the same, the respective impurity profiles, the synthetic method and synthetic efficiency is different. Specifically, the '814 patent references produce products in lower yields and is not suitable to scale-up for large-scale pharmaceutical use because of overall synthetic efficiency. If the process for producing a product according to a product-by-process claim imparts distinctive structural and functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable). Additionally, a source limitation present in the claim can impart structural and functional differences in the product. *Amgen*, 580 F.3d at 1367-68. Additionally, Sandoz fails to demonstrate that the product of the '814 patent references are structurally and functionally the same as the claimed product.

	Sandoz has already expressly admitted that "early preparations [of treprostinil] resulted in complex mixtures of diastereomers requiring separation and low yields" and "[o]ther early efforts by Upjohn in optimizing the preparation of treprostinil focused on closure strategies for the center ring, which also suffered from lack of sufficient stereocontrol and/or low yields due to lengthy synthetic sequences." Sandoz I Initial Invalidity Contentions at 47. Sandoz's admission is further supported by the disclosure of the '393 patent itself, which referenced the '814 patent, on its face. *See* '393 patent References Cited. The products of the '393 patent are structurally and functionally different than the products of the '814 patent references. Upjohn's early syntheses yielded inadequate products in terms of impurities, yield, and other analytical data.[2] For example, the SynQuest Process Optimization For the Manufacture of UT-15 report dated December 28, 2007, states that an early Aristoff synthesis of treprostinil (being an optimized version of the '814 patent synthesis) "yielded a diastereomeric mixture of [treprostinil intermediate]" and subsequent steps added additional chiral centers, thus the Aristoff synthesis "could not allow the production of large-scale quantities of [treprostinil] in an economical way because of extensive separation problems which resulted from the plethora of stereomers formed in this non-stereoselective process." UTC-Sand-Rem00000177. *see also* UTC-Sand-Rem0000177-180 (abandoning the attempt to improve Aristoff synthesis); 180-182; *see generally*, UTC-Sand-Rem-0000145-358. The report also notes that the Upjohn chemists "obtained a crude product corresponding to a mixture of diastereomers [of treprostinil]. Five to ten recrystallizations were necessary…This prior work did not offer much guidance for our purification of the final product [treprostinil] because they had a mixture of stereomers at this stage." UTC-Sand-Rem-00000216. The '814 patent references does not disclose a pure treprostinil product, and while the '814 patent also does not disclose the need for five to ten recrystallizations or other extensive work-up procedures the Synquest report

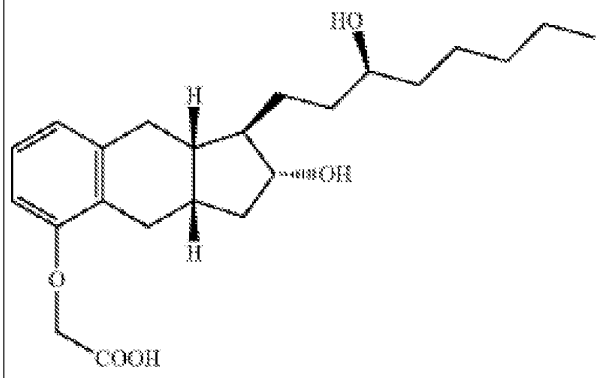
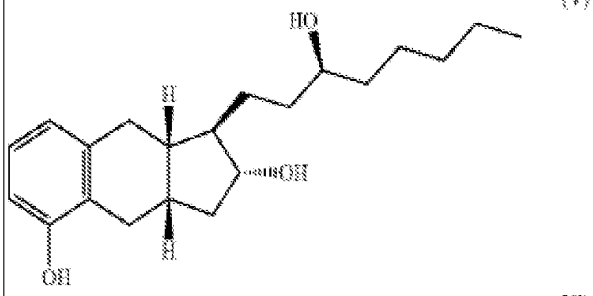
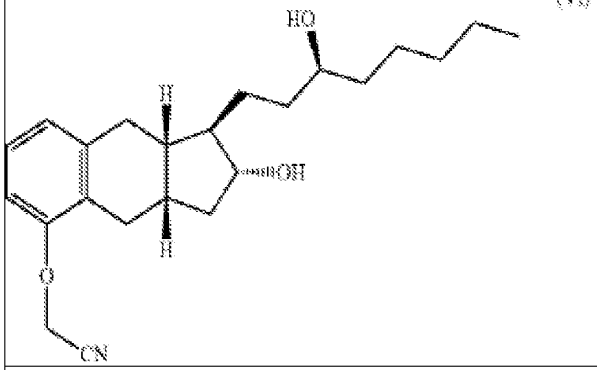
[2] UTC reserves the right to use the entire documents Sandoz cited in their narrative contention response.

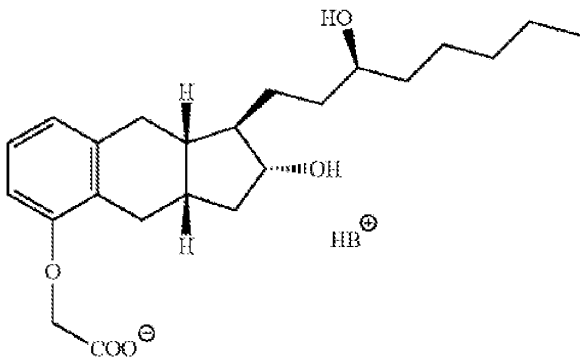
	makes clear that the product of the '814 patent was inadequate even with additional purification techniques not disclosed in the references themselves. Additionally, the lots produced by the prior Upjohn optimized synthesis have a different impurity profile, different average optical rotation, and lower average yield (even after multiple recrystallizations) than lots produced using the '393 patent synthesis that were referenced by Sandoz. SIC at 57-60; *see, also*, UTC-Sand-Rem00061829-62075 at 62013-62015; *see also* UTC-Sand-Rem00022256-22299; UTC-Sand-Rem00025786-26109; and UTC-Sand-Rem00045530-45996. Additionally, a person of ordinary skill in the art would understand that the scale of a chemical reaction can greatly affect the yield and level of impurities. The scale of the reactions disclosed in the '814 patent reference is on the gram scale. Likewise, the lots made from the Upjohn synthesis were made on a smaller scale than several of the later development and commercial lots of treprostinil made using the '393 patent synthesis. *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. A person of ordinary skill in the art would therefore understand that any improvements in the commercial lots of treprostinil made using the '393 patent synthesis is further magnified over the Upjohn synthesis products given their small scale. Sandoz has therefore failed to show the '814 patent references disclose the same pure treprostinil products claimed in the '393 patent. Thus, the '814 patent references fail to anticipate claim 1 of the '393 patent. Sandoz claims that the 1.2g sample of treprostinil in Example 3 of the '814 patent is 95% pure and anticipates the claim, however, there is no evidence within the '814 patent or EP '784 as to the purity of that sample. Sandoz previously admitted that "early preparations [of treprostinil] resulted in complex mixtures of diastereomers requiring separation and low yields…Other early efforts by Upjohn in optimizing the preparation of treprostinil focused on closure strategies for the center ring, which also suffered from lack of sufficient stereocontrol and/or low yields due to lengthy synthetic sequences." Sandoz I Invalidity Contentions at 47. In addition the '075 patent, the '814 patent is the only other Upjohn route and therefore Sandoz was

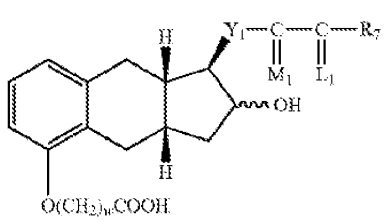
	referring to that route as well. Sandoz' previous Invalidity Contentions operate as an admission of a party opponent, and confirm that even Sandoz itself recognizes the validity of the '393 patent, and the superiority of the product produced by the claimed process of the '393 patent. For these reasons, the '814 patent references do not anticipate claim 1 of the '393 patent.
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III)  wherein w=1, 2, or 3;	Sandoz fails to identify any disclosure of step (a) in the '814 patent references and has therefore waived any argument that the '814 patent references disclose step (a).

Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=C$(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
(b) hydrolyzing the product of formula III of step (a) with a base,	Sandoz fails to identify any disclosure of step (b) in the '814 patent references and has therefore waived any argument that the '814 patent references disclose step (b).
(c) contacting the product of step (b) [sic] with a base B to form a salt of formula I_S (I_S)  and 	Sandoz fails to identify any disclosure of step (c) in the '814 patent references and has therefore waived any argument that the '814 patent references disclose step (c).
(d) optionally reacting the salt formed in step (c) with	Sandoz fails to identify any disclosure of step (d) in the

an acid to form the compound of formula I.	'814 patent references and has therefore waived any argument that the '814 patent references disclose step (d).
Claim 2	
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	The '814 patent references do not disclose any product of formula I (including treprostinil) with a purity of at least 99.5%. In fact, the only reference Sandoz contends discloses treprostinil with at least 99.5 % purity is the Moriarty 2004 reference. During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Indeed, the Moriarty 2004 reference itself specifies how poor the '814 patent references were and identified multiple problems with the products of the '814 patent references. UTC-Sand-Rem00069614-16. Moreover, as described above, even with multiple recrystallizations not described in the '814 patent, the product could not be improved to a higher purity for scale up. Thus, a person of ordinary skill in the art would not combine the teachings of the '814 patent references and Moriarty 2004.
Claim 4	
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	Sandoz fails to identify any disclosure of step (b) or use of NaOH or KOH in the '814 patent references and has therefore waived any argument that the '814 patent references disclose these claim limitations.
Claim 8	
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Sandoz fails to identify any disclosure of not purifying the compound of formula (III) and has therefore waived any argument that the '814 patent references disclose these claim limitations.
Claim 9	
9. A product comprising a compound having formula IV	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 is applicable to claim 9. *See*, claim 1.

 or a pharmaceutically acceptable salt thereof,	
wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, (V)  (VI) 	
(b) hydrolyzing the product of formula VI of step (a) with a base,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 is applicable to claim 9. *See*, claim 1.
(c) contacting the product of step (b) with a base B to	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the

form a salt of formula IV_s, and 	synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 is applicable to claim 9. *See*, claim 1.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 is applicable to claim 9. *See*, claim 1.
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	The only difference between claim 16 and claim 8 of the '393 patent is their dependence of claims 9 and 1, respectively. Thus, each of the arguments for claim 8 is applicable to claim 16. *See*, claim 8.

Anticipation and/or Obviousness based on 2006 Remodulin Package Insert, Prior Sale of Remodulin, U.S. Patent No. 6,765,117 ("the '117 patent") and J. Org. Chem. 2004, 69, 1890-1902 (2004) ("Moriarty 2004") (collectively, "the Moriarty references") including Anticipation by Moriarty 2004	
Claim	**Deficiencies in Prior Art**
Claim 1	
1. A product comprising a compound of formula I  (I)	The '117 patent and Moriarty 2004 references disclose the same synthesis for treprostinil. Additionally, the treprostinil referenced in the 2006 Remodulin Package Insert and the Remodulin on sale prior to the priority date of the '393 patent were also made by the '117 patent process.[3] Since the synthetic method for treprostinil described in each of these references is the same as that set forth in the '117 patent, they will be considered together ("the Moriarty references").

[3] Indeed, the 2006 Remodulin Package Insert does not disclose any synthesis and the "sale" of Remodulin similarly does not disclose any specific synthesis. In fact, Sandoz has admitted that the '393 patent process was not used to make Remodulin (and therefore not "on sale") until after the priority date of the '393 patent. See, SIC at 61 ("By mid-2008, UTC had modified its manufacturing process to include the process steps claimed in the '393 patent.").

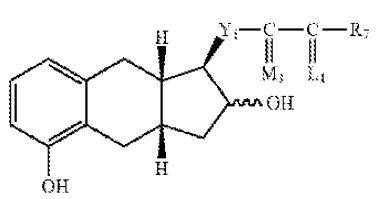
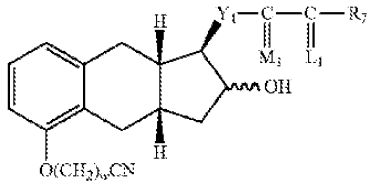
or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Claim 1 of the '393 patent is not anticipated by the Moriarty references because the product produced by the claimed method is different from the product of the Moriarty references. While the chemical structure of treprostinil may be the same, the respective impurity profiles, the synthetic method and synthetic efficiency is different. Specifically, the Moriarty references produce products in lower yields with more impurities. If the process for producing a product according to a product-by-process claim imparts distinctive structural and functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable). During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference (and the '117 patent) because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Contrary to Sandoz' allegations, the Walsh declaration did not require that the '393 patent provide only a certain subset of impurities, but was used to show that there were less total impurities present and less overall impurities. Indeed, the batch record used by Walsh to show the differences was a representative example. On average, the batches of treprostinil made by the '393 patent have less number of impurities and less total impurities than an average of treprostinil made by the '117 patent. The products of the '393 patent are structurally and functionally different than the products of the Moriarty references.[4] Indeed, Sandoz only looks at the first 5 Process Optimization batches of the '393 patent treprostinil for comparison to prior batches made by the Moriarty process, but then also only looks at the last few years of the Moriarty process when it was fully optimized and run at scale. SIC at 55-61; *see also* UTC-Sand-Rem01096535-36. First, a comparison of the first

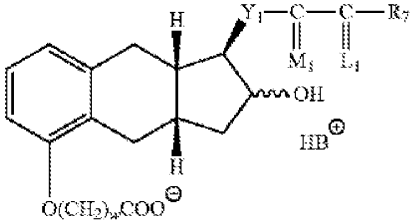
[4] UTC reserves the right to use the entire documents Sandoz cited in their narrative contention response.

	few developmental batches made to years of optimized batches is an unfair comparison. Even under this comparison, however, the 5 '393 patent batches showed that only 1 batch had <0.05% [redacted] impurity, only 1 batch had <0.05% [redacted] impurity, none of the batches had any [redacted] impurity and all batches had <0.05% [redacted] impurity and <0.05% [redacted] impurity. UTC-Sand-Rem01096535-36. This is a very low amount for these impurities given that these were the first few batches made with the process. The last six years of Moriarty batches made, however, had more impurities on average per impurity of several impurities than these 5 initial '393 patent batches. *Id.* A much better comparison, however, would look at the impurity profiles of the first 5 batches of the Moriarty batches (including LRX-97J01, LRX-98A01, LRX-98B01, UT15-98H01, UT15-98I01) as a comparison to these first 5 batches of the '393 patent that Sandoz cites. See, UTC-Sand-Rem00021934-39; UTC-Sand-Rem01156295-295; UTC-Sand-Rem01096536. Indeed, under that analysis, the average '393 patent batch had far less total impurities, and individual impurities as the Moriarty batches had an a much higher average amount of many impurities including [redacted]. *Id.* Additionally, the average Moriarty batch had many times the total impurities of the average '393 patent batch. *Id.* Additionally, beyond the first 5 batches of treprostinil made by the '393 patent, other later batches also confirm that the average batch made by the '393 patent is superior to the batches made by the Moriarty references in terms of quality, impurities present, and total impurities, among other properties. Given the potency of treprostinil, any impurity is a potential safety concern and a person of ordinary skill would want to minimize these impurities. The product of the '393 patent is structurally and functionally different than the products of the prior art that contained treprostinil because the '393 patent has a higher level of average purity, lower number of individual impurities, and better product. For example, in a document entitled Treprostinil Drug Substance Impurities, all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by the '117 patent and Moriarty 2004 process. *See* UTC-Sand-Rem00334054-00334057 and UTC-

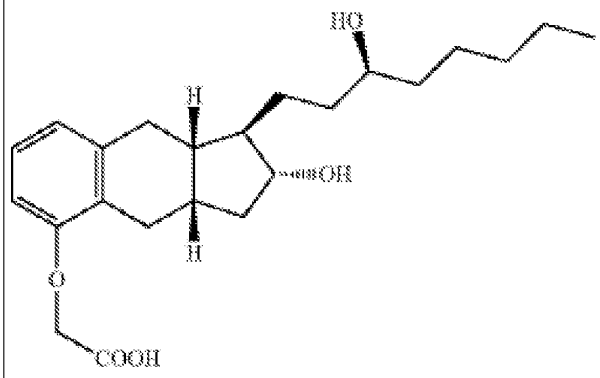
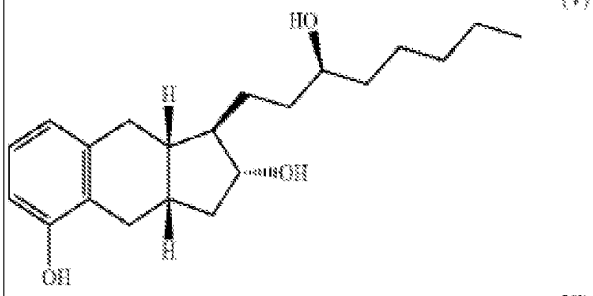
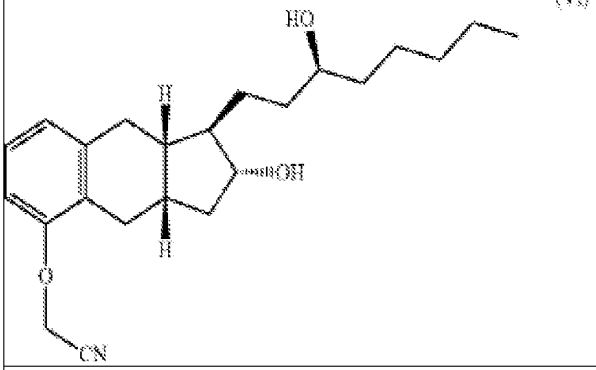
	Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty process. See, e.g., UTC-Sand-Rem01096537, PTX-100a, UTC-Sand-Rem00001673-702; UTC-Sand-Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTC-Sand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTC-Sand-Rem01111355-357; UTC-Sand-Rem01117901-906; UTC-Sand-Rem01117910-912; UTC-Sand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Other documents show that the batches made by the '393 patent process have a better impurity profile on average as well as less total impurities.[5] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the prior art specifies the level of purity or minimal level of impurities that the '393 patent provides. Additionally, a person of ordinary skill in the art would understand that the scale of a chemical reaction can greatly affect the yield and level of impurities. The scale of the reactions disclosed in the Moriarty references on average is smaller than the scale of batches made by the '393 patent. *See* UTC-Sand-

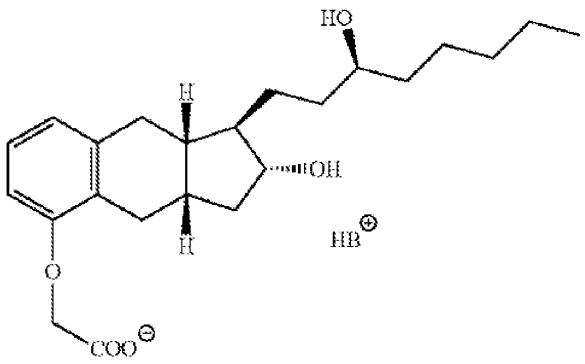
[5] The documents cited herein for batches of treprostinil made by the '117 patent process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different and reserves the right to cite any document from Sandoz's Contentions.

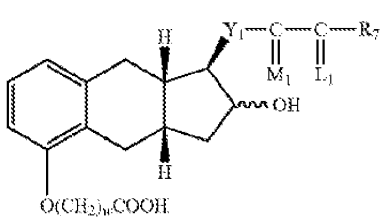
	Rem01096533 ("The following chart lists in detail the changes that occurred in the process between Chicago [using Moriarty process] and Silver Spring [using '393 process]. In Silver Spring, the diethanolamine salt was introduced as a purification step and the batch size was increased from [redacted] to [redacted]."). Despite this jump in batch size, the overall purity of the '393 patent process was reported as 99.9% compared to 99% for the Moriarty process. *Id*. A person of ordinary skill in the art would therefore understand that any improvements in the commercial lots of treprostinil made using the '393 patent synthesis is further magnified over the Moriarty synthesis products given the difference in scale. Sandoz has therefore failed to show the Moriarty references disclose the same pure treprostinil products claimed in the '393 patent. Thus, the Moriarty references fail to anticipate claim 1 of the '393 patent. For these reasons, the Moriarty references do not anticipate claim 1 of the '393 patent.
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III)  wherein w=1, 2, or 3;	See Claim 1.

Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=C$(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
(b) hydrolyzing the product of formula III of step (a) with a base,	*See* Claim 1.
(c) contacting the product of step (b) [sic] with a base B to form a salt of formula I_S  (I_S) and	*See* Claim 1. Sandoz claims that the Moriarty reference teach the performance of step (c) because when the KOH reacts with the treprostinil in step (b), "some molecules of treprostinil acid necessarily and unavoidably react again with KOH to form treprostinil potassium, which is then converted back to treprostinil acid by subsequent addition of HCl." SIC at 75. Not so. As described and claimed, the treprostinil is made in a separate step and not simply in situ with KOH. Indeed, step (c) specifies that it must "contact the product of step (b)" that is, the completed step, before proceeding on to the next step. Thus, Sandoz has failed to show that any of the Moriarty references disclose step (c) of claim 1.

(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See* Claim 1. Because Sandoz has failed to show step (c) of claim 1, they have similarly failed to show step (d) as it requires the salt formed in step (c).
Claim 2	
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	The Moriarty references do not disclose any product of formula I (including treprostinil) with a purity of at least 99.5% except for the one Moriarty 2004 reference. During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Contrary to Sandoz's allegations, the Walsh declaration did not require that the '393 patent provide only a certain subset of impurities, but was used to show that there were less total impurities present and less overall impurities. Indeed, the batch record used by Walsh to show the differences as a representative example. On average, the batches of treprostinil made by the '393 patent have less number of impurities and less total impurities than an average of treprostinil made by the '117 patent. The products of the '393 patent are structurally and functionally different than the products of the Moriarty references. There is no indication of the purification process used in the '393 patent in any Moriarty reference. Thus, a person of ordinary skill in the art would not combine the teachings of the Moriarty references and Moriarty 2004.
Claim 4	
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See* Claim 1.
Claim 8	
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	The Moriarty references indicate that column chromatography is used to purify the compound of formula (III).
Claim 9	
9. A product comprising a compound having formula IV	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.

 or a pharmaceutically acceptable salt thereof,	
wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, (V)  (VI) 	
(b) hydrolyzing the product of formula VI of step (a) with a base,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
(c) contacting the product of step (b) with a base B to	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the

form a salt of formula IV_s, and 	synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	The only difference between claim 16 and claim 8 of the '393 patent is their dependence of claims 9 and 1, respectively. Thus, each of the arguments for claim 8 are applicable to claim 16. *See*, claim 8.

Anticipation and/or Obviousness based on U.S. Patent Application Publication No. 2005/0085540A1 ("Phares") including obviousness based on Phares In Combination with Moriarty 2004, Phares In Combination with Moriarty 2004 and Anderson, N. "Practical Process Research & Development: A Guide for Organic Chemists, p. 13, 223, 226 (2000) ("Anderson")	
Claim	**Deficiencies in Prior Art**
Claim 1	
1. A product comprising a compound of formula I  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Sandoz provides separate charts for 1) Phares (SIC at 61-71), 2) Phares again (SIC at 92-104), 3) Phares in combination with Moriarty 2004 (SIC at 104-125), and 4) Phares in combination with Moriarty 2004 and Anderson (SIC at 126-141). Sandoz repeats many of the same arguments each of the above referenced charts will be addressed together. **Phares** Claim 1 of the '393 patent is not anticipated and/or rendered obvious by Phares because the product produced by the claimed method is different from the product of Phares. Although treprostinil and Remodulin are discussed in Phares, the mere disclosure of treprostinil does not anticipate any claim of the '393

	patent. In fact, contrary to Sandoz's allegations, Phares does not specifically teach the synthesis of treprostinil, but summarily teaches the synthesis of its enantiomer (-)-treprostinil and notes that (+)-treprostinil can be prepared in the same manner. [0143-0145] All that Phares discloses is the synthesis of (-)-treprostinil without indicating how that would be altered to synthesize (+)-treprostinil and is therefore not enabled with regard to teaching a synthesis for (+)-treprostinil. *Id.* Additionally, there is no indication of the purity or potential impurities present in a batch of treprostinil (because no synthesis is disclosed). The product of the Phares publication is structurally and functionally different from the product of Phares. First, as Sandoz admits, Phares does not indicate the purity of diethanolamine. SIC at 112. Instead, Phares only indicates that Form B polymorph of the treprostinil diethanolamine disclosed has a melting point of 107C. [0337] but the data shows a larger range of melting point from about 100-110.[6] The '393 patent, however, indicates that the melting point for Form B is more than 104C. '393 patent, col. 12 ll. 52-55. Thus, it is not clear that the treprostinil diethanolamine from Phares is the same as the treprostinil diethanolamine of the '393 patent. Moreover, Phares does not disclose any purity data for treprostinil diethanolamine. Additionally, Phares was considered by the Patent Office during prosecution and appears on the face of the '393 patent. While the chemical structure of treprostinil and/or treprostinil diethanolamine may be the same, the respective impurity profiles, the unknown synthetic method and resulting product are expected to be different. If the process for producing a product according to a product-by-process claim imparts distinctive structural and functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly

[6] It is also not clear from Phares that 107C is the melting point of Form B of treprostinil diethanolamine. The DSC thermogram shows a single endotherm at 107C and Phares claims "that is consistent with a melting event" but this is not necessarily the correct melting point for treprostinil diethanolamine as the endotherm is much broader than 107C. *See* Phares, [0335, Figures 20 and 21].

	claimed in order to be patentable). Thus, Phares fails to anticipate and/or render obvious claim 1 of the '393 patent. **Phares in combination with Moriarty 2004** The combination of Moriarty 2004 and Phares do not render claim 1 of the '393 patent obvious. As detailed above, Phares alone does not disclose any specific treprostinil product (only its enantiomer) and the treprostinil diethanolamine disclosed is expected to be different than the treprostinil diethanolamine of the '393 patent. Also discussed above, Moriarty 2004 alone does not disclose the same treprostinil product as the treprostinil made has, on average, a lower purity and more impurities present. During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference (and the '117 patent) because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Contrary to Sandoz's allegations, the Walsh declaration did not require that the '393 patent provide only a certain subset of impurities, but was used to show that there were less total impurities present and less overall impurities. Indeed, the batch record used by Walsh to show the differences as a representative example. On average, the batches of treprostinil made by the '393 patent have less number of impurities and less total impurities than an average of treprostinil made by the Moriarty 2004 process. The products of the '393 patent are structurally and functionally different than the products of the Moriarty references.[7] Indeed, Sandoz only looks at the first 5 Process Optimization batches of the '393 patent treprostinil for comparison to prior batches made by the Moriarty process, but then also only looks at the last few years of the Moriarty process when it was fully optimized and run at scale. SIC at 55-61; *see also* UTC-Sand-Rem01096535-36. First, a comparison of the first few developmental batches made to years of optimized batches is an unfair comparison. Even under this comparison, however, the 5 '393 patent batches showed that only 1 batch had <0.05% [redacted] impurity, only 1 batch had <0.05% [redacted] impurity, none of the batches had any [redacted] impurity and all batches had <0.05%

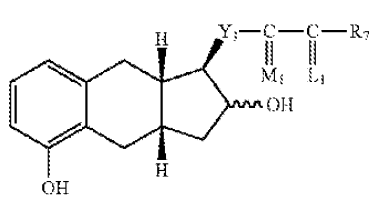
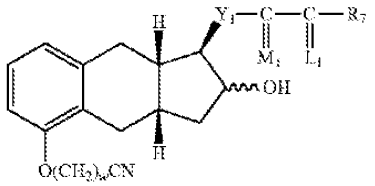
[7] UTC reserves the right to use the entire documents Sandoz cited in their narrative contention response.

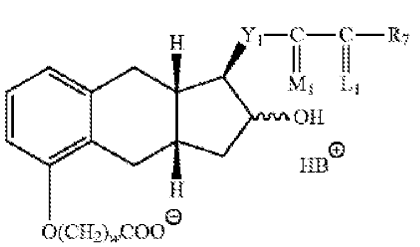
	[redacted] impurity and <0.05% [redacted] impurity. UTC-Sand-Rem01096535-36. This is a very low amount for these impurities given that these were the first few batches made with the process. The last six years of Moriarty batches made, however, had more impurities on average per impurity of several impurities than these 5 initial '393 patent batches. *Id.* A much better comparison, however, would look at the impurity profiles of the first 5 batches of the Moriarty batches (including LRX-97J01, LRX-98A01, LRX-98B01, UT15-98H01, UT15-98I01) as a comparison to these first 5 batches of the '393 patent that Sandoz cites. See, UTC-Sand-Rem00021934-39; UTC-Sand-Rem01156295-295; UTC-Sand-Rem01096536. Indeed, under that analysis, the average '393 patent batch had far less total impurities, and individual impurities as the Moriarty batches had an a much higher average amount of many impurities including [redacted]. *Id.* Additionally, the average Moriarty batch had many times the total impurities of the average '393 patent batch. *Id.* Additionally, beyond the first 5 batches of treprostinil made by the '393 patent, other later batches also confirm that the average batch made by the '393 patent is superior to the batches made by the Moriarty references in terms of quality, impurities present, and total impurities, among other properties. Given the potency of treprostinil, any impurity is a potential safety concern and a person of ordinary skill would want to minimize these impurities. The product of the '393 patent is structurally and functionally different than the products of the prior art that contained treprostinil because the '393 patent has a higher level of average purity, lower number of individual impurities, and better product. For example, in a document entitled Treprostinil Drug Substance Impurities, all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by the '117 patent and Moriarty 2004 process. *See* UTC-Sand-Rem00334054-00334057 and UTC-Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty process. See, e.g., UTC-Sand-Rem01096537, PTX-100a, UTC-Sand-Rem00001673-702; UTC-Sand-

	Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTC-Sand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTC-Sand-Rem01111355-357; UTC-Sand-Rem01117901-906; UTC-Sand-Rem01117910-912; UTC-Sand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Other documents show that the batches made by the '393 patent process have a better impurity profile on average as well as less total impurities.[8] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the prior art specifies the level of purity or minimal level of impurities that the '393 patent provides. Additionally, a person of ordinary skill in the art would understand that the scale of a chemical reaction can greatly affect the yield and level of impurities. The scale of the reactions disclosed in the Moriarty references on average is smaller than the scale of batches made by the '393 patent. *See* UTC-Sand-Rem01096533 ("The following chart lists in detail the changes that occurred in the process between Chicago [using Moriarty process] and Silver Spring [using '393 process]. In Silver Spring, the diethanolamine salt was introduced as a purification step and the batch size was increased from [redacted] to [redacted]."") Despite this jump in batch size, the overall purity of the '393 patent process was reported as

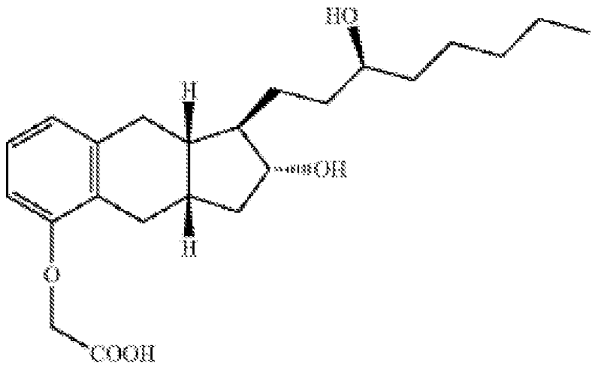
[8] The documents cited herein for batches of treprostinil made by the '117 patent process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different and reserves the right to cite any document from Sandoz's Contentions.

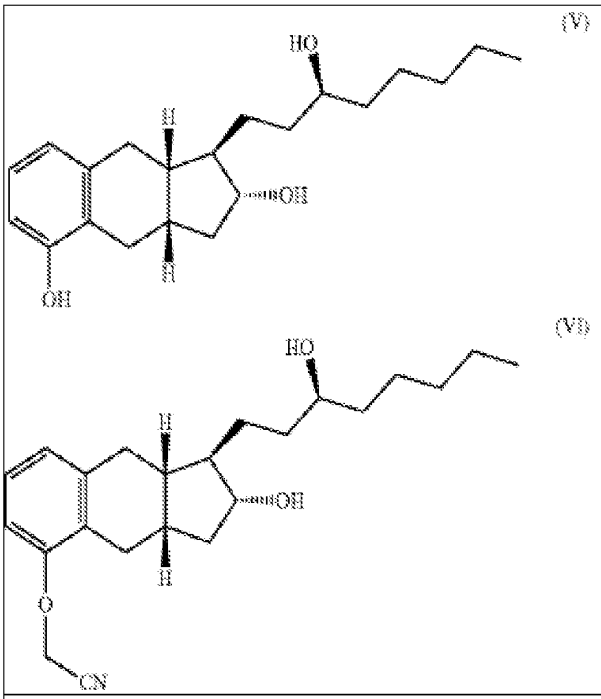
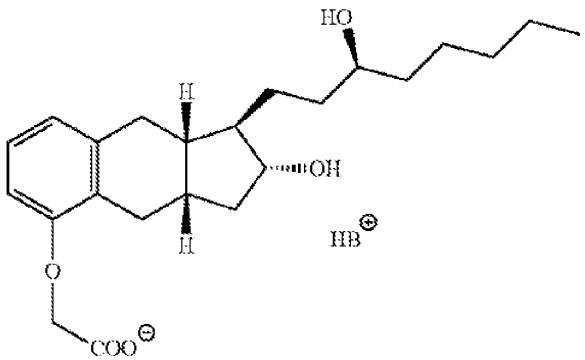
	99.9% compared to 99% for the Moriarty process. *Id.* A person of ordinary skill in the art would therefore understand that any improvements in the commercial lots of treprostinil made using the '393 patent synthesis is further magnified over the Moriarty synthesis products given the difference in scale. Sandoz has therefore failed to show the Moriarty references disclose the same pure treprostinil products claimed in the '393 patent. Both Phares and Moriarty 2004 were disclosed to the Patent Office during prosecution of the '393 patent. Moreover, the batches made by the Moriarty 2004 process are of a lower purity and have a different impurity profile than the treprostinil made by the '393 patent process so even if a person of ordinary skill in the art were to combine these references, Phares does not specify a synthesis for treprostinil so the Moriarty 2004 synthesis would presumably be used to then further make the diethanolamine salt form from Phares. Even if this were the case, however, because both the Moriarty 2004 treprostinil and the Phares treprostinil diethanolamine are of lower and/or different purity, there is no evidence to suggest that the resulting product would be the same as the product of the '393 patent. **Phares in combination with Moriarty 2004 and Anderson** The above response to Phares, Moriarty 2004, and Phares in combination with Moriarty are incorporated herein. Sandoz only cites Anderson for the allegation that "a person of ordinary skill in the art would have been motivated to avoid the 'drawbacks' of column chromatography, which is 'labor intensive; process that is used generally as a last resort and that diethanolamine salts were known and "the solubility of acid salts of the amines (Table 3.7) can provide some operating advantages on scale.". SIC at 127. This is inaccurate, however, as diethanolamine is NOT disclosed in Table 3.7 and is not listed as an "amine useful for scale-up. Anderson, Table 3.7. Instead, only diethylamine is listed, not diethanolamine. *Id.* Regardless of whether a POSA would have preferred to avoid column chromatography, however, is irrelevant. Column chromatography is commonly used for such complicated molecules as treprostinil, which has 5

	chiral centers. Indeed, there is no discussion of using a diethanolamine salt in the Anderson citations provided by Sandoz. As previously described, the combination of Phares and Moriarty 2004 do not render the claims obvious and Anderson does not disclose any information about treprostinil or its synthesis nor even disclose that diethanolamine would have been useful for scale-up. Indeed, it was an unexpected result that the salt step disclosed in the '393 patent worked to remove impurities. Thus, the addition of Anderson to the combination of Phares and Moriarty 2004 does not render claim 1 of the '393 patent obvious.
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,  (II)  (III) wherein w=1, 2, or 3;	See Claim 1, above.

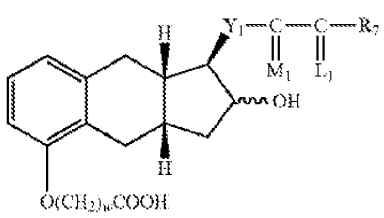
Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=C$(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
(b) hydrolyzing the product of formula III of step (a) with a base,	See Claim 1, above.
(c) contacting the product of step (b) [sic] with a base B to form a salt of formula I_s  (I_s) and	Sandoz claims that Phares discloses this step at [0105]. SIC at 131. The disclosure cited, however, only states that "Treprostinil acid acid [sic] is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling." [0105]. This disclosure, however, does not indicate the source or purity of treprostinil used and as indicated above, there is no indication of the purity of the resulting salt form. Moreover, Sandoz failed to identify step (c) in the Moriarty 2004 disclosure. *See* Claim 1 Moriarty References, above. Sandoz also fails to identify any disclosure in the

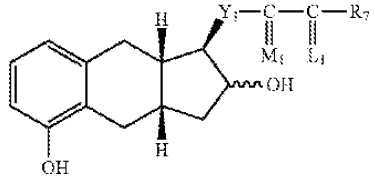
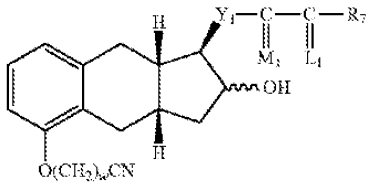
	Anderson reference.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	Sandoz fails to identify any disclosure of step (d) in the Phares or Anderson reference. The Moriarty 2004 reference similarly does not disclose the treprostinil diethanolamine salt that Sandoz cites for step (c) above. Additionally, as previously discussed, the product of the Moriarty 2004 reference is structurally and functionally different than the product of the '393 patent and does not disclose step (d) because Sandoz failed to show it disclosed step (c).
Claim 2	
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	Phares does not disclose a product of Claim 1 with a purity of at least 99.5%. Despite Sandoz's allegations regarding the recystallization process disclosed in Phares, there is no indication that any treprostinil or treprostinil diethanolamine was produced with a purity of at least 99.5%. Anderson does not disclose a product of Claim 1 with a purity of at least 99.5%. Indeed, Anderson does not disclose treprostinil and does not disclose the use of diethanolamine salts. During prosecution of the '393 patent, the Examiner allowed all of the claims of the '393 patent over the Moriarty 2004 reference because of evidence provided that it had a different impurity profile than the prior art. *See, e.g.*, SDZ5499 0004833. Contrary to Sandoz's allegations, the Walsh declaration did not require that the '393 patent provide only a certain subset of impurities, but was used to show that there were less total impurities present and less overall impurities. Indeed, the batch record used by Walsh to show the differences as a representative example. On average, the batches of treprostinil made by the '393 patent have less number of impurities and less total impurities than an average of treprostinil made by the '117 patent. The products of the '393 patent are structurally and functionally different than the products of the Moriarty references. There is no indication of the purification process used in the '393 patent in Moriarty 2004. Thus, claim 2 is not rendered and/or obvious by Phares alone or in combination with Moriarty 2004 and/or Anderson.
Claim 4	
4. The product of claim 1, wherein the base in step (b)	See claim 1.

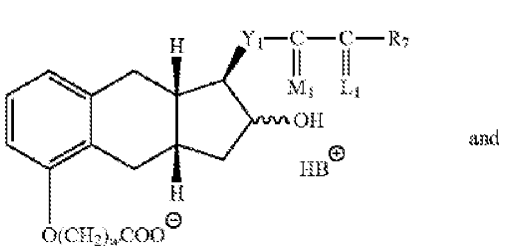
is KOH or NaOH.	
Claim 8	
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Moriarty 2004 indicates that column chromatography is used to purify the compound of formula (III). Similarly, Phares does not disclose the details of the synthesis of treprostinil, however, all synthesis of treprostinil at the time of the Phares invention involved the use of column chromatography. While Anderson indicates that column chromatography is less preferred, there is no indication that would point a POSA to somehow eliminate this purification from existing treprostinil syntheses (or any similarly complex molecules) and does not disclose the use of diethanolamine salt. Thus, claim 8 is not rendered anticipated and/or obvious by Phares alone or in combination with Moriarty 2004 and/or Anderson.
Claim 9	
9. A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Phares does not disclose the synthesis of treprostinil, only its enantiomer. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.

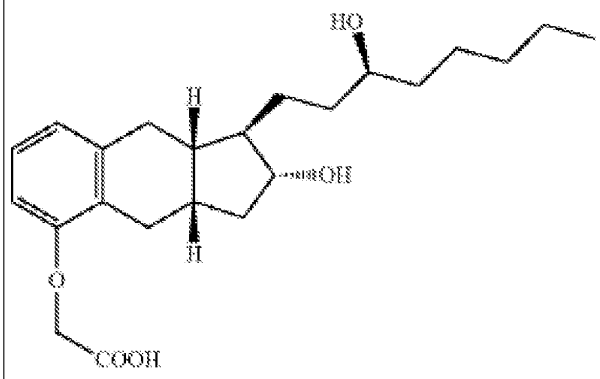
	
(b) hydrolyzing the product of formula VI of step (a) with a base,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
(c) contacting the product of step (b) with a base B to form a salt of formula IV_s, and 	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.

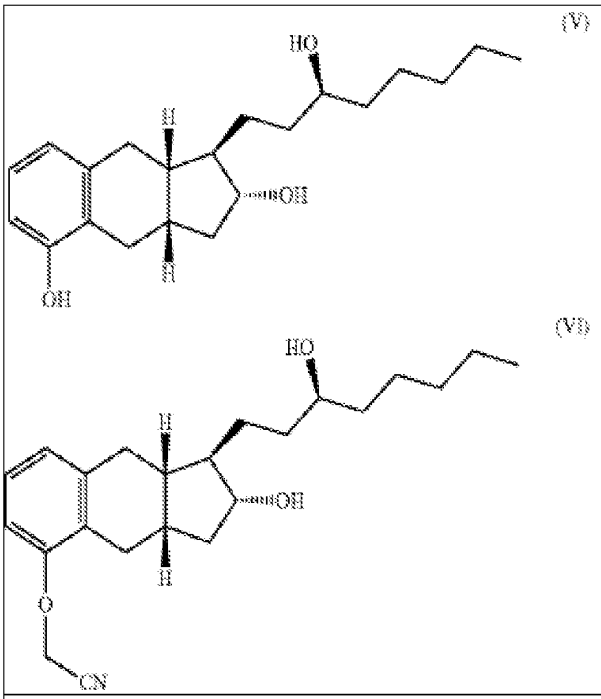
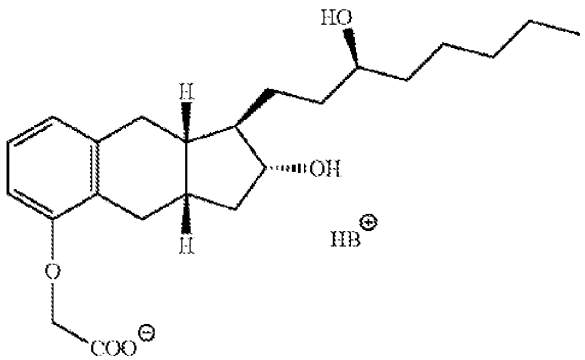
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	The only difference between claim 16 and claim 8 of the '393 patent is their dependence of claims 9 and 1, respectively. Thus, each of the arguments for claim 8 are applicable to claim 16. *See*, claim 8.

Anticipation and/or Obviousness based on "Synthetic Approaches to the 2002 New Drugs" Li, et. al., Mini-Reviews in Medicinal Chemistry, Vol. 4 at pp.207-233 (2004) ("Li") and Sorbera, et. al., "UT-15, Treatment of Pulmonary Hypertension, Treatment of Peripheral Vascular Disease," Drugs of the Future, Vol. 26(4), pp. 364-374 (2001) ("Sorbera") Including Obviousness based on Li	
Claim	**Deficiencies in Prior Art**
Claim 1	
1. A product comprising a compound of formula I  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Both Li and Sorbera only disclose summaries of other known syntheses of treprostinil and disclose no new information on the product, synthesis, or purity/impurity profile of the treprostinil products disclosed in the prior references. Li cites U.S. Patent 6,441,245 ("the '245 patent") and WO 9921830 ("WO '830") for the summary of the treprostinil synthesis disclosed. SDZ5499 0005382-83. Both the '245 patent and WO '830 were disclosed to the Patent Office during prosecution of the '393 patent and listed on the face of the patent. In fact, the '245 patent is cited by the '393 patent "treprostinil, and other prostacyclin derivatives have been prepared as described in...U.S. Patent No. 6,441,245..." '393 patent, Col. 1, ll. 23-26. Although the Li article cites the last step involves titration of treprostinil with NaOH, neither WO '830 or the '245 patent disclose this step. Thus, this step is not supported by the reference and is therefore not enabled as there is no indication that Li actually synthesized anything and is simply reporting previously listed syntheses. Instead, WO '830 and '245 patent discloses the crude product (treprostinil) was purified by column chromatography and no further steps were taken. Sandoz-Trep0007792-93; '245 patent, col. 18, ll. 26-29. Thus, in addition to not disclosing the last salt step, these references use the same synthesis as the '117 patent and Moriarty 2004. Thus, UTC incorporates its arguments regarding the '117 patent and Moriarty 2004 herein. See '117 patent and Moriarty 2004 Claim 1, above. Similarly, Sorbera cites the '075 patent, EP 784, and WO '830 for syntheses of treprostinil and provides no additional information beyond what is in each of these

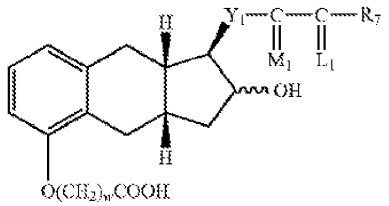
	references regarding the purity, impurity profiles, synthesis or composition of the drug product. As previously discussed, none of these references anticipate and/or render obvious any claim of the '393 patent. See, '075 patent, '814 patent references, and Moriarty references charts above.
(b) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III)  wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=C$(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl;	See claim 1, above. See also, '075 patent, '814 patent references, and Moriarty references charts above.

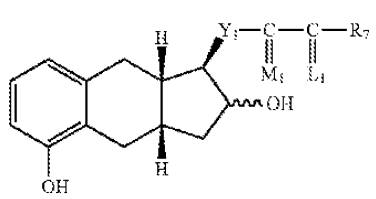
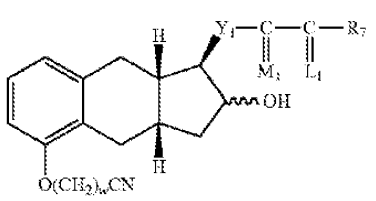
(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
(b) hydrolyzing the product of formula III of step (a) with a base,	See claim 1, above. See also, '075 patent, '814 patent references, and Moriarty references charts above.
(c) contacting the product of step (b) [sic] with a base B to form a salt of formula I_s  (I_s) and	See claim 1, above. See also, '075 patent, '814 patent references, and Moriarty references charts above.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	See claim 1, above. See also, '075 patent, '814 patent references, and Moriarty references charts above.
Claim 2	
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	Neither Li or Sorbera disclose the product of claim 1 with at least 99.5% purity. Additionally, neither Li or Sorbera anticipate and/or render obvious this claim for the same reasons as the '117 patent and Moriarty 2004 do not anticipate and/or render obvious the claim. See claim 1, above. See also '117 patent and Moriarty 2004 charts above.
Claim 4	
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	Neither Li or Sorbera anticipate and/or render obvious this claim for the same reasons as the '117 patent and Moriarty 2004 do not anticipate and/or render obvious the claim. See claim 1, above. See also '117 patent and Moriarty 2004 charts above.
Claim 8	
8. The product of claim 1, wherein the process does	Neither Li or Sorbera anticipate and/or render obvious

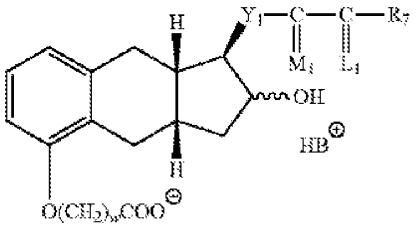
not include purifying the compound of formula (III) produced in step (a).	this claim for the same reasons as the '117 patent and Moriarty 2004 do not anticipate and/or render obvious the claim. See claim 1, above. See also '117 patent and Moriarty 2004 charts above.
Claim 9	
9. A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,	

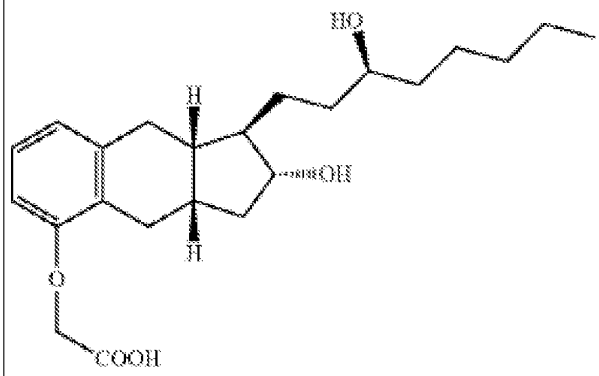
	
(b) hydrolyzing the product of formula VI of step (a) with a base,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
(c) contacting the product of step (b) with a base B to form a salt of formula IV_s, and 	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to claim 9. *See*, claim 1.

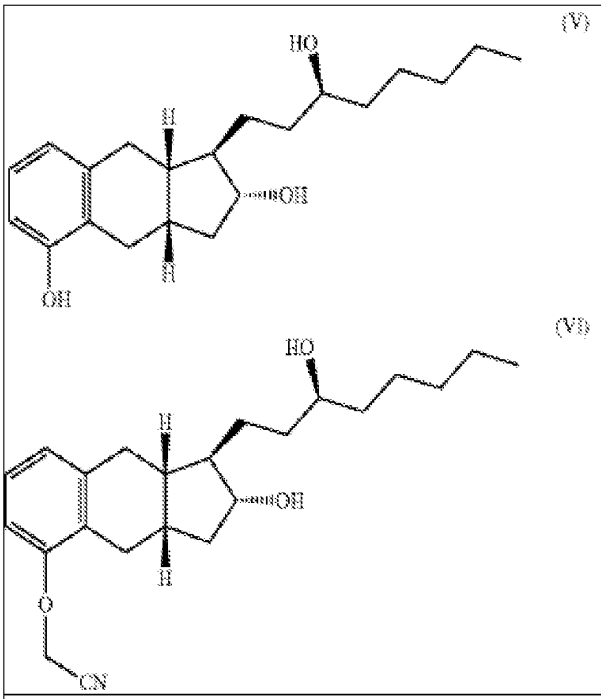
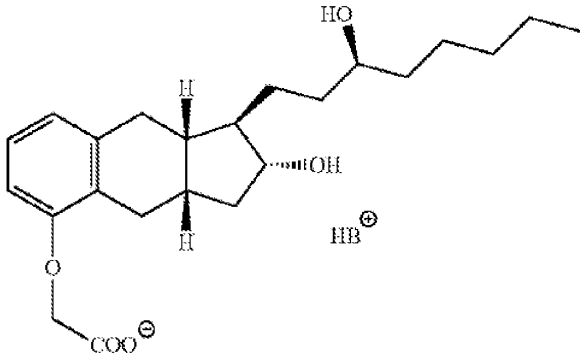
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	The only difference between claim 16 and claim 8 of the '393 patent is their dependence of claims 9 and 1, respectively. Thus, each of the arguments for claim 8 are applicable to claim 16. *See*, claim 8.

Obviousness-Type Double Patenting based on U.S. Patent No. 7,417,070 ("the '070 patent") and U.S. Patent No. 6,765,117 ("the '117 patent")	
Claim	**Deficiencies in Prior Art**
Claim 1	
1. A product comprising a compound of formula I (I)  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Sandoz's entire obviousness-type double-patenting argument with regard to the '070 patent is that because claim 1 of the '070 patent claims a compound having the structure of treprostinil diethanolamine, then that necessarily renders obvious the claims of the '393 patent by the mere disclosure of the structure. SIC at 77-79. Sandoz is wrong. As previously discussed with regard to Phares, the mere disclosure of treprostinil diethanolamine does not render obvious any claim of the '393 patent. Indeed, Sandoz ignores that obviousness-type double patenting requires that only the claims of the prior art must be compared to the asserted claims. The claims of the '393 patent are very different than claim 1 of the '070 patent. Indeed, Sandoz provides no citation for its assertion that process elements are irrelevant specifically when performing an obviousness-type double patenting analysis and no citation that the species/genus argument applies as well. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Moreover, the synthesis used to make the diethanolamine salt in the '070 patent would result in a structurally and functionally different product than the '393 patent for the same reasons as Phares as the '070 patent is the issued patent of the Phares patent publication. Thus, all arguments regarding Phares are incorporated herein. *See* Phares Claim 1 response. Similarly, the claims of the '117 patent are very different than the claims of the '393 patent and would result in different product. Moreover, the '117 patent

	does not specifically disclose treprostinil diethanolamine. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Moreover, the products of the '117 patent and the '393 patent are structurally and functionally different. *See* Moriarty References Claim 1. Other than structural and functional differences, the products of the '117 patent and the '393 patent are also different as the '117 patent product must be stereoselectively produced using the source limitations of starting enyne and cyclized intermediate. Thus, neither the '070 patent nor the '117 patent render the claims of the '393 patent invalid for obviousness-type double patenting.
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III)  wherein w=1, 2, or 3;	Neither the '070 patent claims nor the '117 patent claims disclose step (a) and Sandoz makes no arguments with regard to the obviousness of this step. *See also*, Phares and Moriarty References Claim 1.

Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=C$(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
(b) hydrolyzing the product of formula III of step (a) with a base,	Neither the '070 patent claims nor the '117 patent claims disclose step (b) and Sandoz makes no arguments with regard to the obviousness of this step. *See also*, Phares and Moriarty References Claim 1.
(c) contacting the product of step (b) [sic] with a base B to form a salt of formula I_s (I_s)  and	Neither the '070 patent claims nor the '117 patent claims disclose step (c) and Sandoz makes no arguments with regard to the obviousness of this step. *See also*, Phares and Moriarty References Claim 1.
(d) optionally reacting the salt formed in step (c) with	Neither the '070 patent claims nor the '117 patent

an acid to form the compound of formula I.	claims disclose step (d) and Sandoz makes no arguments with regard to the obviousness of this step. *See also*, Phares and Moriarty References Claim 1.
Claim 2	
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	Neither the '070 patent claims nor the '117 patent claims disclose a compound of formula I in said product is at least 99.5%. Sandoz's obviousness arguments regarding Moriarty 2004 are also incorrect for the reasons stated above. *See also*, Phares and Moriarty References Claim 1.
Claim 4	
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	Neither the '070 patent claims nor the '117 patent claims disclose using KOH or NaOH in step (b) and Sandoz makes no arguments with regard to the obviousness of this step. *See also*, Phares and Moriarty References Claim 1.
Claim 8	
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Neither the '070 patent claims nor the '117 patent claims disclose step (a) and Sandoz makes no arguments with regard to the obviousness of this step. *See also*, Phares and Moriarty References Claim 1.
Claim 9	
9. A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof,	The '070 patent does not disclose treprostinil acid. The '117 patent discloses a different product than claim 9 of the '393 patent for the same reasons as claim 1. See Claim 1.
wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,	*See*, Claim 1.

	
(b) hydrolyzing the product of formula VI of step (a) with a base,	*See,* Claim 1.
(c) contacting the product of step (b) with a base B to form a salt of formula IV_s, and 	*See,* Claim 1.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	See Claim 1.
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	See Claim 8.

BLANK ROME LLP
Stephen M. Orlofsky
David C. Kistler
New Jersey Resident Partners
301 Carnegie Center, 3d Floor
Princeton, NJ 08540
Telephone: (609) 750-7700

OF COUNSEL:
William C. Jackson
BOIES, SCHILLER & FLEXNER LLP
5301 Wisconsin Ave, NW
Washington, DC 20015

Douglas H. Carsten
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real
Suite 200
San Diego, CA 92130

Attorneys for Plaintiff/Counterclaim Defendant
United Therapeutics Corporation

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORP.,	)	
	)	
Plaintiff and Counterclaim-Defendant,	)	
	)	
v.	)	Civil Action No.: 3:14-cv-05498-PGS-LHG
	)	**HIGHLY CONFIDENTIAL-**
TEVA PHARMACEUTICALS USA, INC.,	)	**SUBJECT TO PROTECTIVE ORDER**
	)	
Defendant and Counterclaim-Plaintiff.	)	

UNITED THERAPEUTICS CORP.'S RESPONSES TO TEVA PHARMACEUTICALS USA, INC.'S AMENDED INVALIDITY CONTENTIONS

Plaintiff United Therapeutics Corporation ("UTC") hereby provides its Responses to Teva's Amended Invalidity Contentions, served on April 24, 2015 ("Teva's Amended Contentions"). After making a "finding that Teva's [original] contentions [did] not meet the [Local R]ule or the [Court's O]rder requiring specificity," the Court ordered Teva to redo their contentions in accordance with the Local Rules and the Court's Order. In response, UTC incorporates by reference its previously served March 23, 2015 Responses to Teva's Invalidity Contentions, including the Validity Claim Charts attached thereto ("UTC's March 23 Validity Contentions"), as if fully set forth herein. Additionally, UTC further responds to Teva's Amended Contentions as set forth below.

[redacted]

II. THE ASSERTED CLAIMS OF U.S. PATENT NO. 8,497,393 ARE VALID

Teva, who bears the burden to prove invalidity by clear and convincing evidence, has failed to provide "a chart identifying where specifically in each alleged item of prior art each limitation of each asserted claim is found." L. Pat. R. 3.3(c). With regard to obviousness specifically, Teva has failed to provide "an explanation of why the prior art renders the asserted claim obvious, including an identification of any combinations of prior art showing obviousness." L. Pat. R. 3.3(b). Instead, Teva alleges that "the '393 patent [is] obvious in view of Remodulin, '117 patent, and/or Moriarty 2004 over Monson (1971), Eliel (1994), Jones (1971 or 2000) and/or Wade 2005 in view of the knowledge of one of ordinary skill in the art." Teva's Contentions at p. 77. Thus, rather than provide specific combinations of prior art references, Teva only provides a set of one or more references from a list of three references in combination with one or more references from a list of five references which results in hundreds of possible combinations.[2] Teva fails to provide a description of each of these combinations and UTC is

[2] Teva does, however, provide two example combinations of Moriarty 2004 in view of Monson, Eliel, and Phares 2005 and '117 patent in view of Monson, Jones, and Wade 2005. Other than listing these references, Teva provides no specific arguments to support these combinations. Similarly, Teva makes no mention of Phares 2005 in its original set of possible obviousness combinations in its Amended Contentions adding further confusion as to what combinations of prior art Teva will eventually decide to argue in this case. Teva has therefore waived any other combination of prior art and UTC reserves the right to further amend its

under no requirement to guess as to which combination Teva may wish to assert. Teva has therefore waived any argument regarding any specific combination of these references and to the extent Teva is allowed to argue such combinations, UTC reserves the right to respond and further amend its Validity Contentions at that time. Moreover, Teva also describes multiple other references in its Amended Contentions regarding the '393 patent, but does not include any of these additional references in any possible obviousness combination. Thus, Teva has also waived any further argument regarding any specific obviousness combination as none are identified in Teva's Amended Invalidity Contention Chart or Narrative. Moreover, Teva has failed to provide any reason that would have prompted a person of ordinary skill in the art to arrive at the invention or why they would have a reasonable expectation of success with anything other than hindsight. Accordingly, Teva has waived any argument that any limitation of any claim of the '393 patent is rendered obvious. Accordingly, United Therapeutics' responses cannot properly "follow the order of the invalidity chart...and set forth [United Therapeutics'] agreement or disagreement with each allegation therein" and therefore no response is required. L. Pat. R. 3.4A(d). Without an identification of what combinations of prior art Teva alleges render the claims obvious, United Therapeutics is not able to provide and is thus not required to provide a response.

1. The Scope and Content of the Alleged Teva Prior Art

A brief summary of the prior art below shows that many of the references Teva relies upon to support its invalidity contentions are "non-analogous" prior art or have little to no applicability to benzindene prostacyclin analogues and/or the specific synthetic processes of the

---

contentions and/or strike any of Teva's expert reports that alleges any other combination of prior art not specified in Teva's Contentions.

type claimed in the '393 patent. The discussion below highlights certain representative sections of these and related references to show that their actual teachings do not support Teva's anticipation and/or obviousness arguments. United Therapeutics reserves its right to rely upon other sections of these references and/or additional references to support United Therapeutics' contentions that none of these references, whether considered alone or in combination anticipate and/or render obvious the asserted '393 patent claims, and to more fully expand its contentions during the course of factual and expert discovery in this case. United Therapeutics does not admit that any of Teva's references actually constitute relevant or enabling prior art and also reserves its rights to antedate or otherwise remove any of Teva's alleged prior art.[3]

2. Prosecution History of the '393 Patent Application

It is worth noting that, during prosecution of the '393 patent, the U.S. Patent and Trademark Office considered and rejected many of the same arguments and prior art as those in Teva's Invalidity Contentions. The prior art Teva cites, even if enabling and not cumulative to the art of record, does not refute the PTO's reasons for allowance.

3. The Asserted Claims Of The '393 Patent Are Not Anticipated

UTC incorporates by reference UTC's March 23 Validity Contentions with respect to the alleged anticipation of the '393 patent. United Therapeutics' response to Teva's anticipation and obviousness arguments regarding the '393 patent can be found herein and in the accompanying amended claim chart, as required by the Scheduling Order and Local Patent Rules, attached as Exhibit B, respectively, hereto. In addition, United Therapeutics provides below additional

[3] The Scheduling Order and Local Patent Rules do not require a response to the narrative portion of Teva's Invalidity Contentions. *See, e.g.*, Scheduling Order ¶ 6. By providing this response, United Therapeutics does not hereby waive any rights or arguments with respect to any of the assertions in that narrative.

background information and explanation as to: (a) why the prior art identified by Teva neither anticipates nor renders obvious the claims of the '393 patent; and (b) why the Asserted Claims are not invalid based upon Teva's other invalidity arguments. In brief, the Asserted Claims are not anticipated because no single, enabling reference identified by Teva discloses each and every element of the claimed invention.

Teva's Invalidity Chart and narrative identifies the '117 Patent, Remodulin and Moriarty et al., The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Steroselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil), J.Org. Chemistry., 69(6), 1890-1902 (2004). ("Moriarty 2004") in its anticipation section, but with very limited detail as to why such claims are anticipated other than the fact that treprostinil was disclosed in each of these references. Each of these references, however, were also disclosed to the Patent Office during prosecution of the '393 patent and are listed on the face of the patent. The fact that each reference discloses treprostinil or salts of treprostinil does not mean that the claims are anticipated. Indeed, the Patent Office reviewed many references that disclosed treprostinil and allowed the claims as Teva readily admits. Teva Contentions at 78 ("In fact, the '393 patent incorporates Moriarity [sic] 2004, and the '117 patent, among prior art, that describe purified treprostinil."). Thus the mere disclosure of treprostinil cannot anticipate the claims. Specifically, the '393 patent discloses a different and more pure treprostinil product with less impurities than the prior art. Indeed, during prosecution, the '393 patent was rejected by the Examiner because of the Moriarty 2004 reference (which discloses the same synthesis as the '117 patent) and the Examiner subsequently allowed the claims over the reference because the products were different and the salt step was different. '393 Patent File History, Office Action dated May 15, 2013 (UTC_REM_II_000001424-1429); Office Action Response dated June 5,

2013 (UTC_REM_II_000001436-1444); Notice of Allowance dated June 12, 2013 (UTC_REM_II000001453-1458). Additionally, the specification of the '393 patent details many of the differences between the Moriarty references (identified as "Former Process") and the'393 patent in Example 6 which is incorporated herein. '393 patent, Col. 15:1-17:25.

Because the product produced by the '393 patent is superior, *inter alia* in impurity profiles, purity, yields and other characteristics of the product it is not anticipated or rendered obvious. *See, e.g., Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1308 (Fed. Cir. 2009) (J. Newman, *dissenting*) ("The facts of Thorpe did not concern the exception and expedient where process terms are invoked to describe a new product of complex structure. This exception is rarely invoked. The general rule requiring claims to have a process-free definition of the structure of a new product accommodates most inventions. Some recent exceptions are seen in emerging aspects of biotechnology."); *see also Scripps Clinic & Research Foundation v. Genentech, Inc.,* 927 F.2d 1565 (Fed.Cir.1991) (process to obtain a "highly purified and concentrated" product that was "largely free of contaminants," was not anticipated by previous disclosure of the product), *overruled on other grounds by Abbott Labs v. Sandoz, Inc*., 566 F.3d 1282 (Fed. Cir. 2009). If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable).

First, the product of the '117 patent and Moriarty 2004 are the same as they have the same synthetic process. Additionally, the treprostinil referenced in Remodulin on sale prior to

the priority date of the '393 patent were also made by the '117 patent process.[4] Since the synthetic method for treprostinil described in each of these references is the same as that set forth in the '117 patent, they will be considered together ("the Moriarty references"). The product of the '393 patent is structurally and functionally different than the products of the Moriarty references because the '393 patent has a higher level of average purity, lower number of individual impurities, and is a better product. For example, in a document entitled Treprostinil Drug Substance Impurities, all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by the Moriarty reference process. *See* UTC-Sand-Rem00334054-057 and UTC-Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty process. See, e.g., *See, e.g.*, UTC-Sand-Rem00001673-702; UTC-Sand-Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTC-Sand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTC-Sand-Rem01111355-357; UTC-Sand-Rem01117901-906;

[4] Indeed, Teva provides no evidence of what process Remodulin was made and does not address the impurity profiles previously cited by UTC in its March 23 Validity Contentions regarding the Moriarty References.

UTC-Sand-Rem01117910-912; UTC-Sand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Other documents show that the batches made by the '393 patent process have a better impurity profile on average as well as less total impurities.[5] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the prior art specifies the level of purity or minimal level of impurities that the '393 patent provides.

If the process for producing a product according to a product-by-process claim imparts distinctive structural and functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable). Teva fails to provide any evidence that the two different products are structurally and functionally the same. Additionally, early syntheses of treprostinil such as the Moriarty references yielded less pure products in terms of impurities, yield, and other analytical data.

Claim 2 requires that the product have purity of no less than 99.5%. Moriarty 2004 is the only reference cited by Teva that discloses a purity with at least 99.5%, but as previously described, the product of the Moriarty 2004 reference is different and the Patent Office explicitly considered that claim in relation to the Moriarty 2004 reference and allowed the '393 patent. '393 Patent File History, Office Action dated May 15, 2013 (UTC_REM_II_000001424-1429); Office Action Response dated June 5, 2013 (UTC_REM_II_000001436-1444); Notice of

[5] The documents cited herein for batches of treprostinil made by the Moriarty reference process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different.

Allowance dated June 12, 2013 (UTC_REM_II000001453-1458). Teva provides no additional citations or support for any other asserted claim. Therefore, the '117 patent, Remodulin, and Moriarty 2004 do not anticipate any claim of the '393 patent.

4. The Asserted Claims of the '393 Patent Are Not Rendered Obvious By Teva's Alleged Prior Art

UTC incorporates by reference UTC's March 23 Validity Contentions with respect to the alleged obviousness of the '393 patent. UTC further incorporates by reference its response to Teva's anticipation arguments with respect to the alleged obviousness of the '393 patent. As previously discussed, Teva provides no specific obviousness combination in detail in its Invalidity Chart or narrative, but only a description of possibly hundreds of combinations. None of the references, however, would render obvious any claim of the '393 patent in combination with any other of Teva's cited references. Specifically, Teva cites several references with general statements about purification, but fails to identify how or why any of these references would be used by a person of skill in the art to further purify and optimize the existing prior art treprostinil to arrive at the claims of the '393 patent, nor identifies whether a person of skill in the art would have a reasonable expectation of success in doing so. Indeed, none of the additional prior art cited by Teva references treprostinil or specifies any purification method specifically for benzindene prostacyclin analogues or discloses treprostinil itself.

Specifically, Teva alleges to the extent that the Moriarty references do not anticipate the '393 patent, the claims would be rendered obvious by one or more of the Moriarty references in combination with one or more of Monson (1971), Eliel (1994), Jones (1971 or 2000), and/or Wade 2005. First, Teva cites Monson and Harwood to allege that the use of crystallization and recrystallization as a purification technique was well-known and similarly cite Eliel and Jones to show that "carboxylate ammonium salts are formed from adding a carboxylic acid with an amine

and that those salts can be purified by recrystallization." Teva Contentions at p. 78-79. However, none of these purification references – Monson, Eliel, Jones (1971) or Jones (2000) disclose treprostinil, prostacyclin analogues, or preferred methods of purification for such substances. Indeed, Teva fails to identify how any of these references are relevant to the obviousness analysis of the '393 patent itself. Instead of providing a specific method of purifying complex molecules such as prostacyclin analogues, each only provides a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. Indeed, Teva fails to provide any detail on how or why a person of ordinary skill in the art would look to very basic and sometimes decades old references to determine how to make the highly pure product produced by the '393 patent or have any reasonable expectation of success in doing so. Lastly, Teva only cites Wade 2005 to show that physiologically acceptable salts of treprostinil include salts derived from bases such as ammonia, N-methyl-D-glucamine, magnesium, arginine, and lysine. Teva Contentions at p. 81-82. Once again, however, Teva fails to provide any detail as to how this is relevant to the obviousness of the asserted claims.

In addition to the references that Teva specifically cites as possible references in their alleged obviousness combinations, Teva also cites many additional references that do not appear in any of Teva's alleged combinations. Teva's Contentions at pp. 89-90. Thus, Teva has waived any argument that any claim of the '393 patent is obvious in light of any of these additional references.

First, Teva cites Lin, Aristoff, and McManus for the contention that alkylation using chlorolacetonitrile and subsequent hydrolysis to carboxylic acid was known, but fails to indicate

how this is relevant to the obviousness analysis as the '393 patent itself references other patents that demonstrate those same steps such as the '117 patent.

Second, Teva cites Arumugan, Monson and Yu for the fact that it states "column chromatography is not favored for large-scale production" but fails to identify how this is relevant to obviousness given that Teva fails to identify how or why a person of ordinary skill in the art would look to this reference to make the very pure treprostinil product claimed in the '393 patent or have a reasonable expectation of success in doing so. Third, Teva cites Sorrell, and Pavia, but each only provides a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. Indeed, Teva fails to provide any detail on how or why a person of ordinary skill in the art would look to very basic and sometimes decades old references to determine how to make the highly pure product produced by the '393 patent or have any reasonable expectation of success in doing so.

Lastly, Teva also cites the 2005 Physician's Desk Reference, Burk, Ohno, and Priscinzano for the contention that the diethanolamine salt was known. But the asserted claims of the '393 patent do not require specifically requiring carboxylic ammonium salts are formed from carboxylic acids and amines and do not specifically require the diethanolamine salt. Contrary to Teva's arguments, these references only show very general information that is not directed towards benzindene prostacyclin analogues, much less treprostinil. Indeed, a person of ordinary skill in the art would not have considered these additional basic references to improve the product of the existing prior art treprostinil products and would not have a reasonable expectation of success in combining these very basic references with known syntheses of treprostinil. Accordingly, there would have been no reason or motivation to combine these

references as alleged in Teva's Invalidity Claim Charts, and they do not render the claims obvious.

5. Secondary Considerations

Teva has not established a *prima facie* case of obviousness. Thus, United Therapeutics is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirms that the claims of the '393 patent are not obvious and UTC incorporates by reference UTC's March 23 Validity Contentions with respect to the objective indicia of non-obviousness of the '393 patent. Indeed, Teva in its amended contentions, completely ignores the secondary considerations that UTC already put forth in its March 23 Validity Contentions stating, "Teva is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '393 patent. If UTC relies on any secondary considerations of non-obviousness, Teva reserves the right to supplement its contentions." Teva's Contentions at p. 86. In UTC's March 23 Validity Contentions, UTC did indeed provide evidence of several secondary considerations of non-obviousness regarding the '393 patent including long-felt need, unexpected results, commercial success, and copying. See, UTC's March 23 Validity Contentions at pp. 21-23. Thus, Teva has waived any argument regarding any secondary consideration set forth by UTC.

6. The Asserted Claims of the '393 Patent are Not Invalid For Obviousness-Type Double Patenting Over the '117 Patent

Teva's entire obviousness-type double-patenting argument with regard to the '117 patent is that because the claims of the '117 patent are directed to the same subject matter, treprostinil and its pharmacologically acceptable salt form, then that necessarily renders obvious the claims

of the '393 patent by the mere disclosure treprostinil. Teva's Contentions at 86-88. Teva is wrong. As previously discussed with regard to the '117 patent, the mere disclosure of treprostinil does not render obvious any claim of the '393 patent. Indeed, Teva ignores that obviousness-type double patenting requires that only the claims of the prior art must be compared to the asserted claims. The claims of the '393 patent are very different than the claims of the '117 patent. Indeed, Teva provides no citation for its assumption that process elements are irrelevant specifically when performing an obviousness-type double patenting analysis. The claims of the '117 patent are very different than the claims of the '393 patent and would result in a different product. Moreover, the '117 patent does not specifically disclose treprostinil diethanolamine salt. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Moreover, the products of the '117 patent and the '393 patent are structurally and functionally different. *See* Moriarty References above. Other than structural and functional differences, the products of the '117 patent and the '393 patent are also different as the '117 patent product must be stereoselectively produced using the source limitations of starting enyne and cyclized intermediate. Indeed, the '117 patent claims do not disclose steps (a), (b), (c), or (d) of the '393 patent claims. Similarly, the '117 patent claims do not disclose a product with at least 99.5% purity as required by claim 2 of the '393 patent. Thus, the '117 patent does not render the claims of the '393 patent invalid for obviousness-type double patenting.

7. The Asserted Claims of the '393 Patent are Not Invalid for Lack of Enablement or Lack of Written Description

Teva entire lack of enablement and written description defense is predicated on what UTC alleges:

> "if Plaintiff contends that it would have required undue experimentation for a person of ordinary skill to apply these prior art procedures to obtain the claimed methods (for example it would have required undue experimentation to find particular bases or a particular alkylating agent), the claims are not enabled. Such a contention by Plaintiff would not be supported by the specification or the prosecution history, and to the extent that Plaintiff contends that certain bases or reaction conditions, for example, are unique and that undue experimentation would have been required to practice the claimed method, then the claims of the '393 patent are not enabled or fail to meet the written description requirement. Moreover, to the extent that Plaintiff takes a broad claim construction position and asserts infringement of certain process and resulting intermediates – such as the use of intermediates or process that are not sufficiently disclosed, taught of claimed in the '393 patent, including the intermediates and process that are used to make Teva's treprostinil, the claims of the '393 patent are not enabled and/or lack written description."

Teva's Contentions at pp. 88-89. Teva conflates the distinct concepts of enablement, written description and undue experimentation, and fails to sufficiently allege invalidity on these bases. Enablement is met "when at the time of filing the application one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (citing *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988)). Therefore, the relevant inquiry as to whether "undue experimentation" is required for purposes of determining enablement is measured from the specification, not the "disclosures in the prior art" as Teva asserts. Further, whether undue experimentation is required "is not a single, simple factual determination, but rather a conclusion reached by weighing many factual considerations." *Id.* Teva fails to even contend relevant factors related to (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6)

the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Accordingly, Teva has failed to even allege facts sufficient to establish by clear and convincing evidence that the asserted claims of the '393 patent are not enabled. Moreover, one skilled in the art, having read the specification, could practice the invention of the '393 patent without undue experimentation given the clear teachings to make the more pure treprostinil product claimed.

Additionally, the test for sufficiency of written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Teva's contentions are insufficient as to written description because they fail to even allege that the disclosures of the '393 patent do not convey to a POSA that UT had possession of the claimed subject matter. Each of the asserted claims of the '393 patent fulfill the requirements of written description by conveying that the inventors were in possession of the claimed subject matter as of the filing date.

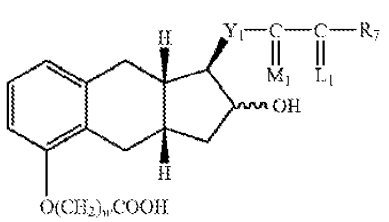
Lastly, both Teva's lack of enablement and written description defenses are based solely on what UTC argues and Teva provides no analysis of any alleged lack of enablement or written description regardless of what UTC's arguments may be. Indeed, UTC already provided responses to Teva's first Invalidity and Infringement Contentions and have already provided terms and constructions for terms, yet Teva provides no new argument regarding lack of enablement or written description. Thus, Teva has waived any argument that the '393 patent is not enabled and/or lacks written description.

EXHIBIT B

UNITED THERAPEUTICS' RESPONSE TO TEVA'S INVALIDITY CONTENTIONS

UNITED STATES PATENT NO. 8,497,393[1]

I. Disclosure of Validity Contentions – United States Patent No. 8,497,393[2]

Claim	Deficiencies in Prior Art
Claim 1	
1. A product comprising a compound of formula I  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	**The '393 Patent is Not Anticipated by the '117 Patent, Remodulin, or Moriarty 2004:** UTC incorporates by reference UTC's March 23 Validity Contentions with respect to the alleged anticipation of the '393 patent. Each of the '117 patent, Remodulin and Moriarty 2004 references ("Moriarty references") were listed by Teva in its narrative as anticipating the claims, but with very limited detail as to why such claims are anticipated other than the fact that treprostinil was disclosed in each of these references. Each of these references, however, were also disclosed to the Patent Office during prosecution of the '393 patent and are listed on the face of the patent. The fact that each reference discloses treprostinil or salts of treprostinil does not mean that the claims are anticipated. Indeed, the Patent Office reviewed many references that disclosed treprostinil and allowed the claims as Teva readily admits. Teva Contentions at 78 ("In fact, the '393 patent incorporates Moriarity [sic] 2004, and the '117 patent, among prior art, that describe purified treprostinil."). Thus the mere disclosure of treprostinil cannot anticipate the claims. Specifically, the '393 patent discloses a different and more pure treprostinil product with less impurities than the prior art. Indeed, during prosecution, the '393 patent was rejected by the

[1] In addition to the references specifically cited herein, United Therapeutics reserves its rights to rely on other materials and information including, but not limited to, the references cited by Teva in its invalidity contentions, expert opinion, and any additional references uncovered during discovery.

[2] Teva provides a laundry list of references in its Invalidity Chart for the '393 patent, but Teva provides no details and no citations to these other references to specify which references allegedly anticipate and/or render obvious any claim of the '393 patent. Teva has therefore waived any argument regarding any alleged anticipation or obviousness based on any of these additional references listed by failing to identify any specific references for anticipation or any specific combination of references for obviousness in their claim chart.

Claim	Deficiencies in Prior Art
	Examiner because of the Moriarty 2004 reference (which discloses the same synthesis as the '117 patent) and the Examiner subsequently allowed the claims over the reference because the products were different and the salt step was different. '393 Patent File History, Office Action dated May 15, 2013 (UTC_REM_II_000001424-1429); Office Action Response dated June 5, 2013 (UTC_REM_II_000001436-1444); Notice of Allowance dated June 12, 2013 (UTC_REM_II000001453-1458). Additionally, the specification of the '393 patent details many of the differences between the Moriarty references (identified as "Former Process") and the'393 patent in Example 6 which is incorporated herein. '393 patent, Col. 15:1-17:25. Because the product produced by the '393 patent is superior, *inter alia* in impurity profiles, purity, yields and other characteristics of the product it is not anticipated or rendered obvious. *See, e.g., Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1308 (Fed. Cir. 2009) (J. Newman, *dissenting*) ("The facts of Thorpe did not concern the exception and expedient where process terms are invoked to describe a new product of complex structure. This exception is rarely invoked. The general rule requiring claims to have a process-free definition of the structure of a new product accommodates most inventions. Some recent exceptions are seen in emerging aspects of biotechnology."); *see also Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed.Cir.1991) (process to obtain a "highly purified and concentrated" product that was "largely free of contaminants," was not anticipated by previous disclosure of the product), *overruled on other grounds by Abbott Labs v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly

Claim	Deficiencies in Prior Art
	claimed in order to be patentable). First, the product of the '117 patent and Moriarty 2004 are the same as they have the same synthetic process. Additionally, the treprostinil referenced in Remodulin on sale prior to the priority date of the '393 patent were also made by the '117 patent process. Since the synthetic method for treprostinil described in each of these references is the same as that set forth in the '117 patent, they will be considered together ("the Moriarty references"). The product of the '393 patent is structurally and functionally different than the products of the Moriarty references because the '393 patent has a higher level of average purity, lower number of individual impurities, and is a better product. For example, in a document entitled Treprostinil Drug Substance Impurities, all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by the Moriarty reference process. *See* UTC-Sand-Rem00334054-057 and UTC-Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty process. See, e.g., *See, e.g.*, UTC-Sand-Rem00001673-702; UTC-Sand-Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTC-Sand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTC-Sand-Rem01111355-357; UTC-Sand-Rem01117901-906; UTC-Sand-

Claim	Deficiencies in Prior Art
	Rem01117910-912; UTC-Sand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Other documents show that the batches made by the '393 patent process have a better impurity profile on average as well as less total impurities.[3] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the prior art specifies the level of purity or minimal level of impurities that the '393 patent provides. Teva fails to provide any evidence that the different products are structurally and functionally the same. Additionally, early syntheses of treprostinil such as the Moriarty references yielded less pure products in terms of impurities, yield, and other analytical data. **The '393 Patent is Not Rendered Obvious by the Prior Art:** UTC incorporates by reference UTC's March 23 Validity Contentions with respect to the alleged obviousness of the '393 patent. UTC further incorporates by reference its response to Teva's anticipation arguments with respect to the alleged obviousness of the '393 patent. As previously discussed, Teva provides no specific obviousness combination in detail in its Invalidity Chart or narrative, but only a description of possibly hundreds of combinations. None of the references, however, would render obvious any claim of the '393 patent in combination with any other of Teva's cited references. Specifically, Teva cites several references with general statements about purification, but fails to identify how or why any of these references would be used by a person of skill in the art to further purify and optimize the existing prior art treprostinil to arrive at the claims of the '393 patent, nor identifies whether a person of skill in the art would have a reasonable expectation of success in doing so. Indeed, none of the additional prior art cited by Teva references treprostinil or specifies any purification method specifically for benzindene prostacyclin analogues or discloses treprostinil itself.

[3] The documents cited herein for batches of treprostinil made by the Moriarty reference process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different.

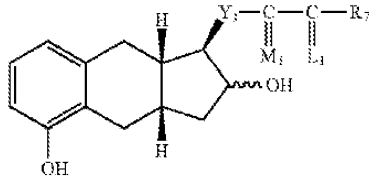
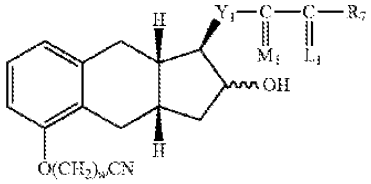
Claim	Deficiencies in Prior Art
	Specifically, Teva alleges to the extent that the Moriarty references do not anticipate the '393 patent, the claims would be rendered obvious by one or more of the Moriarty references in combination with one or more of Monson (1971), Eliel (1994), Jones (1971 or 2000), and/or Wade 2005. First, Teva cites Monson and Harwood to allege that the use of crystallization and recrystallization as a purification technique was well-known and similarly cite Eliel and Jones to show that "carboxylate ammonium salts are formed from adding a carboxylic acid with an amine and that those salts can be purified by recrystallization." Teva Contentions at p. 78-79. However, none of these purification references – Monson, Eliel, Jones (1971) or Jones (2000) disclose treprostinil, prostacyclin analogues, or preferred methods of purification for such substances. Indeed, Teva fails to identify how any of these references are relevant to the obviousness analysis of the '393 patent itself. Instead of providing a specific method of purifying complex molecules such as prostacyclin analogues, each only provides a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. Indeed, Teva fails to provide any detail on how or why a person of ordinary skill in the art would look to very basic and sometimes decades old references to determine how to make the highly pure product produced by the '393 patent or have any reasonable expectation of success in doing so. Lastly, Teva only cites Wade 2005 to show that physiologically acceptable salts of treprostinil include salts derived from bases such as ammonia, N-methyl-D-glucamine, magnesium, arginine, and lysine. Teva Contentions at p. 81-82. Once again, however, Teva fails to provide any detail as to how this is relevant to the obviousness of the asserted claims. In addition to the references that Teva specifically cites as possible references in their alleged obviousness combinations, Teva also cites many additional references that do not appear in any of Teva's alleged combinations. Teva's Contentions at pp. 89-90. Thus, Teva has waived any argument that any claim of the '393 patent is obvious in light of any of these additional references.

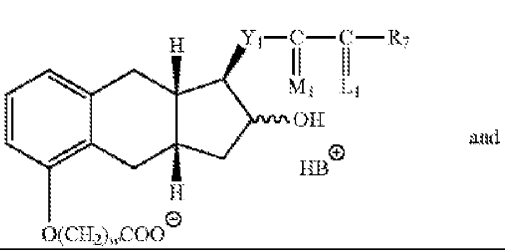
Claim	Deficiencies in Prior Art
	First, Teva cites Lin, Aristoff, and McManus for the contention that alkylation using chlorolacetonitrile and subsequent hydrolysis to carboxylic acid was known, but fails to indicate how this is relevant to the obviousness analysis as the '393 patent itself references other patents that demonstrate those same steps such as the '117 patent. Second, Teva cites Arumugan, Monson and Yu for the fact that it states "column chromatography is not favored for large-scale production" but fails to identify how this is relevant to obviousness given that Teva fails to identify how or why a person of ordinary skill in the art would look to this reference to make the very pure treprostinil product claimed in the '393 patent or have a reasonable expectation of success in doing so. Third, Teva cites Sorrell, and Pavia, but each only provides a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. Indeed, Teva fails to provide any detail on how or why a person of ordinary skill in the art would look to very basic and sometimes decades old references to determine how to make the highly pure product produced by the '393 patent or have any reasonable expectation of success in doing so. Lastly, Teva also cites the 2005 Physician's Desk Reference, Burk, Ohno, and Priscinzano for the contention that the diethanolamine salt was known. But the asserted claims of the '393 patent do not require specifically requiring carboxylic ammonium salts are formed from carboxylic acids and amines and do not specifically require the diethanolamine salt. Contrary to Teva's arguments, these references only show very general information that is not directed towards benzindene prostacyclin analogues, much less treprostinil. Indeed, a person of ordinary skill in the art would not have considered these additional basic references to improve the product of the existing prior art treprostinil products and would not have a reasonable expectation of success in combining these very basic references with known syntheses of treprostinil. Accordingly, there would have been no reason or motivation to combine these references as alleged in Teva's Invalidity Claim Charts, and they do not render the claims obvious.

Claim	Deficiencies in Prior Art
	Accordingly, none of the references cited by Teva anticipate and/or render obvious any asserted claim of the '393 patent. Teva has not established a *prima facie* case of obviousness. Thus, United Therapeutics is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirms that the claims of the '393 patent are not obvious and UTC incorporates by reference UTC's March 23 Validity Contentions with respect to the objective indicia of non-obviousness of the '393 patent. Indeed, Teva in its amended contentions, completely ignores the secondary considerations that UTC already put forth in its March 23 Validity Contentions. Teva Contentions at p. 86. In UTC's March 23 Validity Contentions, UTC did indeed provide evidence of several secondary considerations of non-obviousness regarding the '393 patent including long-felt need, unexpected results, commercial success, and copying. See, UTC's March 23 Validity Contentions at pp. 21-23. Thus, Teva has waived any argument regarding any secondary consideration set forth by UTC. **The '393 Patent is Not Invalid For Obviousness-Type Double Patenting Over the '117 Patent:** Teva's entire obviousness-type double-patenting argument with regard to the '117 patent is that because the claims of the '117 patent are directed to the same subject matter, treprostinil and its pharmacologically acceptable salt form, then that necessarily renders obvious the claims of the '393 patent by the mere disclosure treprostinil. Teva's Contentions at 86-88. Teva is wrong. As previously discussed with regard to the '117 patent, the mere disclosure of treprostinil does not render obvious any claim of the '393 patent. Indeed, Teva ignores that obviousness-type double patenting requires that only the claims of the prior art must be compared to the asserted claims. The claims of the '393 patent are very different than the claims of the '117 patent. Indeed, Teva provides no citation for its assumption that process elements are irrelevant specifically when performing an obviousness-type double patenting analysis. The claims of the '117 patent

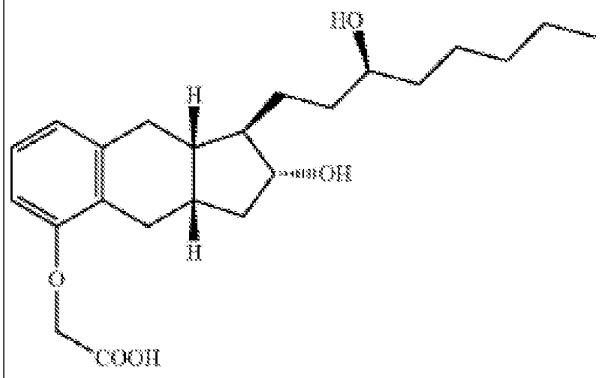
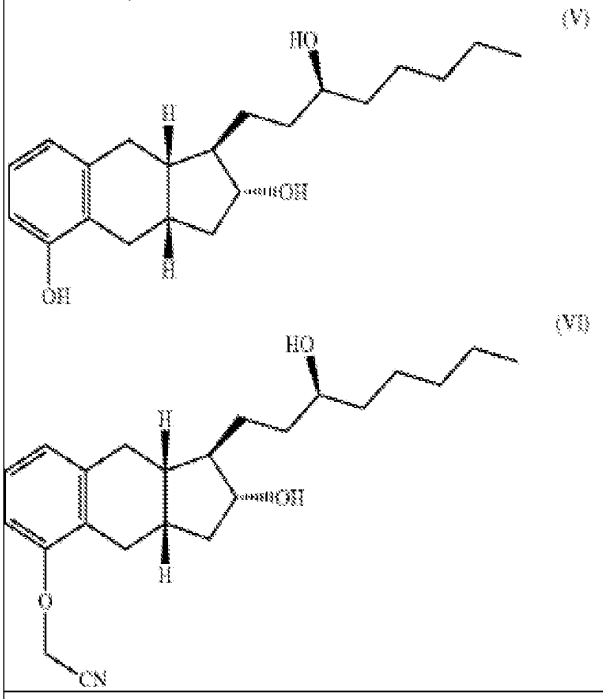
Claim	Deficiencies in Prior Art
	are very different than the claims of the '393 patent and would result in a different product. Moreover, the '117 patent does not specifically disclose treprostinil diethanolamine salt. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Moreover, the products of the '117 patent and the '393 patent are structurally and functionally different. *See* Moriarty References above. Other than structural and functional differences, the products of the '117 patent and the '393 patent are also different as the '117 patent product must be stereoselectively produced using the source limitations of starting enyne and cyclized intermediate. Indeed, the '117 patent claims do not disclose steps (a), (b), (c), or (d) of the '393 patent claims. Thus, the '117 patent does not render the claims of the '393 patent invalid for obviousness-type double patenting. **The '393 Patent is Not Invalid For Lack of Enablement or Lack of Written Description:** Teva's entire lack of enablement and written description defense is predicated on what UTC alleges. Teva's Contentions at pp. 88-89. Teva conflates the distinct concepts of enablement, written description and undue experimentation, and fails to sufficiently allege invalidity on these bases. Enablement is met "when at the time of filing the application one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (citing *In re Wands,* 858 F.2d 731, 736–37 (Fed. Cir. 1988)). Therefore, the relevant inquiry as to whether "undue experimentation" is required for purposes of determining enablement is measured from the specification, not the "disclosures in the prior art" as Teva asserts. Further, whether undue experimentation is required "is not a single, simple factual determination, but rather a conclusion reached by weighing many factual considerations." *Id.* Teva fails to even contend relevant factors related to (1) the quantity of experimentation necessary, (2) the amount of direction

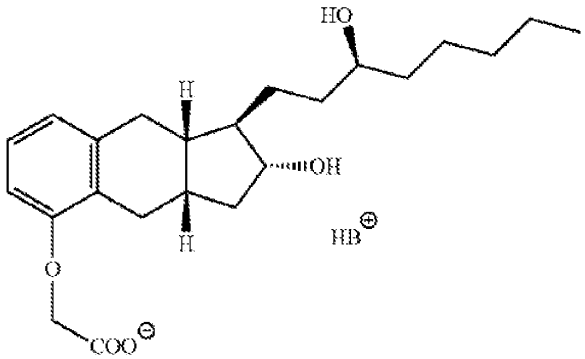
Claim	Deficiencies in Prior Art
	or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Accordingly, Teva has failed to even allege facts sufficient to establish by clear and convincing evidence that the asserted claims of the '393 patent are not enabled. Moreover, one skilled in the art, having read the specification, could practice the invention of the '393 patent without undue experimentation given the clear teachings to make the more pure treprostinil product claimed. Additionally, the test for sufficiency of written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Teva's contentions are insufficient as to written description because they fail to even allege that the disclosures of the '393 patent do not convey to a POSA that UTC had possession of the claimed subject matter. Each of the asserted claims of the '393 patent fulfill the requirements of written description by conveying that the inventors were in possession of the claimed subject matter as of the filing date. Lastly, both Teva's lack of enablement and written description defenses are based solely on what UTC argues and Teva provides no analysis of any alleged lack of enablement or written description regardless of what UTC's arguments may be. Indeed, UTC already provided responses to Teva's first Invalidity and Infringement Contentions and have already provided terms and constructions for terms, yet Teva provides no new argument regarding lack of enablement or written description. Thus, Teva has waived any argument that the '393 patent is not enabled and/or lacks written description.
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,	*See*, claim 1. Teva provides no additional citations or information regarding this claim limitation as the claim chart provided by Teva does not break down each limitation separately.

Claim	Deficiencies in Prior Art
(II)  (III)  wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different. (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=C$(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	

Claim	Deficiencies in Prior Art
(b) hydrolyzing the product of formula III of step (a) with a base,	*See*, claim 1. Teva provides no additional citations or information regarding this claim limitation as the claim chart provided by Teva does not break down each limitation separately.
(c) contacting the product of step (b) [sic] with a base B to form a salt of formula I_s  and	*See*, claim 1. Teva provides no additional citations or information regarding this claim limitation as the claim chart provided by Teva does not break down each limitation separately.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See*, claim 1. Teva provides no additional citations or information regarding this claim limitation as the claim chart provided by Teva does not break down each limitation separately.
Claim 2	
2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	**The '393 Patent is Not Anticipated by the '117 Patent, Remodulin, or Moriarty 2004:** UTC incorporates by reference UTC's March 23 Validity Contentions with respect to claim 2 of the '393 patent and incorporates by reference all arguments regarding Claim 1 above. Claim 2 requires that the product have purity of no less than 99.5%. Moriarty 2004 is the only reference cited by Teva that discloses a purity with at least 99.5%, but as previously described, the product of the Moriarty 2004 reference is different and the Patent Office explicitly considered that claim in relation to the Moriarty 2004 reference and allowed the '393 patent. '393 Patent File History, Office Action dated May 15, 2013 (UTC_REM_II_000001424-1429); Office Action Response dated June 5, 2013 (UTC_REM_II_000001436-1444); Notice of Allowance dated June 12, 2013 (UTC_REM_II000001453-1458). Thus, the '117 patent and Remodulin cannot anticipate Claim 2 because the purity requirement of 99.5% is not explicitly disclosed and Moriarty 2004 does not anticipate the claim because the product of Moriarty 2004 and the product of Claim 2 are different, as described in the prosecution history of the '393 patent.

Claim	Deficiencies in Prior Art
	The '393 Patent is Not Rendered Obvious by the Prior Art: UTC incorporates by reference UTC's March 23 Validity Contentions with respect to claim 2 of the '393 patent and incorporates by reference all arguments regarding Claim 1 above. As previously discussed, Moriarty 2004 is the only reference cited by Teva that discloses a purity with at least 99.5%, but no combination of prior art with Moriarty 2004 would result in the same product with the same purity requirement as the '393 patent. For the same reasons as claim 1, none of the prior art references render claim 2 obvious. Additionally, UTC incorporates by reference all secondary considerations disclosed in UTC's March 23 Response to Teva's Invalidity Contentions. **The '393 Patent is Not Invalid For Obviousness-Type Double Patenting Over the '117 Patent:** UTC incorporates by reference UTC's March 23 Validity Contentions with respect to claim 2 of the '393 patent and incorporates by reference all arguments regarding Claim 1 above. More specifically, the '117 patent does not disclose a purity of 99.5%. Additionally, for the same reasons as claim 1, the '117 patent does not render claim 2 of the '393 patent invalid for obviousness-type double patenting. **The '393 Patent is Not Invalid For Lack of Enablement or Lack of Written Description:** UTC incorporates by reference UTC's March 23 Validity Contentions with respect to claim 2 of the '393 patent and incorporates by reference all arguments regarding Claim 1 above. Teva fails to identify any specific disclosure that is not enabled or lacks written description. For the same reasons as Claim 1 above, Claim 2 is enabled and does not lack written description.
Claim 4	
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See*, claim 1. Teva does not allege this claim is anticipated, lacks written description, is not enabled, nor is invalid for obviousness-type double patenting in its claim chart and therefore waives each of these arguments with respect to this claim. UTC incorporates by reference UTC's March 23 Validity Contentions with respect to claim 4 of the '393 patent and incorporates by reference all arguments regarding Claim

Claim	Deficiencies in Prior Art
	1 above.
Claim 9	
9. A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof,	The difference between claim 9 and claim 1 is that the structures displayed are limited to synthesis of treprostinil. Teva provides no additional citations or information regarding this claim limitation over what was provided for claim 1. UTC incorporates by reference UTC's March 23 Validity Contentions with respect to claim 9 of the '393 patent and incorporates by reference all arguments regarding Claim 1 above.
wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	*See*, claim 1. Teva provides no additional citations or information regarding this claim limitation over what was provided for the previous limitation.
(b) hydrolyzing the product of formula VI of step (a)	*See*, claim 1. Teva provides no additional citations or

Claim	Deficiencies in Prior Art
with a base,	information regarding this claim limitation over what was provided for the previous limitation.
(c) contacting the product of step (b) with a base B to form a salt of formula IV_s, and 	*See*, claim 1. Teva provides no additional citations or information regarding this claim limitation over what was provided for the previous limitation.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See*, claim 1. Teva provides no additional citations or information regarding this claim limitation over what was provided for the previous limitation.

MCCARTER & ENGLISH LLP
William J. O'Shaughnessy
Four Gateway Center
100 Mulberry Street
Newark, NJ 07102
(973) 639-2094

OF COUNSEL:
William C. Jackson
BOIES, SCHILLER & FLEXNER LLP
5301 Wisconsin Ave, NW
Washington, DC 20015

Douglas H. Carsten
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real
Suite 200
San Diego, CA 92130

Attorneys for Plaintiff/Counterclaim Defendant
United Therapeutics Corporation

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORP.,	)	
	)	
Plaintiff and Counterclaim-Defendant,	)	
	)	
v.	)	Civil Action No.: 3:15-cv-05723-PGS-LHG
	)	**HIGHLY CONFIDENTIAL-**
WATSON LABORATORIES, INC.,	)	**ATTORNEYS EYES ONLY**
	)	
Defendant and Counterclaim-Plaintiff.	)	
	)	

UNITED THERAPEUTICS CORP.'S RESPONSES TO WATSON LABORATORIES, INC.'S INVALIDITY CONTENTIONS

Plaintiff United Therapeutics Corporation ("United Therapeutics") hereby provides its Responses to Watson Laboratories, Inc.'s ("Watson") Invalidity Contentions ("Responses") under Local Patent Rule 3.4A, as modified by the Scheduling Order.[1] D.I. 35. The Responses include the following:

Local Patent Rule 3.4A(a) For each item of asserted prior art, the identification of each limitation of each asserted claim that United Therapeutics believes is absent from the prior art;

Local Patent Rule 3.4A(b) If obviousness is alleged, an explanation of why the prior art does not render the asserted claim obvious;

Local Patent Rule 3.4A(c) The Responses follow the order of the invalidity chart required under Local Patent Rule 3.3(c), and set forth in United Therapeutics' agreement or disagreement with each allegation therein and the written basis thereof; and

Local Patent Rule 3.4A(d) United Therapeutics will make available for inspection and copying any document or thing that it intends to rely on in support of its Responses herein.

I. Watson's Contentions are Deficient Under the Local Patent Rules and Scheduling Order

[1] Watson is limited to the prior art asserted in its December 11, 2015 Invalidity Contentions, regardless of its assertions to the contrary. Local Patent Rule 3.3(a) requires Watson to provide in its Invalidity Contentions: "[t]he identity of each item of prior art that allegedly anticipates each asserted claim or renders it obvious." Further, Local Patent Rule 3.7 states that: "[a]mendment of any contentions, disclosures, or other documents required to be filed or exchanged pursuant to these Local Patent Rules may be made only by order of the Court upon a timely application and showing of good cause." *See also Merck Sharp & Dohme Corp. v. Sandoz, Inc.*, C.A. No. 12-3289, 2014 U.S. Dist. LEXIS 52548, at *31 (D.N.J. Apr. 16, 2014) (Denying Defendant's motion to amend its invalidity contentions to add new prior art).

As a preliminary matter, Watson, who bears the burden to prove invalidity by clear and convincing evidence, has failed to provide "a chart identifying where specifically in each alleged item of prior art each limitation of each asserted claim is found." L. Pat. R. 3.3(c). Watson's L. Pat. R. 3.3(c) chart erroneously labels each claim a "Claim Term" and simply lists references that purport to disclose "Prior Art Where Limitation Is Found" with no corresponding reference to which limitation within the claim Watson purports to address. Watson also fails to identify each prior art as required by Local Rule 3.3(a), including by date of issue. This is particularly egregious where Watson lists several references, without identification of date, author, or inventor that it purports to be "prior art references" that "invalid[ate] as anticipated and/or obvious" the claims of the asserted patents, where it does not even discuss said references, and where several such references are after the priority date of the asserted patents. Accordingly, Watson has not properly identified the prior art on which it intends to rely and has not identified with specificity where a single limitation of a single claim is found in the prior art in contravention to the Court's Scheduling Order and this Court's local patent rules. Accordingly, Watson has waived any argument that any limitation of any claim of the '212 patent is found in the prior art unless it shows good cause shown to amend its contentions. Due to Watson's failure to abide by its obligations, United Therapeutics' responses cannot properly "follow the order of the invalidity chart . . . and set forth [United Therapeutics'] agreement or disagreement with each allegation therein" and therefore no response is required, L. Pat. R. 3.4A(d). United Therapeutics nevertheless attempts herein to respond to Watson's contentions to the extent they can be understood and with a degree of guessing and searching at what Watson might have meant. United Therapeutics accordingly reserves its right to bring a Motion to Strike or bring

this matter to the attention of the Court.[2] *See Merck Sharp & Sohme Corp. v. Sandoz, Inc.*, 2014 WL 997532 (D.N.J. 2014) (Goodman, MJ) (finding arguments not made in original invalidity contentions were waived); *Anascape, Ltd. v. Microsoft Corp.*, 2008 WL 7180756, *1-4 (E.D. Tex. 2008) (Clark, J)[3] (granting patentee's motion to strike certain invalidity contentions that merely generally referenced a prior art item without specifically mapping aspects of the prior art reference to each element of the claim; denying motion of accused infringer to amend its invalidity contentions to correct the deficiencies) ("Defendants' invalidity contentions simply assume that Anascape can guess what controllers correspond to which disclosed prior art reference. Allowing such a 'mix-and-match' [invalidity] contention disclosure game to stand would encourage violation of the rules and discourage the voluntary exchange of information.").

IV. THE ASSERTED CLAIMS OF U.S. PATENT NO. 8,497,393 ARE VALID

1. The Scope and Content of the Alleged Watson Prior Art

Watson cites a number of references in its Invalidity Chart, without reference or explanation as to what limitation is purportedly met by such references, nor does it properly address the scope and content of those alleged references. In response to Watson's arguments, the discussion below and the accompanying claim chart at Exhibit C discuss the scope and content of the alleged Watson prior art. These sections highlight certain representative sections of these and related references to show that their actual teachings do not support Watson's anticipation and/or obviousness arguments. United Therapeutics reserves its right to rely upon other sections of these references and/or additional references to support United Therapeutics' contentions that none of these references, whether considered alone or in combination, anticipate and/or render obvious the asserted '393 patent claims, and to more fully expand its contentions

during the course of factual and expert discovery in this case. United Therapeutics does not admit that any of Watson's references actually constitute relevant or enabling prior art and also reserves its rights to antedate or otherwise remove any of Watson's alleged prior art.[7]

2. Prosecution History of the '393 Patent Application

It is worth noting that, during prosecution of the '393 patent, the USPTO considered and rejected many of the same arguments and prior art as those in Watson's Invalidity Contentions. As discussed further below, the USPTO already considered and found that the '393 Patent was patentable over the same arguments Watson now makes. The prior art Watson cites, even if enabling and not cumulative to the art of record, does not refute the USPTO's reasons for allowance.

3. The Asserted Claims Of The '393 Patent Are Not Anticipated

United Therapeutics' response to Watson's anticipation and obviousness arguments regarding the '393 patent can be found herein and in the accompanying claim chart, attached as Exhibit C, respectively, hereto. In addition, United Therapeutics provides below additional background information and explanation as to: (a) why the prior art identified by Watson neither anticipates nor renders obvious the claims of the '393 patent; and (b) why the Asserted Claims are not invalid based upon Watson's other invalidity arguments. In brief, the Asserted Claims are not anticipated because no single, enabling reference identified by Watson discloses each and every element of the claimed invention.

---

[7] The Scheduling Order and Local Patent Rules do not require a response to the narrative portion of Watson's Invalidity Contentions. *See, e.g.*, Scheduling Order ¶ 6. By providing this response, United Therapeutics does not hereby waive any rights or arguments with respect to any of the assertions in that narrative.

Watson's Invalidity Chart does not specify which references allegedly anticipate the '393 patent, but Watson's narrative identifies the '117 Patent, Moriarty et al., The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil), J.Org. Chemistry., 69(6), 1890-1902 (2004) ("Moriarty 2004"), United Therapeutics' own Remodulin® drug product, and U.S. Patent Publication No. 2005/0085540 (April 2005), ("Phares") in its anticipation section, but with very limited detail as to why such references anticipate the claims other than the allegation that treprostinil was disclosed in each of these references. The fact that each reference discloses treprostinil or salts of treprostinil does not mean that the claims are anticipated. Indeed, the USPTO reviewed many references that disclosed treprostinil (including each of the published documents Watson cites) and allowed the claims, as Watson acknowledges. *See* WIC at 35 (citing to United Therapeutics' discussion of the development of treprostinil in the '393 patent, which cites Moriarty 2004, Phares, and the '117 patent). Thus the mere disclosure of treprostinil cannot anticipate the claims. Specifically, the '393 patent discloses a different and more pure treprostinil product with less impurities than the prior art. Indeed, during prosecution, the '393 patent was rejected by the Examiner in view of the Moriarty 2004 reference (which discloses the same synthesis as the '117 patent) and the Examiner subsequently allowed the claims over the reference because the products were different. '393 Patent File History, Office Action dated May 15, 2013 (UTC_WAT_00001465-1470); Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001494-1499). Additionally, the specification of the '393 patent details many of the differences of the '117 patent and Moriarty 2004 (identified as "Former Process") as

compared to the '393 patent in Example 6 which is incorporated herein. '393 patent, Col. 15:1-17:25.

As an initial matter, United Therapeutics notes that the synthesis disclosed in the '117 patent and Moriarty 2004, are essentially the same. *See* '117 patent, Col. 7-10; Moriarty 2004 at 1894-96. Additionally, the Remodulin treprostinil products, on sale prior to the priority date of the '393 patent, were also made by the '117 patent process.[8] Since the synthetic method for treprostinil described in each of these references is essentially the same as that set forth in the '117 patent, they will be considered together ("the Moriarty references"). The Phares reference, however, does not disclose a synthesis for treprostinil, but only its enantiomer. Thus, it is unclear what process Watson is alleging was used to make the treprostinil referenced in Phares. Regardless, none of the allegedly anticipating references disclose, explicitly or inherently, the synthesis process recited in the '393 patent's claims. Indeed, Watson does not even argue that they do.

Moreover, the product of the '393 patent is structurally and functionally different than the products of the Moriarty references and Phares because the '393 patent has a higher level of average purity, lower number of individual impurities, and better product. For example, in a document entitled "Treprostinil Drug Substance Impurities", all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by Moriarty references' process. *See* UTC-Sand-Rem00334054-057 and UTC-Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and

[8] Indeed, Watson provides no evidence of which process produced the asserted prior art Remodulin product.

other lots made by the Moriarty references' process. *See, e.g.*, UTC-Sand-Rem00001712-741; UTC-Sand-Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTC-Sand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTC-Sand-Rem01111355-357; UTC-Sand-Rem01117901-906; UTC-Sand-Rem01117910-912; UTC-Sand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Still other documents show that the batches made by the '393 patent process have a better impurity profile on average as well as less total impurities.[9] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the alleged prior art specifies the level of purity or minimal level of impurities that the '393 patent provides.

Additionally, the FDA accepted a new purity specification when United Therapeutics implemented the inventions of the '393 patent. For example, a process validation report (Protocol No. "VAL-00131") states that it applies to "production of treprostinil diethanolamine intermediate (UT-15C-I), a chemical intermediate used for the production of active

[9] The documents cited herein for batches of treprostinil made by the Moriarty references' process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, United Therapeutics reserves the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different.

pharmaceutical ingredients treprostinil (UT-15) and treprostinil diethanolamine (UT-15C)." Validation Report at 8 (UTC-Sand-Rem00092436-449). This validation report also shows that each of steps (a)-(c) of the claims of the '393 patent are carried out in this new process. *Id.* at 5-7.

A Process Optimization Report also provides results for batches resulting from step (d) of the claims of the '393 patent, which was performed on specific batches of the diethanolamine salt intermediate produced by steps (a)-(c) that are referenced in the Validation Report. Process Optimization at p. 2 (UTC-Sand-Rem01104769-779) (*compare* batch numbers 03L6002, 03L6003, 03M6004, and 03M6006, which are the same UT-15C batch numbers of Validation Report at p. 4). The Process Optimization Report also states that "diethanolamine salt (UT-15C intermediate) of UT-15 is converted to UT-15 [treprostinil] by an acid-extraction removal of the diethanolamine to give UT-15 [treprostinil]…" The percent yield and purity levels of the final treprostinil product are compared to the former process therein, further demonstrating the differences that result in the final treprostinil product when all of steps (a)-(d) of the '393 patent are performed. Process Optimization Report at p. 3

Additionally, a letter from United Therapeutics to the FDA, which references the Validation Report, states as follows:

Validation Report at p. 2. The Validation Report further states:

> In all lots, the total unidentified impurity level (%AUC) decreased from triol to UT-15C intermediate. [redacted]

Id. at p. 3. Finally, this FDA Letter states that, when the new process was implemented, "it was observed that the purity of the treprostinil improved close to 100%", and the letter proposes that "the range of the specification for the HPLC assay for treprostinil be shifted from 97-101% to 98-102% so that it is centered at 100%." *Id.* at p. 3-4. The FDA subsequently approved the Patent Owner's proposed implementation of the '393 process and the increased purity standard. FDA Approval Letter, UTC-Sand-Rem00087652-53.

Because the product produced by the '393 patent is superior, *inter alia* in impurity profiles, purity, yields and other characteristics of the product, it is not anticipated or rendered obvious. *See, e.g., Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1308 (Fed. Cir. 2009) (J. Newman, *dissenting*) ("The facts of Thorpe did not concern the exception and expedient where process terms are invoked to describe a new product of complex structure. This exception is rarely invoked. The general rule requiring claims to have a process-free definition of the structure of a new product accommodates most inventions. Some recent exceptions are seen in emerging aspects of biotechnology."); *see also Scripps Clinic & Research Foundation v. Genentech, Inc.,* 927 F.2d 1565 (Fed.Cir.1991) (process to obtain a "highly purified and concentrated" product that was "largely free of contaminants," was not anticipated by previous disclosure of the product), *overruled on other grounds by Abbott Labs v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d

276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable); *and United Therapeutics Corp. v. Sandoz, Inc.*, Civ. Nos. 12-1617, 13-316, 2014 U.S. Dist. LEXIS 121573 at *140-149 (D.N.J. Aug. 29, 2014) (finding that the '117 patent was not anticipated by prior art disclosures of treprostinil due to a differentiating structure implied by the claimed process). Watson fails to provide any evidence that the alleged prior art products and the '393 patent's product are structurally and functionally the same. Additionally, early syntheses of treprostinil by the Moriarty references' process yielded less pure products in terms of impurities, yield, and other analytical data.

With respect to the Phares reference, it does not disclose what starting treprostinil material is used and therefore cannot anticipate (explicitly or inherently) the final treprostinil product of the '393 patent because each method of producing treprostinil would contain its own distinct impurity profile. In fact, the process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *United Therapeutics*, 2014 WL 4259153 at 53-55. Accordingly, Watson cannot establish anticipation based on a teaching of any treprostinil salt product that does not also identify the source of its starting treprostinil material. Indeed, Petitioner fails to identify any specific purity in Phares that would anticipate any claim of the '393 patent.

Claim 2 requires that the product have a purity of no less than 99.5%. Moriarty 2004 is the only reference cited by Watson that discloses a purity with at least 99.5%, but as previously described, the product of the Moriarty 2004 reference is different and the USPTO explicitly considered that claim in relation to the Moriarty 2004 reference and allowed the '393 patent.

'393 Patent File History, Office Action dated May 15, 2013 (UTC_WAT_00001465-1470); Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001494-1499). Watson provides no additional citations or support for any other asserted claim. Therefore, the '117 patent, Phares, United Therapeutics' Remodulin®, and Moriarty 2004 do not anticipate any claim of the '393 patent.

Further, dependent claims 2-8 and 10-22 are not anticipated by the cited references because they depend from a novel base claim, as well as because they recite additional limitations which further distinguish these claims over the prior art.

4. The Asserted Claims of the '393 Patent Are Not Rendered Obvious By Watson's Alleged Prior Art

As previously discussed, Watson provides no specific obviousness combinations in its Invalidity Chart. Instead, in its narrative, Watson presents "numerous different combinations", having hundreds of permutations. WIC at 44. Specifically, Watson alleges the '393 patent's claims would be rendered obvious by one or more of the Moriarty references in various combination with one or more of Monson[10], Eliel[11], Jones[12], Kawakami[13], Ege[14], and/or Wade[15]. *Id.* Nevertheless, despite proposing hundreds of combinations, Watson provides *no analysis* as

---

[10] Monson, ADVANCED ORGANIC SYNTHESIS, METHODS AND TECHNIQUES, 178-188 (1971) ("Monson").

[11] Eliel, STEREOCHEMISTRY OF ORGANIC COMPOUNDS, 322-325 (1994) ("Eliel").

[12] Jones, ORGANIC CHEMISTRY, 153-155 (2nd ed. 2000) ("Jones").

[13] Japanese Patent App. No. 56-122328A, September 1981 ("Kawakami"). United Therapeutics objects to Watson's purported translation of Kawakami as it is unclear as to whether this is a valid translation, particularly because there is no indication as to who performed the translation.

[14] Ege, S., Organic Chemistry Second Edition, 543-547 (1989) ("Ege").

[15] U.S. Patent Publication No. 2005/0165110 July 2005, Wade et al. ("Wade").

to why or how a skilled artisan would make *even one* of these listed combinations. Watson's narrative is merely a meandering recital of various disclosures in the prior art—including the reliance on references *not* listed in any proposed combinations—without any effort made to put forward a *prima facie* case of why or how a skilled artisan would take these teachings to arrive at the process for making the highly pure treprostinil claimed by the '393 patent, or whether a skilled artisan would even have a reasonable expectation of success in doing so. Accordingly, Watson has waived its obviousness defenses because they have failed to recite even one *prima facie* case of obviousness. *See, e.g., Horizon Pharma AG v. Watson Labs., Inc.*, C.A. No. 13-5124, 2015 U.S. Dist. LEXIS 80853, at *14-18 (D.N.J. Feb. 24, 2015)(Denying defendant's motion to amend its contentions, finding that the Defendant had not acted "diligently" and noting that the local rules "require parties to crystallize their theories of the case early in the litigation and to adhere to these theories once they have been disclosed") (citing *Nova Measuring Instruments Ltd. v. Nanometrics, Inc.*, 417 F. Supp. 2d 1121, 1122-23 (N.D. Cal. 2006)). Regardless, none of the references cited by Watson, alone or in combination, would render obvious any claim of the '393 patent.[16]

First, Watson's contentions regarding the alkylation and hydrolysis steps do not advance their obviousness allegations. For example, Watson cites McManus[17] for the contention that alkylation using chloroacetonitrile and subsequent hydrolysis to a carboxylic acid was known, but fails to indicate how this is relevant to the obviousness analysis because the '393 patent itself references disclosures that demonstrate those same steps—such as the '117 patent and Moriarty

[16] In addition the nonobviousness contentions presented herein and in the accompanying chart, United Therapeutics incorporates by reference the novelty arguments presented above and in the accompanying chart into its contentions of nonobviousness.

[17] McManus et al., Tetrazole Analogs of Plant Auxins, J. Org. Chemistry. 1959, 24, 1464-467 ("McManus").

2004—and the USPTO already considered and found that the '393 patent was distinguishable over those disclosures. *See* WIC at 35, 37; '393 Patent at 1:22-28; '393 Patent File History: Office Action dated May 15, 2013 (UTC_WAT_00001465-1470), Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485), Notice of Allowance dated June 12, 2013 (UTC_WAT_00001494-1499). Further, Watson cites Lin[18] and Aristoff[19], but these references fail to even disclose treprostinil and discuss other prostaglandins not related to the product of the '393 patent. Indeed, most the references identified in Watson's Invalidity Chart do not disclose treprostinil.

Second, Watson cites several references discussing "purification" steps, but Watson fails to identify how or why any of these references would be used by a person of skill in the art to further purify and optimize the existing prior art treprostinil to arrive at the claims of the '393 patent, and fails to discuss whether a person of skill in the art would have a reasonable expectation of success in doing so. *See* WIC 35-37.

Specifically, Watson cites Monson, Arumugan[20] and Yu[21] for the fact that "column chromatography is not favored for large-scale production", cites Monson and Harwood[22] to

---

[18] Lin et al., Benzindene Prostaglandins. Synthesis of Optically Pure 15-Deoxy-U68, 215 and Its Enantiomer via a Modified Intramolecular Wadsworth-Emmons-Wittig Reaction, J. Org. Chemistry, 1987, 52, 5594-5601 ("Lin").

[19] Aristoff et al., Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emmons-Wittig Reaction, J. Am. Chem. SOC. 1985, 107, 7967-7974 ("Aristoff").

[20] Arumugan et al., A New Purification Process for Pharmaceutical and Chemical Industries, Organic Process Research & Development 2005, 9, 319-320 ("Arumugan").

[21] Yu et al., Novel Synthetic Route of a Pivotal Intermediate for the Synthesis of 1â-Methyl Carbapenem Antibiotics, Organic Process Research & Development 2006,10, 829-832 ("Yu").

[22] Harwood, Experimental organic chemistry: Principles and Practice, 127-134 (1989) ("Harwood").

support its allegations that the use of crystallization and recrystallization as a purification technique was well-known, and similarly cites Eliel and Jones to show that "carboxylate ammonium salts are formed from adding a carboxylic acid with an amine and that those salts can be purified by recrystallization." *See* WIC at 35-36. Watson then concludes "a POSA would have been motivated to [modify the prior art synthesis of trepostinil utilizing column chromatography] by applying an obvious form of purification, salt crystallization, to form known salt forms of treprostinil." Watson's conclusion fails for several reasons. As examples, Watson fails to provide any evidence, or indeed argue, that the substitution would have been expected to result in the highly pure treprostinil claimed in the '393 patent, and Watson fails to discuss whether crystallization/recrystallization would even address the issues as to why column chromatography is allegedly not favored in large-scale production. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (a claim is not proved obvious merely by demonstrating that something was possible or known in the prior art).

Additionally, Watson has failed to show that step (c) of the '393 patent would necessarily lead to the same final product if made from different starting treprostinil materials than that made from steps (a) and (b). The process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *United Therapeutics*, 2014 WL 4259153 at 53-55. During prosecution, United Therapeutics demonstrated that the final treprostinil product from the '393 patent is physically different than that of the Moriarty references. Thus, even if the Moriarty references' treprostinil products were used as a starting point, Watson has failed to provide any evidence that, if step (c) was somehow obvious to apply, that the resulting treprostinil product would necessarily be the same as the products claimed in the '393 patent. For example, the declaration of Dr. Walsh submitted during original prosecution

shows that certain impurities in representative examples are reduced below detectable amounts by step (c), while others are still present in detectable amounts, such as treprostinil stereoisomer 3AU90. '393 Patent File History at p. 346-350. Both the type of impurity, as well as the relative amount of that impurity in the starting treprostinil material, may impact the impurity profile of the final product after step (c), yet there is absolutely no disclosure of any specific impurities or total amount of impurities by Watson on this point.

Watson also cites Sorrell[23], Wiberg[24], Schoffstall[25], and Pavia[26], but each only provides a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. *See* WIC at 36, 38. In fact, most of Watson's purification references do not disclose treprostinil, prostacyclin analogues, or preferred methods of purification for such substances. And instead of providing a specific method of purifying complex molecules such as prostacyclin analogues, Watson's cited references largely provide a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. Moreover, Watson fails to provide any detail on how or why a person of ordinary skill in the art would look to very basic and sometimes decades old references to determine how to make the highly pure product produced by the '393 patent or have any reasonable expectation of success in doing so.

---

[23] Sorrell, ORGANIC CHEMISTRY, 755-758 (1999) ("Sorrell").

[24] Wiberg, LABORATORY TECHNIQUE IN ORGANIC CHEMISTRY, 112 (1960) "Wiberg").

[25] Schoffstall, et al., MICROSCALE AND MINISCALE ORGANIC CHEMISTRY LABORATORY EXPERIMENTS, 200-202 (2d ed.) (2004) ("Schoffstall").

[26] Pavia, INTRODUCTION TO ORGANIC LABORATORY TECHNIQUES, 648 (1998) ("Pavia").

Third, Watson also cites the 2005 Physician's Desk Reference[27], Burk[28], Ohno[29], and Priscinzano[30] for the contention that the diethanolamine salt was known and preferred. *See* WIC at 36. But the asserted claims of the '393 patent do not all require specifically that carboxylic ammonium salts are formed from carboxylic acids and amines and do not specifically require the diethanolamine salt. Contrary to Watson's arguments, these references only show very general information that is not directed towards benzindene prostacyclin analogues, much less treprostinil. Indeed, a person of ordinary skill in the art would not have considered these additional basic references to improve the product of the existing prior art treprostinil products and would not have a reasonable expectation of success in combining these very basic references with known syntheses of treprostinil.

Fourth, Watson cites Wade to show that physiologically acceptable salts of treprostinil include salts derived from bases such as ammonia, N-methyl-D-glucamine, magnesium, arginine, and lysine. WIC at 36. Once again, however, Watson fails to provide any detail as to how this is relevant to the obviousness of the asserted claims.

Fifth, Watson also cites Phares, Kawakami, and Ege for the proposition that steps (c) and (d) of the '393 patent were obvious. None of these references, however, disclose steps (c) or (d) as claimed in the '393 patent. Specifically, Watson alleges that it would have been obvious to a

---

[27] The 2005 Physicians' Desk Reference for Bicillin® L-A (penicillin G benzathine suspension) ("2005 Physician's Desk Reference" or "PDR 2005").

[28] Burk, An Enantioselective Synthesis of (S)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation, J. Org. Chem. 2003, 68,5731-5734 ("Burk")

[29] Ohno, Development of Dual-Acting Benzofurans for Thromboxane A2 Receptor Antagonist and Prostacyclin Receptor Agonist: Synthesis, Structure-Activity Relationship, and Evaluation of Benzofuran Derivatives, J. Med. Chem. 2005, 48, 5279-5294 ("Ohno").

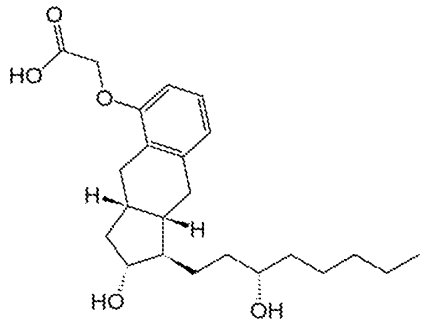
[30] Priscinzano, Piperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909): High Affinity Ligands for the Dopamine Transporter, J. Med. Chem. 2002, 45, 4371-4374 ("Priscinzano")

person of ordinary skill in the art to contact "a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt" and that this salt "can be further precipitated and purified" or dissolved into its fee-acid form. *See* WIC at 38-39. These references alone or in combination, however, do not establish that the '393 patent's claims were obvious.

Watson apparently cites Phares at page 24 for teaching step (c); however, the cited portion merely describes an example of how to make treprostinil diethanolamine from a starting material of treprostinil acid, but provides no detail whatsoever about how the starting treprostinil acid was made or where it comes from. Similarly, Watson cites Phares pages 85-93 as relevant to the teachings of step (c), but these portions describe a clinical study of sustained release capsules and tablets of treprostinil diethanolamine and to a polymorph characterization study of treprostinil diethanolamine. Again, there is no indication in this portion of Phares what process was actually used to make the starting "treprostinil acid" for the treprostinil diethanolamine. And, as discussed above, Phares fails to disclose the synthetic route or purity of the claimed treprostinil product. However, the process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *See United Therapeutics*, 2014 WL 4259153 at *53-55. Accordingly, by failing to show that performing step (c) on a starting treprostinil material, which has a different impurity profile than a starting treprostinil material made by performing steps (a) and (b) of the asserted claims, would necessarily lead to an identical product, Watson's arguments relating to obviousness over Phares necessarily fail.

Regarding Kawakami, Watson has failed to establish that the '393 patent is obvious over any Kawakami combination. Simply put, Kawakami is directed to entirely different compounds with entirely different impurity profiles than the '393 patent. The alleged "prostacyclin compound" disclosed in Kawakami is a two ring structure, yet the core three ring structure of

treprostinil is key to its pharmaceutical usefulness (*United Therapeutics*, 2014 WL 4259153 at *4-5) and is also present in every structure of every step of the '393 patent. *See, e.g.*, '393 patent claim 1.



Treprostinil

"prostacyclin compound" in Kawakami

Indeed, nothing in Kawakami comes close to even addressing the treprostinil product of the '393 patent much less how a skilled artisan would or would not go about synthesizing or purifying the product. Thus, a skilled artisan would have had no motivation to combine Kawakami with, for example, Phares or the Moriarty references, and would have had no reasonable expectation of success of obtaining the same high purity treprostinil product of the '393 patent. Additionally, to the extent Watson is alleging that Kawakami could remedy the deficiencies of the prior art treprostinil compounds (e.g., Moriarty references compounds) to disclose the impurity profile of the claimed treprostinil products, Watson has failed to establish a motivation to combine or reasonable expectation of success of forming a salt of the prior art treprostinil compounds with a purity profile of the products in the claims.

Indeed, Watson offers no basis from which to draw any conclusion about whether an impurity reduction step in Kawakami would possibly have any relevance to a process to

synthesize and or purify a totally different structure such as treprostinil. To illustrate this point further, Kawakami is directed to purifying E- and Z-isomers of "prostacyclin compounds" from one another. In order for the E- and Z-isomers to exist, the "prostacyclin compound" must have an alkene. Treprostinil, on the other hand, contains no mixture of E/Z isomers. In fact, it cannot because it does not contain an alkene capable of E/Z isomerization. Watson has failed to provide a factual basis as to how or why the separation of E/Z isomers of an alkene would provide a motivation to combine or reasonable expectation of success in a compound not containing an alkene capable of E/Z isomerization, such as treprostinil. For these reasons, a skilled artisan would have no motivation to look at Kawakami in order to arrive at the claimed invention of the '393 patent.

Similarly, Ege provides no additional support for Watson's obviousness contentions. Ege is merely an undergraduate chemistry textbook with only generalized descriptions of carboxylic acids and related synthetic procedures, and discloses nothing about any prostacyclin derivative, much less treprostinil free acid. Indeed, Ege fails to disclose anything about the synthesis of pharmaceuticals at all. Ege merely shows it was known to form a free acid from treatment of the corresponding carboxylate salt with a strong acid, but this fact alone provides no reason why a skilled artisan, based on any reference, would conduct a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step with a reasonable expectation of obtaining the claimed products of the '393 patent's claims. In fact, Ege actually suggests this "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would be relatively useless as a means for purifying treprostinil. *See* Ege at p. 8 (stating that the "properties of carboxylic acids are useful for separating them from reaction mixtures containing neutral and basic compounds", which is irrelevant to the claimed treprostinil process). Thus, Ege would not create an

expectation of success for separating one carboxylic-acid compound (*e.g.,* treprostinil free acid) from other carboxylic-acid containing compounds (*e.g.,* different stereoisomers of treprostinil free acid).

By its invalidity contentions, it is obvious that Watson misunderstands the claims of the '393 patent. For example, the claimed invention is not the discovery that carboxylic acids react with bases, but rather that compounds of Formula (I), and in particular treprostinil or a salt thereof, can be obtained with a superior purity profile compared to the prior art. Specifically, performing step (c) on a product which resulted from steps (a) and (b) provided a product with reduced impurities—which was not disclosed in the Moriarty references and resulted in a significant improvement in the treprostinil product being made at the time of invention. In fact, during prosecution of the '393 patent established the impurity profile of the '393 patent claims is different from the impurity profiles of Moriarty 2004. *See* '393 Patent File History, Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485). Watson appears to argue that the salt formation step would have been obvious to reduce or remove acidic or basic impurities, but each of these reduced or removed impurities are neither strongly acidic or basic as each are either diastereomers of treprostinil—which is very weakly acidic—or similarly neutral ester and triol impurities. The '393 patent therefore not only reduced the weakly acidic impurities present from the Moriarty process, but also unexpectedly reduced or eliminated non-acidic impurities as well. Thus, even under Watson's erroneous understanding, it was unexpected that the salt formation step would remove these additional impurities.

Finally, Watson fails to address the distinctive structural and functional characteristics of the product produced by the '393 patents claims. *See, supra*, Section IV.3. If the process for producing a product according to a product-by-process claim imparts distinctive structural or

functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d at 279; *see also United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573 at *140-149 (finding claims directed to producing a treprostinil product valid over prior art disclosures of treprostinil due to the structural and functional differences of the product produced by the claims). Because Watson failed to provide any evidence that the alleged prior art products—alone or modified by the teachings of other references—and the '393 patent's product are structurally and functionally the same, Watson's obviousness contentions fail.

In sum, Watson fails to identify how or why a person of ordinary skill in the art would look to these twenty-five references to make the very pure treprostinil product claimed in the '393 patent or have a reasonable expectation of success in doing so. Thus Watson has failed to demonstrate essential pieces of a *prima facie* case of obviousness, and thus has failed to clearly and convincingly show that '393 patent is invalid. *See In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 933, (U.S. 2013) (citing Procter & Gamble, 566 F.3d at 994) (To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.") Instead, what Watson has presented is a clear case of hindsight, by using the teachings of the patent as a blue print to pick and choose from the prior art. *See Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into use of hindsight'"); *see also State Industries, Inc. v. A.O. Smith Corp.*, 221 U.S.P.Q. (BNA) 958, 973 (M.D. Tenn. 1983), *aff'd in part, rev'd in part*, 751 F.2d 1226 (Fed. Cir. 1985) (an

infringer's need to cite a large number of prior art references can indicate to a court that the invention was novel and not obvious.). Moreover, there would have been no legitimate reason or motivation for a skilled artisan at the time of invention to combine the cited references, and these references, alone or in combination, do not render the claims obvious.

a) The dependent claims are further patentably distinct due to their additional limitations

Claims 2-8 and 10-22 are nonobvious over the cited references because they depend from valid base claims as well as because they recite additional limitations which further distinguish these claims over the prior art.

For example, Claims 6, 10, 15, and 21-22 are to the free acid of Formula (I) or treprostinil. As mentioned above, all of Watson's alleged combinations of prior art start with a Moriarty Reference. The free acid treprostinil in Moriarty was analyzed by United Therapeutics, and representative samples were found to contain a different impurity profile. *See, supra*, Section IV.3.

As explained previously, the claimed free-acid compounds, including treprostinil, produced by the processes of claims 6, 10, 15, and 21 provided a new product that induced FDA to adopt a new purity standard for treprostinil free acid due to the excellent purity of the final product. *See, supra*, Section IV.3. Furthermore, United Therapeutics demonstrated that treprostinil free acid made by the claimed methods provided a compound without many of the impurities included in the free acid treprostinil of the Moriarty references processes, including the two different stereoisomers of treprostinil.

The prior art does not provide a reason that a skilled artisan would include a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step. For example, Phares merely discloses forming a salt from treprostinil free acid of undisclosed origin. *See, supra*, Section

IV.3. There is no suggestion that this salt should then be converted back to the free acid (e.g., there is no suggestion of using the salt formation as a purification method).

As discussed above, the impurities in representative examples of Moriarty include two different stereoisomers of treprostinil free acid. The Watson prior art, *i.e.*, Ege, however suggests that a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would not remove these compounds from the product. Thus, a skilled artisan looking to make the free acid product of claims 6, 10, 15, and 21-22, such as treprostinil free acid, would have understood the Moriarty references combined with the Watson prior art (e.g. Phares, and Ege) to suggest simply making the treprostinil free acid product of the Moriarty references, and not undergoing the additional time and expense of a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step. In fact, at least one Watson prior art reference, Ege, actually teaches away from the usefulness of this step.

In sum, even though Watson cites prior art (e.g., Phares) that allegedly discloses forming a salt from treprostinil free acid, and prior art (e.g., Ege) that generally discusses that carboxylate salt formation was known in the art, there would have been no motivation or expectation of success in using these teachings on the already-formed free acid disclosed in the Moriarty references, and Watson has failed to establish that a skilled artisan would have carried out steps necessary to inherently obtain the claimed products. Thus, Watson fails to establish prima facie case that claims 6, 10, 15 and 22 are invalid as obvious.

5. Secondary Considerations

Watson has not established a *prima facie* case of obviousness. Thus, United Therapeutics is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirms that the Asserted Claims would not have been

obvious and, in fact, represent a surprising solution to a serious problem of minimizing potentially hazardous impurities and providing a safer and purer treprostinil product.

a) Long felt Unmet Need

At the time of the invention, there was a long-felt need to have a shorter, more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner with fewer impurities. Treprostinil has five chiral centers resulting in 32 possible stereoisomers so the potential for stereoisomeric impurities is high and only the treprostinil stereoisomer has the desired pharmaceutical effect. *United Therapeutics*, 2014 WL 4259153 at *2-3. Treprostinil is also a very potent drug so any stereoisomeric impurities would also potentially be potent and could potentially have deleterious effects. *Id.* Thus, there was a need to reduce the amount of impurities as much as possible and the product of the '393 patent further reduces impurities over the previous treprostinil products made by the prior art.

b) Unexpected Results

The results of the claimed inventions in the '393 patent were unexpected. For example, the use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was unexpected. Moreover, it was unexpected that the salt purification step reduced not only diastereomeric impurities, but also non-acidic impurities as well. Thus, a person of skill in the art would not have expected the results of the '393 patent to be so successful.

c) Commercial Success

The '393 patent is used in the current production of Tyvaso and Remodulin, which both contain treprostinil. The inventions claimed in the '393 patent have reduced the cost of making treprostinil and increased efficiency. Tyvaso and Remodulin are commercially successful

products. Tyvaso and Remodulin compete well against potential alternative products; for example, Remodulin competes well against alternatives such as Flolan. The commercial success of Tyvaso and Remodulin are reflected in both gross sales figures and relevant market share. Specifically, United Therapeutics made approximately $463.1 million, $438.8 million and $325.6 million in Tyvaso revenues, representing 36 percent, 39 percent and 36 percent of our total net revenues for the years ended December 31, 2014, 2013 and 2012, respectively. United Therapeutics (2014), *10-K Report* at p. 8, available at http://ir.unither.com/annuals-proxies.cfm. Also, United Therapeutics made approximately $553.7 million, $491.2 million and $458.0 million in Remodulin revenues, representing 43 percent, 44 percent and 50 percent of our total net revenues for the years ended December 31, 2014, 2013 and 2012, respectively. *Id.* at p. 6. United Therapeutics will make available for inspection and copying documents demonstrating the commercial success of Tyvaso and Remodulin.

d) Copying

The non-obviousness of the '393 patent is evidenced by Watson's own actions. Watson copied not only the active ingredient treprostinil sodium, but also the process claimed in the '393 patent. The non-obviousness of the '393 patent is additionally evidenced by the actions of several other generic pharmaceutical companies who have attempted to copy Remodulin. *See, e.g., United Therapeutics Corp. v. Sandoz, Inc.*, Civil Action No. 3:14-cv-05499-PGS-LHG (D.N.J. 2014); *United Therapeutics Corp. v. Teva Pharma*, Civil Action No. 3:14-cv-05498-PGS-LHG (D.N.J. 2014). As stated, above, the '393 patent product and process is currently used in the production of Remodulin and Tyvaso.

6. The Asserted Claims of the '393 Patent are Not Invalid for Obviousness-Type Double Patenting Over the '117 Patent

Watson's entire obviousness-type double-patenting argument can be summarized as: because the claims of the '117 patent and the '393 patent are both directed to the same chemical compound, treprostinil (and its pharmacologically acceptable salt form), then that mere disclosure of treprostinil in the '117 patent necessarily renders obvious the claims of the '393 patent. *See* WIC 46-47. Watson is wrong. As previously discussed, the mere disclosure of treprostinil does not render obvious any claim of the '393 patent.

Moreover, Watson does not correctly apply the law on obviousness-type double patenting. Inexplicably, Watson recites the rule that obviousness-type double patenting requires that only the claims of the prior art are compared to the asserted claims, but then ignores the rule's application and relies upon each patent being "directed to the product treprostinil and its pharmacologically acceptable salt form". *See* WIC at 46; *see also* Geneva *Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385 (Fed. Cir. 2003) (reciting the law for obviousness-type double patenting). Nevertheless, the claims of the '393 patent are very different than the claims of the '117 patent. Specifically, the '393 patent's claims recite different process elements from the '117 patent's claims. *Compare* '117 patent cl. 1; *with* '393 patent cl. 1. For example, the '117 patent's claims require that treprostinil be stereoselectively produced using the source limitations of starting enyne and cyclized intermediate. Further, the '117 patent claims do not disclose steps (a), (b), (c), or (d) of the '393 patent claims. Also, the '117 patent claims do not disclose a product with at least 99.5% purity as required by claim 2 of the '393 patent. Watson's contentions, however, gloss over the process elements of the claims, while providing no support for its apparent assumption that these process elements are irrelevant to an obviousness-type double patenting analysis. This oversight alone is fatal to this invalidity defense.

Furthermore, not only are the claims of the '117 patent very different than the claims of the '393 patent, but also the patents' resulting products are structurally and functionally different from each other. For example, as described above, the '393 patent produces a treprostinil drug product having a higher level of average purity, lower number of individual impurities, and is a better product as compared to the drug product of the '117 patent. *See* Supra discussion of Moriarty References. Also, the '117 patent does not specifically disclose treprostinil diethanolamine salt. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Because the '393 patent's treprostinil product is structurally and functionally different from the '117 patent's product, it is also patentably distinct. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *and United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573 at *140-149 (finding claims directed to producing a treprostinil product valid over prior art disclosures of treprostinil due to the structural and functional differences of the product produced by the claims). .

Thus, the '117 patent does not render the claims of the '393 patent invalid for obviousness-type double patenting.

7. The Asserted Claims of the '393 Patent are Not Invalid for Lack of Enablement or Lack of Written Description

Watson claims that:

> [I]f plaintiff contends that it would have required undue experimentation for a POSA to apply these prior art procedures to obtain the claimed methods (for example it would have required undue experimentation to find particular bases or a particular alkylating agent), the claims would then be invalid for lack of an enabling description. To the extent that plaintiff contends that certain bases or reaction conditions, for example, are unique and that undue experimentation

> would have been required to practice the claimed method, the claims of the '393 patent are not enabled or fail to meet the written description requirement.

WIC at 47. Watson conflates the distinct concepts of enablement, written description and undue experimentation, and fails to sufficiently allege invalidity on these bases.

Enablement is met "when at the time of filing the application one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (citing *In re Wands,* 858 F.2d 731, 736–37 (Fed. Cir. 1988)). Therefore, the relevant inquiry as to whether "undue experimentation" is required for purposes of determining enablement is measured from the specification, not the "prior art procedures" as Watson asserts. Further, whether undue experimentation is required "is not a single, simple factual determination, but rather a conclusion reached by weighing many factual considerations." *Id.* Watson fails to even contend relevant factors related to (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Accordingly, Watson has failed to even allege facts sufficient to establish by clear and convincing evidence that the asserted claims of the '393 patent are not enabled. Moreover, one skilled in the art, having read the specification, could practice the invention of the '393 patent without undue experimentation given the clear teachings to make the more pure treprostinil product claimed.

Additionally, the test for sufficiency of written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Watson's contentions are insufficient as to written

description because they fail to even allege that the disclosures of the '393 patent do not convey to a POSA that United Therapeutics had possession of the claimed subject matter. Each of the asserted claims of the '393 patent fulfill the requirements of written description by conveying that the inventors were in possession of the claimed subject matter as of the filing date.

William J. O'Shaughnessy
MCCARTER & ENGLISH LLP
Four Gateway Center
100 Mulberry Street
Newark, NJ 07102
(973) 639-2094
woshaughnessy@mccarter.com

Of Counsel

William C. Jackson
BOIES, SCHILLER & FLEXNER LLP
5301 Wisconsin Ave, NW
Washington, DC 20015

Veronica S. Ascarrunz
WILSON SONSINI GOODRICH & ROSATI
1700 K Street, NW
Suite 500
Washington, DC 20006

Robert A. Delafield II
WILSON SONSINI GOODRICH & ROSATI
900 S. Capital of Texas Hwy
Las Cimas IV, Fifth Floor
Austin, TX 78746

Dated: January 25, 2016

/s/ Douglas H. Carsten
Douglas H. Carsten
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real
Suite 200
San Diego, CA 92130

Attorneys for Plaintiff/Counterclaim Defendant United Therapeutics Corporation

CERTIFICATE OF SERVICE

I hereby certify that on January 25, 2016, a copy of the foregoing was served on principal counsel of record as set forth below via email.

CONNELL FOLEY LLP
Liza M. Walsh
Tricia B. O'Reilly
Joseph L. Linares
One Newark Center
1085 Raymond Boulevard, 19th Floor
Newark, NJ 07102
(973) 757-1100

OF COUNSEL:

WINSTON STRAWN LLP
Michael K. Nutter
Kurt A. Mathas
35 West Wacker Drive
Chicago, Illinois 60601
Tel: (312) 558-5600
Fax: (312) 558-5700

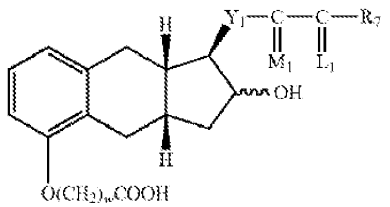
/s/ Douglas H. Carsten
Douglas H. Carsten

EXHIBIT C

UNITED THERAPEUTICS' RESPONSE TO WATSON'S INVALIDITY CONTENTIONS

UNITED STATES PATENT NO. 8,497,393[5]

I. Disclosure of Validity Contentions – United States Patent No. 8,497,393[6]

Claim	Deficiencies in Prior Art
Claim 1	
A product comprising a compound of formula I  (I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	**The '393 Patent is Not Anticipated by the '117 Patent, Remodulin, Phares or Moriarty 2004:** The Asserted Claims are not anticipated because no single, enabling reference identified by Watson discloses each and every element of the claimed invention. Watson's Invalidity Chart does not specify which references allegedly anticipate the '393 patent, but Watson's narrative identifies the '117 Patent, Moriarty et al., The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil), J.Org. Chemistry., 69(6), 1890-1902 (2004) ("Moriarty 2004"), UTC's own Remodulin® drug product, and U.S. Patent Publication No. 2005/0085540 (April 2005), ("Phares") in its anticipation section, but with very limited detail as to why such references anticipate the claims other than the allegation that treprostinil was disclosed in each of these references. The fact that each reference discloses

[5] In addition to the references specifically cited herein, United Therapeutics reserves its rights to rely on other materials and information including, but not limited to, the references cited by Watson in its invalidity contentions, expert opinion, and any additional references uncovered during discovery.

[6] Watson provides a laundry list of references in its Invalidity Chart for the '393 patent, but Watson provides no details and no citations to these other references to specify which references allegedly anticipate and/or render obvious any claim of the '393 patent. Watson has therefore waived any argument regarding any alleged anticipation or obviousness based on any of these additional references listed by failing to identify any specific references for anticipation or any specific combination of references for obviousness in their claim chart.

Claim	Deficiencies in Prior Art
	treprostinil or salts of treprostinil does not mean that the claims are anticipated. Indeed, the Patent Office reviewed many references that disclosed treprostinil (including each of the published documents Watson cites) and allowed the claims, as Watson acknowledges. *See* WIC at 35 (citing to UTC's discussion of the development of treprostinil in the '393 patent, which cites Moriarty 2004, Phares, and the '117 patent). Thus the mere disclosure of treprostinil cannot anticipate the claims. Specifically, the '393 patent discloses a different and more pure treprostinil product with less impurities than the prior art. Indeed, during prosecution, the '393 patent was rejected by the Examiner in view of the Moriarty 2004 reference (which discloses the same synthesis as the '117 patent) and the Examiner subsequently allowed the claims over the reference because the products were different. '393 Patent File History, Office Action dated May 15, 2013 (UTC_WAT_00001465-1470); Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001494-1499). Additionally, the specification of the '393 patent details many of the differences of the '117 patent and Moriarty 2004 (identified as "Former Process") as compared to the '393 patent in Example 6 which is incorporated herein. '393 patent, Col. 15:1-17:25. As an initial matter, United Therapeutics notes that the synthesis disclosed in the '117 patent and Moriarty 2004, are essentially the same. *See* '117 patent, Col. 7-10; Moriarty 2004 at 1894-96. Additionally, the Remodulin treprostinil products, on sale prior to the priority date of the '393 patent, were also made by the '117 patent process.[7] Since the synthetic method for treprostinil described in each of these references is essentially the same as that set forth in the '117 patent, they will be considered together ("the Moriarty references"). The Phares reference, however, does not disclose a synthesis for treprostinil, but only its enantiomer. Thus, it is unclear what process Watson is

[7] Indeed, Watson provides no evidence of which process produced the asserted prior art Remodulin product.

Claim	Deficiencies in Prior Art
	alleging was used to make the treprostinil referenced in Phares. Regardless, none of the allegedly anticipating references disclose, explicitly or inherently, the synthesis process recited in the '393 patent's claims. Indeed, Watson does not even argue that they do. Moreover, the product of the '393 patent is structurally and functionally different than the products of the Moriarty references and Phares because the '393 patent has a higher level of average purity, lower number of individual impurities, and better product. For example, in a document entitled "Treprostinil Drug Substance Impurities", all of the development lots through commercial lots of treprostinil up to March 2004 are compared, which includes lots made by Moriarty references' process. *See* UTC-Sand-Rem00334054-057 and UTC-Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty references' process. *See, e.g.*, UTC-Sand-Rem00001712-741; UTC-Sand-Rem00804699-707; UTC-Sand-Rem00804711-718; UTC-Sand-Rem00804722-730; UTC-Sand-Rem00804744-753; UTC-Sand-Rem00804800-809; UTC-Sand-Rem00804780-790; UTC-Sand-Rem00804838-848; UTC-Sand-Rem00804867-881; UTC-Sand-Rem00956861-956878; UTC-Sand-Rem01085875-877; UTC-Sand-Rem01086040-042; UTC-Sand-Rem01086341-342; UTC-Sand-Rem01086357-359; UTC-Sand-Rem01086816-817; UTC-Sand-Rem01093970-971; UTC-Sand-Rem01093976-977; UTC-Sand-Rem01094378-379; UTC-Sand-Rem01095090-091; UTC-Sand-Rem01102329-330; UTC-Sand-Rem01102331-357; UTC-Sand-Rem01102368-369; UTC-Sand-Rem01102372-427; UTC-Sand-Rem01104987-5002; UTC-Sand-Rem01110528-529; UTC-Sand-Rem01110865-867; UTC-Sand-Rem01117288; UTC-Sand-Rem01111355-357; UTC-Sand-Rem01117901-906; UTC-Sand-Rem01117910-912; UTC-Sand-Rem01118722-727; and UTC-Sand-Rem01126018-020. Still other documents show that the batches made by the '393 patent process have a better impurity profile on average as well as less

Claim	Deficiencies in Prior Art
	total impurities.[8] *See, e.g.*, UTC-Sand-Rem01107146-1107214; UTC-Sand-Rem00794084-794229. Indeed, none of the alleged prior art specifies the level of purity or minimal level of impurities that the '393 patent provides. Additionally, the FDA accepted a new purity specification when United Therapeutics implemented the inventions of the '393 patent. For example, a process validation report (Protocol No. "VAL-00131") states that it applies to "production of treprostinil diethanolamine intermediate (UT-15C-I), a chemical intermediate used for the production of active pharmaceutical ingredients treprostinil (UT-15) and treprostinil diethanolamine (UT-15C)." Validation Report at 8 (UTC-Sand-Rem00092436-449). This validation report also shows that each of steps (a)-(c) of the claims of the '393 patent are carried out in this new process. *Id.* at 5-7. A Process Optimization Report also provides results for batches resulting from step (d) of the claims of the '393 patent, which was performed on specific batches of the diethanolamine salt intermediate produced by steps (a)-(c) that are referenced in the Validation Report. Process Optimization at p. 2 (UTC-Sand-Rem01104769-779) (*compare* batch numbers 03L6002, 03L6003, 03M6004, and 03M6006, which are the same UT-15C batch numbers of Validation Report at p. 4). The Process Optimization Report also states that "diethanolamine salt (UT-15C intermediate) of UT-15 is converted to UT-15 [treprostinil] by an acid-extraction removal of the diethanolamine to give UT-15 [treprostinil]…" The percent yield and purity levels of the final treprostinil product are compared to the former process therein, further demonstrating the differences that result in the final treprostinil product when all of steps (a)-(d) of the '393 patent are performed. Process Optimization Report

[8] The documents cited herein for batches of treprostinil made by the Moriarty references' process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information on batches made by each process to further support the fact that the products of the two processes is different.

Claim	Deficiencies in Prior Art
	at p. 3 Additionally, a letter from United Therapeutics to the FDA, which references the Validation Report, states as follows: [redacted] Validation Report at p. 2. The Validation Report further states: In all lots, the total unidentified impurity level (%AUC) decreased from triol to UT-15C intermediate. [redacted] *Id.* at p. 3. Finally, this FDA Letter states that, when the new process was implemented, "it was observed that the purity of the treprostinil improved close to 100%", and the letter proposes that "the range of the specification for the HPLC assay for treprostinil be shifted from 97-101% to 98-102% so that it is centered at 100%." *Id.* at p. 3-4. The FDA subsequently approved the Patent Owner's proposed implementation of the '393 process and the increased purity standard. FDA Approval Letter, UTC-Sand-Rem00087652-53.

Claim	Deficiencies in Prior Art
	Because the product produced by the '393 patent is superior, *inter alia* in impurity profiles, purity, yields and other characteristics of the product, it is not anticipated or rendered obvious. *See, e.g., Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1308 (Fed. Cir. 2009) (J. Newman, *dissenting*) ("The facts of Thorpe did not concern the exception and expedient where process terms are invoked to describe a new product of complex structure. This exception is rarely invoked. The general rule requiring claims to have a process-free definition of the structure of a new product accommodates most inventions. Some recent exceptions are seen in emerging aspects of biotechnology."); *see also Scripps Clinic & Research Foundation v. Genentech, Inc.,* 927 F.2d 1565 (Fed.Cir.1991) (process to obtain a "highly purified and concentrated" product that was "largely free of contaminants," was not anticipated by previous disclosure of the product), *overruled on other grounds by Abbott Labs v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *see also Amgen Inc. v. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1364, 1367, 1370 (Fed. Cir. 2009) (noting that the structural and functional differences do not need to be explicitly claimed in order to be patentable); *and United Therapeutics Corp. v. Sandoz, Inc.*, Civ. Nos. 12-1617, 13-316, 2014 U.S. Dist. LEXIS 121573 at *140-149 (D.N.J. Aug. 29, 2014) (finding that the '117 patent was not anticipated by prior art disclosures of treprostinil due to a differentiating structure implied by the claimed process). Watson fails to provide any evidence that the alleged prior art products and the '393 patent's product are structurally and functionally the same. Additionally, early syntheses of treprostinil by the Moriarty references' process yielded less pure products in terms of impurities, yield, and other analytical data. With respect to the Phares reference, it does not disclose what starting treprostinil material is used and therefore

Claim	Deficiencies in Prior Art
	cannot anticipate (explicitly or inherently) the final treprostinil product of the '393 patent because each method of producing treprostinil would contain its own distinct impurity profile. In fact, the process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *United Therapeutics*, 2014 WL 4259153 at 53-55. Accordingly, Watson cannot establish anticipation based on a teaching of any treprostinil salt product that does not also identify the source of its starting treprostinil material. Indeed, Petitioner fails to identify any specific purity in Phares that would anticipate any claim of the '393 patent. Claim 2 requires that the product have purity of no less than 99.5%. Moriarty 2004 is the only reference cited by Watson that discloses a purity with at least 99.5%, but as previously described, the product of the Moriarty 2004 reference is different and the Patent Office explicitly considered that claim in relation to the Moriarty 2004 reference and allowed the '393 patent. '393 Patent File History, Office Action dated May 15, 2013 (UTC_WAT_00001465-1470); Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001494-1499). Watson provides no additional citations or support for any other asserted claim. Therefore, the '117 patent, Phares, UTC's Remodulin®, and Moriarty 2004 do not anticipate any claim of the '393 patent. Further, dependent claims 2-8 and 10-22 are not anticipated by the cited references because they depend from a novel base claim, as well as because they recite additional limitations which further distinguish these claims over the prior art. **The Asserted Claims of the '393 Patent Are Not Rendered Obvious By Watson's Alleged Prior Art** As previously discussed, Watson provides no specific obviousness combinations in its Invalidity Chart. Instead, in its narrative, Watson presents "numerous different combinations", having hundreds of

Claim	Deficiencies in Prior Art
	permutations. WIC at 44. Specifically, Watson alleges the '393 patent's claims would be rendered obvious by one or more of the Moriarty references in various combination with one or more of Monson[9], Eliel[10], Jones[11], Kawakami[12], Ege[13], and/or Wade[14]. *Id.* Nevertheless, despite proposing hundreds of combinations, Watson provides *no analysis* as to why or how a skilled artisan would make *even one* of these listed combinations. Watson's narrative is merely a meandering recital of various disclosures in the prior art—including the reliance on references *not* listed in any proposed combinations—without any effort made to put forward a *prima facie* case of why or how a skilled artisan would take these teachings to arrive at the process for making the highly pure treprostinil claimed by the '393 patent, or whether a skilled artisan would even have a reasonable expectation of success in doing so. Accordingly, Watson has waived its obviousness defenses because they have failed to recite even one *prima facie* case of obviousness. *See, e.g., Horizon Pharma AG v. Watson Labs., Inc.*, C.A. No. 13-5124, 2015 U.S. Dist. LEXIS 80853, at *14-18 (D.N.J. Feb. 24, 2015)(Denying defendant's motion to amend its contentions, finding that the Defendant had not acted "diligently" and noting that the local rules "require parties to crystallize their theories of the case early in the litigation and to adhere to these theories once they have been disclosed") (citing *Nova Measuring Instruments Ltd. v. Nanometrics, Inc.*, 417 F. Supp. 2d 1121, 1122-23 (N.D. Cal. 2006)). Regardless, none of

[9] Monson, ADVANCED ORGANIC SYNTHESIS, METHODS AND TECHNIQUES, 178-188 (1971) ("Monson").

[10] Eliel, STEREOCHEMISTRY OF ORGANIC COMPOUNDS, 322-325 (1994) ("Eliel").

[11] Jones, ORGANIC CHEMISTRY, 153-155 (2nd ed. 2000) ("Jones").

[12] Japanese Patent App. No. 56-122328A, September 1981 ("Kawakami"). United Therapeutics objects to Watson's purported translation of Kawakami as it is unclear as to whether this is a valid translation, particularly because there is no indication as to who performed the translation.

[13] Ege, S., Organic Chemistry Second Edition, 543-547 (1989) ("Ege").

[14] U.S. Patent Publication No. 2005/0165110 July 2005, Wade et al. ("Wade").

Claim	Deficiencies in Prior Art
	the references cited by Watson, alone or in combination, would render obvious any claim of the '393 patent.[15] First, Watson's contentions regarding the alkylation and hydrolysis steps do not advance their obviousness allegations. For example, Watson cites McManus[16] for the contention that alkylation using chloroacetonitrile and subsequent hydrolysis to a carboxylic acid was known, but fails to indicate how this is relevant to the obviousness analysis because the '393 patent itself references disclosures that demonstrate those same steps—such as the '117 patent and Moriarty 2004—and the Patent Office already considered and found that the '393 patent was distinguishable over those disclosures. *See* WIC at 35, 37; '393 Patent at 1:22-28; '393 Patent File History: Office Action dated May 15, 2013 (UTC_WAT_00001465-1470), Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485), Notice of Allowance dated June 12, 2013 (UTC_WAT_00001494-1499). Further, Watson cites Lin[17] and Aristoff[18], but these references fail to even disclose treprostinil and discuss other prostaglandins not related to the product of the '393 patent. Indeed, most the references identified in Watson's Invalidity Chart do not disclose treprostinil. Second, Watson cites several references discussing "purification" steps, but Watson fails to identify how or why any of these references would be used by a person of skill in the art to further purify and optimize the existing prior art treprostinil to arrive at the claims of the '393 patent, and fails to discuss whether a person of skill in the art would have a reasonable expectation of

[15] In addition the nonobviousness contentions presented herein and in the accompanying chart, United Therapeutics incorporates by reference the novelty arguments presented above and in the accompanying chart into its contentions of nonobviousness.

[16] McManus et al., Tetrazole Analogs of Plant Auxins, J. Org. Chemistry. 1959, 24, 1464-467 ("McManus").

[17] Lin et al., Benzindene Prostaglandins. Synthesis of Optically Pure 15-Deoxy-U68,215 and Its Enantiomer via a Modified Intramolecular Wadsworth-Emmons-Wittig Reaction, J. Org. Chemistry, 1987,52,5594-5601 ("Lin").

[18] Aristoff et al., Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emmons-Wittig Reaction, J. Am. Chem. SOC. 1985, 107, 7967-7974 ("Aristoff").

Claim	Deficiencies in Prior Art
	success in doing so. *See* WIC 35-37. Specifically, Watson cites Monson, Arumugan[19] and Yu[20] for the fact that "column chromatography is not favored for large-scale production", cites Monson and Harwood[21] to support its allegations that the use of crystallization and recrystallization as a purification technique was well-known, and similarly cites Eliel and Jones to show that "carboxylate ammonium salts are formed from adding a carboxylic acid with an amine and that those salts can be purified by recrystallization." *See* WIC at 35-36. Watson then concludes "a POSA would have been motivated to [modify the prior art synthesis of treprostinil utilizing column chromatography] by applying an obvious form of purification, salt crystallization, to form known salt forms of treprostinil." Watson's conclusion fails for several reasons. As examples, Watson fails to provide any evidence, or indeed argue, that the substitution would have been expected to result in the highly pure treprostinil claimed in the '393 patent, and Watson fails to discuss whether crystallization/recrystallization would even address the issues as to why column chromatography is allegedly not favored in large-scale production. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (a claim is not proved obvious merely by demonstrating that something was possible or known in the prior art). Additionally, Watson has failed to show that step (c) of the '393 patent would necessarily lead to the same final product if made from different starting treprostinil materials than that made from steps (a) and (b). The process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *United Therapeutics*, 2014 WL 4259153 at 53-55. During prosecution,

[19] Arumugan et al., A New Purification Process for Pharmaceutical and Chemical Industries, Organic Process Research & Development 2005, 9, 319-320 ("Arumugan").

[20] Yu et al., Novel Synthetic Route of a Pivotal Intermediate for the Synthesis of 1â-Methyl Carbapenem Antibiotics, Organic Process Research & Development 2006,10, 829-832 ("Yu").

[21] Harwood, Experimental organic chemistry: Principles and Practice, 127-134 (1989) ("Harwood").

Claim	Deficiencies in Prior Art
	United Therapeutics demonstrated that the final treprostinil product from the '393 patent is physically different than that of the Moriarty references. Thus, even if the Moriarty references' treprostinil products were used as a starting point, Watson has failed to provide any evidence that, if step (c) was somehow obvious to apply, that the resulting treprostinil product would necessarily be the same as the products claimed in the '393 patent. For example, the declaration of Dr. Walsh submitted during original prosecution shows that certain impurities in representative examples are reduced below detectable amounts by step (c), while others are still present in detectable amounts, such as treprostinil stereoisomer 3AU90. '393 Patent File History at p. 346-350. Both the type of impurity, as well as the relative amount of that impurity in the starting treprostinil material, may impact the impurity profile of the final product after step (c), yet there is absolutely no disclosure of any specific impurities or total amount of impurities by Watson on this point. Watson also cites Sorrell[22], Wiberg[23], Schoffstall[24], and Pavia[25], but each only provides a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. *See* WIC at 36, 38. In fact, most of Watson's purification references do not disclose treprostinil, prostacyclin analogues, or preferred methods of purification for such substances. And instead of providing a specific method of purifying complex molecules such as prostacyclin analogues, Watson's cited references largely provide a general description of purification techniques with absolutely no mention of any benzindene prostacyclin analogue or treprostinil itself. Moreover, Watson fails to provide any detail on how or why a person of ordinary skill in the art would look to very basic and sometimes decades old references

[22] Sorrell, ORGANIC CHEMISTRY, 755-758 (1999) ("Sorrell").

[23] Wiberg, LABORATORY TECHNIQUE IN ORGANIC CHEMISTRY, 112 (1960) "Wiberg").

[24] Schoffstall, et al., MICROSCALE AND MINISCALE ORGANIC CHEMISTRY LABORATORY EXPERIMENTS, 200-202 (2d ed.) (2004) ("Schoffstall").

[25] Pavia, INTRODUCTION TO ORGANIC LABORATORY TECHNIQUES, 648 (1998) ("Pavia").

Claim	Deficiencies in Prior Art
	to determine how to make the highly pure product produced by the '393 patent or have any reasonable expectation of success in doing so. Third, Watson also cites the 2005 Physician's Desk Reference[26], Burk[27], Ohno[28], and Priscinzano[29] for the contention that the diethanolamine salt was known and preferred. *See* WIC at 36. But the asserted claims of the '393 patent do not all require specifically that carboxylic ammonium salts are formed from carboxylic acids and amines and do not specifically require the diethanolamine salt. Contrary to Watson's arguments, these references only show very general information that is not directed towards benzindene prostacyclin analogues, much less treprostinil. Indeed, a person of ordinary skill in the art would not have considered these additional basic references to improve the product of the existing prior art treprostinil products and would not have a reasonable expectation of success in combining these very basic references with known syntheses of treprostinil. Fourth, Watson cites Wade to show that physiologically acceptable salts of treprostinil include salts derived from bases such as ammonia, N-methyl-D-glucamine, magnesium, arginine, and lysine. WIC at 36. Once again, however, Watson fails to provide any detail as to how this is relevant to the obviousness of the asserted claims. Fifth, Watson also cites Phares, Kawakami, and Ege for the proposition that steps (c) and (d) of the '393 patent were obvious. None of these references, however,

[26] The 2005 Physicians' Desk Reference for Bicillin® L-A (penicillin G benzathine suspension) ("2005 Physician's Desk Reference" or "PDR 2005").

[27] Burk, An Enantioselective Synthesis of (S)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation, J. Org. Chem. 2003, 68,5731-5734 ("Burk")

[28] Ohno, Development of Dual-Acting Benzofurans for Thromboxane A2 Receptor Antagonist and Prostacyclin Receptor Agonist: Synthesis, Structure-Activity Relationship, and Evaluation of Benzofuran Derivatives, J. Med. Chem. 2005, 48, 5279-5294 ("Ohno").

[29] Priscinzano, Piperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909): High Affinity Ligands for the Dopamine Transporter, J. Med. Chem. 2002, 45, 4371-4374 ("Priscinzano")

Claim	Deficiencies in Prior Art
	disclose steps (c) or (d) as claimed in the '393 patent. Specifically, Watson alleges that it would have been obvious to a person of ordinary skill in the art to contact "a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt" and that this salt "can be further precipitated and purified" or dissolved into its fee-acid form. *See* WIC at 38-39. These references alone or on combination, however, do not establish that the '393 patent's claims were obvious. Watson apparently cites Phares at page 24 for teaching step (c); however, the cited portion merely describes an example of how to make treprostinil diethanolamine from a starting material of treprostinil acid, but provides no detail whatsoever about how the starting treprostinil acid was made or where it comes from. Similarly, Watson cites Phares pages 85-93 as relevant to the teachings of step (c), but these portions describe a clinical study of sustained release capsules and tablets of treprostinil diethanolamine and to a polymorph characterization study of treprostinil diethanolamine. Again, there is no indication in this portion of Phares what process was actually used to make the starting "treprostinil acid" for the treprostinil diethanolamine. And, as discussed above, Phares fails to disclose the synthetic route or purity of the claimed treprostinil product. However, the process by which a treprostinil product is made will affect the impurity profile and total amount of impurities in the final product. *See United Therapeutics*, 2014 WL 4259153 at *53-55. Accordingly, by failing to show that performing step (c) on a starting treprostinil material, which has a different impurity profile than a starting treprostinil material made by performing steps (a) and (b) of the asserted claims, would necessarily lead to an identical product, Watson's arguments relating to obviousness over Phares necessarily fail. Regarding Kawakami, Watson has failed to establish that the '393 patent is obvious over any Kawakami combination. Simply put, Kawakami is directed to entirely different compounds with entirely different impurity profiles than the '393 patent. The alleged "prostacyclin compound" disclosed in Kawakami is a

Claim	Deficiencies in Prior Art
	two ring structure, yet the core three ring structure of treprostinil is key to its pharmaceutical usefulness (*United Therapeutics*, 2014 WL 4259153 at *4-5) and is also present in every structure of every step of the '393 patent. *See, e.g.*, '393 patent claim 1. Indeed, nothing in Kawakami comes close to even addressing the treprostinil product of the '393 patent much less how a skilled artisan would or would not go about synthesizing or purifying the product. Thus, a skilled artisan would have had no motivation to combine Kawakami with, for example, Phares or the Moriarty references, and would have had no reasonable expectation of success of obtaining the same high purity treprostinil product of the '393 patent. Additionally, to the extent Watson is alleging that Kawakami could remedy the deficiencies of the prior art treprostinil compounds (e.g., Moriarty references compounds) to disclose the impurity profile of the claimed treprostinil products, Watson has failed to establish a motivation to combine or reasonable expectation of success of forming a salt of the prior art treprostinil compounds with a purity profile of the products in the claims. Watson offers no basis from which to draw any conclusion about whether an impurity reduction step in Kawakami would possibly have any relevance to a process to synthesize and or purify a totally different structure such as treprostinil. To illustrate this point further, Kawakami is directed to purifying E- and Z-isomers of "prostacyclin compounds" from one another. In order for the E- and Z-isomers to exist, the "prostacyclin compound" must have an alkene. Treprostinil, on the other hand, contains no mixture of E/Z isomers. In fact, it cannot because it does not contain an alkene capable of E/Z isomerization. Watson has failed to provide a factual basis as to how or why the separation of E/Z isomers of an alkene would provide a motivation to combine or reasonable expectation of success in a compound not containing an alkene capable of E/Z isomerization, such as treprostinil. For these reasons, a skilled artisan would have no motivation to look at Kawakami in order to

Claim	Deficiencies in Prior Art
	arrive at the claimed invention of the '393 patent. Similarly, Ege provides no additional support for Watson's obviousness contentions. Ege is merely an undergraduate chemistry textbook with only generalized descriptions of carboxylic acids and related synthetic procedures, and discloses nothing about any prostacyclin derivative, much less treprostinil free acid. Indeed, Ege fails to disclose anything about the synthesis of pharmaceuticals at all. Ege merely shows it was known to form a free acid from treatment of the corresponding carboxylate salt with a strong acid, but this fact alone provides no reason why a skilled artisan, based on any reference, would conduct a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step with a reasonable expectation of obtaining the claimed products of the '393 patent's claims. In fact, Ege actually suggests this "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would be relatively useless as a means for purifying treprostinil. *See* Ege at p. 8 (stating that the "properties of carboxylic acids are useful for separating them from reaction mixtures containing neutral and basic compounds", which is irrelevant to the claimed treprostinil process). Thus, Ege would not create an expectation of success for separating one carboxylic-acid compound (*e.g.,* treprostinil free acid) from other carboxylic-acid containing compounds (*e.g.,* different stereoisomers of treprostinil free acid). By its invalidity contentions, it is obvious that Watson misunderstands the claims of the '393 patent. For example, the claimed invention is not the discovery that carboxylic acids react with bases, but rather that compounds of Formula (I), and in particular treprostinil or a salt thereof, can be obtained with a superior purity profile compared to the prior art. Specifically, performing step (c) on a product which resulted from steps (a) and (b) provided a product with reduced impurities—which was not disclosed in the Moriarty references and resulted in a significant improvement in the treprostinil product being made at the time of invention. In fact, during prosecution of the '393 patent established the impurity profile of the '393 patent

Claim	Deficiencies in Prior Art
	claims is different from the impurity profiles of Moriarty 2004. *See* '393 Patent File History, Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485). Watson appears to argue that the salt formation step would have been obvious to reduce or remove acidic or basic impurities, but each of these reduced or removed impurities are neither strongly acidic or basic as each are either diastereomers of treprostinil—which is very weakly acidic—or similarly neutral ester and triol impurities. The '393 patent therefore not only reduced the weakly acidic impurities present from the Moriarty process, but also unexpectedly reduced or eliminated non-acidic impurities as well. Thus, even under Watson's erroneous understanding, it was unexpected that the salt formation step would remove these additional impurities. Finally, Watson fails to address the distinctive structural and functional characteristics of the product produced by the '393 patents claims. If the process for producing a product according to a product-by-process claim imparts distinctive structural or functional characteristics to the product, those characteristics must be evaluated when considering patentability. *See In re Garnero*, 412 F.2d at 279; *see also United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573 at *140-149 (finding claims directed to producing a treprostinil product valid over prior art disclosures of treprostinil due to the structural and functional differences of the product produced by the claims). Because Watson failed to provide any evidence that the alleged prior art products—alone or modified by the teachings of other references—and the '393 patent's product are structurally and functionally the same, Watson's obviousness contentions fail. In sum, Watson fails to identify how or why a person of ordinary skill in the art would look to these twenty-five references to make the very pure treprostinil product claimed in the '393 patent or have a reasonable expectation of success in doing so. Thus Watson has failed to demonstrate essential pieces of a *prima facie* case of obviousness, and thus has failed to clearly and

Claim	Deficiencies in Prior Art
	convincingly show that '393 patent is invalid. *See In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 933, (U.S. 2013) (citing Procter & Gamble, 566 F.3d at 994) (To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.") Instead, what Watson has presented is a clear case of hindsight, by using the teachings of the patent as a blue print to pick and choose from the prior art. *See Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into use of hindsight'"); *see also State Industries, Inc. v. A.O. Smith Corp.*, 221 U.S.P.Q. (BNA) 958, 973 (M.D. Tenn. 1983), *aff'd in part, rev'd in part*, 751 F.2d 1226 (Fed. Cir. 1985) (an infringer's need to cite a large number of prior art references can indicate to a court that the invention was novel and not obvious.). Moreover, there would have been no legitimate reason or motivation for a skilled artisan at the time of invention to combine the cited references, and these references, alone or in combination, do not render the claims obvious. **The dependent claims are further patentably distinct due to their additional limitations** Claims 2-8 and 10-22 are nonobvious over the cited references because they depend from valid base claims as well as because they recite additional limitations which further distinguish these claims over the prior art. For example, Claims 6, 10, 15, and 21-22 are to the free acid of Formula (I) or treprostinil. As mentioned above, all of Watson's alleged combinations of prior art start with a Moriarty Reference. The free acid treprostinil in Moriarty was analyzed by United Therapeutics, and representative samples were found to contain a different impurity profile. As explained previously, the claimed free-acid

Claim	Deficiencies in Prior Art
	compounds, including treprostinil, produced by the processes of claims 6, 10, 15, and 21 provided a new product that induced FDA to adopt a new purity standard for treprostinil free acid due to the excellent purity of the final product. Furthermore, United Therapeutics demonstrated that treprostinil free acid made by the claimed methods provided a compound without many of the impurities included in the free acid treprostinil of the Moriarty references processes, including the two different stereoisomers of treprostinil. The prior art does not provide a reason that a skilled artisan would include a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step. For example, Phares merely discloses forming a salt from treprostinil free acid of undisclosed origin. There is no suggestion that this salt should then be converted back to the free acid (e.g., there is no suggestion of using the salt formation as a purification method). As discussed above, the impurities in representative examples of Moriarty include two different stereoisomers of treprostinil free acid. The Watson prior art, *i.e.*, Ege, however suggests that a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would not remove these compounds from the product. Thus, a skilled artisan looking to make the free acid product of claims 6, 10, 15, and 21-22, such as treprostinil free acid, would have understood the Moriarty references combined with the Watson prior art (e.g., Phares, and Ege) to suggest simply making the treprostinil free acid product of the Moriarty references, and not undergoing the additional time and expense of a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step. In fact, at least one Watson prior art reference, Ege, actually teaches away from the usefulness of this step. In sum, even though Watson cites prior art (e.g., Phares) that allegedly discloses forming a salt from treprostinil free acid, and prior art (e.g., Ege) that generally discusses that carboxylate salt formation was known in the art, there would have been no motivation or expectation of success in using these teachings on the

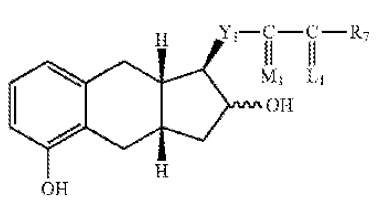
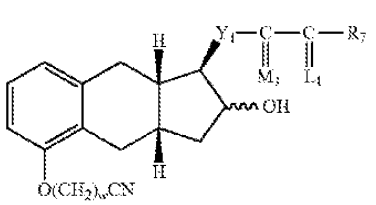
Claim	Deficiencies in Prior Art
	already-formed free acid disclosed in the Moriarty references, and Watson has failed to establish that a skilled artisan would have carried out steps necessary to inherently obtain the claimed products. Thus, Watson fails to establish prima facie case that claims 6, 10, 15 and 22 are invalid as obvious. **Secondary Considerations** Watson has not established a *prima facie* case of obviousness. Thus, United Therapeutics is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirms that the Asserted Claims would not have been obvious and, in fact, represent a surprising solution to a serious problem of minimizing potentially hazardous impurities and providing a safer and purer treprostinil product. **Long felt Unmet Need** At the time of the invention, there was a long-felt need to have a shorter, more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner with fewer impurities. Treprostinil has five chiral centers resulting in 32 possible stereoisomers so the potential for stereoisomeric impurities is high and only the treprostinil stereoisomer has the desired pharmaceutical effect. *United Therapeutics*, 2014 WL 4259153 at *2-3. Treprostinil is also a very potent drug so any stereoisomeric impurities would also potentially be potent and could potentially have deleterious effects. *Id.* Thus, there was a need to reduce the amount of impurities as much as possible and the product of the '393 patent further reduces impurities over the previous treprostinil products made by the prior art. **Unexpected Results** The results of the claimed inventions in the '393 patent were unexpected. For example, the use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was unexpected. Moreover, it

Claim	Deficiencies in Prior Art
	was unexpected that the salt purification step reduced not only diastereomeric impurities, but also non-acidic impurities as well. Thus, a person of skill in the art would not have expected the results of the '393 patent to be so successful. **Commercial Success** The '393 patent is used in the current production of Tyvaso and Remodulin, which both contain treprostinil. The inventions claimed in the '393 patent have reduced the cost of making treprostinil and increased efficiency. Tyvaso and Remodulin are commercially successful products. Tyvaso and Remodulin compete well against potential alternative products; for example, Remodulin competes well against alternatives such as Flolan. The commercial success of Tyvaso and Remodulin are reflected in both gross sales figures and relevant market share. Specifically, United Therapeutics made approximately $463.1 million, $438.8 million and $325.6 million in Tyvaso revenues, representing 36 percent, 39 percent and 36 percent of our total net revenues for the years ended December 31, 2014, 2013 and 2012, respectively. United Therapeutics (2014), *10-K Report* at p. 8, available at http://ir.unither.com/annuals-proxies.cfm. Also, United Therapeutics made approximately $553.7 million, $491.2 million and $458.0 million in Remodulin revenues, representing 43 percent, 44 percent and 50 percent of our total net revenues for the years ended December 31, 2014, 2013 and 2012, respectively. *Id.* at p. 6. United Therapeutics will make available for inspection and copying documents demonstrating the commercial success of Tyvaso and Remodulin. **Copying** The non-obviousness of the '393 patent is evidenced by Watson's own actions. Watson copied not only the active ingredient treprostinil sodium, but also the process claimed in the '393 patent. The non-obviousness of the '393 patent is additionally evidenced by the actions of several other generic pharmaceutical companies who have attempted to copy Remodulin.

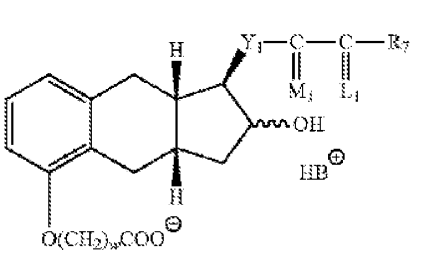
Claim	Deficiencies in Prior Art
	See, e.g., United Therapeutics Corp. v. Sandoz, Inc., Civil Action No. 3:14-cv-05499-PGS-LHG (D.N.J. 2014); *United Therapeutics Corp. v. Teva Pharma*, Civil Action No. 3:14-cv-05498-PGS-LHG (D.N.J. 2014). As stated, above, the '393 patent product and process is currently used in the production of Remodulin and Tyvaso. **The Asserted Claims of the '393 Patent are Not Invalid for Obviousness-Type Double Patenting Over the '117 Patent** Watson's entire obviousness-type double-patenting argument can be summarized as: because the claims of the '117 patent and the '393 patent are both directed to the same chemical compound, treprostinil (and its pharmacologically acceptable salt form), then that mere disclosure of treprostinil in the '117 patent necessarily renders obvious the claims of the '393 patent. *See* WIC 46-47. Watson is wrong. As previously discussed, the mere disclosure of treprostinil does not render obvious any claim of the '393 patent. Moreover, Watson does not correctly apply the law on obviousness-type double patenting. Inexplicably, Watson recites the rule that obviousness-type double patenting requires that only the claims of the prior art are compared to the asserted claims, but then ignores the rule's application and relies upon each patent being "directed to the product treprostinil and its pharmacologically acceptable salt form". *See* WIC at 46; *see also* Geneva *Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385 (Fed. Cir. 2003) (reciting the law for obviousness-type double patenting). Nevertheless, the claims of the '393 patent are very different than the claims of the '117 patent. Specifically, the '393 patent's claims recite different process elements from the '117 patent's claims. *Compare* '117 patent cl. 1; *with* '393 patent cl. 1. For example, the '117 patent's claims require that treprostinil be stereoselectively produced using the source limitations of starting enyne and cyclized intermediate. Further, the '117 patent claims do not disclose steps (a), (b), (c), or (d) of the '393 patent

Claim	Deficiencies in Prior Art
	claims. Also, the '117 patent claims do not disclose a product with at least 99.5% purity as required by claim 2 of the '393 patent. Watson's contentions, however, gloss over the process elements of the claims, while providing no support for its apparent assumption that these process elements are irrelevant to an obviousness-type double patenting analysis. This oversight alone is fatal to this invalidity defense. Furthermore, not only are the claims of the '117 patent very different than the claims of the '393 patent, but also the patents' resulting products are structurally and functionally different from each other. For example, as described above, the '393 patent produces a treprostinil drug product having a higher level of average purity, lower number of individual impurities, and is a better product as compared to the drug product of the '117 patent. *See* Supra discussion of Moriarty References. Also, the '117 patent does not specifically disclose treprostinil diethanolamine salt. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, at *5 (D.N.J. Feb. 21, 2007) ("Defendants have also not persuaded the Court that the rule of anticipation, holding that an earlier claim to a species defeats a later claim to a genus containing that species, controls the result in this case."). Because the '393 patent's treprostinil product is structurally and functionally different from the '117 patent's product, it is also patentably distinct. *See In re Garnero*, 412 F.2d 276, 279 (C.C.P.A. 1979); *and United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. LEXIS 121573 at *140-149 (finding claims directed to producing a treprostinil product valid over prior art disclosures of treprostinil due to the structural and functional differences of the product produced by the claims). . Thus, the '117 patent does not render the claims of the '393 patent invalid for obviousness-type double patenting. **The Asserted Claims of the '393 Patent are Not Invalid for Lack of Enablement or Lack of Written Description**

Claim	Deficiencies in Prior Art
	Watson claims that: [I]f plaintiff contends that it would have required undue experimentation for a POSA to apply these prior art procedures to obtain the claimed methods (for example it would have required undue experimentation to find particular bases or a particular alkylating agent), the claims would then be invalid for lack of an enabling description. To the extent that plaintiff contends that certain bases or reaction conditions, for example, are unique and that undue experimentation would have been required to practice the claimed method, the claims of the '393 patent are not enabled or fail to meet the written description requirement. WIC at 47. Watson conflates the distinct concepts of enablement, written description and undue experimentation, and fails to sufficiently allege invalidity on these bases. Enablement is met "when at the time of filing the application one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (citing *In re Wands,* 858 F.2d 731, 736–37 (Fed. Cir. 1988)). Therefore, the relevant inquiry as to whether "undue experimentation" is required for purposes of determining enablement is measured from the specification, not the "prior art procedures" as Watson asserts. Further, whether undue experimentation is required "is not a single, simple factual determination, but rather a conclusion reached by weighing many factual considerations." *Id.* Watson fails to even contend relevant factors related to (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Accordingly, Watson has failed to even allege facts sufficient to establish by clear and convincing evidence that the asserted claims of the '393 patent are not enabled.

Claim	Deficiencies in Prior Art
	Moreover, one skilled in the art, having read the specification, could practice the invention of the '393 patent without undue experimentation given the clear teachings to make the more pure treprostinil product claimed. Additionally, the test for sufficiency of written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Watson's contentions are insufficient as to written description because they fail to even allege that the disclosures of the '393 patent do not convey to a POSA that United Therapeutics had possession of the claimed subject matter. Each of the asserted claims of the '393 patent fulfill the requirements of written description by conveying that the inventors were in possession of the claimed subject matter as of the filing date.
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,  (II)  (III)	*See*, claim 1. Watson provides no additional citations or information regarding this claim limitation as the claim chart provided by Watson does not break down each limitation separately.

Claim	Deficiencies in Prior Art
wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH—CH_2—CH_3, (5) —$(CH_2)_2$—CH(OH)—CH_3, or (6) —$(CH_2)_3$—CH=C$(CH_3)_2$; —$C(L_1)$—R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,	
(b) hydrolyzing the product of formula III of step (a) with a base,	*See*, claim 1. Watson provides no additional citations or information regarding this claim limitation as the claim chart provided by Watson does not break down each limitation separately.
(c) contacting the product of step (b) [sic] with a base B to form a salt of formula	*See*, claim 1. Watson provides no additional citations or information regarding this claim limitation as the claim chart provided by Watson does not break down each

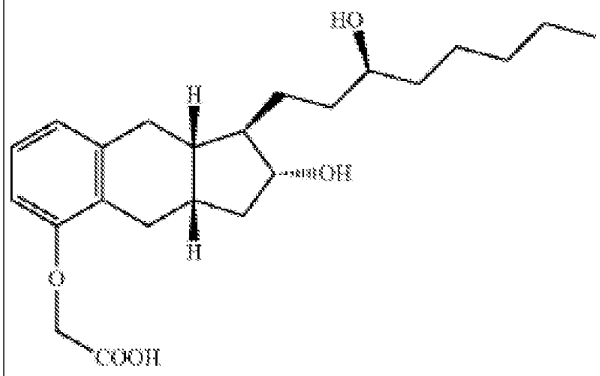
Claim	Deficiencies in Prior Art
I_s  (I$_s$) and	limitation separately.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See*, claim 1. Watson provides no additional citations or information regarding this claim limitation as the claim chart provided by Watson does not break down each limitation separately. Moreover, no prior art reference cited by Watson discloses step (d) after performing steps (a)-(c) on any treprostinil product.
Claim 2	
The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 1". **The '393 Patent is Not Anticipated by the '117 Patent, Remodulin, Phares or Moriarty 2004:** UTC incorporates by reference all arguments regarding Claim 1 above. Claim 2 requires that the product have a purity of no less than 99.5%. Moriarty 2004 is the only reference cited by Watson that discloses a purity with at least 99.5%, but as previously described, the product of the Moriarty 2004 reference is different and the Patent

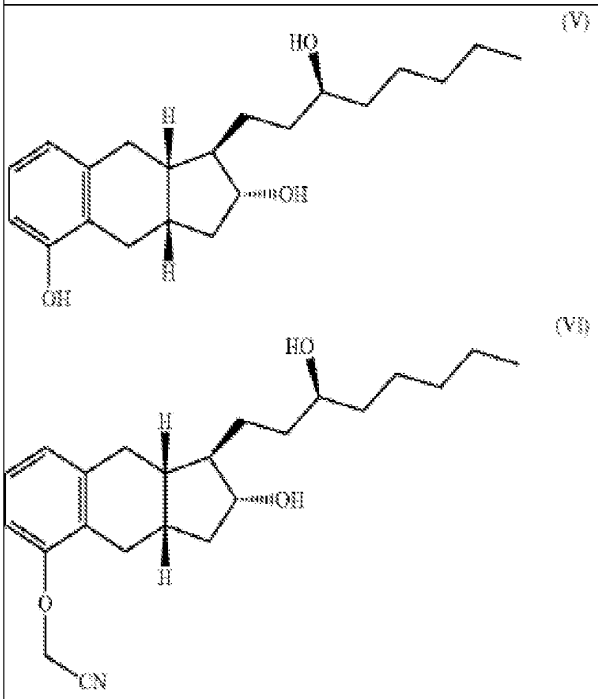
Claim	Deficiencies in Prior Art
	Office explicitly considered that claim in relation to the Moriarty 2004 reference and allowed the '393 patent. '393 Patent File History, Office Action dated May 15, 2013 (UTC_WAT_00001465-1470); Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485); Notice of Allowance dated June 12, 2013 (UTC_WAT_00001494-1499). Thus, the '117 patent, Phares, and Remodulin cannot anticipate Claim 2 because the purity requirement of 99.5% is not explicitly disclosed and Moriarty 2004 does not anticipate the claim because the product of Moriarty 2004 and the product of Claim 2 are different, as described in the prosecution history of the '393 patent. **The '393 Patent is Not Rendered Obvious by the Prior Art:** UTC incorporates by reference all arguments regarding Claim 1 above. As previously discussed, Moriarty 2004 is the only reference cited by Watson that discloses a purity with at least 99.5%, but no combination of prior art with Moriarty 2004 would result in the same product with the same purity requirement as the '393 patent. For the same reasons as claim 1, none of the prior art references render claim 2 obvious. **The '393 Patent is Not Invalid For Obviousness-Type Double Patenting Over the '117 Patent:** UTC incorporates by reference all arguments regarding Claim 1 above. More specifically, the '117 patent does not disclose a purity of 99.5%. Additionally, for the same reasons as claim 1, the '117 patent does not render claim 2 of the '393 patent invalid for obviousness-type double patenting. **The '393 Patent is Not Invalid For Lack of Enablement or Lack of Written Description:** UTC incorporates by reference all arguments regarding Claim 1 above. Watson fails to identify any specific disclosure that is not enabled or lacks written description. For the same reasons as Claim 1 above, Claim 2 is enabled and does not lack written

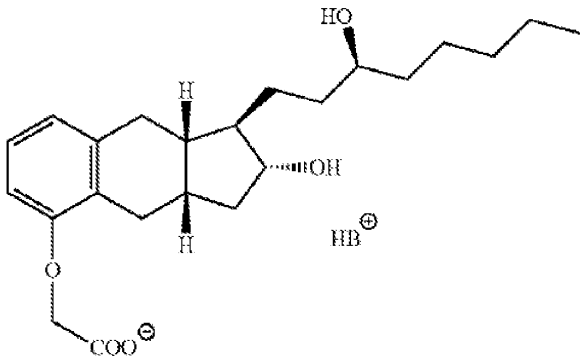
Claim	Deficiencies in Prior Art
	description.
Claim 3	
The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 1". While Watson's narrative alleges that the '117 Patent & Moriarty 2004 disclose "the alkylating agent is $ClCH_2CN$", as described above in connection with claim 1, these disclosures are unavailing as the claimed process steps are distinguishable from these references, which the PTO has already decided. Moreover, the vast majority of the prior art cited by Watson provides no disclosure of these particular alkylating agents whatsoever.
Claim 4	
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 1". While Watson's narrative alleges that certain prior art (i.e., '117 Patent and Moriarty 2004) disclose a KOH or NaOH base, similar to what has been described above in connection with claim 1, this disclosure does not

Claim	Deficiencies in Prior Art
	advance Watson's arguments because it does not teach or suggest that KOH or NaOH is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 5	
The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, Llysine, L-arginine, triethanolamine, and diethanolamine.	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 1". Watson's narrative alleges that Phares discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred," and Wade discloses "physiologically acceptable salts of treprostinil include salts derived from these [claim 13's] bases." However, similar to what has been as described above in connection with claim 1, this disclosure does not advance Watson's arguments because Wade and Phares does not teach or suggest that a base B as defined in this claim is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 6	
The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional

Claim	Deficiencies in Prior Art
	to what Watson "cited above with respect to claim 1." The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (i.e., "reacting the salt formed in step (c) with an acid to form the compound of formula I") And while Watson's narrative alleges that certain prior art (i.e., '117 Patent & Moriarty 2004) discloses that salts of treprostinil could be reacted with diluted HCl to from treprostinil, similar to what has been described above in connection with claim 1, the prior art, alone or in combination, does not disclose or otherwise suggest that claimed step (d) is performed on the treprostinil compound formed by steps (a), (b), and (c), as this claim requires.
Claim 7	
The product of claim 1, wherein Y1 is —CH_2CH_2—; M_1 is α-OH:ß-H or α-H:ß-OH; —$C(L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1.	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 1".
Claim 8	
The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional

Claim	Deficiencies in Prior Art
	to what Watson "cited above with respect to claim 1".
Claim 9	
A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	The difference between claim 9 and claim 1 is that the structures displayed are limited to synthesis of treprostinil. Watson provides no additional citations or information regarding this claim limitation over what was provided for claim 1. UTC incorporates by reference all arguments regarding Claim 1 above.
(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,	*See*, claim 9. Watson provides no additional citations or information regarding this claim limitation over what was provided for the previous limitation.

Claim	Deficiencies in Prior Art
	
(b) hydrolyzing the product of formula VI of step (a) with a base,	*See*, claim 9. Watson provides no additional citations or information regarding this claim limitation over what was provided for the previous limitation.
(c) contacting the product of step (b) with a base B to form a salt of formula IV_s, and	*See*, claim 9. Watson provides no additional citations or information regarding this claim limitation over what was provided for the previous limitation.

Claim	Deficiencies in Prior Art
	
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	*See*, claim 9. Watson provides no additional citations or information regarding this claim limitation over what was provided for the previous limitation.
Claim 10	
The product of claim 9, wherein the purity of product of step (d) is at least 99.5%.	*See*, claims 1, 2 and 9. UTC incorporates by reference all arguments regarding Claims 1, 2 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9". The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (i.e., "reacting the salt formed in step (c) with an acid to form the compound of formula I").
Claim 11	
The product of claim 9, wherein the alkylating agent is	*See*, claims 1 and 9. UTC incorporates by reference all

Claim	Deficiencies in Prior Art
$ClCH_2CN$.	arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9". While Watson's narrative alleges that the '117 Patent & Moriarty 2004 disclose "the alkylating agent is $ClCH_2CN$", as described above in connection with claim 1, these disclosures are unavailing as the claimed process steps are distinguishable from these references, which the PTO has already decided.
Claim 12	
The product of claim 9, wherein the base in step (b) is KOH.	*See*, claims 1 and 9. UTC incorporates by reference all arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9". While Watson's narrative alleges that certain prior art (i.e., '117 Patent and Moriarty 2004) disclose a KOH base, similar to what has been described above in connection with claim 1, this disclosure does not advance Watson's arguments because it does not teach or suggest that KOH is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 13	
The product of claim 9, wherein the base B in step (c)	*See*, claims 1 and 9. UTC incorporates by reference all

Claim	Deficiencies in Prior Art
is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, Llysine, L-arginine, triethanolamine, and diethanolamine.	arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9". Watson's narrative alleges that Phares discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred", and Wade discloses "physiologically acceptable salts of treprostinil include salts derived from these [claim 13's] bases." However, similar to what has been as described above in connection with claim 1, this disclosure does not advance Watson's arguments because Wade and Phares does not teach or suggest that a base B as defined in this claim is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 14	
The product of claim 9, wherein the base B is diethanolamine.	*See*, claims 1 and 9. UTC incorporates by reference all arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9". While Watson's narrative alleges that Phares discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred", similar to what has been described above in connection with claim 1, this disclosure does not advance Watson's arguments because Phares does not

Claim	Deficiencies in Prior Art
	teach or suggest that diethanolamine is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 15	
The product of claim 9, wherein the acid in step (d) is HCl.	*See*, claims 1 and 9. UTC incorporates by reference all arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9". The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (i.e., "reacting the salt formed in step (c) with an acid to form the compound of formula I") And while Watson's narrative alleges that certain prior art (i.e., '117 Patent & Moriarty 2004) discloses that salts of treprostinil could be reacted with diluted HCL to from treprostinil, similar to what has been described above in connection with claim 1, the prior art, alone or in combination, does not disclose or otherwise suggest that claimed step (d) is performed on the treprostinil compound formed by steps (a), (b), and (c), as this claim requires.
Claim 16	
The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	*See*, claims 1 and 9. UTC incorporates by reference all arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument

Claim	Deficiencies in Prior Art
	that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9".
Claim 17	
The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, tricthanolamine, and diethanolamine.	*See*, claims 1 and 9. UTC incorporates by reference all arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9". While Watson's narrative alleges that Phares discloses that "treprostinil can be crystalized, and that the diethanolamine salt of treprostinil is particularly preferred", similar to what has been as described above in connection with claim 1, this disclosure does not advance Watson's arguments because Phares does not teach or suggest that a base B as defined in this claim is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 18	
The product of claim 17, wherein the base B is diethanolamine.	*See*, claims 1 and 9. UTC incorporates by reference all arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9". While Watson's narrative alleges that Phares discloses that "treprostinil can be crystalized, and that the

Claim	Deficiencies in Prior Art
	diethanolamine salt of treprostinil is particularly preferred", similar to what has been described above in connection with claim 1, this disclosure does not advance Watson's arguments because Phares does not teach or suggest that diethanolamine is contacted with a treprostinil compound produced according steps (a) and (b), as claimed.
Claim 19	
The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 1".
Claim 20	
The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, Llysine, L-arginine, triethanolamine, and diethanolamine.	*See*, claims 1 and 9. UTC incorporates by reference all arguments regarding Claims 1 and 9 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 9".
Claim 21	
The product of claim 1, wherein step (d) is performed.	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional

Claim	Deficiencies in Prior Art
	arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 1". The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (i.e., "reacting the salt formed in step (c) with an acid to form the compound of formula I")
Claim 22	
The product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information in its claim chart specific to the particular limitations of this claim, and as such, has waived any additional arguments specific to the invalidity of this particular claim. For example, Watson has waived any argument that a cited reference teaches or suggests the recited claim limitation in any portion of a reference additional to what Watson "cited above with respect to claim 1". The prior art, alone or in combination, does not disclose all limitations of this claim; for example, none of the prior discloses step (d) (i.e., "reacting the salt formed in step (c) with an acid to form the compound of formula I"). Watson's narrative alleges that certain prior art (i.e., Moriarty 2004, Remodulin, '117 Patent, & Phares) disclose treprostinil salts (e.g., treprostinil sodium) being sold as an FDA approved treatment. However, as mentioned above, none of the prior art discloses that the pharmaceutically acceptable salt was "formed from the product of step (d)" as required by this claim.

Electronic Acknowledgement Receipt	
EFS ID:	28022454
Application Number:	14849981
International Application Number:	
Confirmation Number:	6653
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh BATRA
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Strawderman
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1581
Receipt Date:	10-JAN-2017
Filing Date:	10-SEP-2015
Time Stamp:	14:32:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	NtfRltProc.pdf	52384 c44ea6909e65615df10e5aad46bdefd003ffcfa7	no	2

Warnings:

Information:					
2	Miscellaneous Incoming Letter	ActavisInvResponseRedacted.pdf	418592 71cb85dbd669e8f8fa80bd8afef77d6e35b9bcb0	no	59
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	SandozInvResponseRedacted.pdf	339964 5c6416c1a4559cad8808fa80d1a773e08f50ad72	no	68
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	TevaInvResponseRedacted.pdf	259088 d3155e4152aac4002d3ca78783d304f9045aa505	no	30
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	WatsonInvResponseRedacted.pdf	462780 2015e27b71169fd694945e29b5e7fc61b8bd75cf	no	72
Warnings:					
Information:					
		Total Files Size (in bytes):	1532808		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/849,981
Date Submitted: JAN 10 2017				**Filing Date**	9/10/2015
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1672
				Examiner Name	Yevgeny Valenrod
Sheet	1	of	1	Attorney Docket Number	080618-1581

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	E1	Redacted Defendant Watson Laboratories, Inc.'s Invalidity Contentions dated December 11, 2015, *United Therapeutics Corporation (Plaintiff) v. Watson Laboratories, Inc. (Defendant)*, In The United States District Court for the District of New Jersey, Civil Action No. 3:15-cv-05723-PGS-LHG, 35 pages.	

Examiner Signature		Date Considered	

4831-5029-0752.1

Liza M. Walsh
Tricia B. O'Reilly
Joseph L. Linares
CONNELL FOLEY LLP
One Newark Center
1085 Raymond Boulevard, 19th Floor
Newark, NJ 07102
(973) 757-1100

Of Counsel:
Michael K. Nutter (admitted *pro hac vice*)
Kurt A. Mathas (admitted *pro hac vice*)
WINSTON & STRAWN LLP
35 W. Wacker Drive
Chicago, IL 60601-9703
(312) 558-5600

Attorneys for Defendant Watson Laboratories, Inc.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. WATSON LABORATORIES, INC., Defendant.	Civil Action No. 3:15-cv-05723-PGS-LHG Hon. Peter G. Sheridan, U.S.D.J. Hon. Lois H. Goodman, U.S.M.J.

DEFENDANT WATSON LABORATORIES, INC.'S
INVALIDITY CONTENTIONS

Pursuant to Local Patent Rules 3.3 and 3.6 and the proposed Scheduling Order, Watson submits the following invalidity contentions for the asserted claims of United States Patent Nos. 6,521,212, 6,756,033, and 8,497,393.[1]

[1] Nothing in this statement of contentions should be construed as limiting Watson's statutory rights pursuant to 35 U.S.C. § 282, which requires a party asserting invalidity defenses to provide notice of relevant prior art thirty days before trial.

Watson reserves the right to supplement and/or amend these contentions in response to any contentions by plaintiff. Watson further reserves the right to supplement and/or amend these contentions as discovery proceeds, including based on fact or expert discovery disclosures and on any discovery materials that have not yet been produced or provided to Watson, or upon further investigation. Watson further reserves the right to supplement and/or amend these contentions based on any Court decisions in any related cases (including the *United Therapeutics Corp. v. Teva Pharmaceuticals USA, Inc.* case (case no. 3:14-cv-05498)). Watson also reserves the right to supplement and/or amend these contentions when plaintiff provides its infringement allegations, or to the extent any claim construction ruling by the Court modifies Watson's positions herein and/or provides the basis for additional invalidity contentions. Watson otherwise reserves the right to supplement and/or amend these contentions as necessary and appropriate and as provided under the Local Patent Rules or any other applicable rules or order of the Court.

These contentions are made pursuant to Federal Rule of Evidence 502. To the extent these contentions contain any information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, the common interest privilege, or any other applicable privilege or immunity, such disclosure is inadvertent and does not constitute a waiver of any such privilege or immunity. The information set forth in these contentions is provided without waiving: (1) the right to object to the use of any statement for any purpose, in this action or any other, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided below at any time.

These contentions should not be taken as an indication of Watson's position with regard to the proper construction of any claim term.[2] Rather, Watson has made reasonable assumptions, to the extent necessary and appropriate, as to the meaning of claim terms for the purpose of these contentions only and has used those meanings to prepare these contentions. To the extent that Watson determines that a different meaning is appropriate for any claim term, it will assert that meaning in connection with the claim construction proceedings, and Watson reserves the right to amend these contentions as a result of the *Markman* hearing, or any other subsequent clarification or alteration of the meaning of claim terms.

Watson's invalidity positions in these contentions and the accompanying charts may be in the alternative and do not constitute any concession by Watson for purposes of infringement. *See, e.g.*, *Vanmoor v. Wal-Mart Stores, Inc.*, 201 F.3d 1363, 1366 (Fed. Cir. 2000).

In accordance with 21 U.S.C. § 355(j)(2)(B)(ii), Watson provided notice in the form of a "notice letter" to UTC that it sought FDA approval to market drug products under its Abbreviated New Drug Application before the expiration date of the '212, '033 and '393 patents. The notice letter set forth, among other things, the factual and legal bases that the claims of the patents are not infringed, invalid, and/or unenforceable by the proposed treprostinil products described in the ANDA at issue in this case. Watson hereby incorporates by reference the sections of its notice letter.

As discussed in more detail below, at this early stage of the litigation, Watson contends that the relevant prior art—standing alone or in combination with the knowledge of a person of

[2] Any reference in these contentions to the preamble of any claim of the patents-in-suit, including any word or any phrase appearing in such preamble, shall not be taken as an admission that the referenced language of the preamble is or is not a claim limitation. Watson reserves the right to contend that any word or any phrase in the preamble of any claim of the patents-in-suit is or is not a claim limitation.

ordinary skill in the art—renders the asserted claims of the '212, '033 and '393 patents invalid as anticipated under 35 U.S.C. § 102 and/or obvious under 35 U.S.C. § 103.

Pursuant to Local Patent Rule 3.6(c) and 3.3(a)-(b), Watson herein identifies each item of prior art known at this time that allegedly renders each claim invalid as anticipated and/or obvious, and includes an explanation of why the prior art renders the claim invalid. Charts relevant to the patents-in-suit, setting forth the information required under Local Patent Rule 3.6(c) and 3.3(c), are included herein. Further pursuant to Local Patent Rule 3.6(c) and 3.3(c), Watson currently contends that no claim elements are subject to 35 U.S.C. § 112, sixth paragraph. Contemporaneously with this submission, Watson is also producing the documents required under Local Patent Rule 3.6(d) and 3.4, to the extent the same are not already in the possession of plaintiff or have not been otherwise previously produced. Watson reserves the right to supplement this identification should additional documents become relevant during the continuing course of discovery.

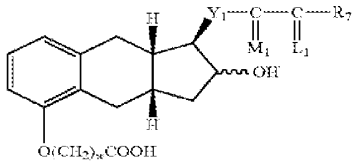
[redacted]

B. The '393 Patent

The '393 patent issued on July 30, 2013 from U.S. Application Serial No. 13/548,446, filed on July 13, 2012. The '446 application claims priority to U.S. Application Serial No. 12/334,731, filed on December 15, 2008, which issued on August 14, 2012 as U.S. Patent No. 8,242,305. The '731 application claimed priority to U.S. Provisional Patent Application No. 61/014,232, filed on December 17, 2007. Therefore, according to the face of the '393 patent, the earliest possible priority date and also the earliest effective filing date for the '393 patent is December 17, 2007.

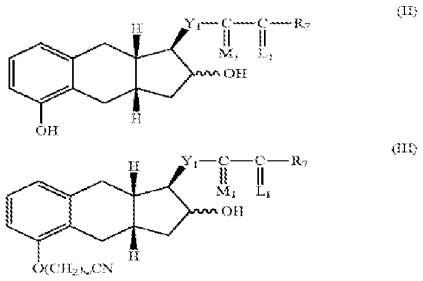
The '393 patent has twenty-two claims, including independent claims 1 and 9, all of which are asserted against Watson. Claims 1-22 are product-by-process claims directed to treprostinil or its pharmaceutically acceptable salt. The claimed process involves the alkylation of a triol compound to a benzindene nitrile compound, hydrolysis of the nitrile compound, formation of a salt using "a base B," and optionally reacting the salt with an acid to form treprostinil. Claim 1 is exemplary:

A product comprising a compound of formula I



or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is

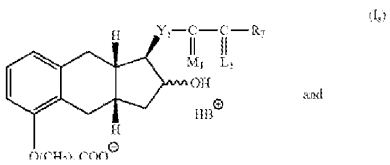
(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH–CH_2–CH_3,
(5) –$(CH_2)_2$–CH(OH)–CH_3, or
(6) –$(CH_2)_3$–CH=$C(CH_3)_2$; –$C(L_1)$–R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;
(2) 2-(2-furyl)ethyl,
(3) 2-(3-thienyl)ethoxy, or
(4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,

(b) hydrolyzing the product of formula III of step (a) with a base,

(c) contacting the product of step (h) with a base B to form a salt of formula I_s.



(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

See '393 patent at claim 1.

II. IDENTIFICATION OF PRIOR ART UNDER L. PAT. R. 3.3(a)

Watson relies on at least the following prior art in support of its invalidity contentions. Watson reserves the right to rely upon additional prior art as discovery progresses, to the extent not addressed herein. Watson further reserves the right to rely on all prior art cited or discussed during the prosecution of any patent claiming priority to the '232 provisional application or the '999 provisional application, as well as any related patents and applications, and any prior art identified in any other actions involving the patents-in-suit or related patents. Watson further reserves the right to identify and rely on additional art or teachings within the art in the event that

Watson's evaluation of the prior art teachings is in any way contested, including to the extent plaintiff seeks to claim an earlier priority date for the asserted claims.

Unless otherwise stated, it should be presumed that Watson intends to rely upon each reference in its entirety to the extent relevant and/or appropriate, including references cited in and/or referenced within the references identified below. Watson also incorporates, in full, all prior art references cited in the '212, '033 and '393 patents, their prosecution histories, and related patents and applications and their prosecution histories.

[redacted]

Claims 1–22 of the '393 patent are invalid as anticipated and/or obvious in view of at least the following prior art references, which are exemplary of the state of the art at the time of the filing of the '393 patent.

- U.S. Patent No. 6,765,117
- Moriarty et al., The Intramolecular Asymmetric Pauson-Khan Cyclization as a Novel and General Steroselective Route to Benzidindene Protacyclins: Synthesis of UT-15 (Treprostinil) J. Org. Chemistry. 2004, 69(6), 1890-1902 ("Moriarty 2004")
- Remodulin®
- Remodulin® Label
- Lin et al., Benzindene Prostaglandins. Synthesis of Optically Pure 15-Deoxy-U-68,215 and Its Enantiomer via a Modified Intramolecular Wadsworth-Emmons-Wittig Reaction, J. Org. Chemistry, 1987,52,5594-5601 ("Lin 1987")
- Aristoff et al., Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emmons-Wittig Reaction, J. Am. Chem. SOC. 1985, 107, 7967-7974 ("Aristoff 1985")
- McManus et al., Tetrazole Analogs of Plant Auxins, J. Org. Chemistry. 1959, 24, 1464-1467 ("McManus 1959")
- Ege, S., *Organic Chemistry Second Edition*, 543-547 (1989) ("Ege 1989")
- U.S. Patent Publication No. 2005/0085540 April 2005, Phares et al. ("Phares 2005")
- U.S. Patent Publication No. 2005/0165110 July 2005, Wade et al. ("Wade 2005")
- Japanese Patent App. No. 56-122328A, September 1981 ("Kawakami 1981")
- Arumugan et al., A New Purification Process for Pharmaceutical and Chemical Industries, Organic Process Research & Development 2005, 9, 319-320 ("Arumugan 2005")
- Yu et al., Novel Synthetic Route of a Pivotal Intermediate for the Synthesis of 1â-Methyl Carbapenem Antibiotics, Organic Process Research & Development 2006, 10, 829-832 ("Yu 2006")

- Monson, ADVANCED ORGANIC SYNTHESIS, METHODS AND TECHNIQUES, 178-188 (1971) ("Monson 1971")

- Harwood, *Experimental organic chemistry: Principles and Practice*, 127-134 (1989) ("Harwood 1989")

- Eliel, STEREOCHEMISTRY OF ORGANIC COMPOUNDS, 322-325 (1994) ("Eliel 1994")

- Jones, ORGANIC CHEMISTRY, 153-155 (2nd ed. 2000) ("Jones 2000")

- Sorrell, ORGANIC CHEMISTRY, 755-758 (1999) ("Sorrell 1999")

- Pavia, INTRODUCTION TO ORGANIC LABORATORY TECHNIQUES, 648 (1998) ("Pavia 1998")

- Priscinzano, Piperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909): High Affinity Ligands for the Dopamine Transporter, J. Med. Chem. 2002, 45, 4371-4374 ("Priscinzano 2002")

- Ohno, Development of Dual-Acting Benzofurans for Thromboxane A2 Receptor Antagonist and Prostacyclin Receptor Agonist: Synthesis, Structure-Activity Relationship, and Evaluation of Benzofuran Derivatives, J. Med. Chem. 2005, 48, 5279-5294 ("Ohno 2005")

- Burk, An Enantioselective Synthesis of (S)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation, J. Org. Chem. 2003, 68, 5731-5734 ("Burk 2003")

- Wiberg, LABORATORY TECHNIQUE IN ORGANIC CHEMISTRY, 112 (1960) ("Wiberg 1960")

- Schoffstall, et al., MICROSCALE AND MINISCALE ORGANIC CHEMISTRY LABORATORY EXPERIMENTS, 200-202 (2d ed.) (2004) ("Schoffstall 2004")

- The 2005 Physicians' Desk Reference for Bicillin® L-A (penicillin G benzathine suspension) ("PDR 2005 Bicillin® L-A")

- The references cited or disclosed during prosecution of the '393 patent

- All references cited above for the '212 and '033 patents

II. EXPLANATION OF ANTICIPATION AND/OR OBVIOUSNESS UNDER L. PAT. R. 3.3(b)

As reflected below, all the asserted claims of the patents-in-suit are invalid under 35 U.S.C. §§ 102 and 103 as anticipated and/or obvious over the prior art, including the specific references listed above and further discussed below. A patent is anticipated under § 102 when a reference (1) discloses each and every element of the claimed invention, whether it does so explicitly or inherently; and (2) enables one of ordinary skill in the art to make the invention without undue experimentation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). A patent would have been obvious under § 103 if it claims "the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007).

C. Invalidity of the '393 Patent

The '393 patent contains product-by-process claims that cover making treprostinil. The focus of the invalidity analysis for a product-by-process claim is the product produced by the claimed process. *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1369-70 (Fed. Cir. 2009). The prior art does not need to teach the process limitations so long as the prior art product is the same as the claimed product. *Id.* UTC asserts that Watson infringes claims 1-22

of the '393 patent. As explained below, Watson hereby contends that all claims are invalid as anticipated or obvious.

1. Claims 1-22 Of The '393 Patent Are Anticipated by the '117 patent, Moriarty 2004, Remodulin®, and/or Phares 2005.

Claims 1–22 of the '393 patent are invalid as anticipated by at least the '117 patent, Moriarty 2004, UTC's own Remodulin® drug product (first approved by the FDA in May 2002 and offered for sale to the public in 2002) and Phares 2005. In the case of product-by-process claims, the focus of the anticipation analysis is the product produced by the claimed process. *See Amgen Inc.*, 580 F.3d at 1369-70. Here, as explained in further detail below, the prior art discloses the same product, treprostinil, or its pharmaceutically acceptable salt, as the claimed product and thus anticipates the claims.

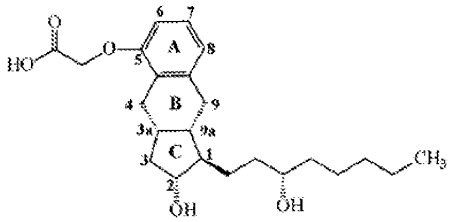
a. The '117 Patent

The '117 patent issued on July 20, 2004. As such, it is prior art under 35 U.S.C. § 102(b). The '117 patent is entitled "Process for Stereoselective Synthesis of Prostacyclin Derivatives." The face of the '117 patent indicates that it is assigned to UTC and includes one inventor in common with the '393 patent (Raju Penmasta). The '117 patent is listed in the Orange Book as covering Tyvaso® and Remodulin® (treprostinil) and claims the same compound and its salt form as the '393 patent. '117 patent at col. 20, l. 10–col. 21, l. 12, claims 1-4. Where the '117 patent discloses each of the limitations of the asserted claims is included in the chart below.

b. Moriarty 2004

Moriarty 2004 is a 2004 article published in the Journal of Organic Chemistry by the named inventors of the '117 patent discussing the synthesis of UT-15 (treprostinil). As such, it is prior art under 35 U.S.C. § 102(b). Similar to the disclosures of the '117 patent, Moriarty 2004

discloses compound 7 (page 1892), the same compound that falls within the claimed compound for all of the claims of the '393 patent.

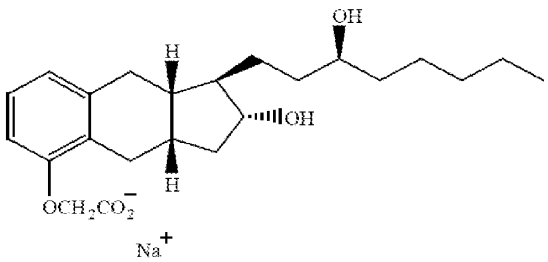


7

Moriarty 2004 discloses an improved "route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale." Moriarty 2004 at Abstract. With the exception of claims 2 and 10, there are no purity requirements in the asserted claims, and thus those claims cannot be used to distinguish the prior art. *See Cubist Pharm., Inc. v. Hospira, Inc.*, No. CA 12-367-GMS, 2014 WL 6968046, at *19-20 (D. Del. Dec. 8, 2014). Claims 2 and 10 require a purity of the product of at least 99.5%, but Moriarty 2004 discloses that the compound is produced with 99.7% purity (page 1902) and thus anticipates those claims. Where Moriarity 2004 discloses each of the limitations of the asserted claims is included in the chart below.

c. Remodulin®

The treprostinil that was used in UTC's commercial embodiment Remodulin®, first approved, marketed, and sold to the public in 2002, with all its attributes and inherent qualities, also anticipates the '393 patent. Remodulin® was approved in 2002 and was publicly available at least one year prior to the application of the '393 patent. *See, e.g.*, Phares 2005 (disclosing the availability of treprostinil sodium (Remodulin®) [0004]); *see also* Wade 2005 at [0021, 0024] (disclosing treprostinil used in Remodulin® and its salt forms). As such, it is prior art under 35 U.S.C. § 102(b). According to its prescribing information, Remodulin® is a treprostinil sodium having the following structural formula:



Where Remodulin® discloses each of the limitations of the asserted claims is included in the chart below.

d. Phares 2005

Phares 2005 is the publication of a patent application by Ken Phares and David Mottola, which was assigned to UTC, and which published on April 21, 2005. As such, it is prior art under 35 U.S.C. § 102(b). Phares 2005 also discloses the claimed compound of the '393 patent in at least two salt forms and further discloses that the sodium salt of the compound is sold as Remodulin®. Phares 2005 para. [0051]. Where Phares 2005 discloses each of the limitations of the asserted claims is included in the chart below.

2. Claims 1-22 Would Have Been Obvious In View Of the Prior Art.

If the Court concludes that claims 1-22 are not anticipated, they are invalid as obvious to a POSA in view of the prior art. As discussed above, claims 1-22 are product-by-process claims directed to treprostinil or its pharmaceutically acceptable salt. The claimed process involves an alkylation of triol compound to a benzindene nitrile compound, hydrolysis of the nitrile compound, formation of a salt using "a base B," and optionally reacting the salt with an acid to form treprostinil. As noted above, in the case of a product-by-process claim, the focus of the invalidity analysis is the product produced by the claimed process. *See Amgen Inc.*, 580 F.3d at 1369-70. The prior art does not need to teach the process limitations so long as "the product in a

product-by-process claim is the same as or obvious from a product of the prior art." *Id.* at 1366. Here, the prior art discloses obvious variations of the same product, treprostinil and the pharmacologically acceptable salt form of treprostinil, as well as all of the process limitations.

As discussed in the anticipation section above, treprostinil and its pharmaceutically acceptable salts as claimed in the '393 patent were well-known in the art at the time as of the '393 priority date. *See* Remodulin® product; the '117 patent, col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902; Phares 2005 para. [0051]. As the applicants conceded, treprostinil (the claimed product and active ingredient in Remodulin®) was well known and first described in U.S. Pat. No. 4,306,075, which issued on December 15, 1981. '393 patent, col. 1, lines 22-28. Indeed, the applicants further admitted that "[t]reprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in J. Org. Chem. 2004, 69, 1890-1902 …, 6,765,117 and 6,809,223." *Id.* An improved process for making treprostinil is disclosed in U.S. Patent No. 4,668,814, which issued on May 26, 1987, and the '117 patent discloses a further improved process for making treprostinil.

The prior art shows that it would have been well known to a POSA to synthesize treprostinil via alkylation of benzindene triol followed by the hydrolysis of benzindene nitrile. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Such alkylation reactions adding $ClCH_2CN$ and then subsequent hydrolysis to the carboxylic acid would have also been well-known in the art. *See, e.g.*, Lin 1987 at p. 5595; Aristoff 1985 at p. 7971; McManus 1959 at pp. 1465-1467.

The prior art also teaches a POSA that the synthesis of treprostinil utilizing purification by column chromatography. *See* '117 Patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. The prior art further teaches that purification by chromatography is not

favored for large-scale industrial production. *See* Monson 1971 p. 185; Arumugam 2005 p. 319; Yu 2006 p. 832. The use of crystallization and recrystallization as a purification technique was well-known. *See e.g.* Monson 1971 pp. 181–83; Harwood 1989 pp. 127–34; Pavia 1998 p. 648. In fact, it was known since at least 1853 (from the work of Louis Pasteur) that carboxylate ammonium salts are formed from adding a carboxylic acid with an amine, and that those salts can be purified by recrystallization. *See* Eliel 1994 p. 322; *see also* Jones 2000 pp. 153–55; Sorrell, 1999 pp. 755–58. Additionally, carboxylate ammonium salts are very common and well known for use in drugs and drug targets, including diethanolamine salts. *See e.g.*, Priscinzano 2002 pp. 4371–74; Ohno 2005 pp. 5279–94, compound 7; Burk 2003 pp. 5731–34; PDR 2005 Bicillin® L-A.

The prior art also teaches a POSA that treprostinil can be crystallized and that the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051], figures 15-22; Moriarty 2004 p. 1892 compound 7, p. 1902. The prior art further discloses that other physiologically acceptable salts of treprostinil include salts derived from bases, such as ammonia, N-methyl-D-glucamine, magnesium, arginine and lysine. *See* Wade 2005 para. [0024]. It was also known in the art that salts of treprostinil could be reacted with diluted HCl to form treprostinil. *See* '117 Patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. In view of the known fact that purification by chromatography is not favored for large-scale industrial production, a POSA would have been motivated to address the problem by applying an obvious form of purification, salt crystallization, to form known salt forms of treprostinil.

As discussed below in Watson's invalidity charts, each step of independent claims 1 and 9 was known and disclosed in the prior art, and it would have been obvious to a POSA to combine these well-known and standard steps to synthesize treprostinil.

Step (a) – Alkylation: The prior art discloses alkylation of benzindene triol with an alkylating agent to produce benzindine nitrile. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Such alkylation reactions adding $ClCH_2CN$ for subsequent hydrolysis to the carboxylic acid were well-known in the art. *See e.g.*, Lin 1987 p. 5595; Aristoff 1985 p. 7971; McManus 1959 pp. 1465-1467.

Step (b) – Hydrolysis: The prior art discloses the hydrolysis of benzindene nitrile. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Such alkylation reactions adding $ClCH_2CN$ and then subsequent hydrolysis to the carboxylic acid compound were well-known in the art. *See e.g.*, Lin 1987 p. 5595; Aristoff 1985 p. 7971; McManus 1959 pp. 1465–67.

Step (c) – formation of salt with base B: The prior art discloses the synthesis of treprostinil. As noted above, the prior art further describes the well-known technique of purification by crystallization or recrystallization. *See, e.g.*, Monson 1971 pp. 181–83; Harwood 1989 pp. 127–34; Pavia 1998 p. 648; Eliel 1994 p. 322; *see also* Jones 2000 pp. 153–55; Sorrell 1999 pp. 755–57; Priscinzano 2002 pp. 4371–74; Ohno 2005 pp. 5279–94, compound 7; Burk 2003 pp. 5731–34; PDR 2005 Bicillin® L-A. Moreover, the prior art teaches a POSA that treprostinil can be crystallized, and that the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051], figures 15–22; Moriarty 2004 p. 1892 compound 7, p. 1902. The prior art also discloses that other physiologically acceptable salts of treprostinil

include salts derived from bases, such as ammonia, N-methyl-D-glucamine, magnesium, arginine and lysine. *See* Wade 2005 para. [0024].

Step (d) – optional reaction of the salt with acid to form the neutral compound: Step (d) is optional, but the prior art teaches a POSA that salts of treprostinil could be reacted with diluted HCl acid to form treprostinil. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Therefore, it would have been obvious to react the salt formed during the crystallization step with an acid to form treprostinil.

Indeed, Steps (c) and (d) of Claims 1 and 9 disclose standard well-known organic chemistry techniques for purification of a carboxylic acid, such as treprostinil acid. The formation of a carboxylate salt, by the addition of a weak base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in steps (c) and (d), was a well-known purification technique. Such techniques were included in introductory organic chemistry textbooks, well before the December 17, 2007. For example, Wiberg 1960, an organic chemistry lab textbook from 1960 states:

> A typical example is the purification of a water-insoluble solid carboxylic acid by dissolving it in sodium hydroxide solution, filtering, precipitating the compound by the addition of acid. A similar procedure may be used with amines: dissolve the compound in acid and precipitate it with a base. These procedures usually work quite well in that they utilize a chemical reaction to aid in separation from nonacidic or nonbasic impurities.

(Wiberg, 1960 p. 6); *see also* Schoffstall 2004 at pgs. 3-40 (describing an experiment in which carboxylic acid is separated from neutral and basic organic compounds by conversion to a salt; addition of an acid, such as HCl, then regenerates the carboxylic acid, which can then be filtered or extracted into an organic solvent).

More specifically, contacting a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt, followed by the addition of a strong acid to regenerate the

carboxylic acid, was well-known in the prior art. For example Phares 2005 discloses that the preparation of treprostinil diethanolamine includes the step of adding and dissolving diethanolamine (*i.e.*, a base) to treprostinil that is dissolved in a 1:1 molar ratio mixture of ethanol:water. (Phares 2005 p. 24). This treprostinil diethanolamine can be further precipitated and purified to form the purer and more stable crystal form called "Form B." (*Id.* pp. 85-93). *See also* Kawakami at pg. 6 (disclosing the preparation and use of dicyclohexylamine (*i.e.*, a base) to form a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, in order to purify the methanoprostacyclin); Ege 1989 at pg. 8 (disclosing that sodium benzoate (*i.e.*, a carboxylate salt) can be converted back to benzoic acid (*i.e.*, a carboxylic acid) by treatment with the acid HCl. (*Id.* pg. 8).

Dependent claims 2 and 10 claim the product of claims 1 and 9, respectively, wherein the purity of compound is at least 99.5%. These claims are rendered obvious for the same reasons as stated above. Additionally, Moriarty 2004 discloses 99.7% purity for treprostinil. p. 1902.

Dependent claim 3 claims the product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$. This claim is rendered obvious for the same reasons as above. Additionally, the prior art discloses that the alkylating agent is $ClCH_2CN$. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

Dependent claim 4 claims the product of claim 1, wherein the base in step (b) is KOH or NaOH. This claim is rendered obvious for the same reasons as above. Additionally, the prior art discloses that the base in step (b) is KOH. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

Dependent claim 5 claims the product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine,

magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above. Also, the claim includes commonly known and utilized bases, and it would have been a matter of routine experimentation for a POSA to choose the bases included. In particular, the prior art specifically discloses that physiologically acceptable salts of treprostinil include salts derived from these bases. *See* Wade 2005 para. [0024]. Furthermore, the prior art also discloses that treprostinil can be crystallized and the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [0051]. Thus, it would have been obvious for a POSA to choose a base that was already known to form a salt with treprostinil.

Dependent claim 6 claims the product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4. This claim is rendered obvious for the same reasons as above. Additionally, the prior art discloses salts of treprostinil could be reacted with diluted HCl to form treprostinil. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Therefore, it would have been obvious to react the salt formed during the crystallization step with diluted HCl to form treprostinil.

Dependent claim 7 claims the product of claim 1, wherein Y_1 is —CH_2CH_2—; M_1 is α-OH:β-H or α-H:β-OH; —$C(L_1)$-R_7 taken together is —$(CH_2)_4CH_3$; and w is 1. This claim is rendered obvious for the same reasons as above.

Dependent claim 8 claims the product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a). This claim is rendered obvious for the same reasons as above.

Dependent claim 11 claims the product of claim 9, wherein the alkylating agent is $ClCH_2CN$. This claim is rendered obvious for the same reasons as above. Additionally, the

prior art discloses that the alkylating agent is $ClCH_2CN$. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

Dependent claim 12 claims the product of claim 9, wherein the base in step (b) is KOH. This claim is rendered obvious for the same reasons as above. Additionally, the prior art discloses that the base in step (b) is KOH. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902.

Dependent claim 13 claims the product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above. Also, the claim includes commonly known and utilized bases, and it would have been a matter of routine experimentation for a POSA to choose the bases included. In particular, the prior art specifically teaches a POSA that physiologically acceptable salts of treprostinil include salts derived from these bases. *See* Wade 2005 para. [0024]. Furthermore, the prior art also discloses that treprostinil can be crystallized and the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051]. Thus, it would have been obvious for a POSA to choose a base that was already known, like those listed in claim 13, to form a salt with treprostinil.

Claim 14 claims the product of claim 9, wherein the base B is diethanolamine. This claim is rendered obvious for the same reasons as above. The prior art also discloses that treprostinil can be crystallized and the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051]. Thus, it would have been obvious for a POSA to choose a base that was already known to form a salt with treprostinil.

Claim 15 claims the product of claim 9, wherein the acid in step (d) is HCl. This claim is rendered obvious for the same reasons as above. Additionally the prior art discloses that salts of treprostinil could be reacted with diluted HCl to form treprostinil. *See* '117 patent col. 20, l. 10–col. 21, l. 12; Moriarty 2004 p. 1892 compound 7, p. 1902. Therefore, it would have been obvious for a POSA to react the salt formed during the crystallization step with diluted HCl to form treprostinil.

Dependent claim 16 claims the product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a). This claim is rendered obvious for the same reasons as above.

Dependent claim 17 claims the product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above. Also, the claim includes commonly known and utilized bases, and it would have been a matter of routine experimentation for a POSA to choose the bases included. In particular, the prior art specifically discloses that physiologically acceptable salts of treprostinil include salts derived from these bases. *See* Wade 2005 para. [0024]. Furthermore, the prior art also discloses that treprostinil can be crystallized and the diethanolamine salt of treprostinil is particularly preferred. *See* Phares 2005 para. [00051]. Thus, it would have been obvious for a POSA to choose a base that was already known to form a salt with treprostinil.

Dependent claim 18 claims the product of claim 17, wherein the base B is diethanolamine. This claim is rendered obvious for the same reasons as above. Further, the prior art discloses that treprostinil can be crystallized, and that the diethanolamine salt of

treprostinil is particularly preferred. *See* Phares 2005 para. [00051]. Thus, it would have been obvious for a POSA to choose a base that was already known to form a salt with treprostinil.

Dependent claim 19 claims the product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 in step (c) is selected from the group consisting of ammonia[,] N-methyl glucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above.

Dependent claim 20 claims the product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. This claim is rendered obvious for the same reasons as above.

Dependent claim 21 claims the product of claim 1, wherein step (d) is performed. This claim is rendered obvious for the same reasons as above.

Dependent claims 22 claims the product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d). This claim is rendered obvious for the same reasons as above. Additionally, Moriarty 2004, on p. 1902 discloses that "[c]ompound 7 was identical in all respects to an authentic sample of UT-15" and as disclosed on p. 1890, UT-15 is Remodulin (Treprostinil Sodium). Furthermore, the '117 patent teaches a POSA the claimed compound in salt form. *See* '117 patent col. 20, l. 10–col. 21, l. 12. Phares 2005 further teaches a POSA the claimed compound in at least two salt forms and additionally discloses that the sodium salt of the compound was being commercially sold as Remodulin® which is an FDA approved treatment. Phares 2005 para. [0051].

Plaintiffs have not set forth any evidence of secondary considerations of non-obviousness, and Watson is not aware of any such secondary considerations that, when

considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '393 patent. If UTC relies on any secondary considerations of non-obviousness, Watson reserves the right to supplement its contentions.

As explained above, the claims would have been obvious in view of a host of prior art references because the steps described in the claims were well-known procedures that would have been obvious to apply. Consequently, there are numerous different combinations of these prior art references and many exemplary references that teach each standard step. By way of example, the following combinations render the asserted claims obvious:

- Moriarty 2004 in combination with Monson 1971, Eliel 1994, Kawakami 1981, Ege 1989, and/or Phares 2005
- Moriarty 2004 in combination with Monson 1971, Jones 2000, and/or Wade 2005
- '117 patent in combination with Monson 1971, Eliel 1994, Kawakami 1981, Ege 1989, and/or Phares 2005
- '117 patent in combination with Monson 1971, Jones 2000, and/or Wade 2005
- Remodulin® in combination with Monson 1971, Eliel 1994, Kawakami 1981, Ege 1989, and/or Phares 2005
- Remodulin® in combination with Monson 1971, Eliel 1994, Jones 2000 and/or Wade 2005
- Moriarty 2004 and/or the '117 patent in combination with Phares 2005 and/or Kawakami 1981
- Moriarty 2004 and/or the '117 patent in combination with Phares 2005 and/or Kawakami 1981 and in further view Ege 1989

A POSA would have been motivated to combine the teachings of these references with a reasonable expectation of success in light of the fact that each of the references taught well known synthesis techniques for the synthesis of compounds such as treprostinil. In addition, Watson's invalidity charts set forth where each prior art reference discloses the limitations of the asserted claims.

Watson reserves the right to set forth additional such examples as discovery continues.

3. The '393 Patent Is Invalid For Obviousness-Type Double Patenting Over the '117 Patent.

The '393 patent is invalid for obviousness-type double patenting over the '117 patent. The doctrine of obviousness-type double patenting forbids obtaining more than one patent on the same invention, and is grounded in Section 101 of the Patent Act. 35 U.S.C. § 101 ("Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, . . . may obtain a patent therefor."); *see also In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985); *Boehringer Ingelheim Int'l. GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1346 (Fed. Cir. 2010); *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001). Through judicial interpretation, "this prohibition has been extended to preclude a second patent on an invention which 'would have been obvious from the subject matter of the claims in the first patent, in light of the prior art.'" *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 940 (Fed. Cir. 1992) (quoting *In re Longi*, 759 F.2d at 893). Accordingly, a claim in an issued patent that is not "patentably distinct" from an earlier issued claim in a separate patent is invalid for non-statutory double patenting, so long as the patents have at least one common inventor. *See, e.g.*, *Eli Lilly & Co.*, 251 F.3d at 970-71; *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377-78 (Fed. Cir. 2003); *see also In re Hubbell*, 709 F.3d 1140, 1145-46 (Fed. Cir. 2013) (requiring only an "overlap in the inventors," not "identity of inventors"); *In re Longi*, 759 F.2d at 892.

An obviousness-type double patenting analysis begins by comparing the invention defined by the properly construed claims of the earlier-expiring patent (the "reference claims") with the claims of the later-expiring patent in a manner analogous to an anticipation analysis under 35 U.S.C. § 102 or an obviousness analysis under 35 U.S.C. § 103, except that the reference claims rather than the patent disclosure are the subject of the comparison. *See In re Braithwaite*, 379 F.2d 594, 597 n.4 (C.C.P.A. 1967). A later-expiring claim is invalid where the alleged invention "would have been obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill of the art and prior art other than the invention claimed in the [reference] patent." *In re Longi*, 759 F.2d at 893 (quoting *In re Zickendraht*, 319 F.2d 225, 232 (C.C.P.A. 1963) (Rich, J., concurring)). The supporting patent disclosures may be relevant for interpreting the scope and meaning of the reference and rejected claims. *In re Vogel*, 422 F.2d 438, 441-42 (C.C.P.A. 1970) ("[[T]he patent disclosure] may be used as a dictionary to learn the meaning of terms in a claim"); *see also Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1378-79 (Fed. Cir. 2012); *In re Avery*, 518 F.2d 1228, 1232 (C.C.P.A. 1975); *In re Zickendraht*, 319 F.2d at 228.

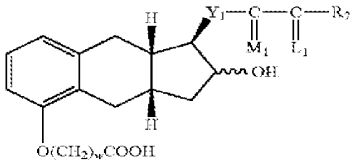
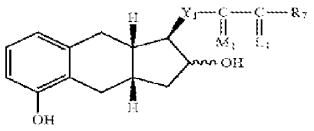
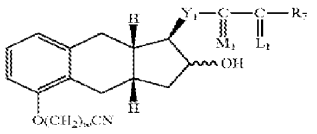
Here, the '117 and '393 patents share at least one common inventor (Raju Penmasta) and the same owner (United Therapeutics Corporation). The claims of the '117 patent are directed to the same subject matter, treprostinil and its pharmacologically acceptable salt form. *See* '117 patent, claims 1–4. There should be no dispute that the claims of the '393 patent, like the claims of the '117 patent, are also directed to the product treprostinil and its pharmacologically acceptable salt form. *See* '393 patent, claims 1–22. Any limitations not expressly claimed in the '117 patent would have been either inherent in the claims of the '117 patent or obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill of the

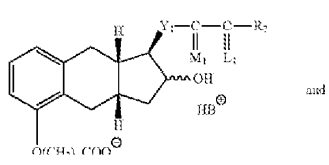
POSA and the prior art. Therefore, for the reasons explained in more detail above in the anticipation and obviousness analyses, the '393 patent is invalid for obviousness type double patenting over the '117 patent.

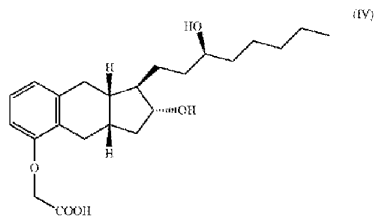
4. Claims 1-22 Of The '393 Patent Are Not Enabled Or Fail To Meet The Written Description Requirement.

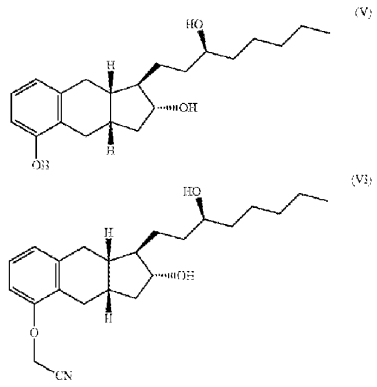
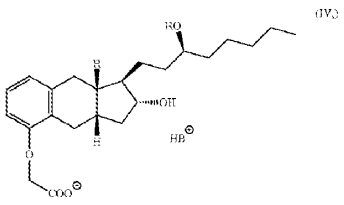
As discussed in the previous sections, it would have been obvious for a POSA to practice the claimed invention by applying known procedures described in the prior art. But if plaintiff contends that it would have required undue experimentation for a POSA to apply these prior art procedures to obtain the claimed methods (for example it would have required undue experimentation to find particular bases or a particular alkylating agent), the claims would then be invalid for lack of an enabling description. To the extent that plaintiff contends that certain bases or reaction conditions, for example, are unique and that undue experimentation would have been required to practice the claimed method, the claims of the '393 patent are not enabled or fail to meet the written description requirement. Moreover, to the extent that plaintiff takes a broad claim construction position and asserts infringement of certain processes and resulting intermediates—such as the use of intermediates or processes that are not sufficiently disclosed, taught or claimed in the '393 patent, including the intermediates and processes that are used to make the treprostinil used in Watson's ANDA product— the claims of the '393 patent are not enabled and/or lack written description.

C. The '393 Patent

	Claim Term	Prior Art Where Limitation Is Found
1	A product comprising a compound of formula I  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising (a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III, (II)  (III)  wherein w=1, 2, or 3; Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_{2)m}$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted	• '117 patent at col. 20, l. 10-col. 21, l. 12, claims 1-4 • Phares 2005 at pp. [0004], [0024], [0041-42], [0051], [0085-93], [99], figures 15-22, claim 49 • Remodulin® • Remodulin® Label • Moriarty 2004 at Abstract, pp. 1892, 1895, compound 7, p. 1902 • '075 patent at col. 14, ll. 5-43, Example 33 • Wade 2005 at paras. [0021], [0024] • Kawakami 1981 at 6 • Monson 1971 at pp. 181-183, 185 • Eliel 1994 at p. 322 • Jones 2000 at pp. 153-155 • Lin 1987 at p. 5595 • Aristoff 1985 at p. 7971 • McManus 1959 at pp. 1465-1467 • Ege 1989 at 8 • Arumugan 2005 at p. 319 • Yu 2006 at p. 832 • Harwood 1989 at pp. 127-134 • Pavia 1998 at p. 648 • Sorrell 1999 at pp. 755-758 • Priscinzano 2002 at pp. 4371-4374 • Ohno 2005 at pp. 5279-5294, compound 7 • Burk 2003 at pp. 5731-5734 • Wiberg, 1960 p. 6 • Schoffstall 2004 at 3-40 • PDR 2005 Bicillin® L-A

	Claim Term	Prior Art Where Limitation Is Found
	phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different, (3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, (4) cis-CH=CH–CH_2–CH_3, (5) –$(CH_2)_2$–CH(OH)–CH_3, or (6) –$(CH_2)_3$–CH=C$(CH_3)_2$; –C(L_1)–R_7 taken together is (1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro, (b) hydrolyzing the product of formula III of step (a) with a base, (c) contacting the product of step (h) with a base B to form a salt of formula I_s.  (I$_s$) and (d) optionally reacting the salt	

	Claim Term	Prior Art Where Limitation Is Found
	formed in step (c) with an acid to form the compound of formula I.	
2	The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.	• *See* prior art cited above with respect to claim 1
3	The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	• *See* prior art cited above with respect to claim 1
4	The product of claim 1, wherein the base in step (b) is KOH or NaOH.	• *See* prior art cited above with respect to claim 1
5	The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 1
6	The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.	• *See* prior art cited above with respect to claim 1
7	The product of claim 1, wherein Y_1 is $\_CH_2CH_2\_$; M_1 is α-OH:β-H or α-H:β-OH; $\_C(L_1)\text{-}R_7$ taken together is $\_(CH_2)_4CH_3$; and w is 1.	• *See* prior art cited above with respect to claim 1
8	The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	• *See* prior art cited above with respect to claim 1
9	A product comprising a compound having formula IV  (IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising (a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula	• '117 patent at col. 20, l. 10-col. 21, l. 12, claims 1-4 • Phares 2005 at pp. [0004], [0024], [0041-42], [0051], [0085-93], [99], figures 15-22, claim 49 • Remodulin® • Remodulin® Label • Moriarty 2004 at Abstract, pp. 1892, 1895, compound 7, p. 1902 • '075 patent at col. 14, ll. 5-43, Example 33 • Wade 2005 at paras. [0021], [0024] • Kawakami 1981 at 6 • Monson 1971 at pp. 181-183, 185 • Eliel 1994 at p. 322 • Jones 2000 at pp. 153-155 • Lin 1987 at p. 5595 • Aristoff 1985 at p. 7971 • McManus 1959 at pp. 1465-1467

	Claim Term	Prior Art Where Limitation Is Found
	VI,  (b) hydrolyzing the product of formula VI of step (a) with a base, (c) contacting the product of step (h) with a base B to form a salt of formula IV_s, and  (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	• Ege 1989 at 8 • Arumugan 2005 at p. 319 • Yu 2006 at p. 832 • Harwood 1989 at pp. 127-134 • Pavia 1998 at p. 648 • Sorrell 1999 at pp. 755-758 • Priscinzano 2002 at pp. 4371-4374 • Ohno 2005 at pp. 5279-5294, compound 7 • Burk 2003 at pp. 5731-5734 • Wiberg, 1960 p. 6 • Schoffstall 2004 at 3-40 • PDR 2005 Bicillin® L-A
10	The product of claim 9, wherein the purity of product of step (d) is at least 99.5%.	• *See* prior art cited above with respect to claim 9
11	The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.	• *See* prior art cited above with respect to claim 9
12	The product of claim 9, wherein the base in step (b) is KOH.	• *See* prior art cited above with respect to claim 9
13	The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine,	• *See* prior art cited above with respect to claim 9

	Claim Term	Prior Art Where Limitation Is Found
	and diethanolamine.	
14	The product of claim 9, wherein the base B is diethanolamine.	• *See* prior art cited above with respect to claim 9
15	The product of claim 9, wherein the acid in step (d) is HCl.	• *See* prior art cited above with respect to claim 9
16	The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	• *See* prior art cited above with respect to claim 9
17	The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysinc, L-arginine, tricthanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 9
18	The product of claim 17, wherein the base B is diethanolamine.	• *See* prior art cited above with respect to claim 9
19	The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 1
20	The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	• *See* prior art cited above with respect to claim 9
21	The product of claim 1, wherein step (d) is performed.	• *See* prior art cited above with respect to claim 1
22	The product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).	• *See* prior art cited above with respect to claim 1

Dated: December 11, 2015

CONNELL FOLEY LLP
Attorneys for Defendant Watson Laboratories, Inc.

By: */s/ Liza M. Walsh*
Liza M. Walsh

Of Counsel:
Michael K. Nutter (admitted *pro hac vice*)
Kurt A. Mathas (admitted *pro hac vice*)
WINSTON & STRAWN LLP
35 W. Wacker Drive
Chicago, IL 60601-9703
(312) 558-5600

CERTIFICATION OF SERVICE

I certify that on the 11th day of December, 2015, a true and correct copy of the foregoing, **DEFENDANT WATSON LABORATORIES, INC.'S INVALIDITY CONTENTIONS** was served upon the following counsel by e-mail:

William J. O'Shaughnessy
McCARTER & ENGLISH LLP
Four Gateway Center
100 Mulberry Street
Newark, New Jersey 07102
(973) 639-2094

Douglas Carsten
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real
Suite 200
San Diego, California 92130

Veronica S. Ascarrunz
WILSON SONSINI GOODRICH & ROSATI
1700 K Street, NW
Suite 500
Washington, D.C. 20006

William C. Jackson
BOIES, SCHILLER & FLEXNER LLP
5301 Wisconsin Avenue, NW
Washington, D.C. 20015

Attorneys for Plaintiff United Therapeutics Corporation

/s/ Liza M. Walsh
Liza M. Walsh
lwalsh@connellfoley.com

Dated: December 11, 2015

Electronic Acknowledgement Receipt	
EFS ID:	28022515
Application Number:	14849981
International Application Number:	
Confirmation Number:	6653
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh BATRA
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Strawderman
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1581
Receipt Date:	10-JAN-2017
Filing Date:	10-SEP-2015
Time Stamp:	14:34:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDS.pdf	150742 86e420af4f40836ccacf18c43a57c56164e67b52	yes	3

	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	3	
Warnings:					
Information:					
2	Other Reference-Patent/App/Search documents	WatsonInvContRedacted.pdf	352468 4af6e6411f4f38b2bfe1b4d969251912debd3a50	no	35
Warnings:					
Information:					
		Total Files Size (in bytes):	503210		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Application No.:	14/849,981
Filing Date:	9/10/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation No.:	6653

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a

competent reference any document submitted herewith. However, in accordance with MPEP § 609.04(a)(I), Applicant hereby states that for items for which the date of publication supplied does not include the month of publication, the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue.

CONCISE EXPLANATION OF RELEVANCE

An invalidity contention filed against parent U.S. Patent 8,497,393 is filed with this submission. Certain information not related to the '393 patent is redacted.

TIMING OF THE DISCLOSURE

The listed document is being submitted in compliance with 37 CFR §1.97(b), before the mailing of a first Office action after the filing of a RCE.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account Number 19-0741.

Respectfully submitted,

Date Jan. 10, 2017

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	14/849,981
Appl. Filing Date:	9/10/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6653

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application. This RCE and the enclosed items listed below are being filed prior to the earliest of: (1) payment of the issue fee (unless a petition under 37 C.F.R. § 1.313 is granted); (2) abandonment of the application; or (3) the filing of a notice of appeal to the U.S. Court of Appeals for the Federal Circuit under 35 U.S.C. §141, or the commencement of a civil action under 35 U.S.C. §145 or §146 (unless the appeal or civil action is terminated).

1. Submission **required** under 37 C.F.R. §1.114: (check items that apply)

   a. Previously submitted:

[ ] Please enter and consider the amendment and/or reply previously filed on __.

[ ] Please consider the Affidavit(s)/Declaration(s) previously filed on __ but not considered.

[ ] Please consider the arguments in the Appeal Brief or Reply previously filed on __.

[ ] Other Documents .

b. Enclosed are:

[**X**] Amendment/Reply.

[**X**] Terminal Disclaimer.

[**X**] Information Disclosure Statement, Form PTO/SB/08

Miscellaneous:

[ ] Suspension of action of the above-identified application is requested under 37 C.F.R. § 1.103(c) for a period of __ months.

The filing fee is calculated below at the large entity rate:

	Claims as Amended		Previously Paid For	Extra Claims Present		Rate		Fee Totals
RCE Fee 1.17(e):						$1,200.0 0	=	$1,200.00
Total Claims:	9	-	20	= 0	x	$80.00	=	$0.00
Independents	2	-	3	= 0	x	$420.00	=	$0.00
First presentation of any Multiple Dependent Claims:					+	$780.00	=	$0.00
CLAIMS FEE TOTAL:							=	$1,200.00

[ ] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[ ]	Extension for response filed within the first month:	$200.00	0	$0.00
[ ]	Extension for response filed within the second month:	$600.00		$0.00
[ ]	Extension for response filed within the third month:	$1,400.00		$0.00
[ ]	Extension for response filed within the fourth month:	$2,200.00		$0.00
[ ]	Extension for response filed within the fifth month:	$3,000.00		$0.00
		EXTENSION FEE SUBTOTAL:		$0.00
		EXTENSION FEE ALREADY PAID:	-	$0.00
		EXTENSION FEE TOTAL		$0.00
		CLAIMS AND EXTENSION FEE TOTAL:		$1,200.00
		Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)		$0.00
		Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)		$0.00
		Publication Fee		$0.00
[ ]	Suspension of action requested under 37 C.F.R. § 1.103(c)			$0.00
		TOTAL FEE:		$1,200.00

The above-identified fees of $1,200.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date DEC 29 2016

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	14/849,981
Filing Date:	9/10/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6653

REPLY UNDER 37 C.F.R. § 1.114

Mailstop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the outstanding Final Office Action mailed on November 30, 2016, and is accompanied by a Request for Continued Examination.

The listing of claims begins on page 2 of this document.

Remarks begin on page 4 of this document.

Listing of Claims:

1. (Previously Presented) A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

2. (Previously Presented) The pharmaceutical composition of claim 1, wherein the salt is isolated in crystalline form.

3. (Canceled).

4. (Previously Presented) The pharmaceutical composition of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

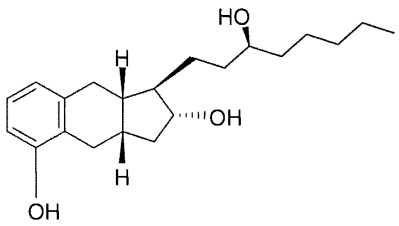
5. (Previously Presented) The pharmaceutical composition of claim 4, wherein the base is diethanolamine.

6. (Previously Presented) The pharmaceutical composition of claim 1, wherein the base is combined with treprostinil that has not been previously isolated.

7. (Previously Presented) The pharmaceutical composition of claim 1, wherein the isolated salt is stored at ambient temperature.

8. (Previously Presented) The pharmaceutical composition of claim 1, which is a pharmaceutical solution.

9. (Previously Presented) A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising alkylating a triol intermediate of the formula:



hydrolyzing the resulting compound to form treprostinil, forming a salt of treprostinil stable at ambient temperature, storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage, wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof.

10. (Previously Presented) A pharmaceutical product prepared by the process of claim 9.

11. (Previously Presented) The process as claimed in claim 9, wherein forming the salt of treprostinil stable at ambient temperature is performed by adding diethanolamine to treprostinil.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

Status of Claims

Claims 1, 2, and 4-11 are pending.

Double Patenting

Claims 1, 2, and 4-11 stand rejected as unpatentable on the ground of non-statutory double patenting over claims 24 and 26 of US Patent No. 8,242,305. Claims 1, 2, and 4-11 also stand provisionally rejected as unpatentable on the ground of non-statutory double patenting over claims 1-3 and 8-14 of co-pending Application No. 14/754,932, which was allowed on November 9, 2016. Without acquiescing in the correctness of the rejections, Applicants submit herewith a terminal disclaimer over the '305 patent and the '932 application to obviate the double patenting rejections.

Concluding Remarks

Applicants believe that the application is in condition for allowance. Favorable reconsideration is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date DEC 29 2016

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

TERMINAL DISCLAIMER	Docket Number (Optional) 080618-1581

In re Application of: United Therapeutics Corporation

Application No.: 14/849,981

Filed: 9/10/2015

For: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

The applicant, United Therapeutics Corporation, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration dates of the full statutory term of prior patent No. **8,242,305** as the term of said prior patent is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent is commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later: expires for failure to pay a maintenance fee; is held unenforceable; is found invalid by a court of competent jurisdiction; is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321; has all claims canceled by a reexamination certificate; is reissued; or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

And

The applicant, United Therapeutics Corporation, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on co-pending U.S. Patent Application No. **14/754,932, filed June 30, 2015**, as such term is defined in 35 U.S.C. 154 and 173, and as the term of any patent granted on said co-pending application may be shortened by any terminal disclaimer filed prior to the grant of any patent on said co-pending application. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on said co-pending application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of any patent granted on said co-pending application, as the term of any patent granted on said co-pending application may be shortened by any terminal disclaimer filed prior to the grant of any patent on said co- pending application, in the event that any such patent granted on said co-pending application: expires for failure to pay a maintenance fee is held unenforceable; is found invalid by a court of competent jurisdiction; is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1,321; has all claims canceled by a reexamination certificate; is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 35264

Signature — Date: DEC 29 2016

Stephen B. Maebius
Typed or printed name

(202) 672-5574
Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

4838-2214-2753.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR 2016-00006

Patent No. 8,497,393B2

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE TO PETITION

37 C.F.R. § 42.23

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

Page

Petitioner SteadyMed, Ltd. submits this reply pursuant to 37 C.F.R. § 42.23.

I. SUMMARY OF THE ARGUMENT

As SteadyMed explained in its Petition, purifying by crystallization is taught in undergraduate chemistry courses: it's Organic Chemistry 101. Even Patent Owner United Therapeutics' (UT) expert recognizes this fact:

> Q: How long has crystallization been around as a method of purification?
>
> A: I don't know how long it's been around.
>
> Q: Before 2007?
>
> A: Oh, yes.
>
> Q: Did you learn about it when you were in college at the university?
>
> A: Yes, I did. […]
>
> Q: And when did you go to college?
>
> A: In 1968 I started. In 1968.
>
> ...
>
> Q: ... But how far back does doing that process you just described, how far back does that go?
>
> The Witness: Decades.

(Ex. 2058, 175:19-176:22, 179:11-17).

Even though the purification process claimed in the '393 Patent is so trivial an undergraduate student in the late 1960s would know how to do it, UT maintains that a product made by the '393 Patent process is "materially and functionally" distinct from products of the prior art Moriarty (Ex. 1004) and Phares (Ex. 1005) references. UT relies on 175 measurements showing the average purity of products

made by one process included in the '393 Patent's claims is [redacted]. (Resp., 34; Ex. 2020, ¶¶ 94-99.) And it relies on measurements alleged to show that one version of the Moriarty process produced an average purity of 99.0%. (Ex. 2020, ¶ 98.) Except that the 99.0% value is a distortion of this data, that required UT, and its attorneys who actually performed this calculation (Ex. 2059, 79:3-10, 81:2-13, 104:14-20), to select 10 data points from another source to lower the purity results (*id.*, 112:22-113:20).

As confirmed by Dr. Williams (*id.*, 218:3-219:16), a fair analysis of the data without the 10 data points shows that the value of [redacted], reported in [redacted] itself, is consistent with UT's purity measurements for batches made according to the Moriarty process (Ex. 2059, 219:17-20). Data purporting to show a lower purity, including UT's Walsh Declaration, mischaracterizes the Moriarty process' purity.

UT's expert Dr. Williams initially believed UT's counsel's calculations. But Dr. Williams conceded that: (1) he performed no calculations on this data himself; (2) he only "spot-checked" the data that was selected by counsel; and (3) he "did not know" whether the 10 data points were produced under the Moriarty process. (Ex. 2059, 81:2-13; 82:1-11; 103:24-104:20; 112:24-114:2). Accordingly, no weight should be afforded to his declaration, or UT's reliance on his declaration. Dr. Williams agreed that SteadyMed's calculation of [redacted] purity was correctly

performed, and should be relied upon (*id.*, 217:11-219:20). This corrected calculation supported what SteadyMed stated in its Petition: that the [redacted] showed that treprostinil made by Moriarty was of similar purity, and similarly, the particular example of treprostinil diethanolamine salt made by Phares was as pure as the examples in the '393 Patent. This calculation confirms that the '393 Patent claims merit cancellation.

UT relies on these now-discredited differences in purity values to argue there was a "long-felt unmet need" for more pure treprostinil. (Resp., 12, 47-48; Ex. 2022, ¶¶ 70-72). But UT's long-felt-need expert Dr. Ruffolo concedes that the claims are not limited to treprostinil, nor treprostinil salt, but include hundreds of thousands of other compounds, for which UT provides no evidence regarding long-felt need or impurities. (Ex. 2059, 71:17-72:17; Ex. 2058, 234:16-235:17.) Except for those claims that are limited to treprostinil alone (only claims 10 and 15), or treprostinil diethanolamine salt (claims 14 and 17), Dr. Ruffolo is not offering an opinion that there is a long-felt need for any other claims. (Ex. 2058, 109:18-121:23.) And even for the products in claims 10, 14, 15, and 17, Dr. Ruffolo concedes that: (1) the FDA requires only a [redacted] purity level, which is *much lower* than any levels produced by the prior art, (Ex. 2058, 159:20-161:7); and, (2) the FDA would allow treprostinil batches produced by the Moriarty process to be sold, (Ex. 2058, 179:23-180:17), since Moriarty products are "highly, highly pure,"(*id.*

217:11-218:5). *See also* (Ex. 2059, 151:2-25).

UT devotes much of its Response to argue that the common patent claim terms "product" and "comprising" were improperly construed by the Board, and should not have their usual legally defined meaning. (Resp., 5, 13-15). UT contends these terms should have special meaning in the '393 Patent, although UT's expert concedes that a plain and ordinary meaning should apply, and that the patent and prosecution history contain no language that redefine these terms. (Ex. 2059, 248:24-249:13.) UT cannot show "clear and unambiguous disclaimer" of the plain meaning of these terms.

II. UT MISCHARACTERIZES ITS OWN DATA.

A. UT's Moriarty Batches Have an Average Purity of [redacted].

In its Response and supporting Williams Declaration (Ex. 2020), UT uses Dr. Williams to present the average purity of treprostinil made by the Moriarty prior-art method, in order to contrast it to the '393 Patent product. Specifically, Dr. Williams relied on 56 batch Certificates of Analysis of treprostinil that were allegedly produced under the Moriarty method (*see* Ex. 2020, Appx. A), and contended that the treprostinil product produced by the '393 Patent process had a higher average purity than the Moriarty product ([redacted]% v. 99.05%), and thus "the treprostinil product of the '393 patent has an average purity that is [redacted] higher than that of Moriarty's." (Ex. 2020, ¶ 98; Resp., 4, 34, and 45). But UT's counsel

selected batches to include in its calculation, and cherry-picked 10 batches to drive down the average purity value of the Moriarty product from [redacted] to 99.05%. These 10 "development" batches, as UT calls them, come from a separate source, and may not have been produced by the Moriarty method. When instead, the 46 "production" batches made by the Moriarty method, and under the same analytical methods, are examined, the correct conclusion is that the Moriarty method produces the *same product as the product of the '393 Patent*: a product with [redacted] purity, just as Moriarty himself reported in his JOC article (Ex. 1004).

Because Dr. Williams and Dr. Ruffolo relied on UT's counsel's incorrect calculation, UT's experts' opinions on differences between the Moriarty product and the '393 Patent product should be disregarded.

1. UT's Data Sources.

UT attaches three exhibits that contain purity information for treprostinil made under the Moriarty method: Exhibits 2036, 2052, and 2053. (Ex. 2020, Appx. A.) Exhibit 2036 is the main source of this data, and contains 44 Certificates of Analysis from either Magellan Laboratories or Cardinal Health for commercial lots of treprostinil. Exhibit 2053 is UT's NDA Annual Report from 2003, which summarizes Certificates of Analysis and purity information from 32 commercial lots, including 30 lots that were already included in Exhibit 2036, plus two additional lots not included in Exhibit 2036. Thus, Exhibits 2036 and 2053 contain

purity data for 46 lots of treprostinil.

Exhibit 2052 is an undated but older document entitled "UT-15 Injection Drug Substance Volume 1.2 Chemistry, Manufacturing and Controls, NDA 21-272," and appears to be a portion of UT's original New Drug Application to sell treprostinil. It contains a summary of purity analyses for 13 lots of treprostinil made by third party companies called "[redacted]" "[redacted]," and "[redacted]" (Ex. 2052, 25-30.) The two [redacted] lots, made in 1986, were not included in UT's Appendix A. "These lots were manufactured by [redacted] using a slightly different route of synthesis." (*id.*, at 25 n.4.) [redacted] was also not included in UT's Appendix A. [redacted], "which was deliberately spiked for use in toxicology studies," (*id.*, at 29 n.2) was included by UT, as were "[redacted], and [redacted] [which] were tested and released using different analytical procedures previously submitted," and for which "the listed specifications do not apply ...," (*id.*, at 25 n.3). The 10 samples selected from the 13 samples in Ex. 2052 were manufactured several years before Moriarty's 2004 Journal of Organic Chemistry article (Ex. 1004). As Dr. Williams confirmed, there is no information provided on what method was used to make these lots, other than the fact that the methods used for many of them were similar to methods [redacted] used in 1986. These 10 data points have purity values far below the values reported in Exhibits 2036 and 2053.

2. Are the 10 Batches Even Moriarty Samples?

The dates of manufacture and footnotes recorded in Exhibit 2052 associated with UT's 10 cherry-picked samples make it unlikely that they were representative of treprostinil made by the Moriarty process:

> Q You don't know the details of how all these lots were made?
>
> A No. I haven't seen the detailed batch records of what went into those lots.
>
> Q Okay. So you don't know whether or not these lots were made by the '393 process, the Moriarty process, the older Aristoff process; is that right?
>
> THE WITNESS: Um, you know, I -- I'd have to investigate further. I don't know.
>
> Q Right. You -- you don't know if any of these are from the Moriarty process? At least not the ones on page 25?
>
> A So the Moriarty paper came out in 2003.
>
> ...
>
> A So I don't think it's possible that any of these could have been made by Moriarty process just based on the dates.

(Ex. 2059, 112:20-113:20). While Dr. Williams contends that these 10 samples represent "development" batches included for "fairness" (*id.*, at 81:23-82:7), he had no explanation for why he included 10 development batches out of 56 samples for his analysis of Moriarty batches, but only 5 development batches out of 157 samples for his analysis of '393-Patent batches. (*Id.*, at 270:15-271:6).

3. 46 Known Moriarty Samples Average to [redacted].

Once the cherry-picked data points are eliminated, the average purity of the 46 remaining samples increases from 99.05% to [redacted]: *the same purity as the product produced by the '393 Patent process*. SteadyMed prepared an Excel spreadsheet containing these 46 data points (Ex. 1021), and had Dr. Williams review every data point and calculation at his deposition to confirm that the [redacted] number is correct, and consistent with the number reported in Ex. 1004:

> Q: Okay. So now that we've – now that you've checked every single data point and looked at the calculations, you agree with me that this calculation of the purity is fair and accurate?
>
> A: The overall purity. But this does not reflect impurity profile.
>
> Q: Yeah I understand. I'm just talking about the overall – the level of purity.
>
> A: Yes.
>
> […]
>
> Q: Okay. And so it is correct that for the samples from Exhibits 2036 and 20[5]3, the 46 samples, the average level of purity was [redacted] percent for the samples made under the Moriarty process?
>
> A: Yes.
>
> Q: Okay. That [redacted] value, that is consistent with the value that [redacted]?
>
> A: They're the same numbers.

(Ex. 2059, 218:25-219:20). By contrast with Dr. Williams' careful review of SteadyMed's calculation, Dr. Williams did not perform any calculations on UT's

data in Appendices A and B, having relied solely on counsel's work. (*id.*, 81:2-13; 82:1-11; 103:24-104:20; 112:24-114:2).

When the science is done properly, UT's data proves that Dr. Moriarty's [redacted] reported value in Ex. 1004 is correct.

4. Any Difference in "Impurity Profiles" is Meaningless.

UT still argues that the exact identity of the impurities generated by each process in the tiny [redacted] set of impurities matters. UT ignores that the '393 Patent claims contain at least hundreds of thousands of compounds (Ex. 2059, 71:17-22), for which none of the impurities have ever been characterized, (*id.*, 72:12-17). And the '393 Patent does not even characterize the impurities of treprostinil (Ex. 2058, 234:16-235:12), which UT maintains as a trade secret requiring a protective order, (Ex. 2058, 93:19-94:24, 233:5-12). As UT's expert Dr. Ruffolo conceded, "I see primarily purities of the parent compound, which is what I believe the invention is related to" and "so I see comparisons between the old process and new process with purities, but – but I don't see, unless I've missed it, I don't see the impurities." (Ex. 2058, 235:6-12.) Secret impurities not identified in the '393 patent for treprostinil, or for hundreds of thousands of other compounds, cannot make the claims patentable.

In any event, neither Dr. Williams nor Dr. Ruffolo opined that the impurity profile of treprostinil mattered:

Q: Do ... any of these particular impurities have deleterious biological consequences? [...]

A: I'm not a clinician, so I don't know.

Q: You don't know?

A: I don't know.

(Ex. 2059, 47:4-13; *see also* Ex. 2058, 257:22-258:9.)

Dr. Ruffolo agrees that both the prior-art and '393 Patent treprostinil are "highly, highly pure." (Ex. 2058, 217:24-218:5.) The FDA only requires [redacted] purity for treprostinil, so achieving higher purity is immaterial to the product, (Ex. 2058, 159:20-161:7), and Moriarty-process treprostinil was, and can still be, sold to the public, (Ex. 2058, 179:23-180:17). Where Moriarty and '393-Patent treprostinil have the same purity, as proven by the [redacted]-purity level, there are no functional differences between them, as Dr. Williams conceded. (Ex. 2059, 67:2-15.)

B. The Walsh Declaration Is Questionable.

During prosecution of the '393 Patent, UT relied on the Walsh Declaration, and differentiated the '393 Patent product from Moriarty's product by showing a "representative sample" of Moriarty product containing 0.6% impurities, which was contrasted with '393 Patent treprostinil diethanolamine salt and treprostinil having 0.1% and 0.2% impurities, respectively. (Ex. 1002 at 343-350.). As noted by UT, the '393 Patent claims were allowed after submission of the Walsh Declaration. (Resp., 5).

The 46 samples contained in Exhibits 2036 and 2053, and a new exhibit submitted by UT—Exhibit 2006—contradict the Walsh Declaration. As Dr. Winkler observed, the data in the Walsh Declaration was derived from a single sample, and significant batch-to-batch variations in the impurity profile of each batch of treprostinil could affect the results. (Ex. 1009, ¶ 66).

Dr. Winkler's concern is confirmed by UT's results from the 46 batches. For example, Moriarty Batch No. [redacted], dated January 25, 2004, and having a purity of [redacted] which is the [redacted] for these batches, had only [redacted]: [redacted]. (Ex. 2036, 5.) According to Dr. Walsh's June 4, 2013 Declaration, "treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application has only three impurities ...." (Ex. 1002, 348-49.) Moreover, "each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of 'Moriarty' at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of "Moriarty." (Ex. 1002, 349.) Yet Moriarty Batch No. [redacted] did not contain detectable amounts of any of these impurities either, proving that

Dr. Walsh could not make his conclusion.

UT told the FDA that treprostinil diethanolamine salt made in accordance with the '393 Patent "[redacted]." (Ex. 2006, 3-6.) Yet these impurities, supposedly removed by carrying out step (d) in the '393 Patent's claims, are not described in the Walsh Declaration, which instead presents "Impurities ... [Total Related Substances]" as 0.2% for the free acid, and 0.1% for the salt, (Ex. 1002, 348), meaning that the free acid is *less pure* than the diethanolamine salt, and not more pure as UT represented to the FDA in Exhibit 2006. Dr. Williams could not provide an explanation for this discrepancy (Ex. 2059, 199:6-18), which contradicts the Walsh Declaration.

III. DR. WILLIAMS' TESTIMONY CONFIRMS THAT PHARES ANTICIPATES CERTAIN '393 PATENT CLAIMS.

Phares (Ex.1005) makes the same treprostinil diethanolamine salt claimed in every claim of the '393 Patent where optional step (d) is not completed, as explained in SteadyMed's Petition and Dr. Winkler's Declaration (Ex. 1009, ¶¶ 44-71.) UT responds by rejecting the Board's claim construction, discussed later in this Reply, and with three factual arguments: (1) that SteadyMed cannot show that Phares used the Moriarty process, claimed in steps (a) and (b) of the '393 Patent's claims; (2) that SteadyMed cannot show that Phares' treprostinil diethanolamine

Form B salt has the same purity level as the '393 Patent's Form B salt; and (3) that HPLC Assay Analysis can measure purity better than 0.4%, even though Dr. Winkler pointed out that the error in UT's own equipment is at least 0.4%, (Ex. 1009, ¶ 70).

But Dr. Williams concedes that the process in Phares for making treprostinil's (-)-enantiomer carries out the same alkylation step (a) and hydrolysis step (b) in the '393 Patent's claims, thus disclosing these steps for treprostinil. And the attached Declaration of Robin D. Rogers (Ex. 1022), SteadyMed's polymorph expert, explains why the melting point of treprostinil diethanolamine salt Form B can be compared between the '393 Patent and Phares reference, and that the particular sample in Phares had at least the same purity as the '393 Patent's examples. Finally, UT's own data showed that the average purity of Moriarty samples was [redacted], proving that batch variation is at least [redacted] and UT's representation to the FDA stated that treprostinil purity will be maintained between [redacted], (Ex. 2006), proving a [redacted] variability applies to purity measurements.

A. Phares discloses steps(a) and (b) of the '393 Patent.

"Q. Okay. So what we see here is there's an alkylating step (a) and a hydrolyzing step (b) on page 42 of the Phares reference. A. Yes." (Ex. 2059, 190:16-19). On Phares page 42 (Ex. 1005), as Dr. Williams concedes in this testimony, steps (a) and (b) are carried out on the mirror image version of the

compounds described in the '393 Patent claims, and as Dr. Winkler explains, the Phares patent at page 42 states that the enantiomer procedure is the same procedure used to make "the commercial drug (+)-Treprostinil." (Ex. 1009 ¶ 56; Ex. 1005, 42.) Thus, in describing that the process for making both enantiomers uses steps (a) and (b), and explaining that the process for the (-)-enantiomer is merely a variation on the already known (+)-enantiomer process, Phares inherently discloses steps (a) and (b) to create the (+)-enantiomer.

B. Phares' Higher Melting Point Means It is at Least Equally Pure.

Dr. Winkler explained that since the Phares treprostinil diethanolamine salt Form B melted at 107°C, but the same Form B in the '393 Patent melted at around 106.6 °C, the Phares sample was necessarily as pure as the '393 Patent's samples. Dr. Williams, who is "not a polymorph expert," (Ex. 2059, 158:17-18; 156:25-157:2), contends nevertheless that the melting point of two samples of the same polymorph (crystal form) cannot be compared to determine their relative purities. (Ex. 2020 ¶ 75.) According to UT and Dr. Williams, how a polymorph is made, including what solvents are used, can affect its melting point, even if the polymorphs are identical. (Resp., 22-24; Ex. 2020 ¶ 75.)

As set forth in Dr. Rogers' Declaration (Ex. 1022, ¶¶ 49-52) and admitted by Dr. Williams, melting point is one of the most common ways to identify different polymorphs. (Ex. 2059, 158:20-25); *see also* Exs. 1024-1026. Dr. Williams

concedes that in the '393 Patent, treprostinil diethanolamine salt is identified as being Form B based solely on its melting point. (Ex. 2059, 170:24-171:3.) And Dr. Williams concedes that the same treprostinil diethanolamine salt polymorph—Form B—is presented in the Phares reference and '393 Patent. (*Id.*, 168:6-11).

While Dr. Williams relies on his "personal experience" observing different melting points for crystals made with different solvents, he conceded that he knew of no literature to support his opinion. (*Id.*, 184:22-185:2.) Dr. Williams conceded that the one article he relied upon in his declaration, Ex. 2030, in fact describes different crystal forms having different melting points, and not the same crystal form having different melting points. (*Id.*, 180:9-25.)

By contrast, Dr. Rogers' Declaration cites several literature sources explaining that melting point uniquely identifies a polymorph. (Ex. 1022, ¶¶ 49-52). Thus, for the same polymorph, if the melting point differs, it is due to impurities contained in the sample having a lower melting point. (*Id.*, ¶ 64.) Dr. Rogers concludes that Phares' higher melting point is necessarily due to higher or at least identical purity. (*Id.*, ¶ 74.) Moreover, the width of the DSC peak in the Phares reference is very narrow, consistent with a very pure material. (*Id.*, ¶ 84.)

C. HPLC Analysis Has Error Bars Too Large to Distinguish the Tiny Differences in Purity Levels UT Relies Upon.

As Dr. Winkler explained, it is not possible to measure treprostinil purity levels better than 0.4%, as shown by UT's own data. (Ex. 1009, ¶ 70.) Now that UT has

provided multiple certificates of analysis for treprostinil, it is now confirmed that UT's Moriarty purity varies by at least [redacted], and indeed, Dr. Williams conceded he had no reason to disagree with this [redacted] value. (Ex. 2059, 218:22-24.)

UT's own exhibits confirm that HPLC assay analysis has a wide error range: "[redacted]." (Ex. 2006, 3.) UT's expert Dr. Williams agrees with this statement and that "[redacted]" refers to the HPLC assay for purity. (Ex. 2059, 133:17-25, 134:24-135:4.)

UT discounts that HPLC assay analysis has a wide error range by suggesting that purity should instead be measured by totaling up "total related substances," which are measurements of particular impurities identified in the HPLC analysis. (Resp., 2-3, 29-30.) But as acknowledged by Dr. Williams, some impurities will not be detected in a total-related-substance analysis (Ex. 2059, 140:5-9.). UT's expert Dr. Ruffolo confirmed that in the '393 Patent, all of the analyses are HPLC analyses of the total treprostinil against a reference standard, and not measurements of total related substances. (Ex. 2058, 153:16-154:7.) And both UT experts acknowledged that the FDA uses HPLC assay analysis to evaluate the overall purity of treprostinil, and to decide whether that treprostinil meets a [redacted] purity requirement that would allow it to be sold. (Ex. 2058, 159:20-161:7; Ex.

2059, 150:23-151:25.)

UT criticizes Dr. Winkler, falsely stating that Dr. Winkler does not understand HPLC analysis, and does not know anything about the error in UT's HPLC equipment. (Resp., 3, 30.) Dr. Winkler instead testified that there is no information regarding the error in the amount of "[redacted]," an impurity present in UT's treprostinil at about [redacted]. (Ex. 2051, 63:3-14.) The error in the [redacted] measurement is irrelevant to the error in treprostinil purity, especially where treprostinil purity is a number near [redacted] ([redacted]), 1000 times larger than the amount of [redacted]. Regarding error in HPLC Analysis of treprostinil purity, Dr. Winkler was unequivocal at his deposition:

> I think the thing that I am able to conclude from the data that is on page 6 of this, of this letter is that the error in the HPLC assay could be as high as 1 percent in the first column and by my analysis could be as high as 2 percent in the second column.

(Ex. 2051, 88:12-18.)

IV. UT'S EXPERTS CONFIRM THE CLAIMS' OBVIOUSNESS.

A. Moriarty Was Recognized as the Best Method to Make Treprostinil Before the Phares Reference was Published.

UT contends that Phares does not anticipate because it does not disclose the first two steps, steps (a) and (b), which were used in the Moriarty process. As explained above, this contention is wrong. But even if it were true, UT's expert Dr. Williams provided testimony confirming that there was a strong reason to combine

Moriarty with Phares: Moriarty was well-known to be the best way to make treprostinil, and would have been the way Dr. Williams' own graduate students would have made the treprostinil in Phares before turning it into its salt.

First, Dr. Williams confirmed that steps (a) and (b) in the '393 Patent claims were disclosed by the Moriarty patent, Ex. 1003. (Ex. 2059, 53:19-54:7). Second, Dr. Williams confirmed that "a person of ordinary skill in the art in 2005 reading the Phares reference, that person would know that the best way to make treprostinil is the Moriarty method ...." (*id.*, 240:2-7). And third, he confirmed that "a typical person of ordinary skill in the art, typical graduate student, they would have found the Moriarty paper and used that technique to make treprostinil in 2005." (*Id.*, 244:10-21.) While UT's expert Dr. Ruffolo disagrees with Dr. Winkler regarding the appropriate level of skill, it is Dr. Ruffolo's opinion that the skill level should be higher than Dr. Winkler's, and that a person of ordinary skill should at least have a Ph.D. (Ex. 2058, 52:2-17.) If a graduate student would use Moriarty, then certainly a Ph.D. would do so. Thus, UT's experts essentially confirm that a person of ordinary skill in the art would combine Moriarty with Phares when making Phares' treprostinil salt.

B. UT's Experts Confirm That Crystallization Through A Salt To Purify Is Organic Chemistry 101.

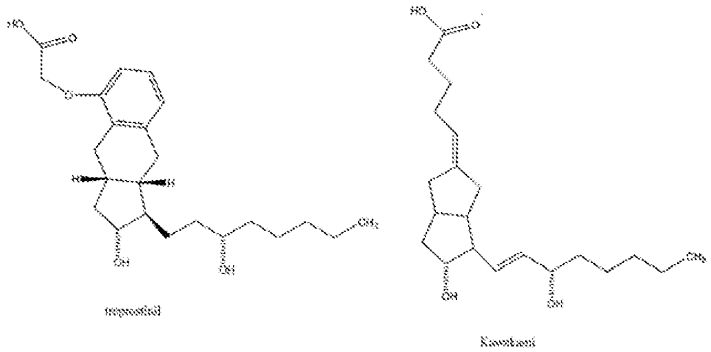
As shown by UT expert Dr. Ruffolo's testimony, *supra*, the process steps (c) and (d), which crystallize a compound as its salt and then convert the salt back to

the acid, have been around for "decades," at least as far back as the late 1960s. (Ex. 2058, 175:19-176:22, 179:11-17.) "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007). UT cannot claim that using this elementary chemistry technique is nonobvious merely because UT applied it to treprostinil.

UT also argues that the particular impurities found in treprostinil, which are said to be stereoisomers, would not have been removed using crystallization. First, there is no teaching in the '393 Patent or the prior art of record regarding what kinds of impurities are present in treprostinil, or, as conceded by UT's experts, of the hundreds of thousands of other compounds included in the claims. (Ex. 2059, 74:18-25; Ex. 2058, 234:16-235:17.) UT maintains the identity of these impurities as a trade secret, necessitating a Protective Order to cover these proceedings so that information on these impurities is not revealed. UT's secret information regarding these impurities' identity cannot be the basis for why a person of ordinary skill in the art would not use crystallization here.

Second, the Kawakami reference, Ex. 1007, used crystallization to separate stereoisomers, as confirmed by Dr. Winkler under UT's counsel's cross-examination. (Ex. 2051, 203:4-204:20.) UT distinguishes Kawakami on grounds

that it concerns a different prostacyclin, not treprostinil, and offers chemical drawings making Kawakami's prostacyclin look different from treprostinil. (Resp., 40.) But SteadyMed has generated more fair drawings of these two structures, and Dr. Williams confirmed that these drawings accurately depict the structures. (Ex. 2059, 245:23-247:1). These new drawings are submitted as Ex. 1028:



When properly depicted, treprostinil and Kawakami are similar compounds.

Finally, treprostinil can be made in any purity desired, as Dr. Williams admitted, by prior-art purification processes like chromatography, since "you could repurify and purify anything you want by chromatography to 99.99999 percent if you wanted to." (Ex. 2059, 94:8-12). While Dr. Williams contends that would be an impractical approach in large-scale manufacturing, he concedes that the '393 Patent's claims are not limited to large-scale manufacturing. (*Id.*, 187:18-188:3.) Thus, there was no barrier to making treprostinil of any purity, and while doing so by using crystallization is obvious, a product having any desired purity can be made by any method, so purer treprostinil is obvious.

V. THE BOARD CONSTRUED THE CLAIMS CORRECTLY.

UT challenges the Board's construction of the legal terms "comprising" and "product," which is surprising since that the Board generally accepted UT's constructions from UT's Preliminary Response. UT had argued that "comprising" should mean "included but not limited to." (Paper 10, at 23). And the Board agreed. (Paper 12, at 13). Now UT contends that "comprising" should not be given its usual open-ended construction. (Resp., 13.) UT points to the prosecution history as effecting a disclaimer of the usual meaning of "comprising," but "[a] statement in the prosecution history can only amount to disclaimer if the applicant clearly and unambiguously' disavowed claim scope." *Toshiba Corp. v. Imation Corp.*, 681 F. 3d 1358, 1370 (Fed. Cir. 2012). UT points to no statements in the prosecution history regarding the meaning of "comprising," but, argues that since the examiner allowed the claims, he must have construed "comprising" according to UT's non-open construction. (Resp., 16.) If that were a clear and unambiguous disavowal, every Patent Owner could argue that its claims should be construed narrowly enough to make them valid, since the initial examiner allowed them.

UT also objects to the Board's plain and ordinary meaning for the term "product," and contends that "product" should be narrowly construed. But this narrow construction is not supportable, and even UT's expert Dr. Williams conceded that "product" is broadly used in the art, assuming that it is even a term

of art and not a legal term. First, Dr. Williams acknowledged that "chemists use the word 'product' in two different contexts, routinely." (Ex. 2059, 248:4-5.) "Product" can mean in chemistry a product and its impurities, or the molecular structure alone. (*Id.*, 248:13-23.) Second, Dr. Williams conceded that the '393 Patent and prosecution history do not provide definitions for "product." (*Id.*, 248:24-249:13.) Third, Dr. Williams' Declaration recognizes that "product" is a term in patent law relating to "product-by-process" claims, (Ex. 2020, ¶ 30), but does not explain why this legal definition should not apply here. Fourth, Dr. Williams' own example of "product" in his own writing—Ex. 2028—uses "product" to mean a product created by nature, and not by a chemical reaction, when it refers to "the natural product from marine sources." (Ex. 2020, ¶ 63.) And fifth, while Dr. Winkler testified that "product" includes the product of a chemical reaction, he testified that "product" was a broad term that encompassed more. (Ex. 2051, 152:21-154:21.)

It is unclear how UT's claim constructions matter. UT seeks a construction limiting the claims by impurity profile, (Resp., 18), but UT cannot articulate how its proposed constructions for "comprising" and "product" effect this result. There is no record evidence showing that the claimed processes and their products have unique impurity profiles, and the '393 Patent lacks information regarding the impurity profiles of treprostinil or its many salts, or for the thousands of compounds in its claims. (Ex. 2059, 71:17-72:17, 74:18-25; Ex. 2058, 234:16-

235:17.) The impurity profiles are not unique to each claim, but depend on unclaimed elements like what solvents were used, (Ex. 2058, 239:22-241:14), whether the intermediate products were purified, (Ex. 2058, 239:8-20, Ex. 2059, 69:17-71:9), and what bases, acids, or other reactants that the claims allow were used. Product-by-process claims would have no definite scope under UT's analysis.

VI. NO LONG-FELT NEED FOR THESE CLAIMS' PRODUCTS.

While UT suggests there was a long-felt need for these claims' products, its long-felt-need expert Dr. Ruffolo testified otherwise: "there's nothing I can tell you about the long-felt need for those other compounds [of claim 1]," (Ex. 2058, 65:4-13); or of claim 9 (Ex. 2058, 69:20-70:11); or of claims 12, 13, 16, 17, 21, or 22 (Ex. 2058, 110:17-111:9, 114:16-117:3, 118:2-5; 118:23-119:23, 121:5-23); or of any claim that was not limited to treprostinil and treprostinil diethanolamine salt, (Ex. 2058, 68:14-25). Only claims 10, 14, 15, and 17 are limited to treprostinil or its salt.

Regarding treprostinil or its diethanolamine salt, Dr. Ruffolo conceded that he had no idea if FDA had asked for a change in purity, (*id.*, 45:15-22), nor could he identify anyone who expressed a particular desire for greater purity, (*id.*, 130:16-25.) He also recognized that one could usually purify a drug further by running purification procedures repeatedly, (*id.*, 46:9-18), which Dr. Williams confirmed was true for treprostinil, (Ex. 2059, 94:8-12), and proves that there was no need for

the "invention." Dr. Ruffolo also conceded, contrary to UT's arguments, that a change in purity specifications is not a major amendment, (Ex. 2058, 310:5-13), but that the other changes UT applied for—changing starting materials and manufacturing facilities, were major amendments (*id.*, 310:13-18).

Regarding claims 10, 14, 15, and 17, Dr. Ruffolo concedes that: (1) the FDA requires only a [redacted] purity level, which is *much lower* than any levels produced by the prior art, (*id.*,159:20-161:7); (2) the FDA would allow batches of treprostinil produced by the Moriarty process to be sold, (*id.*,179:23-180:17), since Moriarty products are "highly, highly pure," (*id.*, 217:11-218:5); and (3) there is no clinical difference between the prior-art Moriarty product and the '393 Patent product (*id.* 315:15-23). Thus, the FDA expressed no need for a purer product. Moreover, Dr. Ruffolo does not know if UT's products that he relies upon are covered by these claims. (*Id.*, 292:25-293:2.)

Dr. Ruffolo's opinion relies on Dr. Williams' incorrect calculation showing 99.0% purity, but Dr. Ruffolo concedes he did not review that calculation, nor speak to Dr. Williams, and depends entirely on Dr. Williams. (*Id.*, 262:4-263:5.) Since Dr. Williams now concedes that the correctly performed calculation shows a [redacted] purity, (Ex. 2059, 218:3-8), Dr. Ruffolo's opinions should be disregarded.

Date: September 27, 2016

Respectfully submitted,

/s Stuart E. Pollack /
Stuart E. Pollack, J.D. Ph.D.
Reg. No. 43,862
DLA Piper LLP (US)

/s Lisa A. Haile /
Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
DLA Piper LLP (US)

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned attorney for Petitioner certifies that the document contains 5,599 words in 14-point Times New Roman font, excluding the parts of the document that are exempted by 37 C.F.R. § 42.24(a)(1), according to the word count tool in Microsoft Word.

Date: September 27, 2016

Respectfully submitted,

/s Stuart E. Pollack /
Stuart E. Pollack, J.D. Ph.D.
Reg. No. 43,862
DLA Piper LLP (US)

/s Lisa A. Haile /
Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
DLA Piper LLP (US)

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the attached Petitioner's Reply was served via electronic mail to the following:

Stephen B. Maebius
George Quillin
FOLEY & LARDNER LLP
UT393-IPR@foley.com

Shaun R. Snader
UNITED THERAPEUTICS CORP.
ssnader@unither.com

Douglas Carsten
Richard Torczon
Robert Delafield
WILSON, SONSINI, GOODRICH & ROSATI
dcarsten@wsgr.com
rtorczon@wsgr.com
bdelafield@wsgr.com

Date: September 27, 2016

/s Stuart E. Pollack /
Stuart E. Pollack, J.D., Ph.D.
Reg. No. 43,862
DLA Piper LLP (US)

/s Lisa A. Haile /
Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
DLA Piper LLP (US)

Paper _____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR 2016-00006

Patent No. 8,497,393

DECLARATION OF ROBIN D. ROGERS IN SUPPORT OF PETITIONER'S REPLY

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

I. OVERVIEW

1. I have been retained by counsel for the Petitioner, SteadyMed Ltd., to offer technical opinions with respect to certain technical matters relating to the *inter partes review* proceedings concerning U.S. Patent No. 8,497,393 ("the '393 Patent") and certain prior art references cited in regard to the '393 Patent.

2. In particular, I have been asked to opine regarding crystal forms of organic molecules, also known as "polymorphs," the melting points of polymorphs, how melting point and purity of polymorphs are related, how differential scanning calorimetry and other analytical techniques are used to analyze polymorphs, and how some of these analytical techniques can be used to compare the purity of two samples.

3. This declaration presents my opinion that the treprostinil diethanolamine Form B polymorph made in the Phares Reference, Ex. 1005, is at least as pure as the same Form B polymorph made in the '393 Patent, Ex. 1001, and is likely purer, based on comparing their melting points.

4. I also opine that the method of making a particular polymorph, such as Form B, and the solvents used, are irrelevant to the properties of the polymorph: two crystals of Form B have the properties of Form B, including melting point and PXRD pattern, regardless of how they were made. Differences present here between two Form B crystals made using different solvents are due to different

impurity profiles and different levels of impurities. In fact, the '393 Patent contains six examples, called Example 3 Batches 1-4 and Example 4 Batches 1 & 2, where the melting points, and thus the impurity level and profile, were each different.

II. QUALIFICATIONS

5. I am currently Canadian Excellence Research Chair in Green Chemistry and Green Chemicals at McGill University, Montreal, Quebec, Canada, a position I started January 1, 2015. Prior to this appointment I served as Distinguished Research Professor in the Department of Chemistry at The University of Alabama, Tuscaloosa, Alabama, USA, where I was Robert Ramsay Chair of Chemistry and the Director of the Center for Green Manufacturing also at The University of Alabama. Since 2009, I have held the title of Honorary Professor in the Institute for Process Engineering at The Chinese Academy of Sciences in Beijing, China. A copy of my curriculum vitae and list of publications is attached as Ex. 1023.

6. I received a B.S. in chemistry (*summa cum laude*) in 1978 and a Ph.D. in chemistry in 1982 from The University of Alabama. During the period 1982–1996, I was successively an assistant, associate, full, and Presidential Research Professor at Northern Illinois University. During the period of 1991–1998, I also held a faculty appointment at the Argonne National Research Laboratory, Argonne, Illinois. In 1996, I became a Professor of Chemistry at The University of

Alabama and, in 1998 I was named Director of The University of Alabama's Center for Green Manufacturing. I was awarded the titles Distinguished Research Professor in 2004 and Robert Ramsay Chair of Chemistry in 2005. From 2007 to 2009, I held a joint appointment as Chair in Green Chemistry in the School of Chemistry & Chemical Engineering and Director of the Queen's University Ionic Liquid Laboratory ("QUILL") at The Queen's University of Belfast, Belfast, Northern Ireland, UK.

7. I am a member of various professional societies, including the American Association for the Advancement of Science (Fellow), American Chemical Society (Fellow), American Crystallographic Association, American Institute of Chemical Engineers, Materials Research Society, American Association of Crystal Growth, and Royal Society of Chemistry (Fellow).

8. In 1989, I joined the Editorial Board of the *Journal of Chemical Crystallography* (then named *Journal of Crystallographic and Spectroscopic Research*). I became Associate Editor of the journal in 1993 and was the Editor from 1996 to 2000. In 1998, I founded the journal *Crystal Engineering* and served as Editor until 1999. In 2000, I was asked by the American Chemical Society ("ACS") to found a new journal called *Crystal Growth & Design*, for which I currently serve as Founding Editor-in-Chief. I also have served or currently serve as editor or on the editorial board of the following journals:

- *Separation Science and Technology*: Associate Editor, 1996-99; Editorial Board, 1999-;
- *Industrial & Engineering Chemistry Research*: Editorial Board, 1999-2001;
- *Journal of Chromatography, B*, Guest Editor, Volume 743 (1 + 2), 2000;
- *Solvent Extraction and Ion Exchange*, Editorial Board, 2002-;
- *Green Chemistry*, International Advisory Board, 2002-;
- *Chemical Communications*, Editorial Advisory Board, 2005-;
- *Accounts of Chemical Research*, Guest Editor (with G. A. Voth), Special Issue on Ionic Liquids, Volume 40(11), 2007
- *ChemSusChem*, International Advisory Board, 2008-;
- *Chemistry Letters*, Advisory Board, 2010-;
- *Australian Journal of Chemistry*, Guest Editor, Research Front on Crystal Engineering, Volume 63(4), 2010;
- *Separation Science & Technology*, Guest Editor (with H. Rodriguez and J. Chen), Special Issue on Ionic Liquids (2012);
- *Chemical Communications* Guest Editor (with D. MacFarlane and S. Zhang), Special Issue on Ionic Liquids (2012);
- *Science China – Chemistry* Guest Editor (with S. Zhang), Special Issue on Ionic Liquids (2012); and

- *Catalysis Today* Guest Editor (with S. Zhang), Special Issue on Ionic Liquids (2012). *Green Chemistry and Sustainable Technology*, Springer, Heidelberg, Germany, Book Series Editor (with L.-N. He, D. Su, P. Tundo, and Z. C. Zhang).
- *Chimica Oggi/Chemistry Today*, Scientific Advisory Board, 2014-
- *Green Energy & Environment*, 2016-

9. In 2002, the ACS asked me to organize and chair a specialty meeting devoted to the topic of polymorphism (*Polymorphism in Crystals: Fundamentals, Prediction, and Industrial Practice*, Tampa, FL, February 23–27, 2003). I was asked to organize and chair follow-up meetings in 2004 (*Polymorphism in Crystals*, Tampa, FL, February 8–11, 2004), in 2006 (*Process Crystallization in the Pharmaceutical and Chemical Industries*, Philadelphia, PA, April 25–27, 2006), and in 2007 (*Crystallization Process Development: Case Studies and Research*, Boston, MA, February 26–27, 2007).

10. In 2010, I was co-founder, co-organizer, and Vice Chair of the first Gordon Research Conference devoted to the topic of Crystal Engineering (Waterville Valley Resort, NH, June 6-11, 2010). I was the organizer and Chair of the second Gordon Research Conference on Crystal Engineering, which was held in June of 2012.

11. I have published more than 760 articles in refereed journals, edited 14 books, and have been named as an inventor on 50 domestic and foreign patents. I have also given over 1,000 presentations before regional, national and international meetings, and over 200 seminars worldwide. In both 2014 and 2015 I have been named to the Thomson Reuters Highly Cited Researchers List, ranking among the top 1% most cited in chemistry.

12. Since 1996, I have had a leadership role in the development of the field of ionic liquids (pure salts liquid at low temperature); probing their fundamental nature while advancing their technological relevance in areas which include crystallization and novel pharmaceutical forms. These efforts have been recognized with several awards including the 2005 Presidential Green Chemistry Challenge Award, the 2011 American Chemical Society Award in Separations Science and Technology, and in recently being elected as a Fellow of the American Association for the Advancement of Science.

13. I use and have used over the past 40 years X-ray diffraction techniques, Differential Scanning Calorimetry ("DSC"), and Thermogravimetric Analysis ("TGA"), among other techniques, in my research efforts. I have also used other spectroscopic techniques to analyze crystalline and amorphous forms, including Infra-red ("IR"), and Raman spectroscopy ("Raman").

14. I have collaborated with organic chemists in industry and in academia as part of a team in the discovery and characterization of novel drug compounds. I have also acted as a consultant in industry in the development of pharmaceutical drug compounds. I have also trained students in organic synthesis and supervised their Ph.D. research. Within my research group, I regularly hire and supervise Ph.D. organic chemists and direct their research in the synthesis and characterization of novel forms of active pharmaceutical ingredients.

15. In my position as Founding Editor-in-Chief of the American Chemical Society journal *Crystal Growth & Design*, I regularly evaluate and judge suitability for publication of numerous manuscripts which utilize and study crystal engineering, polymorphism, and crystal growth and the characterization of solid state materials. Accordingly, I am quite familiar with the academic and scientific standards for experimental work in this field.

16. In 2004, 2005, and 2008, I organized three special issues of *Crystal Growth & Design* dedicated to the phenomenon of polymorphism, and in 2009, I organized a special issue dedicated to pharmaceutical co-crystals. Many of these papers addressed pharmaceutical compounds, hydration, salt selection, and the use of X-ray diffraction.

17. Based on my experience and qualifications, I consider myself an expert in the field of solid-state chemistry including crystal engineering,

crystallization, hydration, solvate formation, and polymorphism, including the isolation and characterization of solvates and hydrates of organic compounds and their applications in pharmaceutical products. Accordingly, I believe that I am more than competent to express the opinions set forth below.

18. Additional details of my education and experience, and a complete list of my publications are set forth in my curriculum vitae, Ex. 1023.

III. MATERIALS CONSIDERED

19. In forming my opinions, I had the materials cited in the Petition, including the '393 Patent (Ex. 1001), Patent Owner's Response, and the Phares Reference (Ex. 1005), the materials cited in this report, Dr. Williams' Declaration (Ex. 2020), Dr. Ruffolo's Declaration (Ex. 2022), Dr. Winkler's Declaration (Ex. 1009), Dr. Williams' and Dr. Ruffolo's deposition transcripts, and have also relied on my own known and my numerous publications listed on my *curriculum vitae* (Ex. 1023).

IV. MY ROLE AND SUMMARY OF MY OPINIONS

20. I am not offering an opinion on the invalidity of the '393 Patent's claims, or commenting on Dr. Winkler's or Dr. Williams' opinions on that ultimate issue.

21. I am offering opinions only on certain scientific questions that are within my expertise, regarding polymorphs, measurement of polymorphs, melting

points of polymorphs, techniques to analyze polymorphs, purity and how melting point relates to purity, and other related issues.

22. I am also offering an opinion about the ability to compare the melting point of samples of a polymorph.

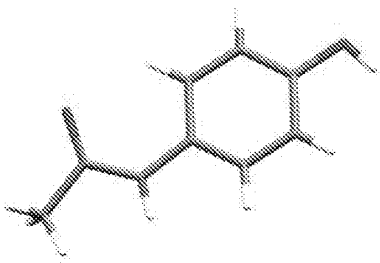
23. I also conclude that a sample of treprostinil diethanolamine salt Form B made by Phares, Ex. 1005, is at least as pure, and likely purer, than samples made and described in columns 12 and 13 of the '393 Patent, Ex. 1001.

V. BACKGROUND

A. Polymorphism

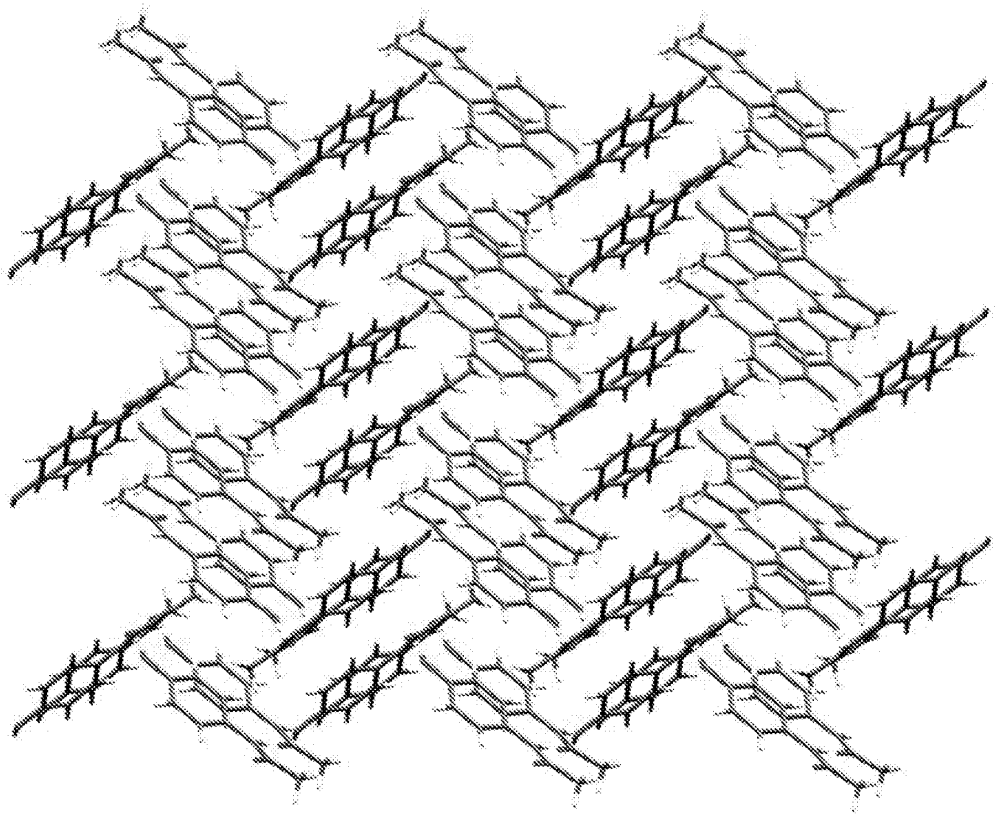
24. Before addressing what a "polymorph" is, it is helpful to begin with a short explanation of what crystals are. Crystals are solids made up of highly organized molecules arranged in a regularly repeating three-dimensional array. These highly organized arrangements of regularly repeating molecules form what are known as crystal lattices.

25. I will explain these concepts using acetaminophen as an example. A single molecule of acetaminophen has the following structure below:



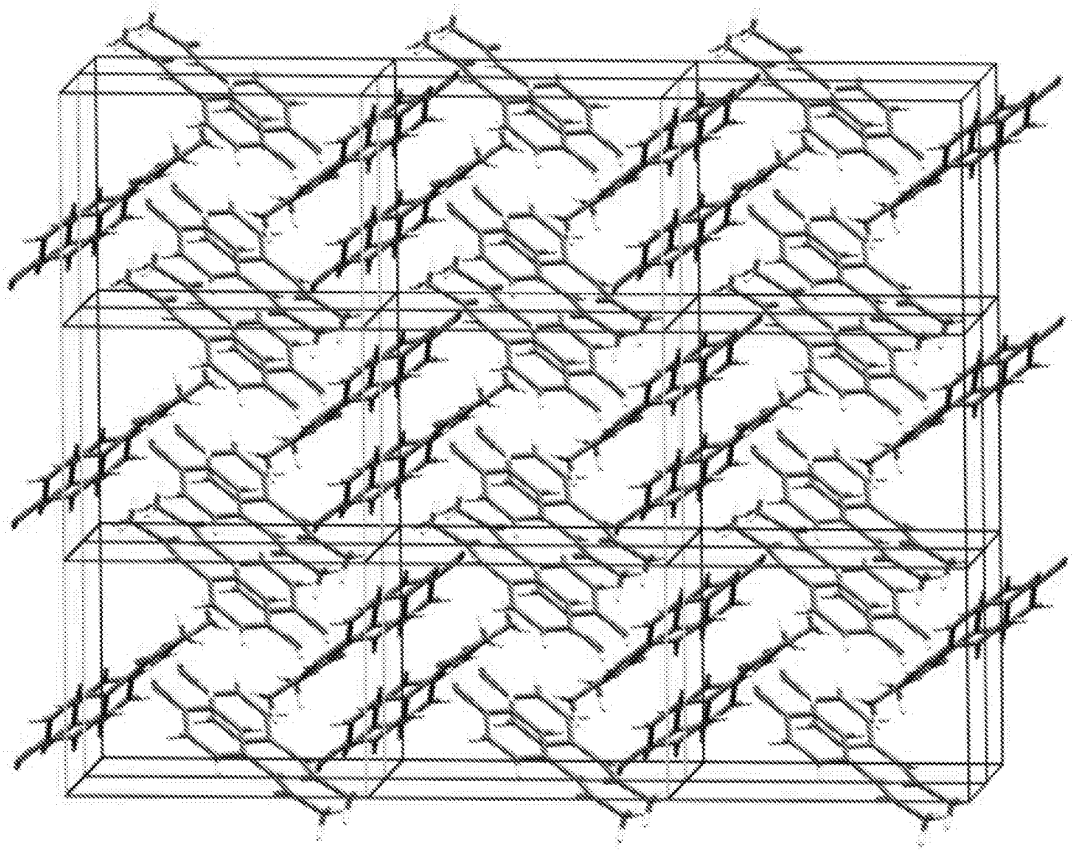
Acetaminophen Molecule

26. When a sample of acetaminophen is crystallized, the molecules in the sample can arrange themselves into a regularly repeating three-dimensional pattern as shown below:



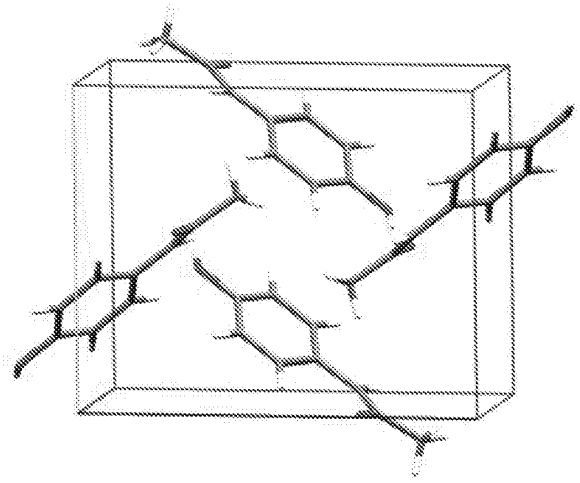
Regularly Repeating 3-D Array of Acetaminophen Molecules

27. This three-dimensional arrangement of molecules is the crystalline lattice, which is like a framework of molecules packed in a regular and repeating manner:



Crystal Lattice of Acetaminophen

28. The smallest repeating unit of the crystalline lattice is known as the unit cell. The crystalline lattice of acetaminophen shown above can also be depicted in terms of the unit cell, shown below.

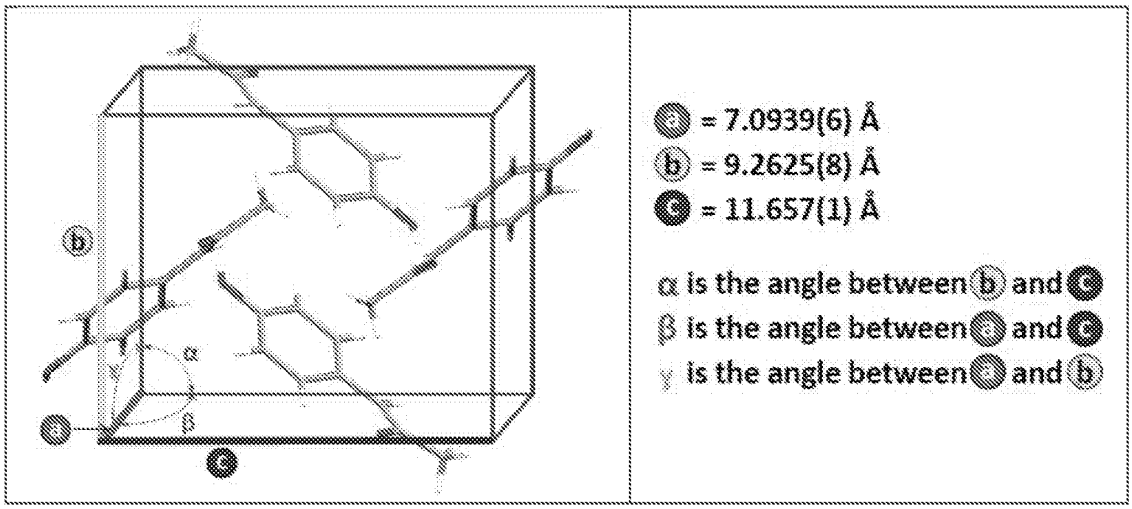


Acetaminophen Unit Cell

29. As can be seen above, the unit cell is a theoretical construct that aids scientists in studying and characterizing crystals, and does not correspond to the shape of the molecules themselves. The ways in which the molecules of the compound (acetaminophen in my example) arrange themselves in space determine the size and shape of the unit cell. Each unit cell is like a brick and the crystal lattice a three-dimensional brick structure. A crystalline solid therefore can be described by the shape and size of a single unit cell because its three-dimensional crystal structure is simply a lattice of those unit cells repeating in all three dimensions.

30. The unit cell is characterized in terms of three lengths, *a*, *b*, and *c*, and three angles, α, β, and γ. These lengths and angles are known as the unit cell parameters. Different unit cells have different values of *a*, *b*, *c*, α, β, and γ, and

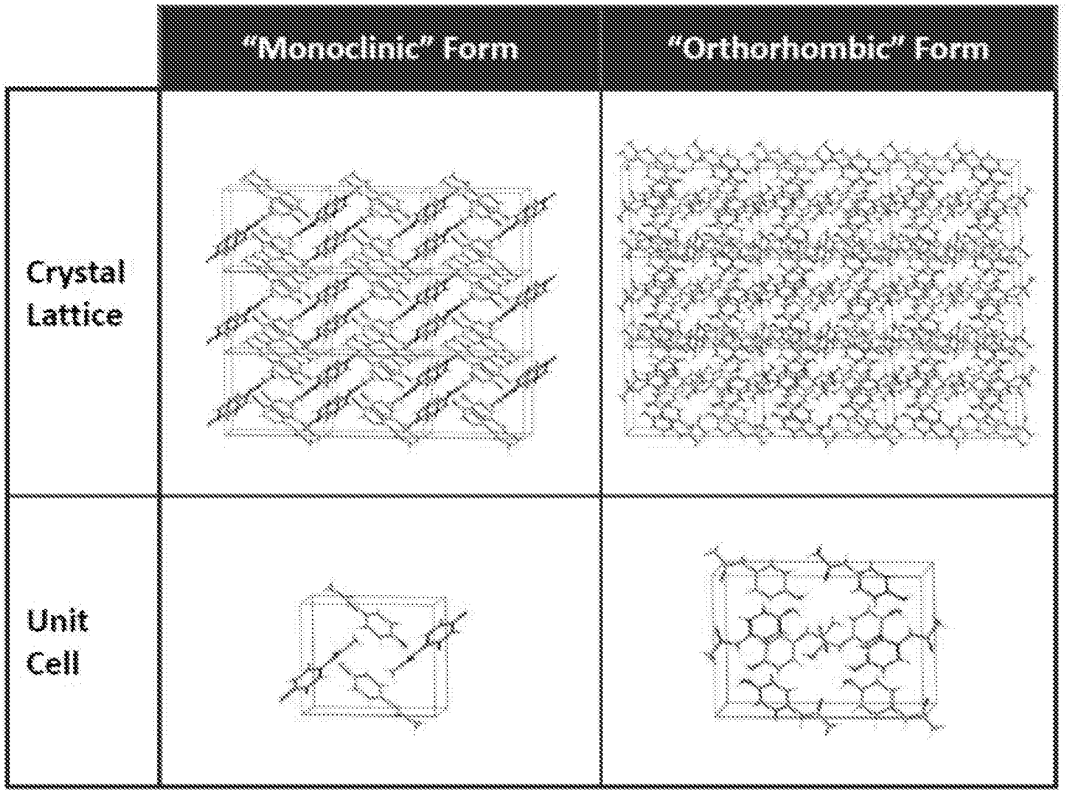
thus have different sizes and shapes. The unit cell parameters for the crystalline acetaminophen in my example are shown below.



Unit Cell Parameters for Acetaminophen

31. Molecules of a compound may arrange, or "pack" themselves in more than one way, which can give rise to different crystalline structures or "forms." Many substances, including pharmaceutical compounds, can exist in more than one crystal form, each form having a different crystalline lattice and different unit cell. This phenomenon is termed "polymorphism" and the different crystal forms are called "polymorphs." A classic example is that of carbon, where one crystal form is diamond, and another crystal form of the same substance is graphite.

32. Two different crystalline forms of acetaminophen, referred to as "monoclinic" and "orthorhombic" are shown below.[1]



Two Different Crystal Forms of Acetaminophen

33. As shown in this example, the size and shape of the unit cell can differ, depending on how the molecules in the lattice of a particular polymorph are organized. Different polymorphs of pharmaceutical compounds may exhibit

[1] The terms "monoclinic" and "orthorhombic" refer to a specific type of crystal lattice. However, for convenience, forms are often named "Form I," Form II," Form III," etc. without any indication of its physical properties.

different properties, such as crystal shape, melting temperature, solubility, and stability.

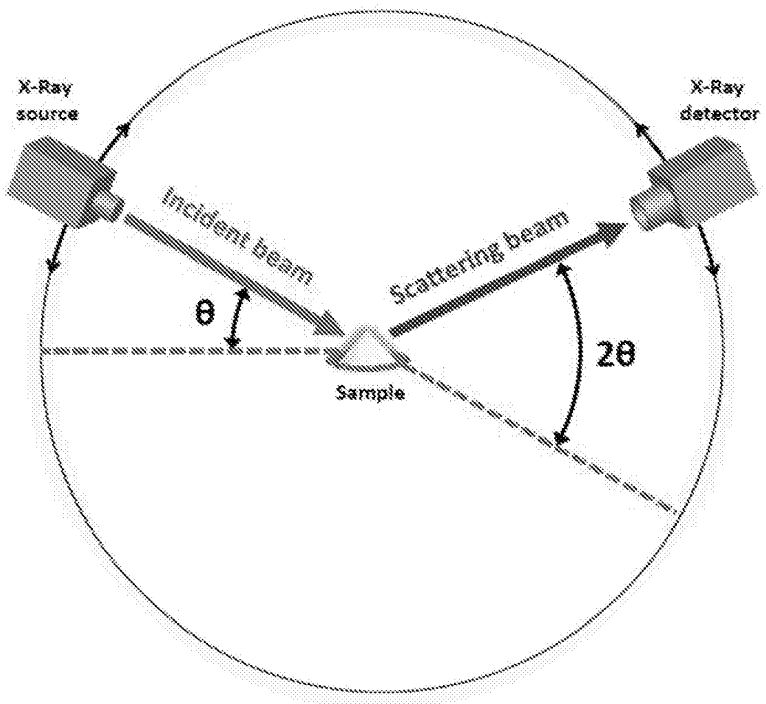
B. Characterizing crystals

34. Because each crystal form, or polymorph, has its own unique unit cell and thus three-dimensional lattice, that particular crystal form can be identified by certain characteristics associated with its crystal lattice (and unit cell). For example, different polymorphs "diffract" (*i.e.*, reflect) X-rays differently. Thus, one technique that can be used to identify the crystal structure of a crystalline compound and to distinguish different polymorphs of the same compound is X-ray diffraction ("XRD"), which when carried out on compounds in powder form is called powder X-ray diffraction ("PXRD").[2]

35. The molecules within each unit cell of the crystal lattice will diffract incident radiation, such as X-rays, in a specific pattern due to the orientation of those molecules within the unit cell. Each different crystal form will diffract X-rays at different "scattering angles" (the angle of the incident X-ray beam to the crystal where scattering of the X-rays is observed) and at differing "intensities" (how many X-rays are scattered). The scattering angles (as shown below) are measured and reported as diffraction peaks 2θ ("two theta"), and can also be referred to as the 2θ values or 2θ peaks.

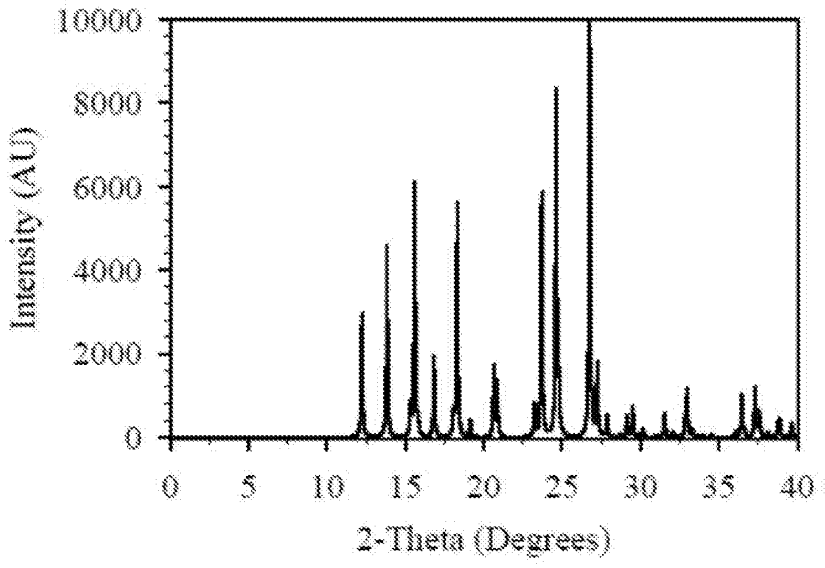
---

[2] PXRD can also be referred to as X-ray powder diffraction, or "XRPD."



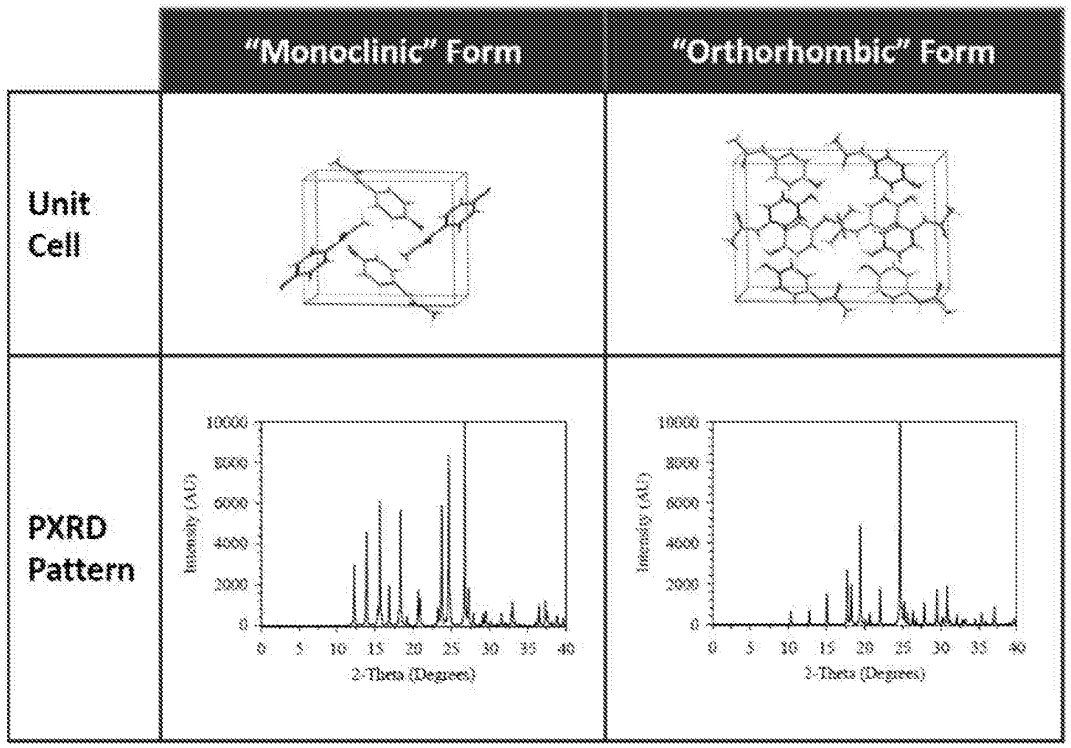
X-Ray Diffraction

36. A given crystalline form of a compound will always diffract X-rays at the same scattering angles. By measuring the scattering angles (2θ) and intensities of X-rays diffracted from a given sample of a polymorph, the 2θ values can be plotted against the differing intensities, as "lines" or "peaks," to produce a specific "X-ray diffraction pattern" for each polymorph. An X-ray diffraction pattern, therefore, can act as a fingerprint for that polymorph. For example, this is the X-ray diffraction pattern for one of the crystalline polymorphs of acetaminophen I discussed above:



X-Ray Diffraction Pattern of Acetaminophen

37. As discussed above, the X-ray diffraction patterns (or "diffractograms") obtained from PXRD analysis are unique to a particular crystal form. The positions of the diffraction peaks provide information about the size and shape of the unit cell, and the intensities of the peaks provide information as to the contents of the unit cell, *i.e.*, the arrangement of atoms within the unit cell. The intensities of the peaks in a given PXRD pattern can be compared to each other. Different crystal forms yield different diffractograms and the technique can be used to distinguish one form from another, as shown below for two polymorphs of acetamimophen.



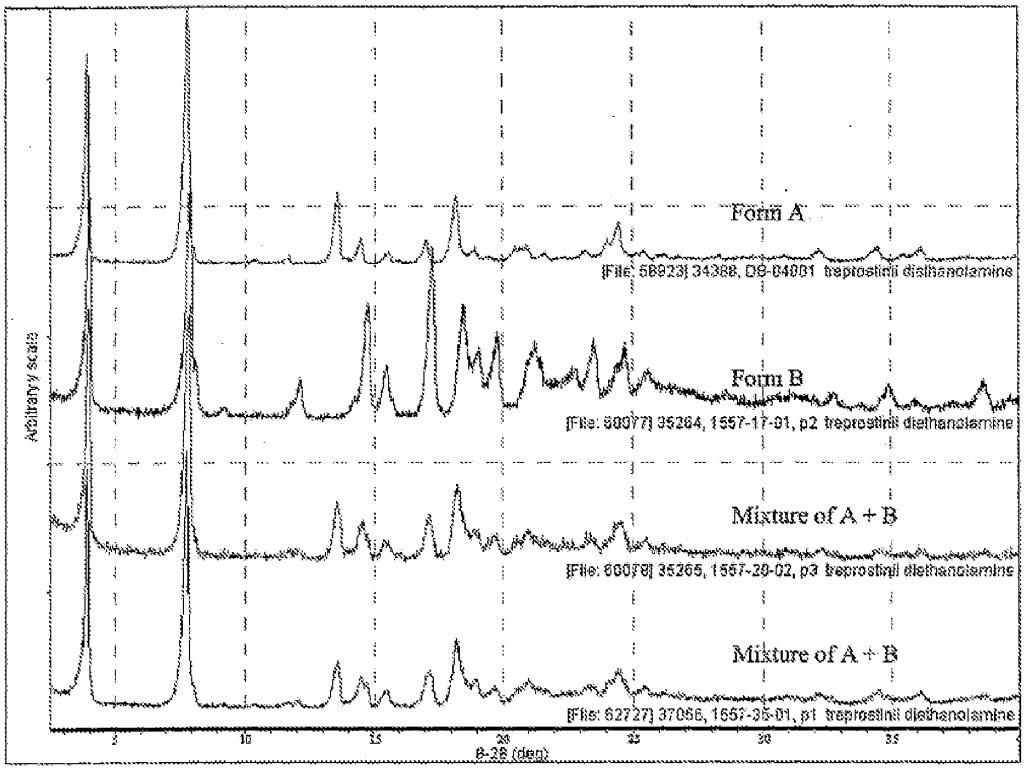
X-Ray Diffraction Patterns of Different Crystal Forms of Acetaminophen

C. Identifying crystals

38. Once a reference PXRD pattern has been established for a particular polymorph, an unknown sample can be identified as that polymorph if its PXRD pattern corresponds to that of the reference PXRD pattern.

39. For example, the Phares Reference, Ex. 1005, provides a comparison of the PXRD patterns for treprostinil diethanolamine salt Form A and Form B:

FIGURE 20



(Ex. 1005 at 120.) The technique can accurately distinguish Form B from Form A, and can even be used to quantitatively assess mixtures of Form A and B.

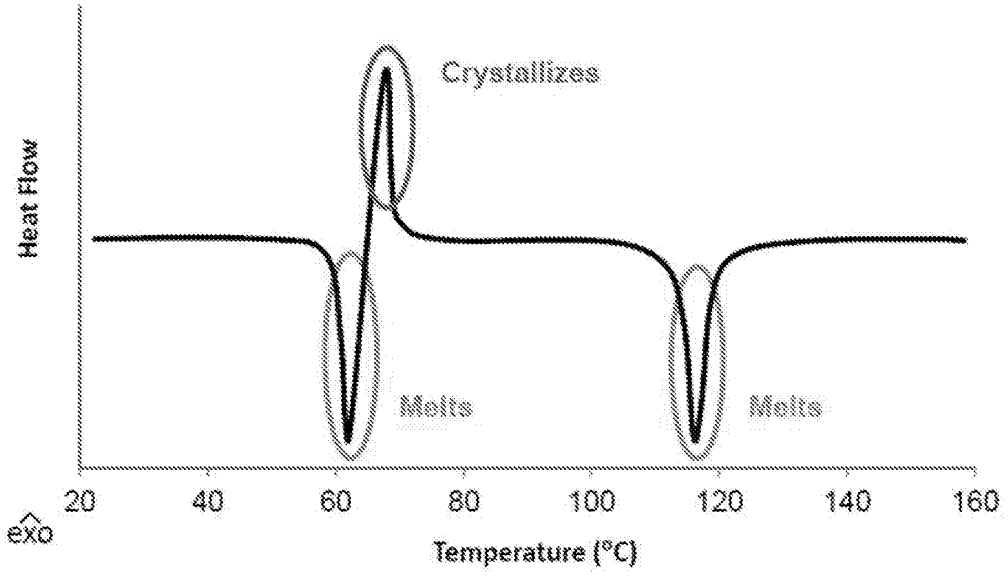
D. Other techniques for characterizing crystals

40. There are other commonly-used analytical techniques besides PXRD for studying or characterizing crystal forms. While PXRD relays information about the inherent structure of a crystal form, and is therefore considered the best method for identifying crystal forms, visual and thermal techniques provide additional information about the physicochemical properties of a sample.

41. Microscopy (visual observation under a microscope) can reveal the morphology (size and shape) of the crystals themselves. In hot-stage microscopy, a sample can be observed as it is heated and/or cooled, which allows one to observe how the sample changes forms (between different crystal forms, or between liquid and solid), and at which temperatures they occur.

42. Thermal analyses provide quantitative information about different crystal forms. A material can go through changes in physical state when it is heated, for example, melt, crystalize, or change crystal forms. Each of these changes in physical state, also called phase transitions, is accompanied by either an absorption (endotherm) or release (exotherm) of heat. When a material melts, it absorbs heat, resulting in an endotherm, and when it crystallizes, it releases heat, resulting in an exotherm.

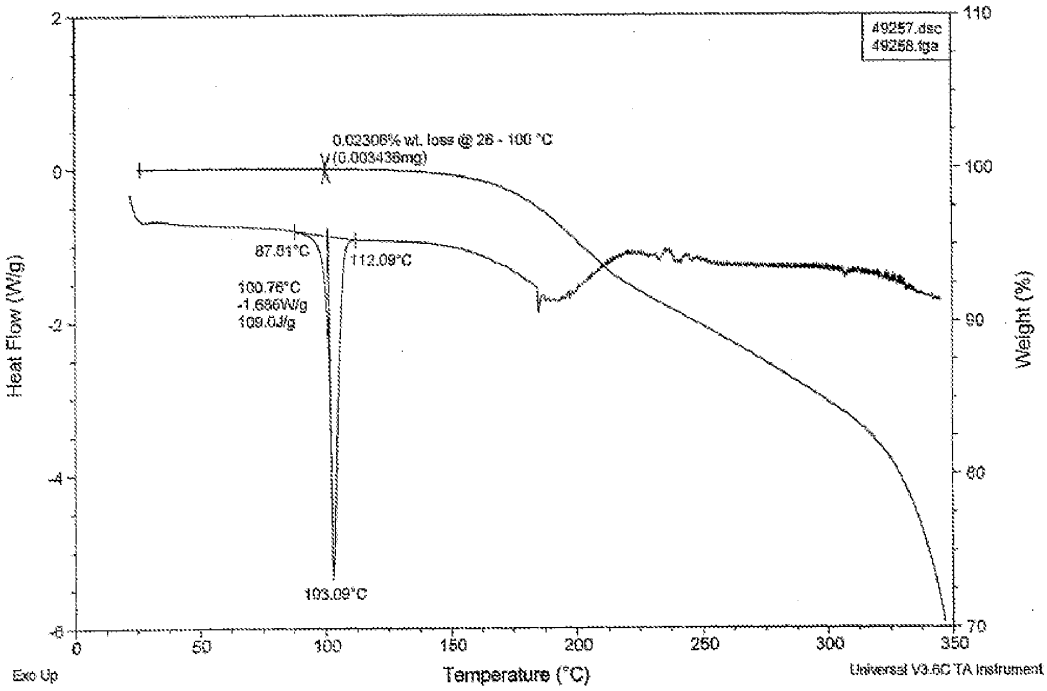
43. Differential scanning calorimetry (DSC) is a method of analysis that allows scientists to track these changes in physical state of a sample as it is heated, by detecting any endotherms (indicative of melting) and/or exotherms (indicative of crystallizations or changes of form) that occur. For example, in the hypothetical DSC plot below, the sample melts at about 62°C (endothermic event, resulting in a downward pointing peak), immediately recrystallizes (exothermic event, resulting in an upward pointing peak), then melts again at about 118 °C (endothermic event, resulting in a downward pointing peak).



Illustrative DSC

44. In the Phares Reference (Ex. 1005) melting point data taken using DSC is used to distinguish and verify the identities of Form A and Form B treprostinil diethanolamine crystals. The melting point data for Form A shows that it melts at 103.09°C.

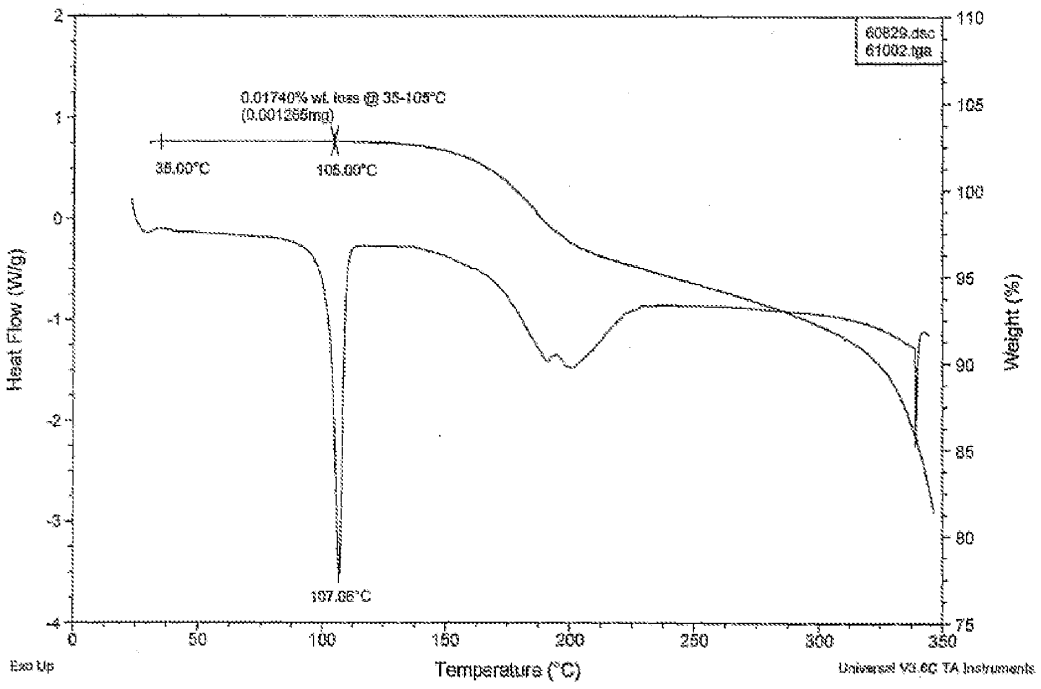
FIGURE 18



(Ex. 1005 at 118.)

45. Similarly, the melting point of a Form B crystal was also measured in the Phares Reference:

FIGURE 21



(Ex. 1005 at 121.) A computer has automatically marked the position of the melting point for this particular Form B crystal, which is indicated as 107.06°C. And this melting point value is reported in the text as 107°C. (Ex. 1005 at 91.)

46. In fact, the '393 Patent recognizes the importance of melting point in identifying which polymorph is present:

> At this stage, if melting point of the treprostinil diethanolamine salt is more than 104° C., it was considered polymorph B. There

> is no need of recrystallization. If it is less than 104°C. it is recrystallized in EtOH-EtOAc to increase the melting point.

(Ex. 1001 col.12 ll.52-56.)

47. Thermogravimetric analysis, known as "TGA" or "TG," is another technique for analyzing polymorphs, and is also used in the Phares Reference, Ex. 1005. TG can be used to determine if a material is a solvate or hydrate. If, upon heating, the weight of the crystal drops, it may indicate that a solvent has been released, due to conversion of the crystal from a pseudo-polymorph where the solvent (or water in the case of a hydrate) is incorporated in the crystal form, to a real polymorph containing the organic chemical alone.

48. For example, in the Phares Reference, Figures 18 and 21 show, in addition to DSC data, a TGA result, which is the upper curve, whose y-axis is the "Weight (%)" at the right. If there is virtually no weight loss at temperatures at or below the melting event, it means the crystal is not a solvate or hydrate. In the Phares Reference, it was demonstrated that neither Form A nor Form B were solvates or hydrates. (Ex. 1005 at 90 ("The TG data [for Form A] shows no measurable weight loss up to 100 °C, indicating that the material is not solvated."); Ex. 1005 at 91 ("The TG [of Form B] shows minimal weight loss up to 100 °C.".)

E. What role does melting point play in polymorph identification?

49. Melting point is so closely associated with the identity of polymorphs, that it has been proposed that polymorphs be identified by their melting points, instead of by their order of discovery.

50. For example, in Stephen R. Byrn *et al.*, *Solid-State Chemistry of Drugs*, Chapter 10, "Polymorphs," 143-231 (2d ed. 1999), a textbook on crystals of drugs, it states:

> It has been suggested that polymorphs be numbered consecutively in the order of their stability at room temperature or by their melting point.

(Ex. 1024, at 2.) This shows that melting point is so closely identified with the identity of a polymorph that melting point has been proposed as a means of distinguishing and identifying polymorphs.

51. Similarly, in Terence L. Threlfall, "Analysis of Organic Polymorphs: A Review," *Analyst* 120(10): 2435 (1995) it is stated that:

> Arbitrary systems are to be discouraged, but numbering based either on order of melting point or of room temperature stability have been recommended.

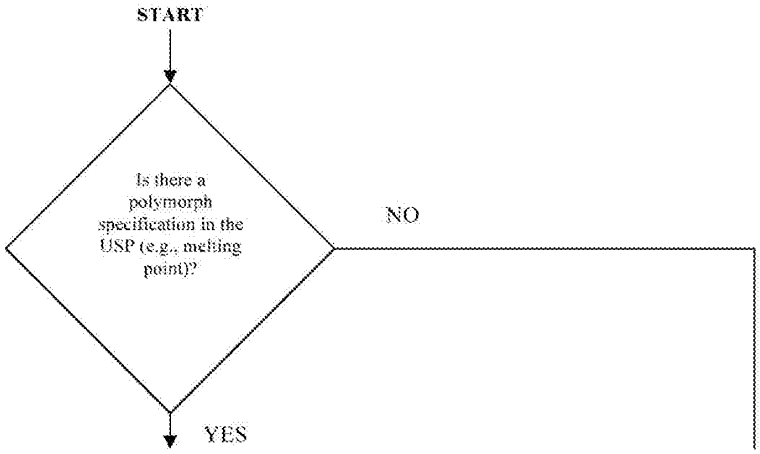
(Ex. 1025, at 1.)

52. As yet one more example, in the FDA Guidance for Industry, *ANDAs: Pharmaceutical Solid Polymorphism--Chemistry, Manufacturing, and Controls*

Information, melting point is particularly pointed out as a distinguishing property of polymorphs:

ATTACHMENT 2 – DECISION TREE 2

Decision Tree 2 Setting specifications for polymorphs in drug substances for solid oral and suspension dosage form products.



(Ex. 1026, at 12.)

VI. MELTING POINT AND THE PURITY OF A CRYSTAL

53. As stated in many textbooks, the purity of a crystal can be related to its melting point:

> The method [of differential scanning calorimetry] can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

$$T_s = T_0 - \frac{T_o^2 R X_i}{F \Delta H_f} \qquad (5.2)$$

where T_s, is the sample temperature, T_0 is the melting point of the pure compound, R is the gas constant, X_i, is the mole fraction of the impurity, F is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus $1/F$ should give a straight line whose slope is proportional to X_i (Brittain *et al*., 1991).

Stephen R. Byrn *et al.*, *Solid-State Chemistry of Drugs*, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027, at 84.)

54. This phenomenon, known as melting-point depression, may be familiar, since it is used to melt ice on the roads in the winter. Salt, which can dissolve in water, is added to roads so that when the water on the road freezes, it contains salt impurities which lower the melting point. The melting point of ice is 0°C (T_0 in the equation above), but it is lower when the ice contains salt as an impurity. Therefore, even if the road temperature is 0°C, the water on the roads will be above the melting point T_s of ice containing salt, and thus, will be a liquid.

55. To simplify, although there is a complex relationship between the amount of impurities (X_i) and the observed melting point (T_s), the melting point will decrease if there are more impurities in the sample from the melting point in a 100% pure sample, which is designated T_0. The decrease will be greater the more impurities there are in the sample.

56. The value T_0 is unique for each polymorph. If I have two crystals that are known from their PXRD patterns to be Form B crystals, then both crystals have the identical T_0 value, regardless of how the crystals were made and what solvents were used to make them.

57. Thus, if the measured melting point of a Form B crystal, T_s, is below 107°C, then the sample contains impurities, in an amount X_i, that is causing a decrease in the observed melting point.

58. As explained in Stephen R. Byrn *et al.*, *Solid-State Chemistry of Drugs*, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027), differential scanning calorimetry or DSC is used to determine the melting point and then the purity of a crystalline sample using Equation 5.2. Another technique, thermal microscopy, is also used for this purpose, and is the technique used in the '393 Patent.

VII. THE CRYSTAL FORMS THAT I HAVE REVIEWED

59. The Phares Reference (Ex. 1005), discussed above, is International Publication No. WO 2005/007081 to Phares, *et al.*, entitled "Compounds and Methods for Delivery of Prostacyclin Analogs," and published January 27, 2005, and is assigned to United Therapeutics. I have been told that there is no dispute that it is prior art to the '393 Patent, but whether it is or not is not relevant to my opinions in this Declaration.

60. The Phares Reference (Ex. 1005) provides a detailed description of the manufacture and characteristics of treprostinil diethanolamine salt, Form A and Form B, using many different solvent systems. It also provides the PXRD patterns, the melting points determined by DSC, the Raman and IR spectra, and the TGA analysis of these crystals.

61. The '393 Patent (Ex. 1001) is also assigned to United Therapeutics. It also describes making treprostinil diethanolamine Form B salt at column 12 and clearly states that Form B is the crystal form that is made. To do so, crystals known to be Form B salt are added to solution, in a process known as seeding. In seeding, by using crystals of a chemical having a known form—here Form B—the same chemical dissolved in that solution will tend to add on to the seed crystal, and thus, will crystallize in accordance with the same crystal pattern, and thus will also form Form B. The '393 Patent authors state that the seed is Form B, which suggests that they must have analyzed its PXRD pattern or had some means to verify this fact.

62. In both the Phares Reference (Ex. 1005) and the '393 Patent (Ex. 1001 col. 12-13), treprostinil diethanolamine salt Form B is made. Phares demonstrated that Form B is the more stable form as compared to Form A. (Ex. 1005 at 88-93). Phares further discloses a Form B melting point for a sample (T_s) determined by DSC of 107° C. (Ex. 1005 at 91 ("Form B appears to be a crystalline material which melts at 107 °C").)

63. The '393 Patent discloses for Form B salt samples having melting point ranges (T_s) determined by thermal microscopy of 104.3-106.3, 105.5-107.2, 104.7-106.6, and 105-108°C, (Ex. 1001 col.12-13, Table,) and 105.0-106.5 and 104.5-105.5°C, (Ex. 1001 col. 13 ll. 50-65).

VIII. NO MATTER HOW FORM B IS MADE, FORM B HAS A SINGLE, DEFINED MELTING POINT

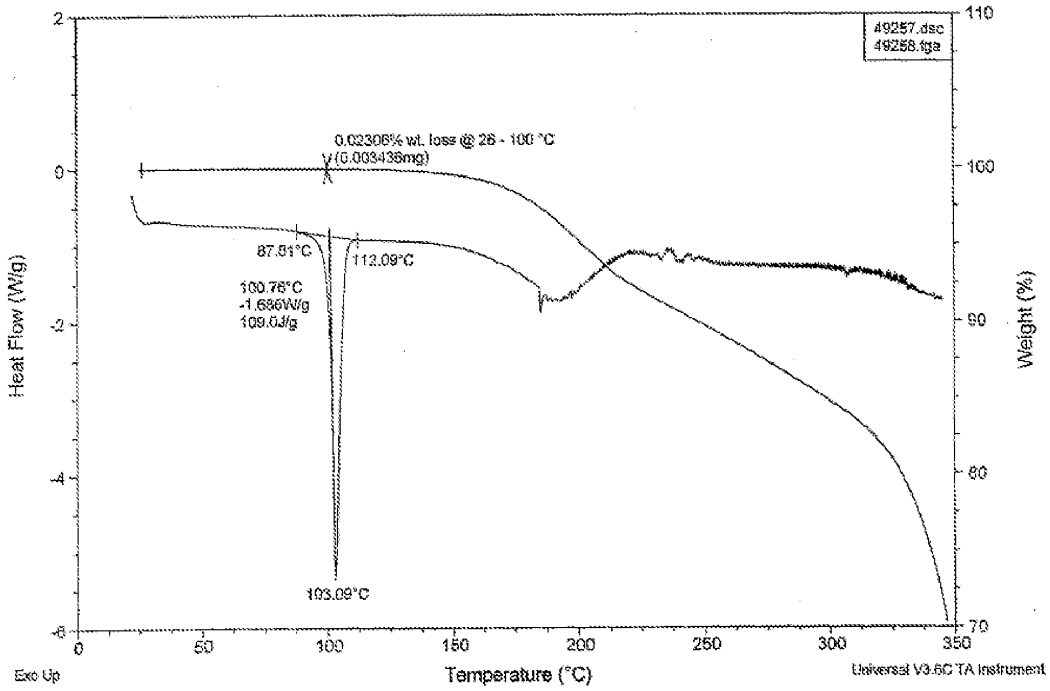
64. No matter how Form B is made, Form B has a single, defined melting point. If impurities are present, the apparent melting point may decrease due to a phenomenon called "melting point depression," but the melting point of a pure substance never changes.

A. Form A Can be Made Using a Number of Different Solvent Systems, But the Result is Still Form A

65. As shown in the Phares Reference, Form A can be made using many different solvents, listed in Table 15, including tetrahydrofuran, toluene:IPA, water, and water:ethanol. (Ex. 1005 at 88-89 (Table 15).) Each of these Form A crystals is the same polymorph, and will have the same melting point for the pure material (T_0 in Equation 5.2). The melting point identified in the Phares Reference for Form A is 103°C.

66. The 103°C corresponds to the following DSC thermogram, depicted in Figure 18 of the Phares Reference (Ex. 1005) below, which shows that the 103°C melting point corresponds to the temperature at the peak.

FIGURE 18



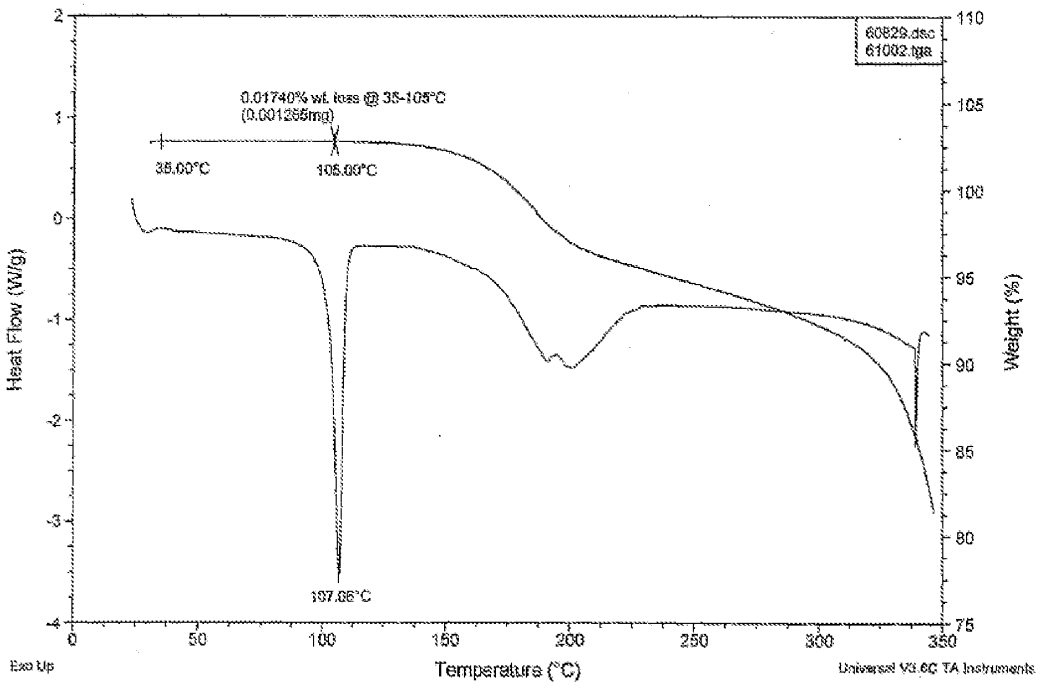
67. The Phares Reference states: "[t]he DSC thermogram shows an endotherm at 103°C that is consistent with melting (from hot stage microscopy)." (Ex. 1005, at 90). In other words, DSC and hot-stage microscopy provide the same result.

B. Form B Can be Made Using a Number of Different Solvent Systems, But the Result is Still Form B

68. As shown in the Phares Reference, Form B can be made using many different solvents, listed in Table 16, including 1,4-dioxane, isopropanol, and toluene. (Ex. 1005 at 89 (Table 16)). Each of these Form B crystals is the same polymorph, and will have the same melting point for the pure material (T_0 in Equation 5.2). The melting point identified in the Phares Reference for Form A is 107°C.

69. The 107°C corresponds to the following DSC thermogram, depicted in Figure 21 of the Phares Reference (Ex. 1005) below, which shows that the 107°C melting point corresponds to the temperature at the peak.

FIGURE 21



70. The Phares Reference states: "[t]he DSC thermogram (Sample ID 1557-17-01) shows a single endotherm at 107°C that is consistent with a melting event (as determined by hotstage microscopy)." (Ex. 1005 at 91). In other words, DSC and hot-stage microscopy provide the same result.

C. The Form B Crystals Made in the Phares Reference Have the At Least the Same Purity as the Form B Crystals Made in the '393 Patent.

71. Since we do not know whether the Form B crystal in the Phares Reference is 100% pure, T_0 (the melting point of 100% pure material) is or exceeds 107°C.

72. As stated above, the observed melting temperature, T_s, for the Form B crystal made in the Phares Reference is 107°C. The '393 Patent reports melting point ranges of 104.3-106.3 °C; 104.7-106.6 °C; 105.0-106.5 °C; and 104.5-105.5 °C. (Ex. 1001, col. 12-13).

73. This comparison of T_s values shows that there is a greater percentage of impurities, X_i, in the '393 Patent Form B batches listed above than in the Phares Reference example. This scientific result is required by Equation 5.2 above, because, for Form B samples, every value in the equation except T_s and X_i is a constant, such that any change in the observed melting temperature, T_s, is necessarily due to a change in impurities, X_i.

74. In conclusion, the higher melting point disclosed in the Phares Reference is consistent with the Form B crystal in the Phares Reference having higher purity than certain of the '393 Patent's Form B crystals, in accordance with Equation 5.2. At the very least, the Phares Reference Form B crystal is at least as pure as any Form B crystal made in the '393 Patent.

D. The *Adhiyaman* reference, Ex. 2030, Does Not Suggest that Form B Crystals Made with Different Solvents Would Have Different Pure Melting Points T_0

75. I understand that United Therapeutics contends that a paper entitled "Crystal modification of dipyridamole using different solvents and crystallization conditions," appearing in *International Journal of Pharmaceutics* 321:27-34 (2006) (Ex. 2030, "Adhiyaman")), supports its contention that two crystals having the same crystal form could have differing T_0 melting point values if made from different solvents. But this paper does not support this conclusion.

76. United Therapeutics argues that, because in the '393 Patent (Ex. 1001 col.12 ll.35-52), treprostinil diethanolamine Form B was made by seeding already-made Form B crystals in a mixed solvent of ethanol and ethanol acetate, while in the Phares Reference (Ex. 1005), treprostinil diethanolamine Form B salt was made by first generating Form A from any of many possible mixed solvents, and then converting Form A to Form B in a second mixed solvent, the two Form Bs could have different T_0 melting point values.

77. As explained above, Form B salt has the same T_0 melting point value, no matter what technique is used to make it.

78. In Adhiyaman, different crystal forms of a drug called "dipyridamole" were made by using three different solvents, including methanol, benzene, and acetonitrile. In each case, the PXRD pattern of the crystals made from each solvent

were different. The differences in PXRD pattern are shown in Figure 3. (Ex. 2030 at 4.)

79. When two crystals have a different PXRD pattern, they are different crystal forms or polymorphs. PXRD patterns are fingerprints for polymorphs.

80. Since each of the crystals generated by using methanol, benzene, and acetonitrile as solvents, in the case of dipyridamole, generate a different crystal form, each crystal form would be expected to have a different T_0 value.

81. By contrast, the crystals generated by United Therapeutics in the '393 Patent and the Phares Reference were both characterized by United Therapeutics as the same crystal form, which United Therapeutics has named Form B.

82. Thus, unlike the case of dipyridamole in Ex. 2030, the crystals being compared in the '393 Patent and Phares Reference are the same crystal form, and thus have the same T_0 pure melting point value. Any difference in their measured melting point, T_s, is due to differing levels of impurities.

E. The Phares Reference Correctly Determined the Melting Point as 107°C, and the Width of the DSC Peak is Narrow

83. I disagree with United Therapeutics' suggestion that the DSC melting point determined in the Phares Reference "shows a broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance." (Patent Owner's Response, at 23.)

84. The peak in the Phares Reference Figure 21 (Ex. 1005 at 121) is quite narrow and sharp. To determine the 107.06°C melting point, most likely the DSC's on-board computer software was used.

85. According to Figure 21, the figure was generated using software called "Universal V3.6C" from TA Instruments, a leading manufacturer of DSC, TGA, and simultaneous DSC/TGA instruments. I am familiar with this manufacturer's equipment, and I know that this equipment comes with on-board software that automatically calculates melting points for the user.

86. The software is designed to correctly assign the melting point and United Therapeutics itself in the Phares Reference confirmed that the value was consistent with hot-stage microscopy.

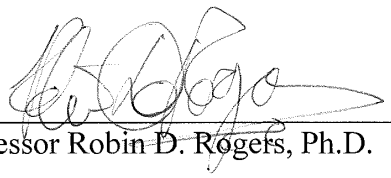
87. The width of the peak is actually very narrow. The onset of the melting event is determined by plotting a tangent straight line (as shown by Figure 18 of the Phares Reference) from the left side of the peak. Such a tangent line is not shown in Figure 21, but is shown on Figure 18 for Form A, where it appears at 100.76°C, which is marked by an "X" on the TGA curve. This same "X" is marked in Figure 21 of Phares at 105.00°C, which marks the onset temperature. Thus, the width of the peak is only 2°C, which is quite narrow and typical of a highly pure chemical.

IX. CONCLUSION

88. In summary, no matter how Form B is made, Form B has a single, defined melting point, and since the Phares Reference (Ex. 1005) discloses the same Form B crystal form as the '393 Patent (Ex. 1001), but a higher melting point than most of the '393 Patent examples, Phares necessarily discloses a salt of at least equal purity to the salt in the '393 Patent, if not higher.

I declare under penalty of perjury that the foregoing is true and correct.

Date: September 27, 2016



Professor Robin D. Rogers, Ph.D.

Dr. Robin D. Rogers
Canada Excellence Research Chair in Green Chemistry and Green Chemicals
Editor, *Crystal Growth & Design*

Department of Chemistry
Otto Maass Chemistry Building
McGill University
801 Sherbrooke St. West
Montreal, QC
Canada H3A 0B8

Email: Robin.Rogers@McGill.ca
URL: http://rdrogers.research.mcgill.ca/
URL (CGD): http://pubs.acs.org/crystal

Date of Birth: March 4, 1957

Schools Attended and Degrees:

1975-1978: The University of Alabama, Tuscaloosa, AL; Chemistry Honors student; B.S. Degree in Chemistry (ACS); Summa Cum Laude.

1978-1982: The University of Alabama, Tuscaloosa, AL; Ph.D. in Inorganic Chemistry; Research Advisor: Professor Jerry L. Atwood.

Positions:

1982-1987:	Assistant Professor, Northern Illinois University, DeKalb, IL, USA
1987-1994:	Associate Professor, Northern Illinois University, DeKalb, IL, USA
1994-1995:	Professor, Northern Illinois University, DeKalb, IL, USA
1995-1996:	Presidential Research Professor, Northern Illinois University, DeKalb, IL, USA
1996-2014:	Professor, The University of Alabama, Tuscaloosa, AL, USA
1998-2014:	Director, The University of Alabama, Center for Green Manufacturing, Tuscaloosa, AL, USA
2004-2014:	Distinguished Research Professor, The University of Alabama, Tuscaloosa, AL, USA
2005-2014:	Robert Ramsay Chair of Chemistry, The University of Alabama, Tuscaloosa, AL, USA
2007-2009:	Chair of Green Chemistry, The Queen's University of Belfast, Belfast, Northern Ireland, United Kingdom
2007-2009:	Director, QUILL Research Centre, The Queen's University of Belfast, Belfast, Northern Ireland, United Kingdom
2015-:	Canada Excellence Research Chair in Green Chemistry and Green Chemicals, McGill University, Montreal, QC, Canada

Adjunct, Honorary, and Visiting:

1982 (summer):	Visiting Assistant Professor, The University of Alabama, Tuscaloosa, AL
1991-1998:	Resident Associate Guest (91-92), Visiting Scientist (92-93), Faculty Appointee (93-97), Guest Appointee (97-98), Argonne National Laboratory, Argonne, IL
1995-1996:	Adjunct Professor, The University of Alabama, Tuscaloosa, AL
1996-1997:	Adjunct Professor, Northern Illinois University, DeKalb, IL
2000 & 2006:	Visiting Professor, Université Louis Pasteur, Strasbourg, France
2004:	Adjunct Professor, Polymer and Fiber Engineering, Auburn University, Auburn, AL
2004:	Adjunct Professor, Department of Biological Sciences, The University of Alabama, Tuscaloosa, AL
2009-:	Honorary Professor, Institute for Process Engineering, Chinese Academy of Sciences, Beijing, China
2010:	Visiting Professor for Senior International Scientists of the Chinese Academy of Sciences, Institute for Process Engineering, Beijing, China
2014:	Adjunct Professor, McGill University, Montreal, QC, Canada
2015-:	Adjunct Professor, The University of Alabama, Tuscaloosa, AL

Memberships and Offices in Societies:

- Phi Beta Kappa; Sigma Xi, American Nuclear Society; American Crystallographic Association; American Institute of Chemical Engineers; Materials Research Society; American Association of Crystal Growth; Fellow of the American Association for the Advancement of Science; Fellow of the Royal Society of Chemistry; Chemical Institute of Canada; National Academy of Inventors.
- American Chemical Society: Rock River Local Section: Chairman Elect (Program Chairman), 1983-84; Chairman, 1984-86; Executive Committee, 1986-87; Secretary-Treasurer, 1988. Separation Science and Technology Subdivision (Industrial and Engineering Chemistry (I&EC)): Program Committee, 1992-2005; Executive Committee, 1993-2006; Vice Chair-Elect, 1993; Chair-Elect, 1994; Chair, 1995; Past-Chair, 1996. Practical Pollution Prevention Subdivision (I&EC): Co-Chair, 1998-99. Green Chemistry & Engineering Subdivision (I&EC): Program Committee, 2000-2006. I&EC Division: Program Committee, 1994-2002; Membership Committee (Academic Chemists Task Force Chair), 1996-2000; Executive Committee, 1995-2006; Program Secretary, 1995-98 ; Chair-Elect, 1998; Chair, 1999; Past-Chair, 2000; Parliamentarian, 2004-2006; I&EC Fellow, 2012. Committee on Science, 2004-06; Fellow of the American Chemical Society, 2009; Committee on Environmental Improvement, Associate 2010-2011; Member 2011-.

Advisory Boards:

- Scientific Advisory Board, EIChroM Industries, Inc., Darien, IL, 1995-2000.
- The University of Alabama College of Arts and Sciences Leadership Board, 1997-2002.
- Technology Review Council, Environmental Technology Demonstration and Commercialization Center (ETDCC), Texas City, TX, 1998-2000.
- Scientific Advisory Board, U.S. Department of Energy Joint Bioenergy Institute, Berkeley, CA, 2010-
- Scientific Advisory Board, Alkermes, Inc., Waltham, MA, 2012.

Editorial Boards and Editorships:

- *Journal of Crystallographic and Spectroscopic Research*: Editorial Board, 1989-93; Associate Editor, 1993
- *Journal of Chemical Crystallography*: Associate Editor, 1994-96; Editor, 1996-2000
- *Separation Science and Technology*: Associate Editor, 1996-99; Editorial Board 1999-
- *Crystal Engineering*: Founding Co-Editor, 1998-99
- *Industrial & Engineering Chemistry Research*: Editorial Board, 1999-2001
- *Journal of Chromatography, B*, Guest Editor, Volume 743 (1 + 2), 2000
- *Crystal Growth & Design*: Founding Editor-in-Chief, 2000-
- *Solvent Extraction and Ion Exchange*, Editorial Board, 2002-
- *Green Chemistry*, Advisory Board, 2002-
- *Chemical Communications*, Advisory Board, 2005-
- *Accounts of Chemical Research*, Guest Editor (with G. A. Voth), Special Issue on Ionic Liquids, Volume 40(11), 2007
- *ChemSusChem*, International Advisory Board, 2008-
- *Chemistry Letters*, Advisory Board, 2010-
- *Australian Journal of Chemistry*, Guest Editor (with K. R. Seddon), Research Front on Crystal Engineering, Volume 63(4), 2010
- *Separation Science & Technology*, Guest Editor (with H. Rodriguez and J. Chen), Special Issue on Ionic Liquids (2012).
- *Chemical Communications* Guest Editor (with D. MacFarlane and S. Zhang), Special Issue on Ionic Liquids (2012).
- *Science China – Chemistry* Guest Editor (with S. Zhang), Special Issue on Ionic Liquids (2012).
- *Catalysis Today* Guest Editor (with S. Zhang), Special Issue on Ionic Liquids (2012).
- *Green Chemistry and Sustainable Technology*, Springer, Heidelberg, Germany, Book Series Editor (with L.-N. He, D. Su, P. Tundo, and Z. C. Zhang).
- *Chimica Oggi/Chemistry Today*, Scientific Advisory Board, 2014-
- *Green Energy & Environment*, Advisory Board, 2016-

National Academy of Sciences Committees:

- National Academy of Sciences Board on Radioactive Waste Management Committee on Long Term Research Needs for High-Level Waste at Department of Energy Sites, 1999-2001.

- National Academy of Sciences Board on Radioactive Waste Management Committee on Risk-Based Approaches for Transuranic and High-Level Radioactive Waste, 2003-2005.
- National Academy of Sciences Board on Radioactive Waste Management Committee Development and Implementation of a Cleanup Technology Roadmap, 2007-2009.

Awards:

- Northern Illinois University Outstanding Faculty Advisor - 1993
- Northern Illinois University Presidential Research Professor – 1995
- American Chemical Society Newsmaker Award – 2001 ("ACS Newsmakers honored in Chicago," *Chemical & Engineering News*, September 24, 2001, p 49.)
- The University of Alabama College of Arts & Sciences Leadership Board Fellow – 2002-2005
- The University of Alabama Burnum Distinguished Faculty Award – 2003.
- The University of Alabama Distinguished Research Professor – 2004
- The University of Alabama Robert Ramsay Chair of Chemistry - 2005
- 2005 Presidential Green Chemistry Challenge Award (Academic): "A Platform Strategy Utilizing Ionic Liquids to Dissolve and Process Cellulose for Advanced New Materials," – 2005 (Ritter, S. K. "Green Success," *Chemical & Engineering News*, June 27, 2005, pp 40-43.)
- Fellow of the Royal Society of Chemistry - 2006
- The University of Alabama Frederick Moody Blackmon – Sarah McCorkle Moody Outstanding Professor Award - 2009
- Fellow of the American Chemical Society – 2009
- Chinese Academy of Sciences Visiting Senior Scientist, Institute for Process Engineering, Beijing, China -2010
- American Chemical Society Award in Separations Science and Technology – 2011
- Fellow of the American Chemical Society Division of Industrial & Engineering Chemistry - 2012
- Fellow of the American Association for the Advancement of Science – 2012
- Paul Walden Award in Ionic Liquids, Presented by the German Science Foundation Priority Program on Ionic Liquids (SPP 1191) – 2013
- Thomson Reuters Highly Cited Researchers List 2014, 2015 (ranking among the top 1% most cited in chemistry).

Student Awards:

- Ann E. Visser: American Institute of Chemical Engineers Separations Division Graduate Student Award in Solvent Extraction – 2002
- Richard P. Swatloski: ACS Kenneth G. Hancock Memorial Student Award in Green Chemistry – 2003 ("2003 Hancock Award Honors Student Research," *Chemical & Engineering News*, July 7, 2003, pp 67-68.)

Research Interest:

Utilizing Ionic Liquids and Green Chemistry for Sustainable Technology Through Innovation. Major thrusts include: **Materials:** Advanced polymeric and composite materials from biorenewables; **Separations**: Novel strategies for separation and purification of value added products from biomass; **Energy:** New lubricant technologies and selective separations; **Medicine/Agrochemicals/Nutraceuticals:** Elimination of waste while delivering improved performance and new applications of pharmaceuticals, agrochemicals, and nutraceuticals.

Statistics:

A. Refereed Publications: > 760
B. Citations; H-Index: > 35,000; 84
C. Patents: 21 issued (plus numerous foreign equivalents); 26 submitted; 9 licensed
D. Books Edited: 14
E. Non-Refereed Reviews, Reports, and Articles: 75
F. Meetings (Symposia) Organized: 33 (37)
G. Presentations (including students and collaborators) before National and International Meetings: 897
H. Presentations (including students and collaborators) before Regional Meetings: 119
I. Seminars: 227
J. PhD (thesis MS) degrees supervised: 27 (4)

Financial Disclosure:

Dr. Robin D. Rogers has partial ownership of 525 Solutions, Inc., Chitinality LLC, and Iolitec, Inc. in addition to financial interest in patents and patent applications through The University of Alabama.

Meetings Organized:

- Chair, *23rd Great Lakes Regional American Chemical Society Meeting*, DeKalb, IL, 1990.
- Conference Chair, *11th International Conference on Partitioning in Aqueous Two-Phase Systems: The Expanding Boundaries of Aqueous Two-Phase Partitioning: Fundamentals and Applications of Environmentally-Benign Polymers in Biological, Industrial and Environmental Processes*, Gulf Shores, AL June 27-July 2, 1999. (Conference URL: http://bama.ua.edu/~rdrogers/aq2phase/11thconf.html.)
- Co-Director (with K. R. Seddon and S. Volkov), NATO Advanced Research Workshop: *Green Industrial Applications of Ionic Liquids*, Crete, Greece, April 12-16, 2000. (Conference URL: http://bama.ua.edu/~rdrogers/NATO.) (Highlighted in Freemantle, M. "Eyes On Ionic Liquids," *Chemical & Engineering News*, May 15, 2000, pp 37-50.)
- Organizer, *Industries of the Future Alabama Symposium: Sustainable Industry through Green Chemistry and Engineering*, Mobile, AL July 27-28, 2000. (Conference URL: http://bama.ua.edu/~rdrogers/IOF/Mobile.)
- Co-Vice Chair (with J. C. Warner), *Gordon Research Conference on Green Chemistry*, Oxford, United Kingdom, September 8-13, 2002.
- Co-Chair (with A. S. Myerson, S. M. Reutzel-Edens, and R. J. Davey), ACS ProSpectives Series: *Polymorphism in Crystals: Fundamentals, Prediction, and Industrial Practice*, Tampa, FL, February 23-27, 2003.
- Co-Chair (with A. S. Myerson, and S. M. Reutzel-Edens), ACS ProSpectives Series: *Polymorphism in Crystals*, Tampa, FL, February 8-11, 2004.
- Organizer, *Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications*, Tuscaloosa, AL, March 23-24, 2004 (Workshop URL: http://www.bama.ua.edu/~rdrogers/ILWorkshop04/).
- Co-Chair (with J. C. Warner), *Gordon Research Conference on Green Chemistry*, Bristol, RI, July 4-9, 2004 (Conference URL: http://bama.ua.edu/~rdrogers/GreenChemistryGRC04).
- U.S. Organizer, NSF Joint China-USA Workshop *Determining the Grand Challenges of Green Chemistry Development and Implementation*, Beijing, China, May 27-31, 2005.
- Organizer, EPA/Green Chemistry Institute Workshop *Incorporating Toxicology into the Design Criteria for New Ionic Liquids Synthesis*, Washington, DC, June 9-10, 2005.
- Program Chair, 2nd International Conference on Green and Sustainable Chemistry; 9th Annual Green Chemistry and Engineering Conference: *Taking Measure of Green Progress: Opportunities to Meet Global Challenges*, Washington, DC, June 20-24, 2005.
- Program Chair, *2005 Rare Earth Research Conference*, Keystone, CO, June 26-30, 2005.
- Co-Organizer (with D. A. Dixon), *Alabama Actinide Day*, April 6, 2005, Tuscaloosa, AL.
- Local Organizer, *Air Force Office of Scientific Research Ionic Liquids Research Workshop*, Tuscaloosa, AL, February 7-8, 2006.
- Organizer, *Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications*, Tuscaloosa, AL, March 23-24, 2006 (Workshop URL: http://www.bama.ua.edu/~rdrogers/ILWorkshop06/).
- Co-Chair (with A. S. Myerson) ACS ProSpectives Series: *Process Crystallization in the Pharmaceutical and Chemical Industries*, Philadelphia, PA, April 25 - 27, 2006.
- Co-Chair (with M. Maase) Intertech Pira Conference *Ionic Liquids: Technical Innovations, Emerging Markets and Applications*, Orlando, FL, December 11-13, 2006.
- Co-Chair (with A. S. Myerson) ACS ProSpectives Series: *Crystallization Process Development: Case Studies & Research*, Boston, MA, February 25-27, 2007.
- Organizing Committee (with K. R. Seddon and J. F. Brennecke), *Biodegradability and Toxicity of Ionic Liquids*, Berlin, Germany, May 6-9, 2007.
- Chair, Intertech Pira Conference *Ionic Liquids: Technical Innovations, Emerging Markets and Applications*, Prague, Czech Republic, October 16-18, 2007.
- Co-Chair (with M. Hong), *5th Chinese National Symposium on Structural Chemistry and Symposium on Chinese Strategy of* Crystal Growth & Design," Fuzhou, China, October 25-31, 2007.
- Conference Chair, *25th Rare Earth Research Conference*, Tuscaloosa, AL, June 22-26, 2008.
- Organizer/Lecturer, *1st Ionic Liquid Workshop Malaysia*, University of Technology PETRONAS, Tronoh, Malaysia, June 30 – July 11, 2008.
- Local Organizing Committee, *15th International Conference on Biopartitioning and Purification*, Brunel University, Uxbridge, UK, June 14-19, 2009.
- Co-Chair (with T. Beyersdorff), Intertech Pira Conference *Ionic Liquids*, Miami Beach, FL, November 18-19, 2009.
- Vice Chair, *Gordon Research Conference on Crystal Engineering*, Waterville Valley, NH, June 6-11, 2010.

- Co-Organizer (with G. Desiraju), *Crystal Growth & Design-India Summit* and *Current Trends in Crystal Engineering Research,* Bangalore, India, December 2-3, 2010.
- Conference Chair, *4th Congress on Ionic Liquids*, Washington, DC, June 15-18, 2011.
- Chair, *Gordon Research Conference on Crystal Engineering*, Waterville Valley, NH, June 10-15, 2012.
- Co-Chair (with S. Zhang*), 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes*, APCIL'12, Beijing, China, September 17-19, 2012.
- Theme Organizer, "Chemistry & Global Stewardship" for the 248th ACS National Meeting (2014), San Francisco, CA, August 10-14 2014.
- Chair, *Gordon Research Conference on Ionic Liquids*, Newry, ME, August 17-22, 2014.
- Organizer/Host, 2015 New Journal of Chemistry Symposium *New Directions in Chemistry*, Montreal, QC Canada, June 3, 2015.

Symposia Organized:

- "Aqueous Biphasic Separations: Biomolecules to Metal Ions," (with C. K. Hall) for the 207th ACS National Meeting (1994), San Diego, CA.
- "Lanthanide Coordination Chemistry," for the Rare Earth Research Conference (1996), Duluth, MN.
- "Current Trends in Applied Chemistry: The Industrial/Academic Interface in Separation Science," for the 213th ACS National Meeting (1997), San Francisco, CA.
- "Recent Advances in Metal Ion Separation and Preconcentration," (with M. L. Dietz and A. H. Bond) for the 214th ACS National Meeting (1997), Las Vegas, NV.
- "Crystal Engineering: Functional Solids by Design," (with M. J. Zaworotko) for the Fifth Chemical Congress of North America (1997), Cancún, Mexico.
- "Transactions Symposium: Crystal Engineering," (with M. J. Zaworotko) for the American Crystallographic Association Annual Meeting (1998), Arlington, VA.
- "Nuclear Separations for Radiopharmacy," (with M. L. Dietz and A. H. Bond) for the 216th ACS National Meeting (1998), Boston, MA.
- "Calixarene Molecules for Separations," (with G. Lumetta and A. S. Gopolan) for the 217th ACS National Meeting (1999), Anaheim, CA.
- "Toward Vision 2000: Sustainable Technology for the Future," (with A. Manheim and A. H. Bond) Poster Session for the 217th ACS National Meeting (1999), Anaheim, CA.
- "Synthesis of New Materials by Coordination Chemistry, Self Assembly and Template Formation," (with M. J. Zaworotko) for the 217th ACS National Meeting (1999), Anaheim, CA.
- "Crystal Engineering," Microsymposium 110D (G. R. Desiraju, Chair; M. J. Zaworotko and R. D. Rogers, Co-Chairs) for the XVIIIth International Union of Crystallography Congress and General Assembly (1999), Glasgow, Scotland, UK.
- "Separation Science and Technology Award Honoring E. Philip Horwitz: Solvent Extraction and Ion Exchange in the 21st Century," (with S. Alexandratos) for the 219th ACS National Meeting (2000), San Francisco, CA.
- "Advances in Solvent Selection and Substitution for Extraction," (with M. Overcash) for the 2000 Spring National AIChE Meeting (2000), Atlanta, GA.
- "Crystal Engineering," (with W. T. Pennington) for the 52nd Southeast/56th Southwest Combined Regional Meeting of the ACS (2000), New Orleans, LA.
- "Separation Science: Trends for the New Century," (with S. Alexandratos, A. Jyo, and M. J. Zaworotko) for the 2000 International Chemical Congress of Pacific Basin Societies, Pacifichem 2000 (2000), Honolulu, HI.
- "Green (or Greener) Industrial Applications of Ionic Liquids," (with K. R. Seddon) for the 221st ACS National Meeting (2001), San Diego, CA (URL: http://bama.ua.edu/~rdrogers/sandiego).
- "Crystal Engineering to Crystal Growth: Design and Function," (with A. S. Myerson and K. R. Seddon) for the 223rd ACS National Meeting (2002), Orlando, FL.
- "Ionic Liquids as Green Solvents: Progress and Prospects," (with K. R. Seddon) for the 224th ACS National Meeting (2002), Boston, MA (URL: http://bama.ua.edu/~rdrogers/Boston).
- "Ionic Liquids III: Fundamentals, Progress, Challenges, and Opportunities," (with K. R. Seddon) for the 226th ACS National Meeting (2003), New York, NY (URL: http://bama.ua.edu/~rdrogers/New York).
- "Ionic Liquids in Polymer Systems," (with C. S. Brazel) for the 227th ACS National Meeting (2004), Anaheim, CA (Highlighted in Freemantle, M. "Designer Liquids in Polymer Systems," *Chemical & Engineering News*, May 3, 2004, pp 26-29.)

- "Polymorphism," Microsymposium MS04 (with E. Vlieg) for the XXth International Union of Crystallography Congress and General Assembly (2005), Florence, Italy.
- "Lanthanide-containing Functional Edifices," (with J.-C. Bunzli, H. Tsukube, and J. Takats) for the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI.
- "Ionic Liquids: Perspectives on the Present, Visions for the Future" (with J. Davis, Jr., D. MacFarlane, and H. Ohno) for the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI.
- "Organic Reactions in Neoteric Media" (with C.-J. Li, T.-H. Chan, D. H. Busch, S. Kobayashi, and P. Jessop) for the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI.
- "Ionic Liquids: Not Just Solvents Anymore OR Ionic Liquids: Parallel Futures," (with J. F. Brennecke and K. R. Seddon) for the 231st ACS National Meeting (2006), Atlanta, GA (URL: http://bama.ua.edu/~rdrogers/Atlanta2006/)
- "Green Chemistry and Engineering" (with M. A. Abraham) within the Joint ACS/AIChE Symposium on "Applied Chemistry and Engineering" for the 233rd ACS National Meeting (2007), Chicago, IL.
- "Award in Separations Science and Technology: Symposium in Honor of Allen S. Myerson," for the 235th ACS National Meeting (2008), New Orleans, LA.
- "Ionic Liquids: From Knowledge to Application," (with J. F. Brennecke and K. R. Seddon) for the 236th ACS National Meeting (2008), Philadelphia, PA (URL: http://bama.ua.edu/~rdrogers/Philadelphia2008/).
- "Green Chemistry for a Sustainable World," for the 239th ACS National Meeting (2010), San Francisco, CA.
- "Symposium in Honor of Allan S. Myerson, I&EC Fellow," for the 239th ACS National Meeting (2010), San Francisco, CA.
- "Ionic Liquids in a Sustainable World (#92)" (with D. MacFarlane and H. Ohno) for the 2010 International Chemical Congress of Pacific Basin Societies, Pacifichem 2010 (2010), Honolulu, HI.
- "Ionic Liquids: Science and Applications" (with A. E. Visser and N. J. Bridges) for the 243rd ACS National Meeting (2012), San Diego, CA.
- "Functional Materials and Ionic Liquids (BBB)" (with S. Dai, T. P. Lodge, P. Wasserscheid, and M. Watanabe) for the 2012 Materials Research Society Spring Meeting (2012), San Francisco, CA.
- "Uranium from Seawater" (with S. Dai and B. Hay) for the 244th ACS National Meeting (2012), Philadelphia, PA.
- "Materials Applications of Ionic Liquids (VV)" (with R. E. Del Sesto, S. Dai, and Y. Yoshida) for the 2013 Materials Research Society Spring Meeting (2013), San Francisco, CA.
- "Uranium from Seawater" (with P. F. Britt) for the 249th ACS National Meeting (2015), Denver, CO.
- "Transactions Symposium: Crystallography for Sustainability," (with C. Lind-Kovacs) for the American Crystallographic Association Annual Meeting (2015), Philadelphia, PA.
- "Connecting Ionic Liquids to Societal Issues: Materials, Medicines, Energy, and Water (#113)" (with D. MacFarlane and H. Ohno) for the 2015 International Chemical Congress of Pacific Basin Societies, Pacifichem 2015 (Dec. 14-21, 2015), Honolulu, HI.
- "Pharmaceutical Ionic Liquids: Understanding, Design, and Utilization," for the Molecules, Materials, Medicines (M3) Meeting (May 14-17, 2016), Solomons Island, MD.

Other Professional Activities:

- International Advisory Board member for the 9th International Conference on Partitioning in Aqueous Two-Phase Systems, Zaragoza, Spain, 1995.
- International Advisory Board member for the 6th Conference on Separation of Ionic Solutes, Piestany Spa, Slovakia, 1995.
- International Scientific Committee member for the 10th International Conference on Partitioning in Aqueous Two-Phase Systems, Reading, United Kingdom, 1997.
- Program Committee for the Tenth Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 1997.
- Program Committee for the Third Department of Energy/Basic Energy Sciences Separations Research Workshop, Savannah, GA, 1999.
- Program Committee for the Eleventh Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 1999.
- Steering Committee Member for *Chemistry in the 21st Century*, *ACS-2000*, San Francisco, CA, 2000.
- Program Committee for IUPAC CHEMRAWN XIV World Conference, Toward Environmentally Benign Processes and Products, Boulder, CO, 2001.

- Program Committee for the Twelfth Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 2001.
- Chair, Scientific Committee for Bio Partitioning & Purification 2003 Conference, Vancouver, BC, Canada, 2003.
- Instructor, NSF/DOE Pan American Advanced Studies Institute (PASI) on Green Chemistry, Montevideo, Uruguay, 2003.
- International Symposium Committee for the First International Symposium on Process Intensification and Miniturisation, Newcastle upon Tyne, United Kingdom, 2003.
- Program Committee for the Thirteenth Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 2003.
- Scientific Committee for the International Conference on Materials for Advanced Technologies (ICMAT 2003)/International Union of Materials Research Societies International Conference in Asia (ICA 2003), Singapore, Symposium D: New Materials by Crystal Engineering Design.
- Group of Advisors, LICP Discussions No. 1 - Ionic Liquids: Progress and Prospects, Lanzhou China, 2004.
- Organizing and Scientific Advisory Committee, Canada-US Joint Workshop on Innovative Chemistry in Clean Media, Montreal, Quebec, Canada, 2004.
- International Program Committee, EUCHEM 2004 Molten Salts Conference, Piechowice, Poland, 2004.
- Instructor, ACS-PRF Summer School on Green Chemistry, Pittsburgh, PA, 2004.
- International Advisory Board, 1st International Congress on Ionic Liquids (COIL), Salzburg, Austria, 2005.
- Program Committee for the Fourteenth Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 2005.
- Advisory Board, Second International Symposium on Green/Sustainable Chemistry, Delhi, India, 2006.
- Organizing Committee 10th Annual Green Chemistry and Engineering Conference: Washington, DC, 2006.
- Scientific Committee, EUCHEM Conference on Molten Salts and Ionic Liquids, Hammamet, Tunisia, 2006.
- International Advisory Committee, International Conference and Exhibition on Green Chemistry, Malaysian Chemical Congress (MCC 2006), Kuala Lumpur, Malaysia, 2006.
- Advisory Committee, DAE-BRNS Biennial Symposium on Emerging Trends in Separation Science and Technology, SESTEC-2006, Mumbai, India, 2006.
- Organizing Committee, 11th Annual Green Chemistry and Engineering Conference, Washington, DC, 2007.
- International Organizing Committee, 2nd International Congress on Ionic Liquids (COIL-2), Yokohama, Japan, 2007.
- Organizing Committee, International Solvent Extraction Conference (ISEC 2008) "Solvent Extraction: Fundamentals to Industrial Applications," Tucson, AZ, 2008.
- International Advisory Board, EUCHEM2008 Conference on Molten Salts and Ionic Liquids, Copenhagen, Denmark, 2008.
- Scientific Advisory Board, Taibah International Chemistry Conference 2009 (TICC-2009), Al-Madinah Al-Munawarah, Saudi Arabia, 2009.
- International Advisory Board for the Joint Conference: The 4th International Conference on Green and Sustainable Chemistry (GSC-4) & the 2nd Asian-Oceanian Conference on Green and Sustainable Chemistry (AOC-2), Beijing, China, 2009.
- International Advisory Committee for the 9th International Workshop on the Crystal Growth of Organic Materials (CGOM9), Singapore, 2010.
- International Advisory Committee for Application of Radiotracers in Chemical, Environmental and Biological Sciences (ARCEBS 10), Kolkata, India, 2010.
- Scientific Committee for 2nd Asian Pacific Conference on Ionic Liquids and Green Processes (APCIL-2), Dalian, China, 2010.
- International Advisory Board for the Green Solvents Conference, Berchtesgaden, Germany, 2010.
- Chair The Rare Earth Research Conference Spedding Award Committee, 2011.
- Technical Committee, International Solvent Extraction Conference (ISEC 2011), Santiago, Chile, 2011.
- International Scientific Committee, 1st International Conference on Ionic Liquids in Separation and Purification Technology, Sitges, Spain, 2011.
- International Advisory Board, EUCHEM2012 Conference on Molten Salts and Ionic Liquids, Newport, South Wales, UK, 2012.
- International Advisory Board, Indo-US Workshop on Green Chemistry for Environments and Sustainable Development, Dehradun, India, March 11-13, 2012.

- International Scientific Committee, 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12, Beijing, China, September 17-19, 2012.
- International Committee, 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT), Toronto, Canada, June 29 – July 2, 2014.
- Advisory Board, 7th Green Solvents Conference, Dresden, Germany, October 19-22, 2014.
- International Advisory Board, Collaborative Conference on Crystal Growth, Phuket, Thailand, Nov. 4-7, 2014.
- International Advisory Board, *6th International Congress on Ionic Liquids (COIL-6),* Jeju, Korea, June 16-20, 2015.
- Invited Expert, meeting of the International Council for Science Project "COncepts and termiNology IN Crystal Engineering" (CONvINCE), Como, Italy, August 30, 2015.
- International Advisory Committee, Collaborative Conference on Crystal Growth (3CG 2015), Hong Kong, China, Dec. 14-17, 2015.
- Advisory Board, International Symposium on Ionic Liquids (ISOIL_2016), Mumbai, India, Jan. 21-22, 2016.
- International Advisory Committee, Energy Materials Nanotechnology Meeting on Cellulose (EMN 2016), Taipei, Taiwan, March 8-11, 2016.
- Scientific Advisory Board, EUCHEM2016, Vienna, Austria, July 3-8, 2016.
- Organizing Committee, Molecules, Materials, Medicines (M3), Solomons Island, MD, May 14-17, 2016.

Books Edited:

1. *Aqueous Biphasic Separations: Biomolecules to Metal Ions*; Rogers, R. D.; Eiteman, M. A., Eds.; Plenum: New York, 1995; 191 pp.
2. *Metal-Ion Separation and Preconcentration, Progress and Opportunities*; Dietz, M. L.; Bond, A. H.; Rogers, R. D., Eds.; ACS Symposium Series 716, American Chemical Society: Washington, DC, 1999; 418 pp.
3. *Crystal Engineering*, Rogers, R. D.; Zaworotko, M. J., Eds.; Transactions of the American Crystallographic Association, Vol. 33; American Crystallographic Association: Buffalo, NY, 1999; 177 pp.
4. *Calixarenes for Separations*; Lumetta, G.; Rogers, R. D.; Gopalan, A. S., Eds.; ACS Symposium Series 757, American Chemical Society: Washington, DC, 2000; 366 pp.
5. *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington, DC, 2002; 474 pp.
6. *Green Industrial Applications of Ionic Liquids*, NATO Science Series II. Mathematics, Physics and Chemistry – Vol. 92, Rogers, R. D.; Seddon, K. R.; Volkov, S. (Eds.); Kluwer: Dordrecht, 2003; 553 pp.
7. *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical Society: Washington, DC, 2003; 599 pp.
8. *Ionic Liquids IIIA: Fundamentals, Progress, Challenges, and Opportunities - Properties and Structure*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 901; American Chemical Society: Washington, DC, 2005; 334 pp.
9. *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities - Transformations and Processes*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington, DC, 2005; 397 pp.
10. *Ionic Liquids in Polymer Systems: Solvents, Additives, and Novel Applications*, Brazel, C. S.; Rogers, R. D. (Eds.); ACS Symposium Series 913; American Chemical Society: Washington, DC, 2005; 206 pp.
11. *Ionic Liquids IV Not Just Solvents Anymore*, Brennecke, J. F.; Rogers, R. D.; Seddon K. R. (Eds.); ACS Symposium Series 975; American Chemical Society: Washington, DC, 2007; 408 pp.
12. *Solvent Extraction: Fundamentals to Industrial Applications - Proceedings of ISEC 2008 International Solvent Extraction Conference, (ISEC 2008)*, Moyer, B. A.; Baron, P.; Chagnes, A.; Cole, P. M.; Cote, G.; Dietz, M. L.; Hatton, T. A.; Horwitz, E. P.; de Ortiz, E. S. P.; Ritcey, G. M.; Robinson, D.; Rogers, R. D.; Sole, K. C.; Tasker, P. A.; Todd, T. A.; Virnig, M. J. (Eds.); Canadian Institute of Mining, Metallurgy and Petroleum: Montréal, 2008; 1661 pp.
13. *Ionic Liquids: From Knowledge to Application*, Plechkova, N. V.; Rogers, R. D.; Seddon K. R. (Eds.); ACS Symposium Series 1030; American Chemical Society: Washington, DC, 2009; 458 pp. ISBN13: 9780841269972; eISBN: 9780841224919; DOI: 10.1021/bk-2009-1030.
14. *Ionic Liquids: Science and Applications*, Visser, A. E.; Bridges, N. J.; Rogers, R. D. (Eds.); ACS Symposium Series 1117; American Chemical Society: Washington, DC, 2012; 313 pp. ISBN 978-0-8412-2763-7; eISBN: 9780841227644; DOI: 10.1021/bk-2012-1117.

Patents:

1. Rogers, R. D.; Horwitz, E. P.; Bond, A. H. "Process for Recovering Pertechnetate Ions from an Aqueous Solution also Containing Other Ions," 2/18/97, U. S. Patent No. 5,603,834.
2. Rogers, R. D.; Horwitz, E. P.; Bond, A. H. "Process for Recovering Chaotropic Ions from an Aqueous Solution also Containing Other Ions," 3/10/99, U. S. Patent No. 5,888,397.
3. Rogers, R. D.; Horwitz, E. P.; Bond, A. H. "Process for Separating and Recovering an Anionic Dye from an Aqueous Solution," 1/13/98, U. S. Patent No. 5,707,525.
4. Mays, J. W.; Bu, L.; Rogers, R. D.; Hong, K.; Zhang, H. "Polymer Formation in Room Temperature Ionic Liquids," 8/2/05, U. S. Patent No. 6,924,341 B2; International Application PCT/US02/10091; International Publication Number WO 02/079269 A1, October 10, 2002.
5. Wu, B.; Reddy, R. G.; Rogers, R. D. "Production, Refining and Recycling of Lightweight and Reactive Metals in Ionic Liquids," 4/19/05, U. S. Patent No. 6,881,321 B2.
6. Holbrey, J. D.; Spear, S. K.; Turner, M. B.; Swatloski, R. P.; Rogers, R. D. "Cellulose Matrix Encapsulation and Method," U.S. Patent No. 6,808,557 B2 (10/26/04); ZA 2005/08446 (04/25/07); EA 009256 (09/12/07); SG 115160 (08/31/07); ZL 200480013560.5 (12/2/09); MX 277934 (08/09/10); KR 10-1064345 (09/05/11); CA 2,519,652 (07/24/12); JP 5213329 (03/08/13).
7. Swatloski, R. P.; Rogers, R. D.; Holbrey, J. D. "Dissolution and processing of cellulose using ionic liquids," U.S. Patent No. 6,824,599 B2 (11/30/04); International Publication Number WO 03/029329 A2 (04/10/03); ZA 2004/2610 (02/23/05); NZ 5,320,076 (01/12/06); ID 0 017 226 (05/4/06); AU 2002347788 (10/26/06); EA 008538 (3/20/07); KR 778793 (11/16/07); ZL 02823875.3 (01/30/08); HK 1076120 (11/28/08); JP 4242768 (01/9/09); MX 26627

(05/11/09); CA 2,462,460 (05/19/09); IL 161124 (06/29/10); EP 1458805 B1 (08/31/11); DE 60240972.1 (08/31/11); PL 206185 (12/14/11); PH 1-2004-500479 (06/29/12); CN ZL200710085298.0 (10/03/12); JP 5148436 (12/07/12); HK1108165 (07/21/13).

8. Swatloski, R. P.; Rogers, R. D.; Holbrey, J. D. "Dissolution and processing of cellulose using ionic liquids," (Divisional Patents), CN ZL200710085298.0 (10/03/12); JP 5148436 (12/07/12); EP 2325246 (11/27/13).
9. Wu, B.; Reddy, R. G.; Holbrey, J. D.; Rogers, R. D. "Ionic Liquid Temperature Sensor," 6/15/04, U. S. Patent No. 6,749,336 B2; International Application PCT/US03/00102; International Publication Number WO 03/058185 A1, July 17, 2003.
10. Holbrey, J. D.; Swatloski, R. P.; Chen, J.; Daly, D. T.; Rogers, R. D. "Polymer Dissolution and Blend Formation In Ionic Liquids." 02/15/11, U. S. Patent No. 7,888,412 B2; PCT Int. Appl. (2005) WO 2005098546 A2; SG 126235 (07/31/07); ZA 2006/08882 (06/25/08); MX 276898 (06/25/10); KR 10-1001533 (12/09/10); AU 2005231083 (03/10/11); NZ 550776 (04/05/11); ID P0028151 (05/02/11); PH 1-2006-501906 (07/22/11); CA 2560680 (11/22/11); EP 1733282 (01/04/12); DE 05729932.3 (01/04/12); JP 5203698 (02/22/13); CN ZL200580016490.3 (08/19/15).
11. Daly, D. T.; Rogers, R. D. "Method of Preparing High Orientation Nanoparticle-Containing Sheets or Films Using Ionic Liquids, and the Sheets or Films Produced Thereby," U.S. Patent No. 7,550,520 B2 (06/23/09); ID P0025079 (02/10/10); SG 137607 (06/30/10).
12. Rogers, R. D.; Daly, D. T.; Turner. M. B.; Spear, S. K.; Holbrey, J. D. "Ionic Liquid Reconstituted Cellulose Composites as Solid Support Matrices." U.S. Patent Application 60/694,902 Filed June 29, 2005; PCT Int. Appl. (2007) WO 2007005388 A3; CN 200680031454.9 (12/21/11); EU 1907470 (04/10/13).
13. Rogers, R. D.; Daly, D. T.; Swatloski, R. P.; Hough, W. L.; Davis Jr., J. H.; Smiglak, M.; Pernak, J.; Spear, S. K. "Multi-Functional Ionic Liquid Compositions for Overcoming Polymorphism and Imparting Improved Properties for Active Pharmaceutical, Biological, Nutritional, and Energetic Ingredients," 7/31/12, U. S. Patent No. 8,232,265; PCT/US2006/039454; WO 2007/044693 A2, April 19, 2007; MX 301158 (07/10/12); CN 200680046195.7 (06/05/13).
14. Rahman, M.; Rodriguez, H.; Sun, N.; Swatloski, R. P.; Daly, D. T.; Rogers, R. D. "Ionic Liquid Systems for the Processing of Biomass, Their Components and/or Derivatives, and Mixtures Thereof," U.S. Patent No. 8,668,807 (03/11/14); PCT Int. Appl. (2009), WO 2009105236 A1 8/27/09.
15. Rogers, R. D.; Daly, D. T.; Swatloski, R. P.; Hough, W. L.; Davis Jr., J. H.; Smiglak, M.; Pernak, J.; Spear, S. K. "Multi-Functional Ionic Liquid Compositions for Overcoming Polymorphism and Imparting Improved Properties for Active Pharmaceutical, Biological, Nutritional, and Energetic Ingredients," 08/12/14, U. S. Patent No. 8,802,596; AU 2012203353 (09/11/14); JP 5713534 (03/20/15).
16. Rogers, R. D.; Myerson, A. S.; Hines, C. C. "Improved Process for the Purification of Aryl Carboxylic Acids," U.S. Patent No. 8,309,760 B2 (11/13/12); PCT/US2008/65348; WO 2008/151034 A1, December 11, 2008.
17. Wu, B.; Reddy, R. G.; Rogers, R. D. "Production, Refining and Recycling of Lightweight and Reactive Metals in Ionic Liquids," 3/28/08, U. S. Patent No. 7,347,920 B2.
18. Spear, Scott K.; Daly, Daniel T.; Frazier, Rachel M.; Rogers, Robin D.; Haque, A. "Conductive composites prepared using ionic liquids," U.S. Patent No. 8,784,691 07/22/14; PCT Int. Appl. (2011), WO 2011011322 A1 1/27/11; U.S. Patent Application US 2012/0241680 A1 09/27/12.
19. DiSalvo, R.; Dykes, H. W. Jr.; Rogers, R. D.; Shamshina, J.; Smiglak, M. "Ionic Liquid Monopropellant Gas Generator," U.S. Patent No. 8,636,860 01/28/14.
20. Daly, D. T.; Rogers, R. D. "Cellulosic Biocomposites as Molecular Scaffolds for Nano-Architectures," US 2012/0122691 A1 05/17/12; U.S. Patent No. 8,883,193 11/11/14.
21. Rogers, R. D.; Myerson, A. S.; Hines, C. C. "Process for Purification of Aryl Carboxylic Acids," U.S. Patent No. 8,859,806 (10/14/14).
22. Frazier, R. M.; Daly, D. T.; Spear, S. K.; Rogers, R. D.; Hough, W. "Organic Photovoltaic-Battery Hybrid Device," (U.S. Application 2012/03818348 A1 12/20/12) U.S. Patent No. 9,073,937 (07/07/15).
23. Qin, Y.; Rogers, R. D.; Daly, D. T. "Process for forming films, fibers, and beads from chitinous biomass," PCT Int. Appl. (2010), WO 2010141470 A2 12/9/10; US 9,096,743 B2 (08/04/15)
24. Rogers, R. D.; Daly, D. T.; MacFarlane, D.; Scott, J. L.; Seddon, K. R.; Gurau, G.; Bica, K.; Turanjanin, J.; Dean, P. M., "Dual Functioning Ionic Liquids and Salts Thereof," PCT Int. Appl. (2010) WO 2010/078300, July 8, 2010; US 2012/0046244 A1 (02/23/12); U.S. Patent No. 9,278,134 (03/08/16).

Patent Applications:

1. Peterson, J. R.; Zjawiony, J. K.; Rogers, R. D. "Synthesis and Optical Resolution of the Taxol Side Chain and Related Compounds," International Application PCT/US1992/009911; International Publication Number WO/1993/010076, May 27, 1993.

2. Daly, D. T.; Spear, S. K.; Frazier, R. M.; Hough-Troutman, W. L.; Rogers, R. D. "Substrates for Delivery of Physiologically Active Agents," PCT Int. Appl. (2009) WO 2009/131692 A1 10/29/09.
3. Rahman, M.; Sun, N.; Qin, Y.; Maxim, M. L.; Rogers, R. D. "Ionic Liquid Systems for the Processing of Biomass, Their Components and/or Derivatives, and Mixtures Thereof," PCT Int. Appl. (2010), WO 2010056790 A1 5/20/10.
4. Frazier, R. M.; Daly, D. T.; Spear, S. K.; Rogers, R. D. "Exfoliation of Graphite using Ionic Liquids," U.S. Provisional Patent filed 11/25/08.; PCT Int. Appl. (2010), WO 2010065346 A1 06/10/10.
5. Rogers, R. D.; Rijksen, C.; Daly, D. T.; Caldwell, K.; Caldwell, G.; Hough-Troutman, W. L.; Bica, K., "Compounds Comprising Two or More Biologically Functional Ions and Method of treating Parkinson's Disease," U.S. Provisional Patent filed 12/29/08; PCT Int. Appl. (2010), WO 2010078258 A1 20100708.
6. Qin, Y.; Rogers, R. D.; Daly, D. T.; "Dissolution of Chitinous Biomass with Ionic Liquids and Making Chitin Film/Fiber/Beads from it," U.S. Patent Application 13/375,245 (U.S. national phase of PCT/US2010/036904) 05/10/12.
7. Pernak, J.; Shamshina, J.; Praczyk, T.; Syguda, A.; Janiszewska, D.; Smiglak, M.; Gurau, G.; Daly, D. T.; Rogers, R. D. "Herbicidal Compositions and Methods of Use," PCT Int. Appl. (2012), WO 2012006313 A2 01/12/12.
8. Rogers, R. D.; Holbrey, J. "Ionic liquid solvents of perhalide type for metals for extraction of radioactive metals from mineral ores," PCT Int. Appl. (2010), WO 2010116167 A1 10/14/10.
9. Rogers, R. D.; Holbrey, J.; Rodriquez, H. "Process for the preparation of heterocyclic chalcogenones via reaction of elemental sulfur, selenium, or tellurium with heterocyclic cationic species," PCT Int. Appl. (2010), WO 2010116166 A2 10/14/10.
10. Rogers, R. D.; Holbrey, J.; Rodriquez, H. "Process for removing metals from hydrocarbons," PCT Int. Appl. (2010), WO 2010116165 A2 10/14/10.
11. Daly, D. T.; Rogers, R. D.; Qin, Y. "Compositions Containing Recylable Ionic Liquids for Use in Biomass Processing," U.S. Patent Application US 20130245336 A1 09/27/12.
12. Riisager, A.; Fehrmann, R.; Rodriguez, R.; Bica, K.; Rogers, R. D.; Daly, D. T.; Gurau, G. "Biologically Active Compounds Supported on Solid Carrier such as Silica for Controlled Release and Improved Thermal Stability," PCT Int. Appl. (2011), WO 2011110662 (2011).
13. Rogers, R. D.; Daly, D. T.; Gurau, G. "Methods for dissolving polymers using mixtures of different ionic liquids and compositions comprising the mixtures," PCT Int. Appl. (2011), WO 2011056924 A2 05/12/2011; US Application 2012/0216705 A1 08/30/12.
14. Rogers, R. D.; Cooke, L. "Fungicidal Compositions and Methods of Use," PCT Int. Appl. (2012), WO 2012021825 02/16/12.
15. Riisager, A.; Fehrmann, R.; Rogers, R. D.; Gurau, G. "Enhancing the thermal stability of ionic compounds by immobilization on porous solid support," PCT Int. Appl. (2013), WO 2013030299 A1 03/07/13.
16. Pernak, J.; Shamshina, J.; Praczyk, T.; Syguda, A.; Janiszewska, D.; Smiglak, M.; Gurau, G.; Daly, D. T.; Rogers, R. D. "Herbicidal Compositions and Methods of Use," US Application (13/808,790) filed 1/7/13; published as US 2013/0109572 A1 05/02/13
17. Swatloski, R. P.; Barber, P. S.; Opichka, T.; Bonner, J. R.; Gurau, G.; Griggs, C. S.; Rogers, R. D. "Process for Electrospinning Chitin Fibers from Chitinous Biomass and Fibers and Articles Produced Thereby," PCT Int. Appl. (2014), WO 2014/01856 A1 01/30/14.
18. Rogers, R. D.; Barber, P. S.; Griggs, C. S.; Gurau, G.; Lu, X; Zhang, S. "Coagulation of Chitin from Solutions of Crustacean Shells in Ionic Liquids using Super-Critical CO_2," US Provisional Application No. 61/764,770 (02/14/13); PCT Int. Appl. (2014), WO 2014125438 A1 20140821; US Patent Application US 2015/0368371 (12/24/15).
19. Rogers, R. D.; Gurau, G.; Shamshina, J.; Daly, D. T. "Chitin and Alginate Composite Fibers," US Patent Application US 2016/0082141 (03/24/16). "Chitin and alginate composite fibers for wound dressings," PCT Int. Appl. (2014), WO 2014172703 A1 20141023.
20. Barber, P. S.; Griggs, C. S.; Rogers, R. D. Shamshina, J. L.; Gurau, G. "Chemical pulping of chitinous biomass for chitin" US Application (62/042,392) filed on 08/27/14.
21. McCrary, P. D.; Rogers, R. D. "Hypergolic Salts with Borane Cluster Anions," US Patent Application US 2014/0373984 A1 filed 06/20/14.
22. Wang, H.-T.; Frazier, R. M.; Guo, L.; Quan, H.; McCrary, P. D.; Rogers, R. D. Exfoliation of thermoelectric Materials and Transition Metal Dichalcogenides using Ionic Liquids," US Patent Application US 2015/0004733 A1 filed 06/27/14; Published 01/01/15.
23. Rogers, R. D. "Nucleoside analog salts with improved solubility," PCT Int. Appl. (2014), WO 2014145464 A1 20140918, Filed 03/17/14, Published 09/18/14); US Patent Application US 2016/0002240 (01/07/16).

A. Refereed Publications:

1. Atwood, J. L.; Rogers, R. D.; Kutal, C.; Grutsch, P. A. "X-ray Crystallographic Characterization of the Single Hydrogen Bridge Attachment of the Tetrahydroborate Group in Tris(methyldiphenylphosphine)tetrahydroboratecopper," *J. Chem. Soc., Chem. Comm.* **1977**, 593-594. **DOI:** 10.1039/C3977000593B.
2. Atwood, J. L.; Crissinger, K. D.; Rogers, R. D. "The Synthesis of $M[Al_2(CH_3)_6NO_3]$ ($M^+ = K^+$, Rb^+, Cs^+, NR_4^+) and the Crystal Structures of $K[Al_2(CH_3)_6NO_3]$ and $K[Al(CH_3)_3NO_3]\bullet C_6H_6$," *J. Organomet. Chem.* **1978**, *155*, 1-14.
3. Atwood, J. L.; Hunter, W. E.; Rogers, R. D.; Holton, J.; McMeeking, J.; Pearce, R.; Lappert, M. F. "Neutral and Anionic Silylmethyl Complexes of the Group 3a and Lanthanoid Metals; the X-ray Crystal and Molecular Structure of $[Li(thf)_4][Yb\{CH(SiMe_3)_2\}_3Cl]$ (thf = Tetrahydrofuran)," *J. Chem. Soc., Chem. Comm.* **1978**, 140-142.
4. Atwood, J. L.; Rogers, R. D.; Hunter, W. E.; Bernal, I.; Brunner, H.; Lukas, R.; Schwarz, W. "X-ray Structure of $[(\eta^5\text{-}C_5H_5)W(CO)_2C_{15}H_{15}]$: a Compound Containing Three Unusually Bonded Five-membered Rings," *J. Chem. Soc., Chem. Comm.* **1978**, 451-452.
5. Guzman, E. C.; Wilkinson, G.; Atwood, J. L.; Rogers, R. D.; Hunter, W. E.; Zaworotko, M. J. "Synthesis and Molecular Structures of Chloro(trimethylphosphine)tris(trimethylsilylmethyl)molybdenum(IV) and Di-μ-Chloro-bis[η^2-trimethylsilylmethylcarbonylbis(carbonyl)trimethylphosphinemolybdenum(II)]," *J. Chem. Soc., Chem. Comm.* **1978**, 465-466.
6. Kutal, C.; Grutsch, P.; Atwood, J. L.; Rogers, R. D. "Structural Characterization of the Single Hydrogen Bridge Attachment of the Tetrahydroborate Group in Tris(methyldiphenylphosphine)(tetrahydroborato)copper," *Inorg. Chem.* **1978**, *17*, 3558-3562.
7. Mattia, J.; Humphrey, M. B.; Rogers, R. D.; Atwood, J. L.; Rausch, M. D. "Syntheses and Molecular Structures of Two Metalloindene Complexes: 1,1-Bis(η^5-cyclopentadienyl)-2,3-bis(pentafluorophenyl)benzotitanole and 1,1-Bis(η^5-cyclopentadienyl)-2-trimethylsilyl-3-phenylbenzotitanole," *Inorg. Chem.* **1978**, *17*, 3257-3264.
8. Rogers, R. D.; Atwood, J. L.; Grüning, R. "The Crystal Structure of *N*-Lithiohexamethyldisilazane, $[LiN(SiMe_3)_2]_3$," *J. Organomet. Chem.* **1978**, *157*, 229-237. **DOI:** 10.1016/S0022-328X(00)92291-5
9. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "Crystal and Molecular Structure of Tetra(cyclopentadienyl)zirconium," *J. Am. Chem. Soc.* **1978**, *100*, 5238-5239. **DOI:** 10.1021/ja00484a069.
10. Atwood, J. L.; Hunter, W. E.; Rogers, R. D.; Carmona-Guzman, E.; Wilkinson, G. "The Crystal Structures of $MoMe_2(\eta^6\text{-}C_6H_6)(PPhMe_2)_2$ and $MoMe_2(\eta^6\text{-}C_6H_5Me)(PPhMe_2)_2$," *J. Chem. Soc., Dalton Trans.* **1979**, 1519-1523. **DOI:** 10.1039/DT9790001519.
11. Rogers, R. D.; Atwood, J. L. "Interaction of Aromatic Hydrocarbons with Organometallic Compounds of the Main Group Elements: VI. Synthesis and Crystal Structure of Cesium Diododimethylaluminate *p*-Xylene Solvate, $Cs[Al(CH_3)_2I_2]\bullet C_6H_4(CH_3)_2$," *J. Cryst. Mol. Struct.* **1979**, *9*, 45-53. **DOI:** 10.1007/BF01370925
12. Rogers, R. D.; Cook, W. J.; Atwood, J. L. "Ferrocenylalanes. 3. Synthesis and Crystal Structure of $(\eta^5\text{-}C_5H_5)Fe[\eta^5\text{-}C_5H_4Al_2(CH_3)_4Cl]$," *Inorg. Chem.* **1979**, *18*, 279-282. **DOI:** 10.1021/ic50192a014
13. Sikora, D. J.; Rausch, M. D.; Rogers, R. D.; Atwood, J. L. "Structure and Reactivity of the First Hafnium Carbonyl, $(\eta^5\text{-}C_5H_5)_2Hf(CO)_2$," *J. Am. Chem. Soc.* **1979**, *101*, 5079-5081. **DOI:** 10.1021/ja00511a056
14. Atwood, J. D.; Janik, T. S.; Atwood, J. L.; Rogers, R. D. "Synthesis of Bis(benzene)tetracarbonyldivanadium, $(C_6H_6)_2V_2(CO)_4$," *Synth. React. Inorg. Met.-Org. Chem.* **1980**, *10*, 397-402. **DOI:** 10.1080/00945718008058251
15. Atwood, J. L.; Rogers, R. D.; Hunter, W. E.; Floriani, C.; Fachinetti, G.; Chiesi-Villa, A. "Crystal and Molecular Structure of Two Early Transition-Metal Dicarbonyldicyclopentadienyl Complexes: $(\eta^5\text{-}C_5H_5)_2Zr(CO)_2$ and $[(\eta^5\text{-}C_5H_5)_2V(CO)_2][B(C_6H_5)_4]$," *Inorg. Chem.* **1980**, *19*, 3812-3817. **DOI:** 10.1021/ic50214a044
16. Bynum, R. V.; Hunter, W. E.; Rogers, R. D.; Atwood, J. L. "Pyrrolyl Complexes of the Early Transition Metals. 1. Synthesis and Crystal Structure of $(\eta^5\text{-}C_5H_5)_2Ti(\eta^1\text{-}NC_4H_4)_2$, $(\eta^5\text{-}C_5H_5)_2Zr(\eta^1\text{-}NC_4H_4)_2$, and $[Na(THF)_6]_2[Zr(\eta^1\text{-}NC_4H_4)_6]$," *Inorg. Chem.* **1980**, *19*, 2368-2374. **DOI:** 10.1021/ic50210a039
17. Carmona, E.; González, F.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. "Alkyl and Acyl Derivatives of Nickel(II) containing Tertiary Phosphine Ligands," *J. Chem. Soc., Dalton Trans.* **1980**, 2108-2116. **DOI:** 10.1039/DT9800002108
18. Çetinkaya, B.; Gümrükçü, I.; Lappert, M. F.; Atwood, J. L.; Rogers, R. D.; Zaworotko, M. J. "Bivalent Germanium, Tin, and Lead 2,6-Di-*tert*-butylphenoxides and the Crystal and Molecular Structures of $M(OC_6H_2Me\text{-}4\text{-}Bu^t_2\text{-}2,6)_2$ (M = Ge or Sn)," *J. Am. Chem. Soc.* **1980**, *102*, 2088-2089. **DOI:** 10.1021/ja00526a054
19. Daniels, P. H.; Wong, J. L.; Atwood, J. L.; Canada, L. G.; Rogers, R. D. "Unreactive 1-Azadiene and Reactive 2-Azadiene in Diels-Alder Reaction of Pentachloroazacyclopentadienes," *J. Org. Chem.* **1980**, *45*, 435-440. **DOI:** 10.1021/jo01291a011
20. Guzman, E. C.; Wilkinson, G.; Rogers, R. D.; Hunter, W. E.; Zaworotko, M. J.; Atwood, J. L. "Synthesis and Crystal Structures of Chloro(trimethylphosphine)tris(trimethylsilylmethyl)molybdenum(IV) and Di-μ-chloro-bis[bis(carbonyl)trimethylphosphine(1-2-η-trimethylsilylmethylcarbonyl)molybdenum(II)]," *J. Chem. Soc., Dalton Trans.* **1980**, 229-234. **DOI:** 10.1039/DT9800000229
21. Paulson, J. A.; Krost, D. A.; McPherson, G. L.; Rogers, R. D.; Atwood, J. L. "Structural, Spectroscopic, and Theoretical Studies of an Exchange-Coupled Manganese(II)-Copper(II) Dimer," *Inorg. Chem.* **1980**, *19*, 2519-2525. **DOI:** 10.1021/ic50211a007
22. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "Synthesis and Structure of $(\eta^5\text{-}C_5H_5)_3Gd\bullet OC_4H_8$," *J. Organomet. Chem.* **1980**, *192*, 65-73. **DOI:** 10.1016/S0022-328X(00)93331-X
23. Rogers, R. D.; Hunter, W. E.; Atwood, J. L. "Nature of the Novel $C_{15}H_{15}$ Ligand in $[W(CO)_2(\eta^5\text{-}C_5H_5)(\eta^3\text{-}C_{15}H_{15})]$," *J. Chem. Soc., Dalton Trans.* **1980**, 1032-1035. **DOI:** 10.1039/DT9800001032

24. Rogers, R. D.; Stone, L. B.; Atwood, J. L. "Tetramethylammonium Iodotrimethylaluminate [NMe_4][$AlMe_3I$]," *Cryst. Struct. Comm.* **1980**, *9*, 143-146.
25. Atwood, J. L.; Hrncir, D. C.; Rogers, R. D.; Howard, J. A. K. "Novel Linear Al-H-Al Electron-Deficient Bond in Na[$(CH_3)_3$Al-H-Al$(CH_3)_3$]," *J. Am. Chem. Soc.* **1981**, *103*, 6787.
26. Calderazzo, F.; Vitali, D.; Mavani, I. P.; Marchetti, F.; Bernal, I.; Korp, J. D.; Atwood, J. L.; Rogers, R. D.; Dalton, M. S. "Preparation, Properties, and Crystal and Molecular Structures of Bis(dialkylamine) Complexes of Rhenium(I)," *J. Chem. Soc., Dalton Trans.* **1981**, 2523-2528.
27. Calderazzo, F.; Vitali, D.; Poli, R.; Atwood, J. L.; Rogers, R. D.; Cummings, J. M.; Bernal, I. "Studies on Organometallic Hetero-multiple-bridged Molecules. Part 7. Synthesis and Properties of Dichalcogenide-bridged Complexes of Rhenium(I) and the Crystal and Molecular Structures of the Diphenyl Ditelluride-bridged Complex, [$Re_2Br_2(CO)_6(Te_2Ph_2)$]," *J. Chem. Soc., Dalton Trans.* **1981**, 1004-1009.
28. Carmona, E.; González, F.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. "Synthesis and Properties of Dialkyl Complexes of Nickel(II). The Crystal Structure of Bis(pyridine)bis(trimethylsilymethyl)nickel(II)," *J. Chem. Soc., Dalton Trans.* **1981**, 777-782.
29. Hrncir, D. C.; Rogers, R. D.; Atwood, J. L. "New Bonding Mode for a Bridging Dioxygen Ligand: Crystal and Molecular Structure of [K•dibenzo-18-crown-6][$Al_2(CH_3)_6O_2$]•1.5C_6H_6," *J. Am. Chem. Soc.* **1981**, *103*, 4277.
30. Liese, W.; Dehnicke, K.; Rogers, R. D.; Shakir, R.; Atwood, J. L. "A Spectroscopic and Crystallographic Study of the [$ReNCl_4$]$^-$ Ion," *J. Chem. Soc., Dalton Trans.* **1981**, 1061-1063.
31. Rogers, R. D.; Atwood, J. L.; Emad, A.; Sikora, D. J.; Rausch, M. D. "The Formation and Molecular Structures of (η^5-$C_5H_5)_3$Y•OC_4H_8 and (η^5-$C_5H_5)_3$La•OC_4H_8," *J. Organomet. Chem.* **1981**, *216*, 383-392.
32. Rogers, R. D.; Atwood, J. L.; Foust, D.; Rausch, M. D. "The Crystal Structure of Vanadocene, (η^5-$C_5H_5)_2$V," *J. Cryst. Mol. Struct.* **1981**, *11*, 183-188.
33. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "First Authentic Example of a Difference in the Structural Organometallic Chemistry of Zirconium and Hafnium: Crystal and Molecular Structure of (η^5-$C_5H_5)_2$Hf(η^1-$C_5H_5)_2$," *J. Am. Chem. Soc.* **1981**, *103*, 692.
34. Rogers, R. D.; Kalyanaraman, B.; Dalton, M. S.; Smith, W.; Kispert, L. D.; Atwood, J. L. "Crystal Structure of Bromoflouroacetic Acid: A Chiral Molecule," *Journal of Crystal and Molecular Stucture* **1981**, *11*, 105-111.
35. Sikora, D. J.; Rausch, M. D.; Rogers, R. D.; Atwood, J. L. "Formation and Molecular Structure of Bis(η^5-cyclopentadienyl)bis(triflourophosphine)titanium," *J. Am. Chem. Soc.* **1981**, *103*, 982-984.
36. Sikora, D. J.; Rausch, M. D.; Rogers, R. D.; Atwood, J. L. "New Syntheses and Molecular Structures of the Decamethylmetallocene Dicarbonyls (η^5-$C_5Me_5)_2$M$(CO)_2$ (M = Ti, Zr, Hf)," *J. Am. Chem. Soc.* **1981**, *103*, 1265-1267.
37. Atwood, J. L.; Honan, M. B.; Rogers, R. D. "Crystal and Molecular Structure of (η^5-C_5H_5)Ta(η^2-$C_2H_4)Cl_2(PMe_2Ph)_2$, a Sterically Crowded Molecule which Exhibits a Distorted η^5-Coordination Mode of the Cyclopentadienyl Ligand," *J. Crystallogr. Spectrosc. Res.* **1982**, *12*, 205-221.
38. Atwood, J. L.; Hrncir, D. C.; Shakir, R.; Dalton, M. S.; Priester, R. D.; Rogers, R. D. "Reaction of Trimethylaluminum with Crown Ethers. The Synthesis and Structure of (Dibenzo-18-crown-6)bis(trimethylaluminum) and of (15-Crown-5)tetrakis(trimethylaluminum)," *Organometallics* **1982**, *1*, 1021-1025.
39. Carmona, E.; Marín, J. M.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D.; Wilkinson, G. "Bis(dinitrogen)- and Diethylene-molydenum(0) Complexes," *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 441-442.
40. Carmona, E.; Marin, J. M.; Poveda, M. L.; Rogers, R. D.; Atwood, J. L. "Preparation and Properties of Dinitrogen Complexes of Molybdenum and Tungsten with Trimethylphosphine as Coligand. III. Synthesis and Properties of *cis*-[$W(N_2)_2(PMe_3)_4$], *trans*-[$W(C_2H_4)_2(PMe_3)_4$] and [$M(N_2)(PMe_3)_5$] (M = Mo, W). The Crystal and Molecular Structure of [$Mo(N_2)(PMe_3)_5$]," *J. Organomet. Chem.* **1982**, *238*, C63-C66.
41. Foust, D. F.; Rogers, R. D.; Rausch, M. D.; Atwood, J. L. "Photoinduced Reactions of (η^5-$C_5H_5)_2MH_3$ and (η^5-$C_5H_5)_2$M(CO)H (M = Nb, Ta) and the Molecular Structure of (η^5-$C_5H_5)_2$Ta(CO)H," *J. Am. Chem. Soc.* **1982**, *104*, 5646-5650.
42. Jones, R. A.; Stuart, A. L.; Atwood, J. L.; Hunter, W. E.; Rogers, R. D. "Steric Effects of Phosphido Ligands. Synthesis and Crystal Structure of Di-*tert*-butylphosphido-Bridged Dinuclear Metal-Metal Bonded Complexes of Fe(II), Co(I, II), and Ni(I)," *Organometallics* **1982**, *1*, 1721–1723.
43. Rausch, M. D.; Edwards, B. H.; Atwood, J. L.; Rogers, R. D. "Formation and Molecular Structure of (η^4-Tetraphenylcyclobutadiene)dicarbonylnitrosylmanganese," *Organometallics* **1982**, *1*, 1567-1571.
44. Rogers, R. D.; Atwood, J. L.; Rausch, M. D.; Macomber, D. W.; Hart, W. P. "The Formation and Molecular Structure of Acetylcyclopentadienylsodium•tetrahydrofuranate," *J. Organomet. Chem.* **1982**, *238*, 79-85.
45. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "Synthesis and Crystal Structure of [(η^5-$C_5H_5)_2$HfO]$_3$•C_6H_5Me," *J. Crystallogr. Spectrosc. Res.* **1982**, *12*, 239-244.
46. Zaworotko, M. J.; Rogers, R. D.; Atwood, J. L. "Interaction of Trimethylaluminum and Trimethylgallium with the Acetate Ion. Synthesis and Crystal Structures of [$N(CH_3)_4$][$Al_2(CH_3)_6CH_3$COO] and Rb[$Ga_2(CH_3)_6CH_3$COO]," *Organometallics* **1982**, *1*, 1179-1183.
47. Atwood, J. L.; Bernal, I.; Calderazzo, F.; Canada, L. G.; Poli, R.; Rogers, R. D.; Veracini, C. A.; Vitali, D. "Studies on Organometallic Hetero-Multiple-Bridged Molecules. 8. Preparation and Crystal and Molecular Structures of Diphenyl Dichalcogenide Complexes of Manganese(I). Kinetic, Spectroscopic, and Equilibrium Data: A Quantitative Assessment of the

Solid-State and Solution Properties within Members of Homogeneous Families of Chalcogenide Low-Valent Metal Complexes," *Inorg. Chem.* **1983**, *22*, 1797-1804.
48. Atwood, J. L.; Hrncir, D. C.; Priester, R. D.; Rogers, R. D. "Decomposition of High-Oxygen Content Organoaluminum Compounds. The Formation and Structure of the $[Al_7O_6Me_{16}]^-$ Anion," *Organometallics* **1983**, *2*, 985-989.
49. Atwood, J. L.; Hrncir, D. C.; Rogers, R. D. "The Use of Crown Ethers to Access New $M[Al_2R_6X]$ Species. Synthesis and Crystal Structure of $[K•dibenzo\text{-}18\text{-}crown\text{-}6][Al_2Me_6C1]•2C_6H_6$," *J. Inclusion Phenom.* **1983**, *1*, 199-207.
50. Atwood, J. L.; Priester, R. D.; Rogers, R. D.; Canada, L. G. "Reaction of Trimethylaluminum with Crown Ethers. II. The Synthesis and Crystal Structure of (Dibenzo-18-crown-6)tris(trimethylaluminum) and of (18-Crown-6)tetrakis(trimethylaluminum)," *J. Inclusion Phenom.* **1983**, *1*, 61-69.
51. Carmona, E.; González, F.; Poveda, M. L.; Marin, J. M.; Atwood, J. L.; Rogers, R. D. "Reaction of *cis*-$[Mo(N_2)_2(PMe_3)_4]$ with CO_2. Synthesis and Characterization of Products of Disproportionation and the X-ray Structure of a Tetrametallic Mixed-Valence Mo^{II}-Mo^{V} Carbonate with a Novel Mode of Carbonate Binding," *J. Am. Chem. Soc.* **1983**, *105*, 3365-3366.
52. Carmona, E.; Marin, J. M.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. "Preparation and Properties of Dinitrogen Trimethylphosphine Complexes of Molybdenum and Tungsten. 4. Synthesis, Chemical Properties, and X-ray Structure of *cis*-$[Mo(N_2)_2(PMe_3)_4]$. The Crystal and Molecular Structures of *trans*-$[Mo(C_2H_4)_2(PMe_3)_4]$ and *trans*, *mer*-$[Mo(C_2H_4)_2(CO)(PMe_3)_3]$," *J. Am. Chem. Soc.* **1983**, *105*, 3014-3022.
53. Carmona, E.; Marín, J. M.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. "Preparation and Properties of Dinitrogen Trimethylphosphine Complexes of Molybdenum and Tungsten-II. Synthesis and Crystal Structures of $[MCl(N_2)(PMe_3)_4]$(M = Mo, W) and *trans*-$[MoCl_2(PMe_3)_4]$," *Polyhedron* **1983**, *2*, 185-193.
54. Carmona, E.; Marín, J. M.; Poveda, M. L.; Sánchez, L.; Rogers, R. D.; Atwood, J. L. "Synthesis of Chloro(trimethylphosphine)tris(trimethylsilymethyl)tungsten(IV); Synthesis and Molecular Structure of Di-μ-chloro-bis[dicarbonyl(trimethylphosphine)(1-2-η-trimethylsilylmethylcarbonyl)tungsten(II)]," *J. Chem. Soc., Dalton Trans.* **1983**, 1003-1005.
55. Carmona, E.; Sánchez, L.; Poveda, M. L.; Marín, J. M.; Atwood, J. L.; Rogers, R. D. "β-C-H Interaction vs. Dihaptoacyl Coordination in a Molybdenum Acetyl Complex. X-ray Crystal Structure of $[Mo(Ac)(S_2CNMe_2)(CO)(PMe_3)_2]$," *J. Chem. Soc., Chem. Comm.* **1983**, 161-162.
56. Edwards, B. H.; Rogers, R. D.; Sikora, D. J.; Atwood, J. L.; Rausch, M. D. "Formation, Reactivities, and Molecular Structures of Phosphine Derivatives of Titanocene. Isolation and Characterization of a Titanium Monoolefin π Complex," *J. Am. Chem. Soc.* **1983**, *105*, 416-426.
57. Herrmann, W. A.; Plank, J.; Hubbard, J. L.; Kriechbaum, G. W.; Kalcher, W.; Koumbouris, B.; Ihl, G.; Schäfer, A.; Ziegler, M. L.; Pfisterer, H.; Pahl, C.; Atwood, J. L.; Rogers, R. D. "Transition Metal Methylene Complexes, LI. Carbocyclic Carbenes, Carbene Bridges, Small Hydrocarbon Ligands, and Metallacycles: Examples of a General Synthetic Concept," *Z. Naturforsch., B: Chem. Sci.* **1983**, *38b*, 1392-1398.
58. Lappert, M. F.; Slade, M. J.; Singh, A.; Atwood, J. L.; Rogers, R. D.; Shakir, R. "Structure and Reactivity of Sterically Hindered Lithium Amides and Their Diethyl Etherates: Crystal and Molecular Structures of $[Li\{N(SiMe_3)_2\}(OEt_2)]_2$ and $[Li(NCMe_2CH_2CH_2CH_2CMe_2)]_4$," *J. Am. Chem. Soc.* **1983**, *105*, 302-304.
59. Rausch, M. D.; Edwards, B. H.; Rogers, R. D.; Atwood, J. L. "Formation of [(Diphenylphosphino)cyclopentadienyl]thallium and Its Utility in the Synthesis of Heterobimetallic Ti-Mn Complexes: The Molecular Structure of (η^5-Cyclopentadienyl)dicarbonyl{(η^5- cyclopentadienyl)[η^5-(diphenylphosphino)cyclopentadienyl]dichlorotitanium-P}manganese]," *J. Am. Chem. Soc.* **1983**, *105*, 3882-3886.
60. Rogers, R. D.; Atwood, J. L. "The Crystal and Molecular Structure of $SnBr[N(SiMe_3)_2]_3$," *J. Crystallogr. Spectrosc. Res.* **1983**, *13*, 1-7.
61. Atwood, J. L.; McMaster, A. D.; Rogers, R. D.; Stobart, S. R. "Stereochemically Nonrigid Silanes, Germanes, and Stannanes. 12. Crystal and Molecular Structures of Tetrakis(η^1-indenyl) Derivatives of Germanium and Tin: Meso Diastereoisomers with S_4 Symmetry," *Organometallics* **1984**, *3*, 1500-1504.
62. Atwood, J. L.; Rogers, R. D.; Bynum, R. V. "Tris(1,2-dimethoxyethane)lithium μ-Chloro-μ-oxo-bis[chloro(pentamethylcyclopentadienyl)(1-pyrrolyl)zirconate(IV)] Dimethoxyethane Solvate, $[Li(C_4H_{10}O_2)_3][Zr_2Cl_3O(C_4H_4N)_2(C_{10}H_{15})_2]•C_4H_{10}O_2$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1984**, *C40*, 1812-1814.
63. Carmona, E.; Paneque, M.; Poveda, M. L.; Rogers, R. D.; Atwood, J. L. "Further Studies on Organonickel Compounds: The Synthesis of Some New Alkyl-, Acyl- and Cyclopentadienyl- Derivatives and the Crystal Structure of *trans*-$[Ni(CH_2SiMe_3)_2(PMe_3)_2]$," *Polyhedron* **1984**, *3*, 317-323.
64. Carmona, E.; Sánchez, L.; Marín, J. M.; Poveda, M. L.; Atwood, J. L.; Priester, R. D.; Rogers, R. D. "η^2-Acyl Coordination and β-C-H Interaction in Acyl Complexes of Molybdenum. Crystal and Molecular Structures of $Mo(\eta^2\text{-}COCH_2SiMe_3)Cl(CO)(PMe_3)_3$ and $Mo(COCH_3)(S_2CNMe_2)(CO)(PMe_3)_2$," *J. Am. Chem. Soc.* **1984**, *106*, 3214-3222.
65. Herrmann, W. A.; Plank, J.; Kriechbaum, G. W.; Ziegler, M. L.; Pfisterer, H.; Atwood, J. L.; Rogers, R. D. "Komplexchemie Reaktiver Organischer Verbindungen XLVII. Synthese, Strukturchemie und Druckcarbonylierung von Metallcarben-Komplexen," *J. Organomet. Chem.* **1984**, *264*, 327-352.
66. Rausch, M. D.; Foust, D. F.; Rogers, R. D.; Atwood, J. L. "The Formation and Molecular Structure of Di-η^5-cyclopentadienyl{2-[(dimethylamino)methyl]phenyl-C,N}yttrium," *J. Organomet. Chem.* **1984**, *265*, 241-248.

67. Rogers, R. D.; Atwood, J. L. "The Crystal and Molecular Structure of [K•DB-18-C- 6][$AlMe_3NO_3$]•0.5C_6H_6," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 1-11.
68. Rogers, R. D.; Atwood, J. L. "Reaction of K_2SO_4 with $AlMe_3$ and the Crystal Structures of $K_2[Al_4Me_{12}SO_4]$ and $K_2[Al_4Me_{12}SO_4]$•0.5*p*-xylene," *Organometallics* **1984**, *3*, 271-274.
69. Rogers, R. D.; Atwood, J. L.; Albright, T. A.; Lee, W. A.; Rausch, M. D. "Structure of (Biphenylene)- and (Triphenylene)$Cr(CO)_3$. An Analysis of the Bonding of $Cr(CO)_3$ to Bicyclic Polyenes," *Organometallics* **1984**, *3*, 263-270.
70. Rogers, R. D.; Baker, J. C.; Atwood, J. L. "The Crystal Structure of [NBu^n_4][AlI_4]," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 333-339.
71. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "Synthesis and Structure of (η^5-$C_5H_5)_2Hf(\eta^1$-$NC_4H_4)_2$," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 21-28.
72. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "The Crystal Structure of LiBr•$(CH_3OCH_2CH_2OCH_3)_2$," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 29-34.
73. Rogers, R. D.; Carmona, E.; Galindo, A.; Atwood, J. L.; Canada, L. G. "Trimethylphosphine Complexes of Molybdenum and Tungsten. The Synthesis and Chemical Properties of $MoCl_4(PMe_3)_3$ and the Crystal and Molecular Structures of $WCl_4(PMe_3)_3$ and $MoO(acac)_2PMe_3$," *J. Organomet. Chem.* **1984**, *277*, 403-415.
74. Rogers, R. D.; Hrncir, D. C. "Structure of (η^5-Cyclopentadienyl)(η^6-tetraphenylborato)iron, [$Fe(C_5H_5)\{B(C_6H_5)_4\}$]," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1984**, *C40*, 1160-1161.
75. Rogers, R. D.; Isci, H.; Mason, W. R. "Structure of Tetra(*n*-butyl)ammonium Tetraiodo-μ,μ'-diiododiplatinate(II), [(n-$C_4H_9)_4N]_2[Pt_2I_6]$," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 383-392.
76. Samuel, E.; Rogers, R. D.; Atwood, J. L. "Synthesis and Crystal Structure of [(η^5- C_9H_{11})TiCl(μ-O)]$_4$," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 573-579.
77. Solar, J. M.; Rogers, R. D.; Mason, W. R. "Synthesis of Some Alkyl Phosphite Complexes of Platinum and Their Structural and Spectral Characterization," *Inorg. Chem.* **1984**, *23*, 373-377.
78. Wayda, A. L.; Dye, J. L.; Rogers, R. D. "Divalent Lanthanoid Synthesis in Liquid Ammonia. 1. The Synthesis and X-ray Structure of $(C_5Me_5)_2Yb(NH_3)(THF)$," *Organometallics* **1984**, *3*, 1605-1610.
79. Atwood, J. L.; Hunter, W. E.; Rogers, R. D.; Weeks, J. A. "Behavior of M[$Al_2Me_6N_3$] (M = K, Rb, Cs) with Aromatic Solvents and the Crystal Structures of Cs[$Al_2Me_6N_3$] 2*p*-xylene and [K•dibenzo-18-crown-6][$Al_2Me_6N_3$]•1.5(1-methylnaphthalene)," *J. Inclusion Phenom.* **1985**, *3*, 113-123.
80. Carmona, E.; Galindo, A.; Poveda, M. L.; Rogers, R. D. "Synthesis and Properties of *cis*-Bis(dinitrogen)tetrakis(trimethylphosphine)tungsten(0). Crystal and Molecular Structures of [$W(N_2)(PMe_3)_5$] and *trans*-[$W(C_2H_4)_2(PMe_3)_4$]," *Inorg. Chem.* **1985**, *24*, 4033-4039.
81. Kool, L. B.; Rausch, M. D.; Rogers, R. D. "The Formation, Crystal and Molecular Structure of (η^5-Pentamethylcyclopentadienyl)(η^7-cycloheptatrienyl)titanium and (η^5- Pentamethylcyclopentadienyl)(η^8-cyclooctatetraene)titanium," *J. Organomet. Chem.* **1985**, *297*, 289-299.
82. Macomber, D. W.; Rogers, R. D. "Preparation and Reactivity of Mononuclear (η^5-Cyclopentadienyl)cobalt Carbene Complexes," *Organometallics* **1985**, *4*, 1485-1487.
83. Medley, J. H.; Fronczek, F. R.; Ahmad, N.; Day, M. C.; Rogers, R. D.; Kerr, C. R.; Atwood, J. L. "The Crystal Structures of $NaAlR_4$, R = Methyl, Ethyl, and *n*-Propyl," *J. Crystallogr. Spectrosc. Res.* **1985**, *15*, 99-107.
84. Rogers, R. D.; Benning, M. M.; Kurihara, L. K.; Moriarty, K. J.; Rausch, M. D. "The Formation and Crystal and Molecular Structures of (η^5-Pentamethylcyclopentadienyl)(η^5- cyclopentadienyl)dichloro-titanium, -zirconium and -hafnium," *J. Organomet. Chem.* **1985**, *293*, 51-60.
85. Vaughn, J. W.; Rogers, R. D. "Structure of *trans*-difluorobis(1,3- propanediamine)chromium(III) perchlorate, *trans*-[$Cr(N_2C_3H_{10})_2F_2$](ClO_4)," *J. Crystallogr. Spectrosc. Res.* **1985**, *15*, 281-287.
86. Wayda, A. L.; Rogers, R. D. "Synthesis, X-ray Crystal Structures, and Reaction Chemistry of Homoleptic and Heteroleptic Organolanthanoid Complexes Incorporating the [(Dimethylamino)methyl]phenyl Ligand," *Organometallics* **1985**, *4*, 1440-1444.
87. Macomber, D. W.; Rogers, R. D. "The Formation and Molecular Structure of (η^5-C_5H_5)Rh(CO)[C(NMe)CH_2CH_2(NMe)]," *J. Organomet. Chem.* **1986**, *308*, 353-360.
88. Rogers, R. D.; Green, L. M. "A Reinvestigation of the Crystal and Molecular Structure of (18-Crown-6)•2CH_3NO_2: D_{3d} Stabilization Via Methyl Hydrogen-Crown Oxygen 'Hydrogen Bonds'," *J. Inclusion Phenom.* **1986**, *4*, 77-84.
89. Rogers, R. D.; Green, L. M.; Benning, M. M. "Crystal and Molecular Structure of a Dinuclear Uranyl(VI) Chloride, [$UO_2Cl_2(THF)_2]_2$," *Lanthanide Actinide Res.* **1986**, *1*, 185-193.
90. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes. 1. Synthesis and Structure of [$Y(OH_2)_8$]Cl_3•(15-crown-5)," *Inorg. Chim. Acta* **1986**, *116*, 171-177.
91. Rogers, R. D.; Kurihara, L. K. "Crystal Structures of Dichlorohexaaquayttrium(III) Chloride, [$YCl_2(OH_2)_6$]Cl, and Dichlorohexaaquaerbium(III) Chloride, [$ErCl_2(OH_2)_6$]Cl," *Lanthanide Actinide Res.* **1986**, *1*, 295-306.
92. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes 2. The Synthesis and Crystal Structure of $Y(NO_3)_3$(12-Crown-4)," *J. Inclusion Phenom.* **1986**, *4*, 351-358.
93. Singh, Y. P.; Rupani, P.; Singh, A.; Rai, A. K.; Mehrotra, R. C.; Rogers, R. D.; Atwood, J. L. "Synthesis and IR, UV, NMR (^{1}H and ^{11}B), and Mass Spectral Studies of New β-Ketoamine Complexes of Boron: Crystal and Molecular Structure of $OC_6H_4OBOC(R)CHC(R')NR$" (R = *p*-ClC_6H_4, R' = C_6H_5, R" = CH_3)," *Inorg. Chem.* **1986**, *25*, 3076-3081.

94. Alt, H. G.; Engelhardt, H. E.; Steinlein, E.; Rogers, R. D. "Acetylenliganden als Bausteine für Carben- und Nitrilliganden. Molekulstrukturen von $C_5H_4Me(CO)_2Mn[C(Me)NH_2]$, $C_5Me_5(CO)_2Mn[C(Me)NH_2]$, $C_5Me_5(CO)_2Mn[C(Me)NMe_2]$ und $C_5Me_5(CO)_2MnNCMe$," *J. Organomet. Chem.* **1987**, *344*, 321-341.
95. Alt, H. G.; Hayen, H. I.; Rogers, R. D. "Preparation and Crystal Structure of the Dinuclear, Asymmetric Dioxo Complex (η^5-C_5Me_5)$(CO)_3$W-W$(O)_2(\eta^5$-$C_5Me_5)$," *J. Chem. Soc., Chem. Comm.* **1987**, 1795-1796.
96. Alt, H. G.; Herrmann, G. S.; Engelhardt, H. E.; Rogers, R. D. "Die Konkurrenz Elecktronischer und Sterischer Substituenteneinflüsse in Metallacyclishen Pentamethylcyclopentadienyl-Alkenylketon-Komplexen des Chroms, Molydäns und Wolframs. Molekulstruktur von $C_5Me_5(CO)_2Cr[HC{=}CPhC(O)Me]$," *J. Organomet. Chem.* **1987**, *331*, 329-339.
97. Hayen, H. I.; Alt, H. G.; Rogers, R. D. "Darstellung, Charakterisierung und Molekulstruktur des η^2-Acylkomplexes $C_5Me_5(CO)(CF_3COO)_2W[\eta^2$-$C(O)CH_2CH_2COMe]$," *J. Organomet. Chem.* **1987**, *323*, 339-351.
98. Rogers, R. D. "Crystal Structure of Dichlorohexaaquadysprosium(III) Chloride, $[DyCl_2(OH_2)_6]Cl$," *Lanthanide Actinide Res.* **1987**, *2*, 41-48.
99. Rogers, R. D. "f-Element/Crown Ether Complexes. 13. Direct Coordination of 12-Crown-4 to Hydrated Terbium Chloride. Synthesis and Crystal Structure of $[Tb(OH_2)_5$(12-crown- 4)$]Cl_3{\bullet}2H_2O$," *Inorg. Chim. Acta* **1987**, *133*, 175-180.
100. Rogers, R. D. "f-Element/Crown Ether Complexes. 16. Synthesis, Crystallization and Crystal Structure of $[Dy(OH_2)_8]Cl_3{\bullet}$18-crown-$6{\bullet}4H_2O$," *Inorg. Chim. Acta* **1987**, *133*, 347-352.
101. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes. 6. Interaction of Hydrated Lanthanide Chlorides with 15-Crown-5: Crystallization and Structures of $[M(OH_2)_8]Cl_3{\bullet}$(15-crown-5) (M = Gd, Lu)," *Inorg. Chim. Acta* **1987**, *130*, 131-137.
102. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes III: Synthesis and Structural Characterization of $[Y(NO_3)_3(OH_2)_5][NO_3]{\bullet}2$(15-*Crown*-5)," *J. Less-Comm. Metals* **1987**, *127*, 199-207.
103. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes. 7. Low Temperature (-150°C) Structure of $[Y(OH_2)_8]Cl_3{\bullet}$(15-crown-5)," *Inorg. Chim. Acta* **1987**, *129*, 277-282.
104. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes. 4. Synthesis and Crystal and Molecular Structures of $[MCl(OH_2)_2$(18-crown-6)$]Cl_2{\bullet}2(H_2O)$ (M = Sm, Gd, Tb)," *Inorg. Chem.* **1987**, *26*, 1498-1502.
105. Rogers, R. D.; Kurihara, L. K.; Benning, M. M. "f-Element/Crown Ether Complexes, 11. Preparation and Structural Characterization of $[UO_2(OH_2)_5][ClO_4]_2{\bullet}3$(15-crown-5)$\bullet CH_3CN$ and $[UO_2(OH_2)_5][ClO_4]_2{\bullet}2$(18-crown-6)$\bullet 2CH_3CN\bullet H_2O$," *J. Inclusion Phenom.* **1987**, *5*, 645-658.
106. Rogers, R. D.; Kurihara, L. K.; Benning, M. M. "Structure of Thorium Nitrate-1,4,7,10,13,16-Hexaoxacyclooctadecane-Water (1/1/3), $[Th(OH_2)_3(NO_3)_4]{\bullet}$18-Crown-6 at 123 K," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1987**, *C43*, 1056-1058.
107. Rogers, R. D.; Kurihara, L. K.; Benning, M. M. "f-Element/Crown Ether Complexes. 10. Oxidation of UCl_4 to $[UO_2Cl_4]^{2-}$ in the Presence of Crown Ethers: Structural Characterization of Crown Ether Complexed Ammonium Ions $[(NH_4)$(15-crown-$5)_2]_2[UO_2Cl_4]{\bullet}2CH_3CN$, $[(NH_4)$(benzo-15-crown-$5)_2]_2[UCl_6]{\bullet}4CH_3CN$, and $[(NH_4)$(dibenzo-18-crown-6)$]_2[UO_2Cl_4]{\bullet}2CH_3CN$ and Synthesis of $[Na$(12-crown-$4)_2]_2[UO_2Cl_4]{\bullet}2OHMe$ and $[UO_2Cl_2(OH_2)_3]{\bullet}$18-crown-$6{\bullet}H_2O{\bullet}OHMe$," *Inorg. Chem.* **1987**, *26*, 4346-4352.
108. Rogers, R. D.; Kurihara, L. K.; Richards, P. D. "Crystallization and Structural Characterization of Dibenzo-18-crown-$6{\bullet}2$(MeCN) and Dibenzo-18-crown-$6{\bullet}2(MeNO_2)$; Assignment of Specific C-H$\bullet\bullet\bullet$O Interactions," *J. Chem. Soc., Chem. Comm.* **1987**, 604-606.
109. Rogers, R. D.; Kurihara, L. K.; Voss, E. J. "f-Element/Crown Ether Complexes. 5. Structural Changes in Complexes of Lanthanide Chloride Hydrates with 18-Crown-6 Accompanying Decreases in Ln^{3+} Ionic Radii: Synthesis and Structures of $[M(OH_2)_7(OHMe)][MCl(OH_2)_2$(18-crown-6)$]_2Cl_7{\bullet}2(H_2O)$ (M = Y, Dy)," *Inorg. Chem.* **1987**, *26*, 2360-2365.
110. Rogers, R. D.; Richards, P. D. "Neutral Solvent/Crown Ether Interactions 3. Reorientation of the Hydrogen Bonds in the Low Temperature (-150°C) Structure of 18-Crown-$6{\bullet}2(CH_3NO_2)$," *J. Inclusion Phenom.* **1987**, *5*, 631-638.
111. Rogers, R. D.; Voss, E. J. "f-Element/Crown Ether Complexes. 14. Synthesis and Crystal Structure of $[Lu(OH_2)_8][Na$(12-crown-$4)_2]Cl_4{\bullet}2H_2O$," *Inorg. Chim. Acta* **1987**, *133*, 181-187.
112. Wayda, A. L.; Mukerji, I.; Dye, J. L.; Rogers, R. D. "Divalent Lanthanoid Synthesis in Liquid Ammonia. 2. The Synthesis and X-ray Crystal Structure of $(C_8H_8)Yb(C_5H_5N)_3{\bullet}1/2C_5H_5N$," *Organometallics* **1987**, *6*, 1328-1332.
113. Alt, H. G.; Engelhardt, H. E.; Razavi, A.; Rausch, M. D.; Rogers, R. D. "Pentamethylcyclopentadienyl-, Acetylcyclopentadienyl-, und Indenyl-dicarbonyl-Acetylenkomplexe des Vanadiums. Molekulstruktur von $C_9H_7V(CO)_2PhC_2H$," *Z. Naturforsch., B: Chem. Sci.* **1988**, *43b*, 438-444.
114. Carmona, E.; Muñoz, M. A.; Rogers, R. D. "Synthesis, Characterization, and Properties of the η^2-Acyl Complexes Mo(η^2-$COCH_2CMe_3)X(PMe_3)_4$ (X = Cl, Br)," *Inorg. Chem.* **1988**, *27*, 1598-1601.
115. Macomber, D. W.; Hung, M.-H.; Verma, A. G.; Rogers, R. D. "A New, General Route to (μ-Bis(carbene))ditungsten Complexes: X-ray Crystal Structure of $(CO)_5W\{C(OCH_3)CH_2[CH(CH_2)_3C(CH_2CH{=}CH_2)]C(OCH_3)\}W(CO)_5$," *Organometallics* **1988**, *7*, 2072-2074.
116. Macomber, D. W.; Liang, M.; Rogers, R. D. "Synthesis and Reactivity of Ditungsten μ-Carbene Complexes: X-ray Crystal Structure of $W_2(CO)_9[\mu$-η^1,η^3-$C(OCH_3)C{=}CH(CH_2)_5CH_2]$," *Organometallics* **1988**, *7*, 416-422.
117. Macomber, D. W.; Verma, A. G.; Rogers, R. D. "Intermolecular [2+2+2] Cycloaddition Reactions of Alkynes and Alkenes Mediated by Cobalt: X-ray Crystal Structures of Two Isomeric (η^5-Cyclopentadienyl)(η^4-1,3-cyclohexadiene)cobalt Complexes," *Organometallics* **1988**, *7*, 1241-1253.
118. Paquette, L. A.; DeRussy, D. T.; Rogers, R. D. "On Possible Redirection of the Course of Anionic Oxy-Cope Rearrangements,"

Tetrahedron **1988**, *44*, 3139-3148.
119. Paquette, L. A.; Lau, C. J.; Rogers, R. D. "Uni- and Biparticulate Electrophilic Additions to Conjugated Bis(bicyclo[1.1.0]butanes)," *J. Am. Chem. Soc.* **1988**, *110*, 2592-2600.
120. Peterson, J. R.; Do, H. D.; Rogers, R. D. "Anticancer-Agent Development: X-ray Structure of Dimethyl 2,3,4,5-Tetrahydro-3-(3,4-methylenedioxybenzoyl)-2-oxo-5β-(3,4,5-trimethoxyphenyl)-3α,4α-furandicarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1786-1789.
121. Peterson, J. R.; Rogers, R. D.; Do, H. D. "Structure of Dimethyl 2,3,4,5-Tetrahydro-2-oxo-5α-(3,4,5-trimethoxyphenyl)-3α,4β-furancarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1784-1786.
122. Robinson, G. H.; Sangokoya, S. A.; Rogers, R. D. "Synthesis and Molecular Structure of the Optically Active Organoaluminum Dimer (S)-(-)-(S)-(-)-[$(C_6H_5)CH(CH_3)NHAl(CH_3)_2]_2$," *Polyhedron* **1988**, *7*, 2727-2730.
123. Rogers, R. D. "f-Element/Crown Ether Complexes. 26. Crystallization of Two Hydrated Forms of Hydrogen Bonded Complexes of $NdCl_3 \bullet nH_2O$ and 15-crown-5. Crystal Structures of $[Nd(OH_2)_9]Cl_3 \bullet$15-crown-5$\bullet H_2O$ and $[NdCl_2(OH_2)_6]Cl \bullet$15-crown-5," *Inorg. Chim. Acta* **1988**, *149*, 307-314.
124. Rogers, R. D. "f-Element/Crown Ether Complexes 15. Synthesis and Crystal Structure of $[Lu(OH_2)_8]Cl_3 \bullet$1.5(12-crown-4)$\bullet 2H_2O$," *J. Coord. Chem.* **1988**, *16*, 415-424.
125. Rogers, R. D. "Neutral Molecule/Crown Ether Interactions 5. Comparison of the C-H Acidic Interactions of Nitromethane and Acetonitrile with 18-crown-6 and Dibenzo-18-crown-6. Crystal Structures of Dibenzo-18-crown-6$\bullet 2CH_3NO_2$ and Dibenzo-18-crown-6$\bullet 2CH_3CN$," *J. Inclusion Phenom.* **1988**, *6*, 629-645.
126. Rogers, R. D. "Structure of Di[bis(1,4,7,10-tetraoxacyclododecane)sodium] Tetrachlorodioxouranate(VI)-Methanol (1/2), $[Na(12\text{-crown-}4)_2]_2[UO_2Cl_4] \bullet$2MeOH," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 638-641.
127. Rogers, R. D.; Benning, M. M. "Synthesis and Structure of Thorium Chloride-1,4,7,10,13-Pentaoxacyclopentadecane-Water-Methanol-Acetonitrile (1/1/2/2/1), $[ThCl_4(OHMe)_2(OH_2)_2] \bullet$15-Crown-5$\bullet CH_3CN$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 641-644.
128. Rogers, R. D.; Benning, M. M. "Preparation and Structure of Bis(1,4,7,10,13,16- hexaoxacyclododecaneammonium) Hexachlorouranate(IV)-Acetonitrile (1/2), $[(NH_4)$(18-crown-6)$]_2[UCl_6] \bullet 2CH_3CN$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1397-1399.
129. Rogers, R. D.; Etzenhouser, R. D. "Structure of $[LuCl_3$(triethylene glycol)$] \bullet$OHMe," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1400-1402.
130. Rogers, R. D.; Etzenhouser, R. D. "Structure of $[DyCl_3$(triethylene glycol)$] \bullet$18-crown-6," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1533-1535.
131. Rogers, R. D.; Kurihara, L. K.; Benning, M. M. "f-Element/Crown Ether Complexes. Part 9. The Role of Solvent Hydrogen Bonding: Synthesis and Crystal Structure of Aquatetrachlorotris(ethanol)thorium(IV)-1,4,7,10,13,16-hexaoxacyclo-octadecane-Water (1/1/1)," *J. Chem. Soc., Dalton Trans.* **1988**, 13-16.
132. Rogers, R. D.; Richards, P. D.; Voss, E. J. "Neutral Solvent/Crown Ether Interactions, 4. Crystallization and Low Temperature (-150 °C) Structural Characterization of 18-crown-6$\bullet 2(CH_3CN)$," *J. Inclusion Phenom.* **1988**, *6*, 65-71.
133. Rogers, R. D.; Rollins, A. N.; Benning, M. M. "f-Element/Crown Ether Complexes. 22. Preparation and Structural Characterization of Lanthanide Chloride Complexes of 12-crown-4," *Inorg. Chem.* **1988**, *27*, 3826-3835.
134. Rogers, R. D.; Shakir, R.; Atwood, J. L.; Macomber, D. W.; Wang, Y.-P.; Rausch, M. D. "The Crystal and Molecular Structures of Formyl-, Cyano-, and Aminocyclopentadienyldicarbonylnitrosylchromium," *J. Crystallogr. Spectrosc. Res.* **1988**, *18*, 767-778.
135. Rogers, R. D.; Teuben, J. H. "The Crystal and Molecular Structures of (η^5- Pentamethylcyclopentadienyl)(η^7-Cyclohepatatrienyl)zirconium and -hafnium," *J. Organomet. Chem.* **1988**, *354*, 169-176.
136. Rogers, R. D.; Voss, E. J. "f-Element/Crown Ether Complexes 12. Synthesis and Crystal Structure of $[Y(NO_3)_3(OH_2)_2$(NCMe)$][Y(NO_3)_3(OH_2)_2$(OHMe)$] \bullet 2$(benzo-15-crown-5)$\bullet$OHMe," *J. Coord. Chem.* **1988**, *16*, 405-414.
137. Rogers, R. D.; Voss, E. J.; Etzenhouser, R. D. "f-Element/Crown Ether Complexes. 17. Synthetic and Structural Survey of Lanthanide Chloride Triethylene Glycol Complexes," *Inorg. Chem.* **1988**, *27*, 533-542.
138. Alt, H. G.; Engelhardt, H. E.; Frister, T.; Rogers, R. D. "Darstellung und Charakterisierung der Isonitril-Hydridkomplexe Cp'$(CO)_2$(CNR)MH (Cp' = η^5-C_5H_5, η^5-C_5Me_5; R = Me, ^{t}Bu; M = Mo, W). Molekülstruktur von $C_5Me_5(CO)_2$(CN^{t}Bu)MoH," *J. Organomet. Chem.* **1989**, *366*, 297-304.
139. Alt, H. G.; Engelhardt, H. E.; Hayen, H. I.; Rogers, R. D. "Umsetzungen des Asymmetrischen, Zweikernigen Dioxokomplexes $C_5Me_5(CO)_3$W-W$(O)_2C_5Me_5$ mit Cl_2, Br_2, I_2, HCl, CF_3COOH, NOCl, NO und Luft. Molekülstruktur von $C_5Me_5W(CO)_2Br_3$," *J. Organomet. Chem.* **1989**, *366*, 287-295.
140. Alt, H. G.; Engelhardt, H. E.; Rogers, R. D. "Die Protonierung von Ylidkomplexen des Mangans mit HBF_4. Die Molekülstruktur von $[C_5H_5(CO)_2MnCH_2CH(PEt_3)]BF_4$," *J. Organomet. Chem.* **1989**, *362*, 117-124.
141. Alt, H. G.; Engelhardt, H. E.; Rogers, R. D.; Abu-Orabi, S. T. "Photoinduzierte Umsetzungen der Komplexe (η^6-$C_6H_3R_3)(CO)_3Cr$ (R = Me, Et) mit den Acetylenen $C_2R'_2$ (R' = H, C_3H_7, $C(OEt)_2H$). Die Molekülstruktur von $(C_6H_3Me_3)(CO)Cr(\mu\text{-}CO)\{\mu\text{-}C_2[C(OEt)_2H]_2\}Cr(CO)_4$," *J. Organomet. Chem.* **1989**, *378*, 33-43.
142. Alt, H. G.; Engelhardt, H. E.; Wrackmeyer, B.; Rogers, R. D. "Die Photoinduzierte Umsetzung der Tricarbonyl-Hydridkomplexe Cp'$W(CO)_3H$ (Cp' = η^5-C_5H_5, η^5-C_5Me_5) mit Methylacetylen und Dimethylacetylen zu η^3-Allyl- und Metallacyclischen Alkenylketon-Komplexen. Molekülstruktur von $C_5Me_5W(CO)_2(\eta^3\text{-}C_3H_5)$," *J. Organomet. Chem.* **1989**, *379*, 289-301.

143. Beachley, O. T., Jr.; Spiegel, E. F.; Kopasz, J. P.; Rogers, R. D. "Indium(III) Compounds Containing the Neopentyl Substituent, $In(CH_2CMe_3)_3$, $In(CH_2CMe_3)_2Cl$, $In(CH_2CMe_3)Cl_2$, and $In(CH_2CMe_3)_2CH_3$. Crystal and Molecular Structure of Dichloroneopentylindium(III), an Inorganic Polymer," *Organometallics* **1989**, *8*, 1915-1921.
144. Burford, N.; Spence, R. E. v. H.; Rogers, R. D. "Preparation, Crystal Structures, and Spectroscopic Characterization of Diaminochalcogenophosphonium Cations," *J. Am. Chem. Soc.* **1989**, *111*, 5006-5008.
145. Hall, T. J.; Bachrach, S. M.; Spangler, C. W.; Sapochak, L. S.; Lin, C. T.; Guan, H. W.; Rogers, R. D. "Structure of All-*trans*-1,6-diphenyl- (*A*) and All-*trans*-1,6-bis(*o*-methoxyphenyl)-1,3,5-hexatriene (*B*)," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 1541-1543.
146. Hall, T. J.; Mertz, C. J.; Bachrach, S. M.; Hipple, W. G.; Rogers, R. D. "The Crystal Structure of $UO_2Cl_2(OH_2)(MeCN)_2 \bullet 2MeCN$," *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 499-505.
147. Heeres, H. J.; Meetsma, A.; Teuben, J. H.; Rogers, R. D. "Mono(pentamethylcyclopentadienyl) Complexes of Cerium(III). Synthesis, Molecular Structure, Thermal Stability, and Reactivity of $(C_5Me_5)CeX_2$ (X = 2,6-Di-*tert*-butylphenoxo, $CH(SiMe_3)_2$, and $N(SiMe_3)_2$) Complexes," *Organometallics* **1989**, *8*, 2637-2646.
148. Heeres, H. J.; Teuben, J. H.; Rogers, R. D. "Novel Monopentamethylcyclopentadienyl Alkoxides of La and Ce; X-ray Crystal Structure of $(C_5Me_5Ce(OCMe_3)_2)_2$," *J. Organomet. Chem.* **1989**, *364*, 87-96.
149. Jaw, H.-R. C.; Savas, M. M.; Rogers, R. D.; Mason, W. R. "Crystal Structures and Solution Electronic Absorption and MCD Spectra for Perchlorate and Halide Salts of Binuclear Gold(I) Complexes Containing Bridging $Me_2PCH_2PMe_2$ (dmpm) or $Me_2PCH_2CH_2PMe_2$ (dmpe) Ligands," *Inorg. Chem.* **1989**, *28*, 1028-1037.
150. Kool, L. B.; Ogasa, M.; Rausch, M. D.; Rogers, R. D. "Synthesis of [η^5-(Diphenylphosphino)cyclopentadienyl][η^7-(diphenylphosphino)cycloheptatrienyl]titanium and Its Utility in the Formation of Heterobimetallic Complexes: The Molecular Structure of Tetracarbonyl{[η^5-(diphenylphosphino)cyclopentadienyl][η^7- (diphenylphosphino)cycloheptatrienyl]titanium-*P*,*P*'}chromium Hemitoluene Solvate," *Organometallics* **1989**, *8*, 1785-1790.
151. Lin, W. O.; da Costa, J. B. N.; Alt, H. G.; Rogers, R. D. "A New System of Ionophores Derived from *o*,*o*'-Biphenyldiol. X-ray Structure of *o*-Hydroxy-biphenyl-*o*'-oxyacetamide," *Z. Naturforsch., B: Chem. Sci.* **1989**, *44b*, 1331-1332.
152. Macomber, D. W.; Madhukar, P.; Rogers, R. D. "Synthesis of [Alkenyl(dimethylamino)carbene]tungsten Complexes using the Peterson Reaction: X-ray Crystal Structure of (*E*)-$(CO)_5W[C(NMe_2)CH{=}CH(\eta\text{-}C_5H_4)Fe(\eta\text{-}C_5H_5)]$," *Organometallics* **1989**, *8*, 1275-1282.
153. Moriarty, K. J.; Rogers, R. D.; Paquette, L. A. "Stereoselective Formation from a (1*S*,5*S*)-(-)-Verbenone-Derived Cyclopentadiene of Dimeric and Mixed Titanium and Zirconium Dichloride Complexes," *Organometallics* **1989**, *8*, 1512-1517.
154. Paquette, L. A.; He, W.; Rogers, R. D. "Comparative Analysis of Molecular-Recognition Levels Attained during Capture of Chiral Cyclopentenyl Organometallics by Conformationally Immobilized Ketonic Systems," *J. Org. Chem.* **1989**, *54*, 2291-2300.
155. Paquette, L. A.; Moriarty, K. J.; McKinney, J. A.; Rogers, R. D. "Analysis of the π-Facial Preference for Complexation of a Camphor-Derived, Enantiomerically Pure Cyclopentadienyl Ligand to $CpMCl_2$ Fragments (M = Ti and Zr)," *Organometallics* **1989**, *8*, 1707-1713.
156. Paquette, L. A.; Moriarty, K. J.; Meunier, P.; Gautheron, B.; Sornay, C.; Rogers, R. D.; Rheingold, A. L. "Stereochemical Course of π-Face Coordination to Isodicyclopentadiene during Formation of Mixed Titanocene and Zirconocene Dichloride Complexes," *Organometallics* **1989**, *8*, 2159-2167.
157. Paquette, L. A.; Moriarty, K. J.; Rogers, R. D. "(1*R*)-(-)-Nopol as the Source of an Optically Pure Fused Cyclopentadienyl Ligand. Stereochemical Course of Complexation to Cyclopentadienyltitanium and -zirconium Dichloride Fragments," *Organometallics* **1989**, *8*, 1506-1511.
158. Paquette, L. A.; O'Doherty, G. A.; Miller, B. L.; Rogers, R. D.; Rheingold, A. L.; Geib, S. L. "Stereochemically Uniform Mode of Iron Carbonyl Complexation to Spirocyclic Isodicyclopentadienes," *Organometallics* **1989**, *8*, 2167-2172.
159. Paquette, L. A.; Vanucci, C.; Rogers, R. D. "Stereochemical Course of Diels-Alder Cycloadditions to Hydroxymethyl-Substituted Plane-Nonsymmetric Cyclopentadienes," *J. Am. Chem. Soc.* **1989**, *111*, 5792-5800.
160. Peterson, J. R.; Do, H. D.; Rogers, R. D. "Platelet Activating Factor Antagonist Design. 2. X-ray Structure of Dimethyl 2,3,4,5-Tetrahydro-5β-(3,4-methylenedioxyphenyl)-2-oxo-3β-(3,4,5-trimethoxybenzoyl)-3α,4α- furandicarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 1059-1063.
161. Peterson, J. R.; Do, H. D.; Rogers, R. D. "Anticancer Agent Development. 3. X-ray Structure of Dimethyl 1-Methoxy-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-*trans*-3,4- dihydronaphthalene-2,3-dicarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 1568-1571.
162. Peterson, J. R.; Horsley, D. B.; Brozik, J. A.; Rogers, R. D. "Platelet Activating Factor Antagonist Design. 3. X-ray Crystal Structure and Intermolecular Crystal Lattice Interactions of Methyl *trans*-4-Acetoxymethyl-4,5-dihydro-2,5-bis(3,4-methylenedioxyphenyl)-3- furancarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 1164-1167.
163. Peterson, J. R.; Smillie, T. J.; Rogers, R. D. "Platelet Activating Factor Antagonist Design: Structure of Methyl *trans*-5-(3,4-Dimethoxyphenyl)-2,3,4,5-tetrahydro-2-oxo-4-furancarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 297-300.
164. Peterson, J. R.; Winter, T. J.; Do, H. D.; Rogers, R. D. "Anticancer Agent Development: X-ray Crystal Structure and Keto-Enol Tautomerism of Dimethyl 1-hydroxy-6,7-methylenedioxy-4- (3',4',5'-trimethoxyphenyl)-*trans*-3,4-dihydronaphthalene-2,3-dicarboxylate," *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 135-145.
165. Peterson, J. R.; Winter, T. J.; Everson, T. P.; Rogers, R. D. "Novel Manganese(III) Oxidation Chemistry: X-ray Crystal Structure

of 5,7,8-Trimethoxy-1-(2,4,5-trimethoxyphenyl)-1,2-dihydronapthalene," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 132-134.
166. Rausch, M. D.; Tsai, W.-M.; Chambers, J. W.; Rogers, R. D.; Alt, H. G. "Synthetic and X-ray Structural Studies on Pentabenzylcyclopentadienyl Derivatives of Manganese, Rhenium, and Iron," *Organometallics* **1989**, *8*, 816-821.
167. Robinson, G. H.; Sangokoya, S. A.; Pennington, W. T.; Self, M. F.; Rogers, R. D. "Unexpected Conformation of the Hydrogen Chloride Salt of [14]aneN$_4$: An X-ray Structural Examination of [H$_2$[14]aneN$_4$H$_2$]Cl$_4$ and Its Role in Organaluminum Host-Guest Chemistry," *J. Coord. Chem.* **1989**, *19*, 287-294.
168. Rogers, R. D. "Macrocycle Complexation Chemistry. 31. The Crystal Structure of [ThCl$_2$(OH$_2$)$_7$]Cl$_2$•18-crown-6•2H$_2$O," *Lanthanide Actinide Res.* **1989**, *3*, 71-81.
169. Rogers, R. D. "f-Element/Crown Ether Complexes: 21. Conformational Changes in Metal Complexed versus Hydrogen Bonded Benzo-15-crown-5 in the Structure of [Y(OH$_2$)$_3$(NCMe)(benzo-15-crown-5)][ClO$_4$]$_3$•benzo-15-crown-5•CH$_3$CN," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, *7*, 277-287.
170. Rogers, R. D.; Alt, H. G.; Engelhardt, H. E. "Umsetzungen des Acetylenkomplexes (C$_6$H$_3$Me$_3$)(CO)$_2$Cr(C$_2$H$_2$) mit PMe$_3$ und HNMe$_2$. Festkörperstrukturen von (C$_6$H$_3$Me$_3$)(CO)$_2$Cr(PMe$_3$) und (C$_6$H$_3$Me$_3$)(CO)$_2$Cr[C(Me)NMe$_2$]," *J. Organomet. Chem.* **1989**, *366*, 305-312.
171. Rogers, R. D.; Benning, M. M.; Etzenhouser, R. D.; Rollins, A. N. "Novel Unidentate Co-ordination of a Crown Ether and of a Polyethylene Glycol to Uranium(VI)," *J. Chem. Soc., Chem. Comm.* **1989**, 1586-1588.
172. Rogers, R. D.; Teuben, J. H. "Structure of (η^5-C$_5$Me$_5$)(η^8-C$_8$H$_8$)Zr, an Aromatic Mixed Sandwich Complex of Zirconium(III)," *J. Organomet. Chem.* **1989**, *359*, 41-47.
173. Spangler, B. D.; Vaný sek, P.; Hernandez, I. C.; Rogers, R. D. "Structure of Crystal Violet Tetraphenylborate," *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 589-596.
174. Spangler, C. W.; Hall, T. J.; Saindon, M. L.; Rogers, R. D.; McCoy, R. K.; Birge, R. R.; Fleitz, P. A.; Zhang, C.-F. "The Relationship between Structure and Nonlinear Optical Properties in Donor-Acceptor Polyenes," *Inst. Phys. Conf. Ser.* **1989**, *103*, 233-238.
175. Alt, H. G.; Palackal, S. J.; Rogers, R. D. "Umsetzungen des 1,2-Bis(3-indenyl)ethan-Dianions mit Photochemisch Aktivierten Carbonylkomplexen des Chroms, Molybdäns und Wolframs. Molekülstruktur von C$_9$H$_7$CH$_2$CH$_2$C$_9$H$_7$ und (η^5:η^5-C$_9$H$_6$CH$_2$CH$_2$C$_9$H$_6$)[W(CO)$_3$Me]$_2$," *J. Organomet. Chem.* **1990**, *388*, 105-116.
176. Banks, M. A.; Beachley, O. T., Jr.; Maloney, J. D.; Rogers, R. D. "The Chemistry of Diphenylphosphine Adducts of Tris(neopentyl) and Tris(trimethylsilylmethyl)gallium and -indium Including the Crystal and Molecular Structure of (Me$_3$CCH$_2$)$_3$Ga•P(H)Ph$_2$," *Polyhedron* **1990**, *9*, 335-342.
177. Burford, N.; Royan, B. W.; Spence, R. E. v. H.; Cameron, T. S.; Linden, A.; Rogers, R. D. "Linear Co-ordinative Bonding at Oxygen: A Spectroscopic and Structural Study of Phosphine Oxide-Group 13 Lewis Acid Adducts," *J. Chem. Soc., Dalton Trans.* **1990**, 1521-1528.
178. Burford, N.; Royan, B. W.; Spence, R. E. v. H.; Rogers, R. D. "Nuclear Magnetic Resonance Spectroscopic Characterization and the Crystal and Molecular Structures of Ph$_3$PS•AlCl$_3$ and Ph$_3$PSe•AlCl$_3$: A Classification of the Co-ordinative Bonding Modes of the Phosphine Chalcogenides," *J. Chem. Soc., Dalton Trans.* **1990**, 2111-2117.
179. Burford, N.; Royan, B. W.; Whalen, J. M.; Richardson, J. F.; Rogers, R. D. "Co-ordinatively Unsaturated Group 15 Elements: The Isolation and Crystal Structure of a Novel Dimeric Dithiarsolidinium Cation," *J. Chem. Soc., Chem. Comm.* **1990**, 1273-1275.
180. Burford, N.; Spence, R. E. v. H.; Rogers, R. D. "Chemistry of the Diaminochalcogenophosphinic Chloride-Aluminum Trichloride System: Preparation and Crystal Structures of New Chalcogenophosphonium Cations," *J. Chem. Soc., Dalton Trans.* **1990**, 3611-3619.
181. Burford, N.; Spence, R. E. v. H.; Whalan, J. M.; Rogers, R. D.; Richardson, J. F. "Syntheses and Crystal Structures for the First Two Examples of the Four-Membered PNSiS Heterocycle," *Organometallics* **1990**, *9*, 2854-2856.
182. Lee, B.; Pennington, W. T.; Robinson, G. H.; Rogers, R. D. "Organogallium Chemistry of Macrocyclic Amines. Synthesis and Molecular Structure of [Ga(CH$_3$)$_3$]$_4$[(CH$_3$)$_4$[14]aneN$_4$] and [Ga(CH$_3$)$_2$][14]aneN$_4$[Ga(CH$_3$)$_3$]$_2$," *J. Organomet. Chem.* **1990**, *396*, 269-278.
183. Murray, C. K.; Warner, B. P.; Dragisich, V.; Wulff, W. D.; Rogers, R. D. "Thermal Reactions of Acyloxy and Alkoxy Carbene Complexes with Imines: Metathesis, Acetate Rearrangements, and a New Route to Imino Carbene Complexes via Peterson Type Eliminations," *Organometallics* **1990**, *9*, 3142-3151.
184. Paquette, L. A.; DeRussy, D. T.; Vandenheste, T.; Rogers, R. D. "Comparative Analysis of Diastereoselection Levels Attainable during Controlled Exo and Endo Addition of Chiral Cyclopentenyl Organometallics to Optically Pure and Racemic 1-Vinylnorbornan-2-ones," *J. Am. Chem. Soc.* **1990**, *112*, 5562-5573.
185. Paquette, L. A.; Kesselmayer, M. A.; Rogers, R. D. "Quantitation of Proximity Effects on Rate. A Case Study Involving Dyotropic Hydrogen Migration within *syn*-Sesquinorbornene Disulfones Carrying Central Substituents Having Different Spatial Demands," *J. Am. Chem. Soc.* **1990**, *112*, 284-291.
186. Paquette, L. A.; Liang, S.; Waykole, L.; DeLucca, G.; Jendralla, H.; Rogers, R. D.; Kratz, D.; Gleiter, R. "[4.4.4]Propellahexaene by Triple Shapiro Degradation. Structural and Electronic Properties of This Maximally Unsaturated Hydrocarbon and Consequences of O-Methylation of Its [4.4.4]Propellatrienetrione Precursors," *J. Org. Chem.* **1990**, *55*, 1598-1611.
187. Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. "[3.3] Sigmatropy within 1-Vinyl-2-alkenyl-7,7-

dimethyl-*exo*-norbornan-2-ols. The First Atropselective Oxyanionic Cope Rearrangement," *J. Am. Chem. Soc.* **1990**, *112*, 277-283.
188. Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. "Boat/Chair Topographic Stereoselection during Anionic Oxy-Cope Rearrangement of 1-Alkenyl-2-cyclopentenyl-*endo*-norbornan-2-ols," *J. Am. Chem. Soc.* **1990**, *112*, 265-277.
189. Peterson, J. R.; Everson, T. P.; Rogers, R. D. "Novel Manganese(III) Oxidation Chemistry: X-ray Crystal Structures of (1α,2α,4β)-1,2-diacetoxy-4-(4-methoxyphenyl)-6-methoxy-1,2,3,4- tetrahydronaphthalene (Compound A) and (1α,2α,4β)-1,2-diacetoxy-4-(2-methoxyphenyl)-8-methoxy-1,2,3,4-tetrahydronaphthalene (Compound B)," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 37-45.
190. Peterson, J. R.; Horsley, D. B.; Brozik, J. A.; Rogers, R. D. "Anticancer Agent Development. 4. X-ray Crystal Structure and Intermolecular Crystal Lattice Interactions of Methyl *Trans*-4,5-dihydro-4-acetoxymethyl-5-(3,4,5-trimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)-3- furancarboxylate," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 47-52.
191. Peterson, J. R.; Horsley, D. B.; Rogers, R. D. "Platelet-Activating-Factor Antagonist Design. 4. Structure and Intermolecular Crystal Lattice Interactions of *cis*-3,4-Dibenzyl-2-oxo-2,3,4,5-tetrahydrofuran," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1990**, *C46*, 872-875.
192. Peterson, J. R.; Peterson, S.; Baker, J. K.; Rogers, R. D. "Anticancer Agent Development. 5. X-ray Structure and ^{1}H NMR Spectral Analysis of (1α,2α,5α,6α)-2,6-bis(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-4,8-dione," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 327-333.
193. Rausch, M. D.; Spink, W. C.; Conway, B. G.; Rogers, R. D.; Atwood, J. L. "Synthetic and Structural Studies on (η^5:η^5-Fulvalene)bimetallic Compounds Derived from (η^5:η^5-Fulvalene)dithallium," *J. Organomet. Chem.* **1990**, *383*, 227-252.
194. Rogers, R. D.; Alt, H. G.; Maisel, H. E. "Die Molekülstruktur des Carbenartigen Ylidkomplexes $(C_5H_4Me)(CO)_2Mn[CHCH(PEt_3)]$," *J. Organomet. Chem.* **1990**, *381*, 233-238.
195. Rogers, R. D.; Atwood, J. L.; Rausch, M. D.; Macomber, D. W. "Crystal Structures of (η^5-C_5H_4COMe)$M(CO)_3Me$ (M = Mo,W)," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 555-560.
196. Rogers, R. D.; Bond, A. H.; Hipple, W. G. "Macrocycle Complexation Chemistry. 33. Preparation of [Ca(12-crown-4)$_2$][UO_2Cl_4] and [$Ca(OH_2)_3$(15-crown-5)][UO_2Cl_4]. Structure of [$Ca(OH_2)_3$(15-crown-5)][UO_2Cl_4]," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 611-616.
197. Rogers, R. D.; Nunez, L. "Macrocycle Complexation Chemistry. 29. Synthesis and Crystal Structure of [CuCl(18-thiacrown-6)]$_n$," *J. Coord. Chem.* **1990**, *21*, 111-118.
198. Rogers, R. D.; Nuñez, L. "Macrocycle Complexation Chemistry. 32. Modification of the Lanthanide Ion Coordination Sphere via Electrocrystallization of Hydrated Lanthanide Chloride Complexes of 12-crown-4," *Inorg. Chim. Acta* **1990**, *172*, 173-180.
199. Rogers, R. D.; Park, M.-G.; Kevill, D. N. "Structure of 3-(4-Methoxyphenyl)-4-phenyl-4*H*-1,2,4-triazole," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1990**, *C46*, 2218-2221.
200. Rogers, R. D.; Rollins, A. N. "Macrocycle Complexation Chemistry 30: Comparison of the Crystal Structures of [$La(NO_3)_3$(15-crown-5)] and [$La(NO_3)_3$(monoaza-15-crown-5)]," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 389-393.
201. Rogers, R. D.; Rollins, A. N.; Etzenhouser, R. D.; Henry, R. F. "f-Element/Crown Ether Complexes. 27. The Synthesis and Crystal Structure of [$Ce(NO_3)_3(OH_2)$(12-crown-4)]•12-crown-4," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1990**, *8*, 375-382.
202. Rogers, R. D.; Royal, J. D.; Bolton, D. M.; Boeyens, J. C. A.; Allen, C. C. "f-Element/Crown Ether Complexes. 20. Synthesis and Structure of [$Y(NO_3)_3(OH_2)_3$]•1.5(15-crown-5)•Me_2CO," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 525-533.
203. Sivik, M. R.; Rogers, R. D.; Paquette, L. A. "Isodicyclopentadienes and Related Molecules LII. Comparative Analysis of the Solid State Structural Features of Bis(η^5-(1*R*,8*R*)- and (η^5-1*R*,8*R*),η^5-(1*S*,8*S*)-7,7,9,9-tetramethyltricyclo[6.1.1.$0^{2,6}$]deca-3,5-dien-2-yl)dichlorotitanium," *J. Organomet. Chem.* **1990**, *397*, 177-185.
204. Wayda, A. L.; Kaplan, M. L.; Lyons, A. M.; Rogers, R. D. "Mixed-Ligand Imidazole Complexes of Organolanthanides," *Polyhedron* **1990**, *9*, 751-756.
205. Alvarez, R.; Atwood, J. L.; Carmona, E.; Pérez, P. J.; Poveda, M. L.; Rogers, R. D. "Formation of Carbonyl-Carbonate Complexes of Molybdenum by Reductive Disproportionation of Carbon Dioxide. X-ray Structure of $Mo_4(\mu_4\text{-}CO_3)(CO)_2(O)_2(\mu_2\text{-}O)_2(\mu_2\text{-}OH)_4(PMe_3)_6$," *Inorg. Chem.* **1991**, *30*, 1493-1499.
206. Beachley, O. T., Jr.; Lees, J. F.; Rogers, R. D. "(Tert-butyl)cyclopentadienylindium(I), In($C_5H_4CMe_3$): Synthesis, Characterization and X-ray Structural Study," *J. Organomet. Chem.* **1991**, *418*, 165-171.
207. Burford, N.; McInnis, J. D.; Schriver, M. J.; Rogers, R. D. "Structure of Bis[bis(trimethylsilyl)methylene]methoxyphosphorane," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1991**, *C47*, 884-885.
208. Carmona, E.; Contreras, L.; Poveda, M. L.; Sánchez, L. J.; Atwood, J. L.; Rogers, R. D. "η^2-Acyl and Methyl Complexes of Tungsten. Crystal and Molecular Structures of W(η^2-C(O)CH_2SiMe_3)Cl(CO)(PMe_3)$_3$ and W(CH_3)(S_2CNMe_2)(CO)$_2$(PMe_3)$_2$," *Organometallics* **1991**, *10*, 61-71.
209. Christie, S.; Dubois, R. H.; Rogers, R. D.; White, P. S.; Zaworotko, M. J. "Air Stable Liquid Clathrates: Solid State Structure and Hydrocarbon Solubility of Organic Cation Triodide Salts," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, *11*, 103-114.
210. Gilbert, T. M.; Rogers, R. D. "Spectroscopic Properties of Conjugated Metal-Carbon Multiple Bonds: Synthesis and Absorption Spectra of the "Dialkylidynes" $(RO)_3W/C\text{-}C/W(OR)_3$ (OR = $OCMe_3$, $OCMe_2CF_3$, $OCMe_2Et$)," *J. Organomet. Chem.* **1991**, *421*, C1-C5.
211. Hufford, C. D.; Badria, F. A.; Abou-Karam, M.; Shier, W. T.; Rogers, R. D. "Preparation, Characterization, and Antiviral

Activity of Microbial Metabolites of Stemodin," *J. Nat. Prod.* **1991**, *54*, 1543-1552.
212. Jürgens, A. R.; McChesney, J. D.; Rogers, R. D. "Synthesis of Hydrophenanthrene Natural Products. Structure of a 17-Nordehydropimarane Derived from Dehydroabietic Acid," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1991**, *C47*, 1675-1678.
213. Macomber, D. W.; Hung, M.-H.; Madhukar, P.; Liang, M.; Rogers, R. D. "Synthesis and Structures of (μ-Bis(carbene))dimetal Complexes of Chromium and Tungsten," *Organometallics* **1991**, *10*, 737-746.
214. Macomber, D. W.; Madhukar, P.; Rogers, R. D. "Unusual Rearrangement of [(α-(Silyl)alkyl)alkoxycarbene]tungsten Complexes: X-ray Crystal Structure of (*E*)-$(CO)_5W[C(N(CH_3)_2)CH_2CH_2CH{=}C(OCH_3)Si(CH_3)_3]$," *Organometallics* **1991**, *10*, 2121-2126.
215. Negri, J. T.; Rogers, R. D.; Paquette, L. A. "Belted Spirocyclic Tetrahydrofurans: A New Class of Preorganized Ionophoric Polyethers. Molecular Structure, Conformation, and Binding to Alkali-Metal Atoms," *J. Am. Chem. Soc.* **1991**, *113*, 5073-5075.
216. Nuñez, L.; Rogers, R. D.; Crabtree, G. W.; Welp, U.; Vandervoort, K.; Umezawa, A.; Fang, Y. "Magnetic and Structural Properties of Fe in Single Crystals of $YBa_2Cu_{3-x}Fe_xO_{7-\delta}$," *Phys. Rev. B: Condensed Matter* **1991**, *44*, 4526-4531.
217. Ogasa, M.; Mallin, D. T.; Macomber, D. W.; Rausch, M. D.; Rogers, R. D.; Rollins, A. N. "Synthetic and Structural Studies on New Vinylcyclopentadienyl Derivatives of Titanium, Iron and Thallium," *J. Organomet. Chem.* **1991**, *405*, 41-52.
218. Ogasa, M.; Rausch, M. D.; Rogers, R. D. "New Heterobimetallic Compounds Derived from [η^5-(Dimethylphosphino)cyclopentadienyl][η^7-(dimethylphosphino)cycloheptatrienyl]titanium," *J. Organomet. Chem.* **1991**, *403*, 279-291.
219. Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Rogers, R. D. "Impact of Substituent Modifications on the Atropselectivity Characteristics of an Anionic Oxy-Cope Ring Expansion," *J. Am. Chem. Soc.* **1991**, *113*, 1335-1344.
220. Paquette, L. A.; Friedrich, D.; Rogers, R. D. "Alkylaluminum-Catalyzed Claisen Expansion Reactions. Scope and Stereochemistry," *J. Org. Chem.* **1991**, *56*, 3841-3849.
221. Paquette, L. A.; Moorhoff, C. M.; Maynard, G. D.; Hickey, E. R.; Rogers, R. D. "Stereochemical Course of the Base-Promoted Aldol Self-Coupling of Racemic 5-Norbornen-2-one and 2-Norbornanone," *J. Org. Chem.* **1991**, *56*, 2449-2455.
222. Paquette, L. A.; O'Doherty, G. A.; Rogers, R. D. "Intramolecular Reaction Rate Is Not Determined Exclusively by the Distance Separating Reaction Centers. The Kinetic Consequences of Modulated Ground State Strain on Dyotropic Hydrogen Migration in Systems of Very Similar Geometric Disposition," *J. Am. Chem. Soc.* **1991**, *113*, 7761-7762.
223. Peterson, J. R.; Do, H. D.; Rogers, R. D. "Anticancer Agent Development; 6. Application of the Heterocycle Annulation-Rearrangement Strategy in the Synthesis of a Podophyllotoxin Precursor," *Synthesis* **1991**, 275-277.
224. Peterson, J. R.; Do, H. D.; Rogers, R. D. "X-ray Structure and Crystal Lattice Interactions of the Taxol Side-Chain Methyl Ester," *Pharm. Res.* **1991**, *8*, 908-912.
225. Piatak, D. M.; Tang, P.-F. L.; Franciskovich, J.; Rogers, R. D. "Stereochemistry of Erysulfone," *J. Nat. Prod.* **1991**, *54*, 902-904.
226. Rausch, M. D.; Ogasa, M.; Ayers, M. A.; Rogers, R. D.; Rollins, A. N. "Formation and Molecular Structure of Hydridotricarbonyl{[η^5-(diphenylphosphino)cyclopentadienyl][η^7- (diphenylphosphino)cycloheptatrienyl]titanium-*P*,*P*'}manganese: A New Chelated Titanium-Manganese Heterobimetallic Compound," *Organometallics* **1991**, *10*, 2481-2484.
227. Rausch, M. D.; Ogasa, M.; Rogers, R. D.; Rollins, A. N. "Synthetic and Structural Studies on Carboxy, Carbomethoxy, and Trimethylsilyl Derivatives of (η^5-Cyclopentadienyl)(η^7- cycloheptatrienyl)titanium," *Organometallics* **1991**, *10*, 2084-2086.
228. Rogers, R. D.; Benning, M. M. "Macrocycle Complexation Chemistry. 37. The Isolation and Crystallographic Characterization of the U^{4+} and UO_2^{2+} Extraction Complexes $[(H_5O_2)(dicyclohexano\text{-}24\text{-}crown\text{-}8)]_2[UO_2Cl_4]\bullet MeOH$ and $[(H_5O_2)(dicyclohexano\text{-}24\text{-}crown\text{-}8)]_2[UCl_6]\bullet MeOH$," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, *11*, 121-135.
229. Rogers, R. D.; Bond, A. H.; Henry, R. F. "Structure of Ammonium *p*-Toluenesulfonate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1991**, *C47*, 168-170.
230. Rogers, R. D.; Bond, A. H.; Hipple, W. G.; Rollins, A. N.; Henry, R. F. "Synthesis and Structural Elucidation of Novel Uranyl-Crown Ether Compounds Isolated from Nitric, Hydrochloric, Sulfuric, and Acetic Acids," *Inorg. Chem.* **1991**, *30*, 2671-2679.
231. Rogers, R. D.; Bond, A. H.; Witt, M. M. "Macrocycle Complexation Chemistry 34. Polyethylene Glycol and Glycolate Complexes of Th^{4+}. Preparation and Structural Characterization of $[ThCl_3(pentaethylene\ glycol)]Cl\bullet CH_3CN$ and the $(Th^{4+})_4$ Cluster, $[Th_4Cl_8(O)(tetraethylene\ glycolate)_3]\bullet 3CH_3CN$," *Inorg. Chim. Acta* **1991**, *182*, 9-17.
232. Rogers, R. D.; Etzenhouser, R. D.; Murdoch, J. S.; Reyes, E. "Macrocycle Complexation Chemistry. 35. Survey of the Complexation of the Open Chain 15-Crown-5 Analogue Tetraethylene Glycol with the Lanthanide Chlorides," *Inorg. Chem.* **1991**, *30*, 1445-1455.
233. Rogers, R. D.; Rollins, A. N.; Henry, R. F.; Murdoch, J. S.; Etzenhouser, R. D.; Huggins, S. E.; Nuñez, L. "Direct Comparison of the Preparation and Structural Features of Crown Ether and Polyethylene Glycol Complexes of $NdCl_3\bullet 6H_2O$," *Inorg. Chem.* **1991**, *30*, 4946-4954.
234. Rogers, R. D.; Weitl, F. L.; Kevill, D. N. "Structure of 1-(1-adamantyl)-5-(α-methylvinyl)tetrazole," *J. Crystallogr. Spectrosc. Res.* **1991**, *21*, 661-665.
235. Zaworotko, M. J.; Sturge, K. C.; Nunez, L.; Rogers, R. D. "Sterically Crowded Organometallics. Influence of Complexation upon the Conformation of Hexakis(phenylethyl)benzene," *Organometallics* **1991**, *10*, 1806-1810.
236. Burford, N.; Mason, S.; Spence, R. E. v. H.; Whalen, J. M.; Richardson, J. F.; Rogers, R. D. ""Genuine Heterocycles" from the Acid-Induced Cyclization of (Silylamino)(imino)(chalcogeno)phosphoranes and as a Result of Chloride Ion Abstraction from Bis[bis(trimethylsilyl)amino]thiophosphoryl Chloride," *Organometallics* **1992**, *11*, 2241-2250.

237. Burford, N.; Spence, R. E. v. H.; Whalen, J. M.; Richardson, J. F.; Rogers, R. D. "Novel Cyclisations of the Chalcogeno-Phosphoryl Unit and the Formation of Genuine Heterocycles," *Phosphorus, Sulfur, and Silicon* **1992**, *64*, 137-144.
238. Gilbert, T. M.; Landes, A. M.; Rogers, R. D. "Synthesis and Electronic Properties of Triply Bonded Hexakis(fluoroalkoxy)dimolybdenum Complexes. Structure of $Mo_2[OCMe(CF_3)_2]_6$ and Investigation of the Nature of the Frontier Orbitals in Triply Bonded M_2X_6 Compounds," *Inorg. Chem.* **1992**, *31*, 3438-3444.
239. Nuñez, L.; Rogers, R. D. "Crystal Structure of [$PrCl_3$(15-crown-5)] Prepared via Electrocrystallization," *J. Crystallogr. Spectrosc. Res.* **1992**, *22*, 265-269.
240. Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. "Regio- and Stereochemical Course of the Ring Expansion of Bridged Bicyclic Ketones to Spirocyclic α-Keto Tetrahydrofurans," *J. Org. Chem.* **1992**, *57*, 3956-3965.
241. Paquette, L. A.; Branan, B. M.; Rogers, R. D. "X-ray Crystallographic Study of α-Brominated Diketo Tetraquinanes. Conformational Effects of the Number of Halogens and their Position on Bond Length and Solid-State Conformation," *Tetrahedron* **1992**, *48*, 297-306.
242. Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. "134. An Enantioselective Approach to the Taxanes: Direct Access to Functionalized *cis*-Tricyclo[9.3.1.$0^{3,8}$]pentadecanes *via* α-Hydroxy Ketone and *Wagner-Meerwein* Rearrangements," *Helv. Chim. Acta* **1992**, *75*, 1755-1771.
243. Paquette, L. A.; Kesselmayer, M. A.; Underiner, G. E.; House, S. D.; Rogers, R. D.; Meerholz, K.; Heinze, J. "Multifaceted Consequences of Holding Two [8] Annulene Rings Face-to-Face. Synthesis, Structural Characteristics, and Reduction Behavior of [2_2](1,5)Cyclooctatetraenophane," *J. Am. Chem. Soc.* **1992**, *114*, 2644-2652.
244. Paquette, L. A.; Negri, J. T.; Rogers, R. D. "Synthesis and Molecular Structure of Belted Spirocyclic Tetrahydrofurans, a New Class of Preorganized Hosts for Cations," *J. Org. Chem.* **1992**, *57*, 3947-3956.
245. Peterson, J. R.; Zjawiony, J. K.; Liu, S.; Hufford, C. D.; Clark, A. M.; Rogers, R. D. "Copyrine Alkaloids: Synthesis, Spectroscopic Characterization, and Antimycotic/Antimycobacterial Activity of A- and B-Ring-Functionalized Sampangines," *J. Med. Chem.* **1992**, *35*, 4069-4077.
246. Rogers, R. D.; Benning, M. M.; Etzenhouser, R. D.; Rollins, A. N. "Synthesis and Structural Characterization of the Monodentate 12-Crown-4 and Hexaethylene Glycol Complexes of Uranium(VI): $[UO_2Cl_2(OH_2)_2$(12-crown-4)]•12-crown-4 and $UO_2Cl_2(OH_2)_2$(hexaethylene glycol)," *J. Coord. Chem.* **1992**, *26*, 299-311.
247. Rogers, R. D.; Bond, A. H. "Crown Ether Complexes of Lead(II) Nitrate. Crystal Structures of the 12-Crown-4, 15-Crown-5, Benzo-15-Crown-5, and 18-Crown-6 Complexes," *Inorg. Chim. Acta* **1992**, *192*, 163-171.
248. Rogers, R. D.; Bond, A. H. "Structure of $[ThCl(OH)(OH_2)_6]_2Cl_4$•18-crown-6•$2H_2O$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1992**, *C48*, 1199-1201.
249. Rogers, R. D.; Bond, A. H. "Structure of [Ca(triethylene glycol)$_2$]Cl_2•$4H_2O$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1992**, *C48*, 1782-1785.
250. Rogers, R. D.; Bond, A. H.; Aguinaga, S. "Alcoholysis of $Bi(NO_3)_3$•$5H_2O$ by Polyethylene Glycols. Comparison with Bismuth(III) Nitrate Crown Ether Complexation," *J. Am. Chem. Soc.* **1992**, *114*, 2960-2967.
251. Rogers, R. D.; Bond, A. H.; Aguinaga, S.; Reyes, A. "Complexation Chemistry of Bismuth(III) Halides with Crown Ethers and Polyethylene Glycols. Structural Manifestations of a Stereochemically Active Lone Pair," *J. Am. Chem. Soc.* **1992**, *114*, 2967-2977.
252. Rogers, R. D.; Bond, A. H.; Hipple, W. G. "Synthesis and Crystal Structure of $[UO_2(NO_3)_2(OH_2)_2]$•2(benzo-15-crown-5)," *J. Crystallogr. Spectrosc. Res.* **1992**, *22*, 365-369.
253. Rogers, R. D.; Etzenhouser, R. D.; Murdoch, J. S. "Triethylene Glycol Complexes of the Early Lanthanide(III) Chlorides," *Inorg. Chim. Acta* **1992**, *196*, 73-79.
254. Rogers, R. D.; Henry, R. F. "Crystal Structure of $[CeCl(OH_2)_3$(EG4)]Cl_2•H_2O (EG4 = Tetraglyme)," *J. Crystallogr. Spectrosc. Res.* **1992**, *22*, 361-364.
255. Rogers, R. D.; Henry, R. F. "Structure of $[PrCl_3$(EO4)$]_2$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1992**, *C48*, 1099-1101.
256. Rogers, R. D.; Henry, R. F.; Rollins, A. N. "Macrocycle Complexation Chemistry. 38. Crystallographic and Ultraviolet/Visible Characterization of Nitrobenzo-15-crown-5, Dinitrobenzo-15-crown-5, and Dinitrodibenzo-18-crown-6•$2CH_3CN$," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 219-232.
257. Rogers, R. D.; Huggins, S. E.; Henry, R. F.; Bond, A. H. "Arene-Substituent Effects in Benzo-15-crown-5 Complexes. The Crystal Structures of 4-Aminobenzo-15-crown-5 and $[KI(OH_2)$(4-nitrobenzo-15-crown-5)$]_2$," *Supramol. Chem.* **1992**, *1*, 59-63.
258. Alt, H. G.; Han, J. S.; Rogers, R. D. "Darstellung und Charakterisierung von Indenyl- und Fluorenylfunktionalisierten Cyclopentadienylcarbonyl-Methylkomplexen des Molybdäns und Wolframs. Molekülstrukturen von (η^5-$C_5H_4CMe_2C_9H_7$)M(CO)$_3$Me (M = Mo,W), (η^5-$C_5H_4CMe_2C_{13}H_9$)M(CO)$_3$Me und (η^5:η^2-$C_5H_4CMe_2C_9H_7$)Mo(CO)$_2$Me," *J. Organomet. Chem.* **1993**, *445*, 115-124.
259. Alt, H. G.; Han, J. S.; Rogers, R. D. "Photoinduzierte Desalkylierungsreaktionen an Indenyl- und Fluorenylfunktionalisierten Cyclopentadienyltricarbonyl-Methylkomplexen des Molybdäns und Wolframs. Molekülstrukturen von (η^5:η^1-$C_5H_4CMe_2C_9H_6$)Mo(CO)$_3$, (η^5:η^1- $C_5H_4CMe_2C_{13}H_8$)W(CO)$_3$, und [(η^5-$C_5H_4(CH_2)_3C_{13}H_9$)W(CO)$_3$]$_2$," *J. Organomet. Chem.* **1993**, *454*, 165-172.
260. Alt, H. G.; Han, J. S.; Rogers, R. D.; Thewalt, U. "Acetylenkomplexe des Wolframs. Molekülstrukturen von (η^5-

$C_5H_4CMe_2C_{13}H_9$)W(CO)(HC$_2$Ph)Me, (η^5:η^1-$C_5H_4CMe_2C_{13}H_8$)W(CO)(C$_2$Ph$_2$) und (η^5-C_5H_5)Cr(CO)(C$_2$H$_2$)NO; ein Vergleich von alkinischen Vier- und Zweielektronenliganden," *J. Organomet. Chem.* **1993**, *459*, 209-217.

261. Beachley, O. T., Jr.; Maloney, J. D.; Rogers, R. D. "Gallium and Indium Compounds Containing Three Different Substituents. Crystal and Molecular Structure of [(Me_3CCH_2)ClGaPPh$_2$]$_3$," *J. Organomet. Chem.* **1993**, *449*, 69-75.
262. Beachley, O. T., Jr.; Maloney, J. D.; Rogers, R. D. "Synthesis of [(Me_3CCH_2)Ga(PPh$_2$)$_2$]$_2$ from [(Me_3CCH_2)ClGaPPh$_2$]$_3$," *Organometallics* **1993**, *12*, 229-232.
263. Burford, N.; Losier, P.; Mason, S.; Royan, B. W.; Spence, R. E. v. H.; Bakshi, P. K.; Borecka, B.; Cameron, T. S.; Richardson, J. F.; Rogers, R. D. "The Stability of *Carbenic* and *Alkenic* Phosphorus Environments," *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *76*, 17-20.
264. Filippou, A. C.; Völkl, C.; Rogers, R. D. "Metal-Centered C-C Coupling of Nitriles with 1- Azaallyl Ligands; Synthesis and Structure of β-Diiminato Complexes of Tungsten," *J. Organomet. Chem.* **1993**, *463*, 135-142.
265. Gilbert, T. M.; Rogers, R. D. "Structure of [W$_2$(μ-C$_2$){OC(CH_3)$_3$}$_6$]: a Dimetallabutadiyne," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1993**, *C49*, 677-680.
266. Hadley, F. J.; Gilbert, T. M.; Rogers, R. D. "Crystal Structures of (η^6-C_7H_8)M(CO)$_3$ (M = Cr, W). Comparisons Among a Homologous Series of Cycloheptatriene Complexes and Experimental Evidence for a Boat Conformation of the Coordinated Ring," *J. Organomet. Chem.* **1993**, *455*, 107-113.
267. Heeres, H. J.; Nijhoff, J.; Teuben, J. H.; Rogers, R. D. "Reversible Carbon-Carbon Bond Formation in Organolanthanide Systems. Preparation and Properties of Lanthanide Acetylides [Cp*$_2$LnC/CR]$_n$ and Their Rearrangement Products [Cp*$_2$Ln]$_2$(μ-η^2:η^2-RC_4R) (Ln = La, Ce, R = alkyl)," *Organometallics* **1993**, *12*, 2609-2617.
268. Horwitz, E. P.; Dietz, M. L.; Diamond, H.; Rogers, R. D.; Leonard, R. A. "Advanced Chemical Separations in Support of the Clean Option Strategy," In *International Conference and Technology Exhibition on Future Nuclear Systems: Emerging Fuel Cycles and Waste Disposal Options Global '93*, American Nuclear Society, Inc.: La Grange Park, IL, 1993; Vol. 1; pp 39-43.
269. Horwitz, E. P.; Dietz, M. L.; Diamond, H.; Rogers, R. D.; Leonard, R. A. "Combined TRU-Sr Extraction/Recovery Process," In *Solvent Extraction in the Process Industries, Proceedings of ISEC '93*; Logsdail, D. H.; Slater, M. J., Eds.; Elsevier: London, 1993; Vol. 3; pp 1805-1812.
270. Hufford, C. D.; Jia, Y.; Croom, E. M., Jr.; Muhammed, I.; Okunade, A. L.; Clark, A. M.; Rogers, R. D. "Antimicrobial Compounds from *Petalostemum purpureum*," *J. Nat. Prod.* **1993**, *56*, 1878-1889.
271. Nuñez, L.; Rogers, R. D. "Utilization of Crown Ether Chemistry to Prepare Bimetallic Compounds: Preparation and Structural Characterization of [Ba(15-crown-5)$_2$][$CuCl_4$]," *J. Coord. Chem.* **1993**, *28*, 347-354.
272. Rogers, R. D.; Alt, H. G. "Crystal Structure of Cr(CO)$_5$($NHMe_2$)," *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 533-535.
273. Rogers, R. D.; Bauer, C. B. "Crystal Structures of [Gd_6(O)(OH)$_8$(NO_3)$_6$(OH_2)$_{12}$][NO_3]$_2$•2H_2O and [NH_4]$_2$[Yb_6(O)(OH)$_8$(NO_3)$_7$(OH_2)$_{10}$][NO_3]$_3$•H_2O," *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 537-545.
274. Rogers, R. D.; Bond, A. H.; Aguinaga, S. "Synthesis and Crystallographic Characterization of [Cd(OH_2)$_2$(μ-Br)$_4$(Cd(2-hydroxyethyl sulfide)(μ-Br))$_2$]$_n$," *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 857-862.
275. Rogers, R. D.; Bond, A. H.; Aguinaga, S.; Reyes, A. "Polyethylene Glycol Complexation of Cd^{2+}. Structures of Triethylene Glycol Complexes of $CdCl_2$, $CdBr_2$ and CdI_2," *Inorg. Chim. Acta* **1993**, *212*, 225-231.
276. Rogers, R. D.; Bond, A. H.; Bauer, C. B. "Aqueous Biphase Systems for Liquid/Liquid Extraction of f-Elements Utilizing Polyethylene Glycols," *Sep. Sci. Technol.* **1993**, *28*, 139-153.
277. Rogers, R. D.; Bond, A. H.; Bauer, C. B. "The Crown Ether Extraction of Group 1 and 2 Cations in Polyethylene Glycol-Based Aqueous Biphasic Systems at High Alkalinity," *Pure Appl. Chem.* **1993**, *65*, 567-572.
278. Rogers, R. D.; Bond, A. H.; Bauer, C. B. "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1993**, *28*, 1091-1126.
279. Rogers, R. D.; Bond, A. H.; Bauer, C. B. "Polyethylene Glycol-Based Aqueous Biphasic Systems for Liquid/Liquid Extraction of Environmentally Toxic Heavy Metals," In *Solvent Extraction in the Process Industries, Proceedings of ISEC '93*; Logsdail, D. H.; Slater, M. J., Eds.; Elsevier: London, 1993; Vol. 3; pp 1641-1648.
280. Rogers, R. D.; Bond, A. H.; Wolff, J. L. "Structural Studies of Polyether Coordination to Mercury(II) Halides: Crown Ether versus Polyethylene Glycol Complexation," *J. Coord. Chem.* **1993**, *29*, 187-207.
281. Rogers, R. D.; Henry, R. F.; Ochrymowycz, L. A.; Toske, S. G. "The Improved Synthesis and Crystal Structure of 20-Thiocrown-4," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1993**, *15*, 145-152.
282. Rogers, R. D.; Macomber, D. W.; Liang, M. "Crystal Structure of a (μ-Bis(carbene))dimetal Complex of Tungsten," *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 623-628.
283. Rogers, R. D.; Rollins, A. N.; Etzenhouser, R. D.; Voss, E. J.; Bauer, C. B. "Structural Investigation into the Steric Control of Polyether Complexation in the Lanthanide Series: Macrocyclic 18-Crown-6 versus Acyclic Pentaethylene Glycol," *Inorg. Chem.* **1993**, *32*, 3451-3462.
284. Rogers, R. D.; Sivik, M. R.; Paquette, L. A. "Isodicyclopentadienes and Related Molecules LVII. Solid State Structural Studies of the Diastereomeric *exo*- and *endo*-(η^5-Cyclopentadienyl)(η^5-1*S*,8*R*)-9,9-dimethyltricyclo[6.1.1.0^{2,6}]deca-2,5-dienyl)dichlorotitaniums and a Stereopure *exo*-(η^5-Pentamethyl-cyclopentadienyl) Congener," *J. Organomet. Chem.* **1993**, *450*, 125-135.
285. Sangokoya, S. A.; Pennington, W. T.; Byers-Hill, J.; Robinson, G. H.; Rogers, R. D. "Toward Unusual Al-O Compounds. Synthesis and Molecular Structure of [$Al_4O(OCH_2CF_3)_{11}$]$^-$: Structural Characterization of a Novel Al_4O_{12} Cluster," *Organometallics* **1993**, *12*, 2429-2431.

286. Donaldson, W. A.; Shang, L.; Rogers, R. D. "Reactivity of Tricarbonyl(pentadienyl)iron(1+) Cations: Preparation of an Optically Pure Tricarbonyl(diene)iron Complex via Second-Order Asymmetric Transformation," *Organometallics* **1994**, *13*, 6-7.
287. Fierro, R.; Rausch, M. D.; Rogers, R. D.; Herberhold, M. "New Sulfur and Selenium Derivatives of (η^5-Cyclopentadienyl)(η^7-cycloheptatrienyl)titanium, and Their Application in the Syntheses of Heterobimetallic Compounds," *J. Organomet. Chem.* **1994**, *472*, 87-95.
288. Gilbert, T. M.; Bond, A. H.; Rogers, R. D. "Structures of a Series of [4-R-C_6H_4-CH(OR')$_2$]Cr(CO)$_3$ Complexes: Evidence Against a Favored Carbonyl Orientation in (*Para*-disubstituted Arene)chromium Tricarbonyl Compounds," *J. Organomet. Chem.* **1994**, *479*, 73-86.
289. Gilbert, T. M.; Hadley, F. J.; Bauer, C. B.; Rogers, R. D. "Organotransition Metal Compounds for Photonics: Syntheses and Structures of a Series of (Nitrostilbene)chromium Tricarbonyl Complexes," *Organometallics* **1994**, *13*, 2024-2034.
290. Gilbert, T. M.; Rogers, R. D. "Structures of Z-(Nitrostilbene)chromium Tricarbonyl Complexes: The Effect of Metal Coordination on the Nonplanarity of the Stilbene System," *J. Chem. Crystallogr.* **1994**, *24*, 315-320.
291. Hasinoff, L.; Takats, J.; Zhang, X. W.; Bond, A. H.; Rogers, R. D. "Application of the Sterically Demanding Hydrotris(3-*tert*-butyl-5-methylpyrazolyl)borate Ligand to Ln(II) Chemistry: Synthesis of a New Class of Mixed-Ligand Yb(II) Complexes," *J. Am. Chem. Soc.* **1994**, *116*, 8833-8834.
292. Ji, Z. P.; Rogers, R. D. "Structure of [La(NO_3)$_3$(OH_2)$_2$(OHMe)(bipy)]•15-crown-5," *J. Chem. Crystallogr.* **1994**, *24*, 415-419.
293. Ji, Z. P.; Rogers, R. D. "The Synthesis and Crystal Structure of [La(OH_2)$_5$(phen)$_2$]Cl_3•4H_2O•phen," *J. Chem. Crystallogr.* **1994**, *24*, 797-800.
294. Khalifa, S. I.; Baker, J. K.; Rogers, R. D.; El-Feraly, F. S.; Hufford, C. D. "Microbial and Mammalian Metabolism Studies of the Semisynthetic Antimalarial, Anhydrodihydroartemisinin," *Pharm. Res.* **1994**, *11*, 990-994.
295. O'Doherty, G. A.; Rogers, R. D.; Paquette, L. A. "Consequences of Modulated Precompression along Reaction Coordinates. Synthesis, Crystallographic Structural Studies, and Rate of Intramolecular Dyotropy in an Extended Series of *syn*-Sesquinorbornene Disulfones," *J. Am. Chem. Soc.* **1994**, *116*, 10883-10894.
296. Okunade, A. L.; Liu, S.; Clark, A. M.; Hufford, C. D.; Rogers, R. D. "Sesquiterpene Lactones from *Peucephyllum schottii*," *Phytochemistry* **1994**, *35*, 191-194.
297. Paquette, L. A.; Branan, B. M.; Friedrich, D.; Edmondson, S. D.; Rogers, R. D. "Analysis of the Conformational Nature, Resolvability, and Thermal Racemization of Hetero 2,3-Dispiro Cyclohexanones. The Weighting of Carbonyl/C-X Stabilization Relative to the Electronic Interaction between the Vicinal Electronegative Substituents," *J. Am. Chem. Soc.* **1994**, *116*, 506-513.
298. Rogers, R. D.; Adrowski, M. J.; Bond, A. H. "Crystal Structure of Pt(S_2COEt)$_2$," *J. Chem. Crystallogr.* **1994**, *24*, 707-710.
299. Rogers, R. D.; Bauer, C. B. "Structure of Diethylenetriammonium Nitrate," *J. Chem. Crystallogr.* **1994**, *24*, 281-283.
300. Rogers, R. D.; Bauer, C. B. "Crystal Structure of Pyridinium Hydrogen Sulfate, [HC_5H_5N][HSO_4]," *J. Chem. Crystallogr.* **1994**, *24*, 285-287.
301. Rogers, R. D.; Bauer, C. B.; Bond, A. H. "Crown Ethers as Actinide Extractants in Acidic Aqueous Biphasic Systems: Partitioning Behavior in Solution and Crystallographic Analyses of the Solid State," *J. Alloys Compd.* **1994**, *213/214*, 305-312.
302. Rogers, R. D.; Jezl, M. L. "Ammonium Heptachlorooxodiantimonate(III), (NH_4)$_3$[Sb_2Cl_7O]," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1994**, *C50*, 1527-1529.
303. Rogers, R. D.; Jezl, M. L.; Bauer, C. B. "Effects of Polyethylene Glycol on the Coordination Sphere of Strontium in $SrCl_2$ and Sr(NO_3)$_2$ Complexes," *Inorg. Chem.* **1994**, *33*, 5682-5692.
304. Rogers, R. D.; Rollins, A. N. "Primary to Secondary Sphere Coordination of 18-Crown-6 to Lanthanide(III) Nitrates: Structural Analysis of [Pr(NO_3)$_3$(18-crown-6)] and [M(NO_3)$_3$(OH_2)$_3$]•18-crown-6 (M = Y, Eu, Tb-Lu)," *J. Chem. Crystallogr.* **1994**, *24*, 321-329.
305. Rogers, R. D.; Rollins, A. N. "Primary to Secondary Sphere Coordination of 15-Crown-5 to Lanthanide(III) Chlorides: Structural Analysis of [MCl_3(15-crown-5)] (M = La, Ce) and [Er(OH_2)$_8$]Cl_3•15-crown-5," *J. Chem. Crystallogr.* **1994**, *24*, 531-537.
306. Bauer, C. B.; Rogers, R. D.; Nuñez, L.; Ziemer, M. D.; Pleune, T. T.; Vandegrift, G. F.; "Review and Evaluation of Extractants for Strontium Removal Using Magnetically Assisted Chemical Separation," Report ANL-95/26, Argonne National Laboratory: Argonne, IL 1995; 25 pp.
307. Beachley, O. T., Jr.; Maloney, J. D.; Banks, M. A.; Rogers, R. D. "Synthesis and Characterization of a Series of Organoindium Phosphides, Including Molecular Structures of [(Me_3CCH_2)$_2$InPEt_2]$_2$ and [(Me_3CCH_2)$_2$InP(H)(C_6H_{11})]$_3$," *Organometallics* **1995**, *14*, 3448-3454.
308. Black, D. G.; Swenson, D. C.; Jordan, R. F.; Rogers, R. D. "Tetraaza Macrocycles as Ancillary Ligands in Early Metal Alkyl Chemistry. Synthesis and Characterization of Out-of-Plane (Me_4taen)ZrX_2 (X = Alkyl, Benzyl, NMe_2, Cl) and (Me_4taen)ZrX_2($NHMe_2$) (X = Cl, CCPh) Complexes," *Organometallics* **1995**, *14*, 3539-3550.
309. Bowen, D. E.; Jordan, R. F.; Rogers, R. D. "Group 4 Metal Mono-Dicarbollide Piano Stool Complexes. Synthesis, Structure, and Reactivity of (η^5-$C_2B_9H_{11}$)M(NR_2)$_2$(NHR_2) (M = Zr, R = Et; M = Ti, R = Me, Et)," *Organometallics* **1995**, *14*, 3630-3635.
310. Dietz, M. L.; Horwitz, E. P.; Rogers, R. D. "Extraction of Strontium from Acidic Nitrate Media Using a Modified PUREX Solvent," *Solvent Extr. Ion Exch.* **1995**, *13*, 1-17.
311. Feil-Jenkins, J. F.; Nash, K. L.; Rogers, R. D. "Lanthanide Complexes with Tetrahydrofuran-2,3,4,5-tetracarboxylic Acid: The Effect of Ligand Rigidity on Cation Size-Selectivity," *Inorg. Chim. Acta* **1995**, *236*, 67-74.
312. Fu, W.; McDonald, R.; Takats, J.; Bond, A. H.; Rogers, R. D. "Cycloheptatrienyl bridged heterobimetallic complexes: fluxional behavior and X-ray crystal structure of *syn*-(μ^3:η^2-C_7H_7)Fe($CO)_3$Pd(η^3-C_3H_5)," *Inorg. Chim. Acta* **1995**, *229*, 307-313.

313. Galindo, A.; Gutiérrez, E.; Monge, A.; Paneque, M.; Pastor, A.; Pérez, P. J.; Rogers, R. D.; Carmona, E. "Dinitrogen, Butadiene and Related Complexes of Molybdenum. Crystal Structures of $Mo(N_2)(PMe_3)_5$ and $[Mo(\eta^3\text{-}CH_3CHCHCH_2)(\eta^4\text{-}C_4H_6)(PEt_3)_2][BF_4]$," *J. Chem. Soc., Dalton Trans.* **1995**, 3801-3808.
314. Horwitz, E. P.; Dietz, M. L.; Diamond, H.; Rogers, R. D.; Leonard, R. A. "Combined TRUEX-SREX Extraction/Recovery Process," In *Chemical Pretreatment of Nuclear Waste for Disposal*; Schulz, W. W.; Horwitz, E. P., Eds.; Plenum: New York, 1995; pp 81-99.
315. Hufford, C. D.; Khalifa, S. I.; Orabi, K. Y.; Wiggers, F. T.; Kumar, R.; Rogers, R. D.; Campana, C. F. "1α-Hydroxyarteether, a New Microbial Transformation Product," *J. Nat. Prod.* **1995**, *58*, 751-755.
316. Paquette, L. A.; Branan, B. M.; Rogers, R. D. "High-Pressure Diels-Alder Reactions of 1-Oxa[4.4.4]propella-5,7-diene Proceed with Framework Isomerization," *J. Org. Chem.* **1995**, *60*, 1852-1855.
317. Paquette, L. A.; Branan, B. M.; Rogers, R. D.; Bond, A. H.; Lange, H.; Gleiter, R. "Heteroatomic Influences on the π-Facial Selectivity of Diels-Alder Cycloadditions to Dispiro[4.0.4.4]tetradeca-11,13-dienes," *J. Am. Chem. Soc.* **1995**, *117*, 5992-6001.
318. Peterson, J. R.; Zjawiony, J. K.; Clark, A. M.; Hufford, C. D.; Rogers, R. D. "Antifungal Copyrine Alkaloids: Crystal Structure of 3-Methylsampangine," *J. Chem. Crystallogr.* **1995**, *25*, 223-226.
319. Rogers, R. D.; Bauer, C. B.; Bond, A. H. "Novel Polyethylene Glycol-Based Aqueous Biphasic Systems for the Extraction of Strontium and Cesium," *Sep. Sci. Technol.* **1995**, *30*, 1203-1217.
320. Rogers, R. D.; Bond, A. H.; Bauer, C. B.; Zhang, J.; Jezl, M. L.; Roden, D. M.; Rein, S. D.; Chomko, R. R. "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems," In *Aqueous Biphasic Separations: Biomolecules to Metal Ions*; Rogers, R. D.; Eiteman, M. A., Eds.; Plenum: New York, 1995; pp 1-20.
321. Rogers, R. D.; Bond, A. H.; Bauer, C. B.; Zhang, J.; Rein, S. D.; Chomko, R. R.; Roden, D. M. "Partitioning Behavior of ^{99}Tc and ^{129}I from Simulated Hanford Tank Wastes Using Polyethylene Glycol-Based Aqueous Biphasic Systems," *Solvent Extr. Ion Exch.* **1995**, *13*, 689-713.
322. Rogers, R. D.; Bond, A. H.; Henry, R. F.; Rollins, A. N. "The Effects of Methylene-Substituents in Crown Ether Backbones. Crystal Structures of $[Na(OH_2)$(methylene-16-crown-5)]I, $[Na(NO_2)$(methylene-16-crown-5)]•0.5(H_2O), 3,16-Dimethylene-26-crown-8, $[Na_4I_4$(3,16-dimethylene-26-crown-8)], and $[Na_2(OH_2)_4$(3,16-dimethylene-26-crown-8)]I_2," *Supramol. Chem.* **1995**, *4*, 191-202.
323. Rogers, R. D.; Rollins, A. N. "Mixed Anion Lanthanide(III) Crown Ether Complexes: Crystal Structures of $[LaCl_2(NO_3)$(12-crown-4)]$_2$, $[La(NO_3)(OH_2)_4$(12-crown-4)]Cl_2•CH_3CN and $[LaCl_2(NO_3)$(18-crown-6)]," *Inorg. Chim. Acta* **1995**, *230*, 177-183.
324. Rogers, R. D.; Rollins, A. N.; Gatrone, R. C.; Horwitz, E. P. "Comparison of the Crystal Structure and Molecular Models of N-N-Diisobutyl-2-(octylphenylphosphinyl)acetamide (CMPO)," *J. Chem. Crystallogr.* **1995**, *25*, 43-49.
325. Rogers, R. D.; Song, Y. "Crystal Structure Analyses of Two Crown Ether Complexes of Copper(II) Nitrate: $[Cu(NO_3)_2$(12-crown-4)] and $[Cu(OH_2)_2$(15-crown-5)]$[NO_3]_2$," *J. Coord. Chem.* **1995**, *34*, 149-157.
326. Rogers, R. D.; Song, Y. "The Crystal Structure of a Heterobimetallic Crown Ether Complex: [Na(dibenzo-18-crown-6)]$[FeCl_4]$," *J. Chem. Crystallogr.* **1995**, *25*, 579-582.
327. Rogers, R. D.; Zhang, J.; Bond, A. H.; Bauer, C. B.; Jezl, M. L.; Roden, D. M. "Selective and Quantitative Partitioning of Pertechnetate in Polyethylene Glycol-Based Aqueous Biphasic Systems," *Solvent Extr. Ion Exch.* **1995**, *13*, 665-688.
328. Whitcomb, D. R.; Rogers, R. D. "The Properties, Crystal, and Molecular Structure of Catena-[(μ-actetato-)(μ-phthalazine)silver(I)dihydrate]: $\{[Ag(\mu\text{-}O_2CCH_3)(\mu\text{-PHZ})(H_2O)_2]_2\}_n$," *J. Chem. Crystallogr.* **1995**, *25*, 137-142.
329. Beachley, O. T., Jr.; Banks, M. A.; Kopasz, J. P.; Rogers, R. D. "Main Group Compounds as Amphoteric Ligands to Transition Metals. Synthesis and Molecular Structure of $Cr(CO)_5[PPhCH_2Ga(CH_2CMe_3)_2$•$NMe_3]$," *Organometallics* **1996**, *15*, 5170-5174.
330. Blair, J. T.; Patel, R. C.; Rogers, R. D.; Whitcomb, D. W. "The Molecular Structure of [bis-(2- (Tribromomethylsulfonyl-benzothiazole)-silver(I)-tetrafluroborate•(acetone)] $[Ag\{(C_7H_4NS)SO_2CBr_3\}_2BF_4$•$Me_2CO]$: A Possible Model for Bromine Elimination of Silver Halide Fog Centers," *J. Imaging Sci. Technol.* **1996**, *40*, 117-122.
331. Brechbiel, M. W.; Gansow, O. A.; Pippin, C. G.; Rogers, R. D.; Planalp, R. P. "Preparation of the Novel Chelating Agent *N*-(2-Aminoethyl)-*trans*-1,2-diaminocyclohexane-*N,N′,N″*-pentaacetic Acid (H_5CyDTPA), a Preorganized Analogue of Diethylenetriaminepentaacetic Acid (H_5DTPA), and the Structures of $Bi^{III}(CyDTPA)^{2-}$ and $Bi^{III}(H_2DTPA)$ Complexes," *Inorg. Chem.* **1996**, *35*, 6343-6348.
332. Brogan, J. B.; Bauer, C. B.; Rogers, R. D.; Zercher, C. K. "Selectivity in the Rearrangements of Oxonium Ylides," *Tetrahedron Lett.* **1996**, *37*, 5053-5056.
333. Chen, M. J.; Nuñez, L.; Rathke, J. W.; Rogers, R. D. "Hydrido(1,4,8,11,15,18,22,25-octa-*n*- pentylphthalocyanato)-rhodium Dimers: Single-Crystal X-ray Structure, and the Isomerization of the Four Isomers," *Organometallics* **1996**, *15*, 2338-2344.
334. Cooke, J.; McClung, R. E. D.; Takats, J.; Rogers, R. D. "Synthesis, Characterization, and Dynamic Behavior of $Os_2Pt(CO)_8(PPh_3)_2$: A Trinuclear Osmium-Platinum Cluster with Flexible Metal Framework," *Organometallics* **1996**, *15*, 4459-4468.
335. Fettinger, J. C.; Mattamana, S. P.; Poli, R.; Rogers, R. D. "Accessibility of 17-Electron Structures for Cyclopentadienylchromium(III) Compounds. 1. Experimental Studies on the Dichloride and Dimethyl Compounds," *Organometallics* **1996**, *15*, 4211-4222.
336. Gilbert, T. M.; Bauer, C. B.; Rogers, R. D. "Structures of (η^6-Benzene dimethylacetal)- and (η^6-Benzene diethylacetal)chromium Tricarbonyl: Structural Evidence for the Near-Electroneutrality of the Dialkylacetal Substituent," *J. Chem. Crystallogr.* **1996**, *26*, 355-360.
337. Gilbert, T. M.; Hadley, F. J.; Simmons, M. D.; Bauer, C. B.; Rogers, R. D. "Syntheses and Structures of

Bis(tricarbonylchromium)-Substituted α, ω-Diphenylhexatriene Complexes," *J. Organomet. Chem.* **1996**, *510*, 83-92.
338. Ji, Z. P.; Rogers, R. D. "The Crystal Structure and Supramolecular Chain of $[La(NO_3)_3(OH_2)_2(phen)]$•15-crown-5," *J. Chem. Crystallogr.* **1996**, *26*, 573-577.
339. Johnson, C. P.; Atwood, J. L.; Steed, J. W.; Bauer, C. B.; Rogers, R. D. "Transition Metal Complexes of *p*-Sulfanatocalix[5]arene," *Inorg. Chem.* **1996**, *35*, 2602-2610.
340. Melendez, R. E.; Sharma, C. V. K.; Zaworotko, M. J.; Bauer, C.; Rogers, R. D. "Toward the Design of Porous Organic Solids: Modular Honeycomb Grids Sustained by Anions of Trimesic Acid," *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2213-2215.
341. Paquette, L. A.; Morwick, T. M.; Negri, J. T.; Rogers, R. D. "Addition of 2,3-Dihydro-5-furanyllithium to Diisopropyl Squarate as a Means for the Rapid Generation of Structurally Complex Oxygen-Containing Tetraquinane Networks," *Tetrahedron* **1996**, *52*, 3075-3094.
342. Paquette, L. A.; Stephanian, M.; Branan, B. M.; Edmondson, S. D.; Bauer, C. B.; Rogers, R. D. "Conformational Analysis of Poly(spirotetrahydrofuranyl)cyclohexyl Systems. The Preference of Multiple C-O Bonds for Equatorial Occupancy," *J. Am. Chem. Soc.* **1996**, *118*, 4504-4505.
343. Rogers, R. D. "The Crystal and Molecular Structure of $[\eta^5\text{-}C_5H_3(SiMe_3)_2]_2Yb(THF)$," *J. Organomet. Chem.* **1996**, *512*, 97-100.
344. Rogers, R. D.; Bauer, C. B. "Water Soluble Calixarenes as Possible Metal Ion Extractants in Polyethylene Glycol-Based Aqueous Biphasic Systems," *J. Radioanal. Nucl. Chem.* **1996**, *208*, 153-161.
345. Rogers, R. D.; Bauer, C. B. "Partitioning Behavior of Group 1 and 2 Cations in Polyethylene Glycol-Based Aqueous Biphasic Systems," *J. Chromatogr., B: Biomed. Appl.* **1996**, *680*, 237-242.
346. Rogers, R. D.; Bauer, C. B. "Structural Chemistry of Metal-Crown Ether and Polyethylene Glycol Complexes Excluding Group 1 and 2," In *Comprehensive Supramolecular Chemistry*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Exec. Eds., Lehn, J. M., Chair. Ed. Bd., Vol. I, *Molecular Recognition: Receptors for Cationic Guests*; Gokel, G. W., Ed.; Pergamon: Exeter, 1996; pp 315-355.
347. Rogers, R. D.; Bond, A. H. "Crown Ether Mediated Cadmium Halide Dimers and Polymers," *Inorg. Chim. Acta* **1996**, *250*, 105-117.
348. Rogers, R. D.; Bond, A. H.; Bauer, C. B.; Griffin, S. T.; Zhang, J. "Polyethylene Glycol-Based Aqueous Biphasic Systems for Extraction and Recovery of Dyes and Metal/Dye Complexes," In: *Value Adding through Solvent Extraction Proceedings of ISEC'96*; Shallcross, D. C.; Paiman, R.; Prvcic, L. M. Eds.; The University of Melbourne: Parkville, Victoria, Australia, 1996; Vol. 2; pp 1537-1542.
349. Rogers, R. D.; Bond, A. H.; Bauer, C. B.; Zhang, J.; Griffin, S. T. "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems: Correlation of Partitioning Behavior with Available Thermodynamic Hydration Data," *J. Chromatogr., B: Biomed. Appl.* **1996**, *680*, 221-230.
350. Rogers, R. D.; Bond, A. H.; Griffin, S. T.; Horwitz, E. P. "New Technologies for Metal Ion Separations: Aqueous Biphasic Extraction Chromatography (ABEC). Part I. Uptake of Pertechnetate," *Solvent Extr. Ion Exch.* **1996**, *14*, 919-946.
351. Rogers, R. D.; Bond, A. H.; Roden, D. M. "Structural Chemistry of Poly(ethylene glycol) Complexes of Lead(II) Nitrate and Lead(II) Bromide," *Inorg. Chem.* **1996**, *35*, 6964-6973.
352. Rogers, R. D.; Bond, A. H.; Zhang, J.; Bauer, C. B. "Polyethylene Glycol Based-Aqueous Biphasic Systems as Technetium-99m Generators," *Appl. Radiat. Isotop.* **1996**, *47*, 497-499.
353. Rogers, R. D.; Zhang, J. "Effects of Increasing Polymer Hydrophobicity on Distribution Ratios of TcO_4^- in Polyethylene/Polypropylene Glycol-Based Aqueous Biphasic Systems," *J. Chromatogr., B: Biomed. Appl.* **1996**, *680*, 231-236.
354. Schulz, S.; Gillan, E. G.; Ross, J. L.; Rogers, L. M.; Rogers, R. D.; Barron, A. R. "Synthesis of Gallium Chalcogenide Cubanes and Their Use as CVD Precursors for Ga_2E_3 (E = S, Se)," *Organometallics* **1996**, *15*, 4880-4883.
355. Steed, J. W.; Tocher, D. A.; Rogers, R. D. "Ruthenium Mediated Cyclodimerisation of Buta-1,3-diene," *Chem. Commun.* **1996**, 1589-1590.
356. Tsai, W.-M.; Rausch, M. D.; Rogers, R. D. "Improved Synthesis of Pentabenzylcyclopentadiene and Study of the Reaction between Pentabenzylcyclopentadiene and Iron Pentacarbonyl," *Organometallics* **1996**, *15*, 2591-2594.
357. Whitcomb, D. R.; Rogers, R. D. "The Molecular Structure of [*bis*-Triphenylphosphine-silver(I)stearate], $[((C_6H_5)_3P)_2Ag(O_2C(CH_2)_{16}CH_3)]$, Solubilization of Long Alkyl Chain Silver Carboxylates," *J. Chem. Crystallogr.* **1996**, *26*, 99-105.
358. Zhao, H.; Heintz, R. A.; Dunbar, K. R.; Rogers, R. D. "Unprecedented Two-Dimensional Polymers of Mn(II) with $TCNQ^{\bullet}$ (TCNQ = 7,7,8,8-Tetracyanoquinodimethane)," *J. Am. Chem. Soc.* **1996**, *118*, 12844-12845.
359. Zong, K.; Chen, W.; Cava, M. P.; Rogers, R. D. "Synthesis and Properties of Bis(2,5-dimethylpyrrolo[3,4-*d*])tetrathiafulvalenes, a Class of Annelated Tetrathiafulvalene Derivatives with Excellent Donor Properties," *J. Org. Chem.* **1996**, *61*, 8117-8124.
360. Adams, R. D.; McBride, K. T.; Rogers, R. D. "A New Route to Polyselenoether Macrocycles. Catalytic Macrocyclization of 3,3-Dimethylselenatane by $Re_2(CO)_9SeCH_2CMe_2CH_2$," *Organometallics* **1997**, *16*, 3895-3901.
361. Beachley, O. T., Jr.; Maloney, J. P.; Rogers, R. D. "Cyclopentadiene Elimination Reaction as a Route to Bis(neopentyl)gallium Phosphides. Crystal and Molecular Structures of $[(Me_3CCH_2)_2GaPEt_2]_2$ and $[(Me_3CCH_2)_2GaP(C_6H_{11})_2]_2$," *Organometallics* **1997**, *16*, 3267-3272.
362. Black, D. G.; Jordan, R. F.; Rogers, R. D. "Structural Trends in Group 4 Metal Tetraaza Macrocycle Complexes. Molecular Structures of $(Me_4taen)Zr(OtBu)_2$ and $(Me_4taen)Hf(NMe_2)_2$," *Inorg. Chem.* **1997**, *36*, 103-108.
363. Bodige, S. G.; Rogers, R. D.; Blackstock, S. C. "Supramolecular Networks *via* Pyridine *N*-oxide CH•••O Hydrogen Bonding in the Crystal Structures of 2,2'-Dithiobis(pyridine *N*-oxide) and its Complexes with 1,2,4,5-Tetracyanobenzene and Pyromellitic

Dianhydride," *Chem. Commun.* **1997**, 1669-1670.

364. Brogan, J. B.; Zercher, C. K.; Bauer, C. B.; Rogers, R. D. "Study of the Rearrangements of Oxonium Ylides Generated from Ketals," *J. Org. Chem.* **1997**, *62*, 3902-2909.
365. Greer, M. L.; McGee, B. J.; Rogers, R. D.; Blackstock, S. C. "Pyrazinedioxide - Tetracyanoethylene Arrays in the Solid State - New Donor-Acceptor Interactions for Crystal Engineering," *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1864-1866.
366. Hennigar, T. L.; MacQuarrie, D. C.; Losier, P.; Rogers, R. D.; Zaworotko, M. J. "Supramolecular Isomerism in Coordination Polymers: Conformational Freedom of Ligands in $[Co(NO_3)_2(1,2\text{-bis}(4\text{-pyridyl})ethane)_{1.5}]_n$," *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 972-973.
367. Hilfiker, K. A.; Brechbiel, M. W.; Rogers, R. D.; Planalp, R. P. "Tricationic Metal Complexes ($[ML][NO_3]_3$, M = Ga, In) of *N*,*N*',*N*"-Tris(2-pyridylmethyl)-*cis*-1,3,5-triaminocyclohexane: Preparation and Structure," *Inorg. Chem.* **1997**, *36*, 4600-4603.
368. Kim, I.; Nishihara, Y.; Jordan, R. F.; Rogers, R. D.; Rheingold, A. L.; Yap, G. P. A. "Synthesis, Structures, Dynamics, and Olefin Polymerization Behavior of Group 4 Metal $(pyCAr_2O)_2M(NR_2)_2$ Complexes Containing Bidentate Pyridine-Alkoxide Ancillary Ligands," *Organometallics* **1997**, *16*, 3314-3323.
369. Luckay, R.; Cukrowski, I.; Mashishi, J.; Reibenspies, J. H.; Bond, A. H.; Rogers, R. D.; Hancock, R. D. "Synthesis, Stability and Structure of the Complex of Bismuth(III) with the Nitrogen-Donor Macrocycle 1,4,7,10-Tetraazacyclododecane. The Role of the Lone Pair on Bismuth(III) and Lead(II) in Determining Coordination Geometry," *J. Chem. Soc., Dalton Trans.* **1997**, 901-908.
370. McChesney, J. D.; Dou, J.; Sindelar, R. D.; Goins, D. K.; Walker, L. A.; Rogers, R. D. "Tirucallane- Type Triterpenoids: NMR and X-ray Diffraction Analyses of 24-*epi*-Piscidinol A and Piscidinol A," *J. Chem. Crystallogr.* **1997**, *27*, 283-290.
371. Morss, L. R.; Rogers, R. D. "Syntheses and Crystal Structures of $[M(NO_3)_2(tpen)][NO_3]\cdot 3H_2O$ (M = La, Tb), Rare Earth Complexes with Strong M-N Bonds," *Inorg. Chim. Acta* **1997**, *255*, 193-197.
372. Nuñez, L.; Rogers, R. D. "Synthesis and Structural Characterization of $[H_2(diaza\text{-}18\text{-}crown\text{-}6)][CuCl_4]\cdot H_2O$," *J. Chem. Crystallogr.* **1997**, *27*, 5-10.
373. Rogers, R. D.; Bond, A. H. "Crystal Structure of $[Pb(cis\text{-}anti\text{-}cis\text{-dicyclohexyl-18-crown-6})(OH_2)_2][ClO_4]_2$," *J. Chem. Crystallogr.* **1997**, *27*, 263-267.
374. Rogers, R. D.; Bond, A. H.; Zhang, J.; Horwitz, E. P. "New Technetium-99m Generator Technologies Utilizing Polyethylene Glycol-Based Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1997**, *32*, 867-882.
375. Rogers, R. D.; Griffin, S. T.; Horwitz, E. P.; Diamond, H. "Aqueous Biphasic Extraction Chromatography (ABEC^{TM}): Uptake of Pertechnetate from Simulated Hanford Tank Wastes," *Solvent Extr. Ion Exch.* **1997**, *15*, 547-562.
376. Rogers, R. D.; Zhang, J. "New Technologies for Metal Ion Separations *Polyethylene Glycol Based-Aqueous Biphasic Systems and Aqueous Biphasic Extraction Chromatography*," In *Ion Exchange and Solvent Extraction*; Vol. 13, Marinsky, J. A.; Marcus, Y., Eds.; Marcel Dekker: New York, 1997; Ch. 4, pp 141-193.
377. Rogers, R. D.; Zhang, J.; Bauer, C. B. "The Effects of Choice of Anion (X = Cl^-, SCN^-, NO_3^-) and Polyethylene Glycol (PEG) Chain Length on the Local and Supramolecular Structures of LnX_3/PEG Complexes," *J. Alloys Compd.* **1997**, *249*, 41-48.
378. Rogers, R. D.; Zhang, J.; Griffin, S. T. "The Effects of Halide Anions on the Partitioning Behavior of Pertechnetate in Polyethylene Glycol-Based Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1997**, *32*, 699-707.
379. Sharma, C. V. K.; Bauer, C. B.; Rogers, R. D.; Zaworotko, M. J. "Interdigitated Supramolecular Laminates," *Chem. Commun.* **1997**, 1559-1560.
380. Simonsen, K. B.; Zong, K.; Rogers, R. D.; Cava, M. P.; Becher, J. "Stable Macrocyclic and Tethered Donor-Acceptor Systems. Intramolecular Bipyridinium and Tetrathiafulvalene Assemblies," *J. Org. Chem.* **1997**, *62*, 679-686.
381. Whitcomb, D. R.; Rogers, R. D. "The Molecular Structure of Catena-[(μ-phthalato)-di-(μ-phthalazine)-di-silver(I)hydrate] $([Ag_2(\mu\text{-}(O_2C)_2C_6H_4)(\mu\text{-}PHZ)_2(H_2O)]_n)$: Carboxylate Control of Side-on versus Stacked Coordination Polymerization," *Inorg. Chim. Acta* **1997**, *256*, 263-267.
382. Whitcomb, D. R.; Rogers, R. D. "Crystal and Molecular Structure of [Ammonia-silver(I)-2-(4-chlorobenzoyl)benzoate]: $[(NH_3)\cdot Ag(C_{14}H_8ClO_3)]$, a Silver Complex Containing Both Linear and Three-Coordinate Silvers," *Polyhedron* **1997**, *16*, 863-868.
383. Bauer, C. B.; Concolino, T. E.; Eglin, J. L.; Rogers, R. D.; Staples, R. J. "Synthesis of Dirhenium Species with Benzamide Ligands *via* Hydrolysis of Benzonitrile," *J. Chem. Soc., Dalton Trans.* **1998**, 2813-2817.
384. Bond, A. H.; Rogers, R. D. "Synthesis and X-ray Crystallographic Characterization of $[Cd(NO_3)_2(15\text{-crown-}5)]$ and $[Cd(NO_3)_2(18\text{-crown-}6)]$," *J. Chem. Crystallogr.* **1998**, *28*, 521-527.
385. Brandon, E. J.; Rogers, R. D.; Burkhart, B. M.; Miller, J. S. "The Structure and Ferrimagnetic Behavior of *meso*-Tetraphenylporphinatomanganese(III) 1,4-Tetrachlorobenzoquinoneide, $[Mn^{III}TPP]^+[QCl_4]^{\bullet-}\cdot PhMe$. Evidence of a Quinoidal Structure for $[QCl_4]^{\bullet-}$," *Chem. Eur. J.* **1998**, *4*, 1938-1943.
386. Bünzli, J.-C. G.; Ihringer, F.; Dumy, P.; Sager, C.; Rogers, R. D. "Structural and Dynamic Properties of Calixarene Bimetallic Complexes: Solution *versus* Solid-State Structure of Dinuclear Complexes of Eu^{III} and Lu^{III} with Substituted Calix[8]arenes," *J. Chem. Soc., Dalton Trans.* **1998**, 497-503.
387. Cannon, R. D.; Jayasooriya, U. A.; Sowrey, F. E.; Tilford, C.; Little, A.; Bourke, J. P.; Rogers, R. D.; Vincent, J. B.; Kearley, G. J. "Concealed Asymmetry in an Exchange-Coupled Trichromium(III) Cluster: Structure and Magnetic Spectrum of $[Cr_3O(OOCPh)_6(py)_3](py)_{0.5}ClO_4$," *Inorg. Chem.* **1998**, *37*, 5675-5677.
388. Huddleston, J. G.; Willauer, H. W., Boaz, K. R.; Rogers, R. D. "Separation and Recovery of Food Coloring Dyes using Aqueous Biphasic Extraction Chromatographic Resins," *J. Chromatogr. B, Biomed. Sci. Appl.* **1998**, *711*, 237-244.
389. Huddleston, J. G.; Willauer, H. W., Swatloski, R. P.; Visser, A. E.; Rogers, R. D. "Room Temperature Ionic Liquids as Novel

Media for 'Clean' Liquid-Liquid Extraction," *Chem. Commun.* **1998**, 1765-1766. (Highlighted in Freemantle, M. "'Green' solution for ionic liquids," *Chemical & Engineering News*, August 24, 1998, p 12; Guterman, L. "Weird mixtures replace toxic solvents," *New Scientist*, September 5, 1998, p 13; WJP "Room-temperature ionic liquids provide a new approach to liquid-liquid extraction of aromatics," *CHEMTECH*, May 1999, p 6. Reported to be the 6th most cited ionic liquids paper by ISI Essential Science Indicators, Special Topics (http://www.esi-topics.com/ionic-liquids/index.html May 2004) with 215 citations at that time. Reported to be the 22nd most cited paper in the 40 year history of *Chemical Communications*; http://www.rsc.org/Publishing/Journals/cc/News/Top40MostCitedArticles.asp September 8, 2005.)

390. Jackson, Y. A.; Rogers, L. M.; Rogers, R. D.; Cava, M. P. "Cycloaddition Products of 3-Oxido-1-phenylpyridinium and 1-Cyanoacenaphthylene," *J. Chem. Soc. Perkin I* **1998**, 1865-1868.
391. Martin, A.; Uhrhammer, R.; Gardner, T. G.; Jordan, R. F.; Rogers, R. D. "Neutral and Cationic Group 4 Metal Compounds Containing Octamethyldibenzotetraazaannulene (Me_8taa^{2-}) Ligands. Synthesis and Reactivity of $(Me_8taa)MX_2$ and $(Me_8taa)MX^+$ Complexes (M = Zr, Hf; X = Cl, hydrocarbyl, NR_2, OR)," *Organometallics* **1998**, *17*, 382-397.
392. Mohanakrishnan, A. K.; Lakskmikantham, M. V.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. "*o*-Quinoid Heterocyclic Compounds: Naphtho[2,3-*c*]thiophene Revisited," *Tetrahedron* **1998**, *54*, 7075-7080.
393. Nash, K. L.; Rogers, R. D.; Ferraro, J.; Zhang, J. "Lanthanide Complexes with 1-Hydroxyethane-1,1-diphosphonic Acid: Solvent Organization and Coordination Geometry in Crystalline and Amorphous Solids," *Inorg. Chim. Acta* **1998**, *269*, 211-223.
394. Paquette, L. A.; Bolin, D. G.; Stephanian, M.; Branan, B. M.; Mallavadhani, U. V.; Tae, J.; Eisenberg, S. W. E.; Rogers, R. D. "Intramolecular Oxymercuration of Stereoisomeric Cyclohexyl-Belted Poly(spirotetrahydrofuranyl) Platforms," *J. Am. Chem. Soc.* **1998**, *120*, 11603-11615.
395. Paquette, L. A.; Rothhaar, R. R.; Isaac, M.; Rogers, L. M.; Rogers, R. D. "Diastereo- and Enantiodifferentiation in Indium-Promoted Allylations of 2,3-Azetidinediones in Water. Definition of Long-Range Stereocontrol Elements on π-Facial Selectivity for β-Lactam Synthesis," *J. Org. Chem.* **1998**, *63*, 5463-5472.
396. Rogers, R. D.; Griffin, S. T. "Partitioning of Mercury in Aqueous Biphasic Systems and on ABEC™ Resins," *J. Chromatogr. B, Biomed. Sci. Appl.* **1998**, *711*, 277-283.
397. Rogers, R. D.; Sharma, C. V. K.; Whitcomb, D. R. "Molecular Tweezers and Pentameric Aggregates: Convergent Hydrogen-Bonded Self-Assembly of 2:1 and 2:3 Cocrystals of Phthalazine:Phthalic Acid," *Crystal Eng. (*Suppl*., Mat. Res. Bull.)* **1998**, *3/4*,255-262.
398. Rogers, R. D.; Willauer, H. D.; Griffin, S. T.; Huddleston, J. G. "Partitioning of Small Organic Molecules in Aqueous Biphasic Systems," *J. Chromatogr. B, Biomed. Sci. Appl.* **1998**, *711*, 255-263.
399. Rogers, R. D.; Zaworotko, M. J. "Whither Crystal Engineering?" In *Crystal Engineering*, Rogers, R. D.; Zaworotko, M. J., Eds.; Transactions of the American Crystallographic Association, Vol. 33; American Crystallographic Association: Buffalo, NY, 1998; pp 1-5.
400. Rogers, R. D.; Zhang, J.; Campbell, D. T. "Crown Ether Complexes of $UO_2(NCS)_2$ and $Th(NCS)_4$: Clues to Solution Behavior or Just Interesting Supramolecular Structures?," *J. Alloys Compd.* **1998**, *271-273*, 133-138.
401. Sharma, C. V. K.; Rogers, R. D. "C-H•••X (X = N,O) Hydrogen Bond-Mediated Assembly of Donors and Acceptors: The Crystal Structures of Phenazine Complexes with 1,4-Dinitrobenzene and TCNQ," *Crystal Eng. (*Suppl*., Mat. Res. Bull.)* **1998**, *1*, 139-145.
402. Sharma, C. V. K.; Rogers, R. D. "Discrete Macrocycles to Infinite Polymeric Frames: Crystal Engineering Studies of Ag(I):Pyrimidine Complexes," *Crystal Eng.* (Suppl., *Mat. Res. Bull.*) **1998**, *1*, 19-38.
403. Sharma, C. V. K.; Griffin, S. T.; Rogers, R. D. "Simple Routes to Supramolecular Squares with Ligand Corners: 1:1 Ag^I:Pyrimidine Cationic Tetranuclear Assemblies," *Chem. Commun.* **1998**, 215-216.
404. Sharma, C. V. K.; Swatloski, R. P.; Rogers, R. D. "4,4'-Dipyridine•$2H_2O$: Complementarity of Hydrogen Bond Donor:Acceptor Ratio," *Crystal Eng. (*Suppl*., Mat. Res. Bull.)* **1998**, *1*, 153-158.
405. Sharma, C. V. K.; Swenson, J. A.; Rogers, R. D. "The Design of Two Dimensional Polymeric Networks: Coordination Complexes of Cadmium Iodide with Bifunctional Ligands," In *Crystal Engineering*, Rogers, R. D.; Zaworotko, M. J., Eds.; Transactions of the American Crystallographic Association, Vol. 33; American Crystallographic Association: Buffalo, NY, 1998; pp 59-66.
406. Uzelmeier, C. E.; Bartley, S. L.; Fourmigué, M.; Rogers, R.; Grandinetti, G.; Dunbar, K. R. "Reaction of Octachlorodirhenate with a Redox-Active Tetrathiafulvalene Phosphine Ligand: Spectroscopic, Magnetic, and Structural Characterization of the Unusual Paramagnetic Salt $[ReCl_2(o\text{-}P2)_2][Re_2Cl_6(o\text{-}P2)]$ (*o*-P2 = *ortho*-$\{P(C_6H_5)_2\}_2(CH_3)_2TTF$)," *Inorg. Chem.* **1998**, *37*, 6706-6713.
407. Wisniewski, K.; Zamojski, A.; Rogers, R. D. "(Phenylthio)acetyliron Complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2SPh]$ Configuration of Aldols," *Tetrahedron* **1998**, *54*, 14201-14212.
408. Ye, N.; Rogers, R. D.; Brechbiel, M. W.; Planalp, R. P. "Synthesis and X-ray Crystal Structure of N,N',N''-Tris(2-thienylmethyl)-cis-1,3,5-triaminocyclohexanecopper(II) Dichloride," *Polyhedron* **1998**, *17*, 603-606.
409. Zhang, L.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. "Synthesis of a Wakayin Model Compound: Oxidative Formation of a New Pyrrole Ring in the Indol-3-yl-indoloquinone System," *Tetrahedron Lett.* **1998**, *39*, 7677-7678.
410. Bartsch, R. A.; Hwang, H.-S.; Talanov, V. S.; Talanova, G. G.; Purkiss, D. W.; Rogers, R. D. "New Proton-Ionizable Lariat Ethers with Picrylamino-Type Side Arms and Their Alkali Metal Salts. Synthesis and Structural Studies," *J. Org. Chem.* **1999**, *64*, 5341-5349.
411. Bond, A. H.; Chang, F. W. K.; Thakkar, A. H.; Williamson, J. M.; Gula, M. J.; Harvey, J. T.; Griffin, S. T.; Rogers, R. D.;

Horwitz, E. P. "Design, Synthesis, and Uptake Performance of ABEC® Resins for the Removal of Pertechnetate from Alkaline Radioactive Wastes," *Ind. Eng. Chem. Res.* **1999**,*38*, 1676-1682.
412. Bond, A. H.; Dietz, M. L.; Rogers, R. D. "Progress in Metal Ion Separation and Preconcentration: An Overview," In *Metal-Ion Separation and Preconcentration, Progress and Opportunities*; Dietz, M. L.; Bond, A. H.; Rogers, R. D., Eds.; ACS Symposium Series 716, American Chemical Society: Washington, DC, 1999; pp 2-12.
413. Bond, A. H.; Gula, M. J.; Harvey, J. T.; Duffey, H. M.; Horwitz, E. P.; Griffin, S. T.; Rogers, R. D.; Collins, J. L. "Flowsheet Feasibility Studies Using ABEC® Resins for the Removal of Pertechnetate from Nuclear Wastes," *Ind. Eng. Chem. Res.* **1999**, *38*, 1683-1689.
414. Bryan, J. C.; Delmau, L. H.; Hay, B. P.; Nicholas, J. B.; Rogers, L. M.; Rogers, R. D.; Moyer, B. A. "Cesium Recognition by Supramolecular Assemblies of 2-Benzylphenol and 2-Benzylphenolate," *Structural Chem.* **1999**, *10*, 187-203.
415. Clark, D. L.; Conradson, S. D.; Donohoe, R. J.; Keogh, D. W.; Morris, D. E.; Palmer, P. D.; Rogers, R. D.; Tait, C. D. "Chemical Speciation of the Uranyl Ion under Highly Alkaline Conditions. Synthesis, Structures, and Oxo Ligand Exchange Dynamics," *Inorg. Chem.* **1999**, *38*, 1456-1466.
416. del Mar Conejo, M.; Parry, J. S.; Carmona, E.; Schultz, M.; Brennann, J. G.; Beshouri, S. M.; Andersen, R. A.; Rogers, R. D.; Coles, S.; Hursthouse, M. "Carbon Monoxide and Isocyanide Complexes of Trivalent Uranium Metallocenes," *Chem. Eur. J.* **1999**, *5*, 3000-3009.
417. Gilbert, T. M.; Bauer, C. B.; Bond, A. H.; Rogers, R. D. "Structures of Homoleptic Triply Bonded $M_2(OR)_6$ Compounds where the Alkoxide is Tertiary: The Effect of Steric Bulk and Alkoxide Conformation on Structural Parameters," *Polyhedron.* **1999**, *18*, 1293-1301.
418. Gilbert, T. M.; Bauer, C. B.; Bond, A. H.; Rogers, R. D. "Syntheses and Structures of Metal-Metal Triply Bonded M_2R_6 Compounds: Consideration of Starting Materials, Stability, and Structural Parameters," *Polyhedron* **1999**, *18*, 1303-1310.
419. Gobley, O.; Gentil, S.; Schloss, J. D.; Rogers, R. D.; Gallucci, J. C.; Meunier, P.; Gautheron, B.; Paquette, L. A. "Magnesiation of Isodicyclopentadiene. Formation of Sandwich and Monomeric Complexes and the Stereoselectivity of Their Reactions with Transition Metal Halides," *Organometallics* **1999**, *18*, 2531-2535.
420. Huddleston, J. G.; Griffin, S. T.; Zhang, J.; Willauer, H. D.; Rogers, R. D. "Metal Ion Separations in Aqueous Biphasic Systems and Using Aqueous Biphasic Extraction Chromatography," In *Metal-Ion Separation and Preconcentration, Progress and Opportunities*; Dietz, M. L.; Bond, A. H.; Rogers, R. D., Eds.; ACS Symposium Series 716, American Chemical Society: Washington, DC, 1999; pp 79-100.
421. Huddleston, J. G.; Ingenito, C. C.; Rogers, R. D. "Partitioning Behavior of Porphyrin Dyes in Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1999**, *34*, 1091-1101.
422. Huddleston, J. G.; Willauer, H. D.; Griffin, S. T.; Rogers, R. D. "Aqueous Polymeric Solutions as Environmentally Benign Liquid/Liquid Extraction Media," *Ind. Eng. Chem. Res.* **1999**, *38*, 2523-2539.
423. Nowak, I.; Rogers, L. M.; Rogers, R. D.; Thrashe, J. S. "Toward the Synthesis of Novel Fluorinated Building Blocks: 3,4-difluorothiophene-1,1-dioxide," *J. Fluorine Chem.* **1999**, *93*, 27-31.
424. Nowak, I.; Rogers, L. M.; Rogers, R. D.; Thrasher, J. S. "The Effect of Fluorine on the Diastereoselectivity of the Addition of α-Oxyradicals to 3-Fluoro-2,3-dihydro-1H-λ^6-thiophene-1,1-dione," *J. Fluorine Chem.* **1999**, *93*, 73-81.
425. Paquette, L. A.; Edmondson, S. D.; Monck, N.; Rogers, R. D. "Studies Directed toward the Synthesis of the Unusual Antileukemic Diterpene Jatrophatrione. 2. Functionalization of Advanced Polycyclic Precursors to the 9-Epi and 8,9-Dehydro Congeners," *J. Org. Chem.* **1999**, *64*, 3255-3265.
426. Paquette, L. A.; Tae, J.; Hickey, E. R.; Rogers, R. D. "A Belted Monofacial Ionophore Featuring High Selectivity for Lithium Ion Complexation," *Angew. Chem. Int. Ed.* **1999**, *38*, 1409-1411.
427. Rapko, B. M.; McNamara, B. K.; Rogers, R. D.; Lumetta, G. J.; Hay, B. P. "Coordination Chemistry of Lanthanide Nitrates with *N*,*N*,*N'*,*N'*-Tetramethylsuccinamide," *Inorg. Chem.* **1999**, *38*, 4585-4592.
428. Rogers, R. D. "Chemical Crystallography in Crystal Engineering," In *Crystal Engineering: The Design and Application of Functional Solids*; Seddon, K. R.; Zaworotko, M. J. Eds., NATO ASI Series, Kluwer: Dordrecht. 1999; pp 155-189.
429. Rogers, R. D.; Visser, A. E.; Swatloski, R. P.; Hartman, D. H. "Metal Ion Separations in Room Temperature Ionic Liquids: Potential Replacements for Volatile Organic Diluents," In *Metal Separation Technologies Beyond 2000: Integrating Novel Chemistry with Processing*; Liddell, K. C.; Chaiko, D. J., Eds.; The Minerals, Metals & Materials Society: Warrendale, PA, 1999; pp 139-147.
430. Sharma, C. V. K.; Broker, G. A.; Huddleston, J. G.; Baldwin, J. W.; Metzger, R. M.; Rogers, R. D. "Design Strategies for Solid-State Supramolecular Arrays Containing Both Mixed-Metallated and Freebase Porphyrins," *J. Am. Chem. Soc.* **1999**, *121*, 1137-1144.
431. Sharma, C. V. K.; Rogers, R. D. "'Molecular Chinese Blinds': Self-Organization of Tetranitrato Lanthanide Complexes Into Open, Chiral Hydrogen-Bonded Networks," *Chem. Commun.* **1999**, 83-84.
432. Talinova, G. G.; Elkarim, N. S. A.; Hanes, Jr., R. E.; Hwang, H.-S.; Rogers, R. D.; Bartsch, R. A. "Extraction Selectivities of Crown Ethers for Alkali Metal Cations: Differences between Single-Species and Competitive Solvent Extractions," *Anal. Chem.* **1999**, *71*, 672-677.
433. Talinova, G. G.; Elkarim, N. S. A.; Talanov, V. S.; Hanes, Jr., R. E.; Hwang, H.-S.; Bartsch, R. A.; Rogers, R. D. "The 'Picrate Effect' on Extraction Selectivities of Aromatic Group-Containing Crown Ethers for Alkali Metal Cations," *J. Am. Chem. Soc.* **1999**, *121*, 11281-11290.
434. Visser, A. E.; Griffin, S. T.; Ingenito, C. A.; Hartman, D. H.; Huddleston, J. G.; Rogers, R. D. "Aqueous Biphasic Systems as a

Novel Environmentally-Benign Separations Technology for Metal Ion Removal," In *Metal Separation Technologies Beyond 2000: Integrating Novel Chemistry with Processing*; Liddell, K. C.; Chaiko, D. J., Eds.; The Minerals, Metals & Materials Society: Warrendale, PA, 1999; pp 119-130.

435. Whitcomb, D. R.; Rogers, R. D. "The Crystal and Molecular Structure of the Tetrameric Methyl-2-mercaptobenzimidazole•AgBr (Acetone Solvate) Complex: Mode of Complex Formation between Silver Bromide and Thione Type Photographic Stabilizers," *J. Imaging Sci. Technol.* **1999**, *43*, 498-502.
436. Whitcomb, D. R.; Rogers, R. D. "Chemistry of Photothermographic Imaging Materials. II," *J. Imaging Sci. Technol.* **1999**, *43*, 517-520.
437. Willauer, H. D.; Huddleston, J. G.; Griffin, S. T.; Rogers, R. D. "Partitioning of Aromatic Molecules in Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1999**, *34*, 1069-1090.
438. Yordanov, A. T.; Gansow, O. A.; Brechbiel, M. W.; Rogers, L. M.; Rogers, R. D. "The Preparation and X-ray Crystallographic Characterization of Lead(II) Calix[4]arenesulfonate Complex," *Polyhedron* **1999**, *18*, 1055-1059.
439. Zhao, H.; Heintz, R. A.; Ouyang, X.; Dunbar, K. R.; Campana, C. F.; Rogers, R. D. "Spectroscopic, Thermal, and Magnetic Properties of Metal/TCNQ Polymers with Extensive Supramolecular Interactions bewteen Layers," *Chem. Mater.* **1999**, *11*, 736-746.
440. Zucchi, Z.; Scopelliti, R.; Pittet, P.-A.; Bünzli, J.-C. G.; Rogers, R. D. "Structural and Photophysical Behavior of Lanthanide Complexes with a Tetraazacyclododecane Featuring Carbamoyl Pendant Arms," *J. Chem. Soc., Dalton Trans.* **1999**, 931-938.
441. Adams, R. D.; Perrin, J. L.; Queisser, J. A.; Rogers, R. D. "Synthesis and Structural Characterization of Chiral Thiacrowns: The Crystal and Molecular Structure of (*R,R,R*)-2,6,10-Trimethyl-1,5,9-trithiacyclododecane," *J. Organomet. Chem.* **2000**, *596*, 115-120.
442. Blair, E.; Nikles, J. A.; Nikles, D. E.; Rogers, L. M.; Rogers, R. D.; Stabler, D.; Street, S. C. "Molecular Structure of the Amine-Quinone Model Compound, 2,4-Bis(dimethylamino)-1,4-benzoquinone," *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2000**, *41*, 317-318.
443. Blais, M. S.; Rogers, R. D.; Rausch, M. D. "Synthesis, Reactions and Structure of Bromo(η^5-diphenylphosphinocyclopentadienyl)nickel(II) Dimer," *J. Organomet. Chem.* **2000**, *593-594*, 142-146.
444. Bond, A. H.; Dietz, M. L.; Rogers, R. D. "Nuclear Separations for Radiopharmacy: The Need for Improved Separations to Meet Future Research and Clinical Demands," *Ind. Eng. Chem. Res.* **2000**, *39*, 3130-3134.
445. Hay, B. P.; Dixon, D. A.; Lumetta, G. J.; Rapko, B. M.; Roundhill, D. M.; Rogers, R. D.; Hutchinson, J. E.; Paine, R. T.; Raymond, K. N. "Architectural Design Criteria for f-Block Metal Ion Sequestering Agents Final Report," Report PNNL-13221, Pacific Northwest National Laboratory: Richland, WA, 2000; 32 pp.
446. Huddleston, J. G.; Griffin, S. T.; Zhang, J.; Willauer, H. D.; Rogers, R. D. "Metal Ion Separations in Aqueous Biphasic Systems and with ABEC™ Resins," In *Aqueous Two-Phase Systems: Methods and Protocols*; Hatti-Kaul, R., Ed.; In *Methods in Biotechnology*, Vol. 11; Walker, J. M., Ed.; Humana Press, Totowa, NJ, 2000, pp 77-94.
447. Huddleston, J. G.; Willauer, H. W.; Rogers, R. D. "Solvatochromic Studies in Polyethylene Glycol-Salt Aqueous Biphasic Systems," *J. Chromatogr. B: Biomed. Sci. Appl.* **2000**, *743*, 137-149.
448. Jensen, M. P.; Beitz, J. V.; Rogers, R. D.; Nash, K. L. "Thermodynamics and Hydration of the Europium Complexes of a Nitrogen Heterocycle Methane-1,1-Diphosphonic Acid," *J. Chem. Soc., Dalton Trans.* **2000**, 3058-3064.
449. Lumetta, G. J.; McNamara, B. K.; Rapko, B. M.; Sell, R. L.; Rogers, R. D.; Broker, G.; Hutchison, J. E. "Synthesis and characterization of mono- and bis-(tetraalkylmalonamide)uranium(VI) complexes," *Inorg. Chim. Acta* **2000**, *309*, 103-108.
450. Paquette, L. A.; Ohmori, N.; Lowinger, T. B.; Rogers, R. D. "Vicinal Tetrahydrofuranyl Substitution of Alkyl Chains. Tetra-, Penta-, and Hexafunctionalized Arrays," *J. Org. Chem.* **2000**, *65*, 4303-4308.
451. Paquette, L. A.; Tae, J.; Hickey, E. R.; Trego, W. E.; Rogers, R. D. "Preorganized ligand arrays based on spirotetrahydrofuranyl motifs. Synthesis of the stereoisomeric 1,8,14-trioxatrispiro[4.1.4.1.4.1]octadecanes and the contrasting conformational features and ionic binding capacities of these belted ionophores," *J. Org. Chem.* **2000**, *65*, 9160-9171.
452. Park, G.; Ye, N.; Rogers, R. D.; Brechbiel, M. W.; Planalp, R. P. "Effect of Metal Size on Coordination Geometry of *N,N',N''*-tris(2-pyridylmethyl)-*cis,cis*-1,3,5-triaminocyclohexane: Synthesis and Structure of $[M^{II}L](ClO_4)_2$ (M = Zn, Cd and Hg)," *Polyhedron* **2000**, *19*, 1155-1161.
453. Rapko, B. M.; McNamara, B. K.; Rogers, R. D.; Broker, G. A.; Lumetta, G. J.; Hay, B. P. "Coordination Chemistry of Lanthanide Triflates and Perchlorates with *N,N,N',N'*-Tetramethylsuccinamide," *Inorg. Chem.* **2000**, *39*, 4858-4867.
454. Rogers, R. D.; Reichert, W. M.; Klingshirn, M. A.; Visser, A. E.; Spear, S. K. "Vision 2020: How Green Chemistry Can Shape the Future of the Sugar Processing Industry," In *Proceedings SPRI 2000 Conference on Sugar Processing Research, April 9-12, 2000, Porto, Portugal*, Godshall, M. A., Ed; Sugar Processing Research Institute, Inc., New Orleans, LA, 2000; pp 20-40.
455. Sharma, C. V. K.; Broker, G. A.; Szulczewski, G. J.; Rogers, R. D. "Self-Assembly of Freebase- and Metalated-Tetrapyridylporphyrins to Modified Gold Surfaces. *Chem. Commun.* **2000**, 1023-1024.
456. Sharma, C. V. K.; Broker, G. A.; Rogers, R. D. "Polymorphous One-Dimensional Tetrapyridylporphyrin Coordination Polymers Which Structurally Mimic Aryl Stacking Interactions," *J. Solid State Chem.* **2000**, *152*, 253-260.
457. Spear, S. K.; Griffin, S. T.; Huddleston, J. G.; Rogers, R. D. "Radiopharmaceutical and Hydrometallurgical Separations of Perrhenate Using Aqueous Biphasic Systems and the Analogous Aqueous Biphasic Extraction Chromatographic Resins," *Ind. Eng. Chem. Res.* **2000**, *39*, 3173-3180.
458. Tae, J.; Rogers, R. D.; Paquette, L. A. "Lithium Ion-Selective Binding Properties of a Conformationally Constrained Tris(spirotetrahydrofuran) Secured to an Inositol Orthoformate Platform," *Org. Lett.* **2000**, *2*, 139-142.

459. Visser, A. E.; Griffin, S. T.; Hartman, D. H.; Rogers, R. D. "Napthol- and Resorcinol-Based Azo Dyes as Metal Ion Complexants in Aqueous Biphasic Systems," *J. Chromatogr. B: Biomed. Sci. Appl.* **2000**, *743*, 107-114.
460. Visser, A. E.; Swatloski, R. P.; Hartman, D. H.; Huddleston, J. G.; Rogers, R. D. "Calixarenes as Ligands in Environmentally-Benign Liquid/Liquid Extraction Media, Aqueous Biphasic Systems and Room Temperature Ionic Liquids," In *Calixarenes for Separations*; Lumetta, G. J.; Rogers, R. D.; Gopalan, A. S., Eds.; ACS Symposium Series 757, American Chemical Society: Washington, DC, 2000; pp 223-236.
461. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Griffin, S. T.; Rogers, R. D. "Traditional Extractants in Nontraditional Solvents: Groups 1 and 2 Extraction by Crown Ethers in Room-Temperature Ionic Liquids," *Ind. Eng. Chem. Res.* **2000**, *39*, 3596-3604.
462. Visser, A. E.; Swatloski, R. P.; Rogers, R. D. "pH-Dependent Partitioning in Room Temperature Ionic Liquids Provides a Link to Traditional Solvent Extraction Behavior," *Green Chem.* **2000**, *2*, 1-4.
463. Willauer, H. D.; Huddleston, J. G.; Li, M.; Rogers, R. D. "Investigation of Aqueous Biphasic Systems for the Separations of Lignins from Cellulose in the paper Pulping Process," *J. Chromatogr. B: Biomed. Sci. Appl.* **2000**, *743*, 127-135.
464. Wu, B.; Reddy, R. G.; Rogers, R. D. "Aluminum recycling via near room temperature electrolysis in ionic liquids," In *Int. Symp. Recycl. Met. Eng. Mater., Proc., 4th*; Stewart, D. L., Jr.; Daley, J. C.; Stephens, R. L., Eds.; The Minerals, Metals & Materials Society, Warrendale, PA, 2000, pp 845-856.
465. Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Broker, G. A.; Willauer, H. D.; Rogers, R. D. "Characterization and Comparison of Hydrophobic and Hydrophilic Room Temperature Ionic Liquids Incorporating the Imidazolium Cation," *Green Chem.* **2001**, *3*, 156-164. (Highlighted in Emsley, J. "Ionic Liquids Poised for a Solvent-Free Atmosphere," *Science Watch* September/October 2003, Vol. 14 No. 5 as the 5th most cited paper in Chemistry for the time period March-April 2003. Among the Top Five most accessed papers for *Green Chem.* May 2004. Reported to be the 11th most cited ionic liquids paper by ISI Essential Science Indicators, Special Topics (http://www.esi-topics.com/ionic-liquids/index.html May 2004) with 123 citations at that time. Reported to be the 5th most accessed article in *Green Chemistry* in 2005 and in 2006.)
466. Kus, P.; Dalley, N. K.; Kuo, X.; Rogers, R. D.; Bartsch, R. A. "X-ray structural investigation of 4-phenyl-, 4-(o-Tolyl)-and 4-(2',4',6'-trimethylphenyl)[2.2]paracyclophanes," *Polish J. Chem.* **2001**, *75*, 1351-1360.
467. Li, M.; Willauer, H. W.; Huddleston, J. G.; Rogers, R. D. "Temperature Effects on Polymer-Based Aqueous Biphasic Extraction Technology in the Paper Pulping Process," *Sep. Sci. Technol.* **2001**, *36*, 835-847.
468. Luo, H.; Eberly, N.; Rogers, R. D.; Brechbiel, M. W. "Syntheses and Characterizations of Metal Complexes Derived from *cis,cis*-1,3,5-Triaminocyclohexane-*N,N',N''*-triacetic Acid," *Inorg. Chem.* **2001**, *40*, 493-498.
469. Luo, H.; Rogers, R. D.; Brechbiel, M. W. „A convenient and selective route to a trans-difunctionalized macrocyclic hexadentate N_4O_2 ligand," *Can. J. Chem.*, **2001**, *79*, 1105-1109.
470. Park, G.; Dadachova, E.; Przyborowska, A.; Lai, S.; Ma, D.; Broker, G.; Rogers, R. D.; Planalp, R. P.; Brechbiel, M. W. "Synthesis of novel 1,3,5-*cis,cis*-triaminocyclohexane ligand based Cu(II) complexes as potential radiopharmaceuticals and correlation of structure and serum stability," *Polyhedron* **2001**, *20*, 3155-3163.
471. Park, G.; Shao, J.; Lu, F. H.; Rogers, R. D.; Chasteen, N. D.; Brechbiel, M. W.; Planalp, R. P. "Copper(II) Complexes of Novel N-Alkylated Derivatives of *cis,cis*-1,3,5-Triaminocyclohexane. 1. Preparation and Structure," *Inorg. Chem.* **2001**, *40*, 4167-4175.
472. Rogers, R. D.; Spear, S. K.; Swatloski, R. P.; Reichert, W. M.; Godshall, M. A.; Johnson, T. P.; Moens, L. "Non-sugar products from sugarcane for the new millennium: green pathways to a carbohydrate-economy?" *Publ. Tech. Pap. Proc. Annu. Meet. Sugar Ind. Technol. (May 6-9, 2001, Taipei, Taiwan)* **2001**, *60*, 291-301.
473. Spear, S. K.; Visser, A. E.; Willauer, H. W.; Swatloski, R. P.; Griffin, S. T.; Huddleston, J. G.; Rogers, R. D. "Green Separations Science & Technology: Replacement of Volatile Organic Compounds in Industrial Scale Liquid-Liquid or Chromatographic Separations," In *Green Engineering*; Anastas, P. T.; Heine, L. G.; Williamson, T. C., Eds.; ACS Symposium Series 766, American Chemical Society: Washington, DC, 2001; pp 206-221.
474. Swatloski, R. P.; Visser, A. E.; Reichert, W. M.; Broker, G. A.; Farina, L. M.; Holbrey, J. D.; Rogers, R. D. "Solvation of 1-butyl-3-methylimidazolium hexafluorophosphate in aqueous ethanol-a green solution for dissolving 'hydrophobic' ionic liquids," *Chem. Commun.* **2001**, 2070-2071. (Highlighted in "'Green' solution for ionic liquids," *Chemical & Engineering News*, October 22, 2001, p 50.)
475. Visser, A. E.; Holbrey, J. D.; Rogers, R. D. "Hydrophobic ionic liquids incorporating N-alkylisoquinolinium cations and their utilization in liquid-liquid separations," *Chem. Commun.* **2001**, 2484-2485.
476. Visser, A. E.; Swatloski, R. P.; Griffin, S. T.; Hartman, D. H.; Rogers, R. D. "Liquid/Liquid Extraction of Metal Ions in Room Temperature Ionic Liquids," *Sep. Sci. Technol.* **2001**, *36*, 785-804.
477. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Mayton, R.; Sheff, S.; Wierzbicki, A.; Davis, Jr. J. H.; Rogers, R. D. "Task-Specific Ionic Liquids for the Extraction of Metal Ions from Aqueous Solutions," *Chem. Commun.* **2001**, 135-136. (Highlighted in Beard, J. "What's Wet and Green?," *The Alchemist*, January 26, 2001, URL: http://www.chemweb.com/alchem/2001/news/nw_010126_ionic.html; last accessed January 30, 2001.)
478. Wu, B.; Reddy, R. G.; Rogers, R. D. "Aluminum reduction via near room temperature electrolysis in ionic liquids," *Light Metals (Proceedings of the Technical Sessions Presented by the TMS Aluminum Committee at the 130th TMS Annual Meeting, New Orleans, LA, February 11-15, 2000)* The Minerals, Metals & Materials Society, Warrendale, PA, 2001; pp 237-243.
479. Wu, B.; Reddy, R. G.; Rogers, R. D. "Novel Ionic Liquid Thermal Storage for Solar Thermal Electric Power Systems," *Proceedings of Solar Forum 2001: Solar Energy: The Power to Choose, April 21-25, 2001, Washington, DC* ASME,

Washington, DC, 2001.

480. Amaresh, R. R.; Lakshmikantham, M. V.; Baldwin, J. W.; Cava, M. P.; Metzger, R. M.; Rogers, R. D. "Condensed Thiophenes and Selenophenes: Thionyl Chloride and Selenium Oxychloride as Sulfur and Selenium Transfer Reagents," *J. Org. Chem.* **2002**, *67*, 2453-2458.
481. Broker, G. A.; Klingshirn, M. A.; Rogers, R. D. "Green Chemistry and Lanthanide-Based Crystal Engineering," *J. Alloys Comp.* **2002**, *344*, 123-127.
482. Chong, H.-s.; Ganguly, B.; Broker, G. A.; Rogers, R. D.; Brechbiel, M. W. "Stereoselective and Regioselective Synthesis of Azepane and Azepine Derivatives via Piperidine Ring Expansion," *J. Chem. Soc. Perkin I* **2002**, 2080-2086.
483. Guo, Z.; Li, M.; Willauer, H. D.; Huddleston, J. G.; April, G. C.; Rogers, R. D. "Evaluation of Polymer-Based Aqueous Biphasic Systems as Improvement for the Hardwood Alkaline Pulping Process," *Ind. Eng. Chem. Res.* **2002**, *41*, 2535-2542.
484. Holbrey, J. D.; Reichert, W. M.; Swatloski, R. P.; Broker, G. A.; Pitner, W. R.; Seddon, K. R.; Rogers, R. D. "Efficient, halide free synthesis of new, low cost ionic liquids: Alkylimidazolium salts containing methyl- and ethyl-sulfate anions" *Green Chem.* **2002**, *4*, 407-413.
485. Holbrey, J. D.; Rogers, R. D. "Green Chemistry and Ionic Liquids - Synergies and Ironies," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 2-14.
486. Holbrey, J. D.; Rogers, R. D. "Green Industrial Applications of Ionic Liquids: Technology Review," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 446-458.
487. Holbrey, J. D.; Shaughnessy, K. H.; Klingshirn, M. A.; Broker, G. A.; Rogers, R. D. "Transition Metal Catalyzed CO/Olefin Co-Polymerization in Room Temperature Ionic Liquids," In *Molten Salts XIII: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2002; Vol. 2002-19, pp 213-223.
488. Hong, K.; Zhang, H.; Mays, J. W.; Visser, A. E.; Brazel, C. S.; Holbrey, J. D.; Reichert, W. M.; Rogers, R. D. "Conventional free radical polymerization in room temperature ionic liquids: A green approach to Commodity Polymers with Practical Advantages," *Chem. Commun.* **2002**, 1368-1369.
489. Huddleston, J. G.; Broker, G. A.; Willauer, H. D.; Rogers, R. D. "Free-Energy Relationships and Solvatochromatic Properties of 1-Alkyl-3-methylimidazolium Ionic Liquids," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 270-288.
490. Huddleston, J. G.; Willauer, H. D.; Rogers, R. D. "The Solvatochromic Properties, α, β, and π^*, of PEG-Salt Aqueous Biphasic Systems," *Phys. Chem. Chem. Phys.* **2002**, *4*, 4065-4070.
491. Katritzky, A. R.; Jain, R.; Lomaka, A.; Petrukhin, R.; Karelson, M.; Visser, A. E.; Rogers, R. D. "Correlation of the Melting Points of Potential Ionic Liquids (Imidazolium Bromides and Benzimidazolium Bromides) Using the CODESSA Program," *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 225-231. [*Erratum: J. Chem. Inf. Mod.* **2005**, *45*, 533-534.]
492. Katritzky, A. R.; Lomaka, A.; Petrukhin, R.; Jain, R.; Karelson, M.; Visser, A. E.; Rogers, R. D. "QSPR Correlation of the Melting Point for Pyridinium Bromides, Potential Ionic Liquids," *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 71-74.
493. Klingshirn, M. A.; Broker, G. A.; Holbrey, J. D.; Shaughnessy, K. H.; Rogers, R. D. "Polar, non-coordinating ionic liquids as solvents for alternating copolymerization of styrene and CO catalyzed by cationic palladium catalysts," *Chem. Commun.* **2002**, 1394-1395.
494. Planalp, R. P.; Przyborowska, A. M.; Ye, N.; Ku, F. H.; Rogers, R. D.; Broker, G. A.; Torti S. V.; Brechbiel, M. W. "Novel Cytotoxic Chelators that Bind Iron(II) Selectively over Zinc(II) under Aqueous Aerobic Conditions," *Biochem. Soc. Trans.* **2002**, *30*, 758-762.
495. Royer, A. C.; Rogers, R. D.; Arrington, D. L.; Street, S. C.; Vincent, J. B. "Spectroscopic studies of the dodecanuclear chromium complex $Cr_{12}O_9(OH)_3(pivalate)_{15}$: confirmation of the presence of twelve Cr(III) centers and the crystal structure of $Cr_{12}O_9(OH)_3(pivalate)_{15}\bullet 2PrOH\bullet 9H_2O$," *Polyhedron* **2002**, *21*, 155-165.
496. Scott, M. P.; Brazel, C. S.; Benton, M. G.; Mays, J. W.; Holbrey, J. D.; Rogers, R. D. "Application of ionic liquids as plasticizers for poly(methyl-methacrylate)," *Chem. Commun.* **2002**, 1370-1371.
497. Scovazzo, P.; Visser, A. E.; Davis, Jr., J. H.; Rogers, R. D.; Koval, C. A.; DuBois, D. L.; Noble, R. D. "Supported Ionic Liquid Membranes (SILMs) and Facilitated Ionic Liquid Membranes (FILMs)," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 69-87.
498. Spear, S. K.; Visser, A. E.; Rogers, R. D. "Ionic Liquids: Green Solvents for Carbohydrate Studies," In *Proceedings of the 2002 Sugar Processing Research Conference, Advances in the Chemistry and Processing of Beet and Cane Sugar, March 10-13, 2002, New Orleans, LA;* Godshall, M. A., Ed; Sugar Processing Research Institute, Inc.: New Orleans, LA, 2002; pp 336-340.
499. Swatloski, R. P.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Ionic Liquids for the Dissolution and Regeneration of Cellulose," In *Molten Salts XIII: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2002; Vol. 2002-19, pp 155-164.
500. Swatloski, R. P.; Spear, S. K.; Holbrey, J. D.; Rogers, R. D. "Dissolution of Cellose with Ionic Liquids," *J. Am. Chem. Soc.* **2002**, *124*, 4974-4975. (Highlighted in "Ionic Liquids Can Dissolve Cellulose," *Chemical & Engineering News*, April 29, 2002, p 24. Reported to be the 18th most cited ionic liquids paper in the previous two-year period by ISI Essential Science Indicators, Special Topics (http://www.esi-topics.com/ionic-liquids/index.html May 2004) with 22 citations at that time.)

501. Swatloski, R. P.; Visser, A. E.; Reichert, W. M.; Broker, G. A.; Farina, L. M.; Holbrey, J. D.; Rogers, R. D. "On the solubilization of water with ethanol in hydrophobic hexafluorophosphate ionic liquids," *Green Chem.* **2002**, *4*, 81-87.
502. Visser, A. E.; Holbrey, J. D.; Rogers, R. D. "Room temperature ionic liquids as alternatives to traditional organic solvents in solvent extraction," In *ISEC 2002, Proceeding of the International Solvent Extraction Conference Cape Town, South Africa 17 to 21 March 200*; Sole, K. C.; Cole, P. M.; Preston, J. S.; Robinson, D. J., Eds.; Chris van Rensburg Publications, Melville, South Africa, 2002; Vol. 1; pp 474-480.
503. Visser, A. E.; Reichert, W. M.; Swatloski, R. P.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "Characterization of Hydrophilic and Hydrophobic Ionic Liquids: Alternatives to Volatile Organic Compounds for Liquid-Liquid Separations," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 289-308.
504. Visser, A. E.; Rogers, R. D. "Actinide Chemistry in Novel Solvent Media: Room Temperature Ionic Liquids," In *Molten Salts XIII: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2002; Vol. 2002-19, pp 516-529.
505. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Mayton, R.; Sheff, S. Wierzbicki, A.; Davis, Jr. J. H.; Rogers, R. D. "Task-Specific Ionic Liquids Incorporating Novel Cations for the Coordination and Extraction of Hg^{2+} and Cd^{2+}: Synthesis, Characterization, and Extraction Studies," *Env. Sci. Technol.* **2002**, *36*, 2523-2529.
506. Willauer, H. D.; Huddleston J. G.; Rogers, R. D. "Solute Partitioning in Aqueous Biphasic Systems Composed of Polyethylene Glycol and Salt: The Partitioning of Small Neutral Organic Species," *Ind. Eng. Chem. Res.* **2002**, *41*, 1892-1904.
507. Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "Solvent Properties of Aqueous Biphasic Systems Composed of Polyethylene Glycol and Salt Characterized by the Free Energy of Transfer of a Methylene Group Between the Phases and by a Linear Solvation Energy Relationship," *Ind. Eng. Chem. Res.* **2002**, *41,* 2591-2601.
508. Yamato, K.; Bartsch, R. A.; Dietz, M. L.; Rogers, R. D. "Improved stereospecific synthesis of the *trans*-isomers of dicyclohexano-18-crown-6 and the solid-state structure of the *trans-syn-trans*-isomer," *Tetrahedron Lett.* **2002**, *43*, 2153-2156.
509. Yamato, K.; Bartsch, R. A.; Dietz, M. L.; Broker, G. A.; Rogers, R. D. "Synthesis of chiral *trans-anti-trans*-isomers of dicyclohexano-18-crown-6 via an enzymatic reaction and the solid-state structure of one enantiomer," *Tetrahedron Lett.* **2002**, *43*, 5805-5808.
510. Zhang, H.; Bu, L.; Li, M.; Hong, K.; Visser, A. E.; Rogers, R. D.; Mays, J. W. "Homopolymerization and Block Copolymer Formation in Room Temperature Ionic Liquids using Conventional Free Radical Initiators," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 114-124.
511. Abraham, M. H.; Zissimos, A. M.; Huddleston, J. G.; Willauer, H. D.; Rogers, R. D.; Acree, Jr., W. E. "Some Novel Liquid Partitioning Systems: Water-Ionic Liquids and Aqueous Biphasic Systems," *Ind. Eng. Chem. Res.* **2003**, *42*, 413-418.
512. Aqad, E.; Lakshmikantham, M. V.; Cava, M. P.; Broker, G. A.; Rogers, R. D. "Synthesis of Benzo[*c*]selenophene and Derivatives via New Routes," *Org. Lett.* **2003**, *5*, 2519-2521.
513. Guo, Z.; Huddleston, J. G.; Rogers, R. D.; April, G. C. "Reaction Parameter Effects in Metal-Salt-Catalyzed Aqueous Biphasic Pulping Systems," *Ind. Eng. Chem. Res.* **2003**, *42*, 248-253.
514. Guo, Z.; Li, M.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "PEG-Based Aqueous Biphasic Systems as Improvement for Kraft Hardwood Pulping Process," *Chem. Eng. Commun.* **2003**, *190*, 1155-1169.
515. Gutowski, K. E.; Bridges, N. J.; Cocalia, V. A.; Spear, S. K.; Holbrey, J. D.; Swatloski, R. P.; Davis, J. H., Jr.; Rogers, R. D. "Approaches to Nuclear Separations Using Room Temperature Ionic Liquids," *American Nuclear Society GLOBAL 2003 Winter Meeting Proceedings* **2003**; pp 1604-1608.
516. Gutowski, K. E.; Broker, G. A.; Willauer, H. D.; Huddleston, J. G.; Swatloski, R. P.; Holbrey, J. H. "Controlling the aqueous miscibility of ionic liquids: Aqueous biphasic systems of water-miscible ionic liquids and water-structuring salts for recycle, metathesis, and separations," *J. Am. Chem. Soc.* **2003**, *125*, 6632-6633.
517. Helm, M. L.; Loveday, K. D.; Combs, C. M.; Bentzen, E. L.; VanDerveer, D. G.; Rogers, R. D.; Grant, G. J. "Heavy Metal Complexes of Macrocyclic Thioethers," *J. Chem. Crystallogr.* **2003**, *33* 447-455.
518. Holbrey, J. D.; Reichert, W. M.; Nieuwenhuyzen, M.;Johnson, S.; Seddon, K. R.; Rogers, R. D., "Crystal polymorphism in 1-butyl-3-methylimidazolium halides: supporting ionic liquid formation by inhibition of crystallization," *Chem. Commun.* **2003**, 1636-1637.
519. Holbrey, J. D.; Reichert, W. M.; Nieuwenhuyzen, M.; Sheppard, O.; Hardacre, C.; Rogers, R. D., "Liquid Clathrate Formation in Ionic Liquid/Aromatic Mixtures," *Chem. Commun.* **2003**, 476-477.
520. Holbrey, J. D.; Reichert, W. M.; Reddy, R. G.; Rogers, R. D. "Heat Capacities of Ionic Liquids and Their Applications as Thermal Fluids," In *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical Society: Washington DC, 2003; pp 121-133.
521. Holbrey, J. D.; Reichert, W. M.; Tkatchenko, I.; Bouajila, E.; Walter, O.; Tommasi, I.; Rogers, R. D. "1,3-Dimethylimidazolium-2-carboxylate: The Unexpected Synthesis of an Ionic Liquid Precursor and Carbene-CO_2 Adduct," *Chem. Commun.* **2003**, 28-29.
522. Holbrey, J. D.; Rogers, R. D. "Physico-chemical properties of ionic liquids: Melting points and phase diagrams," In *Ionic Liquids in Synthesis*; Wasserscheid, P.; Welton, T., Eds.; Wiley-VCH, Weinheim, **2003**; pp 41-55.
523. Holbrey, J. D.; Turner, M. B.; Rogers, R. D. "Selection of Ionic Liquids for Green Chemical Applications," In *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical

Society: Washington DC, 2003; pp 2-12.
524. Holbrey, J. D.; Turner, M. B.; Reichert, W. M.; Rogers, R. D. "New ionic liquids containing an appended hydroxyl functionality from the clean, atom-efficient, one-pot reaction of 1-methylimidazole and acid with propylene oxide," *Green Chem.* **2003**, *5*, 731-736.
525. Holbrey, J. D.; Visser, A. E.; Rogers, R. D. "Physico-chemical properties of ionic liquids: Solubility and solvation in ionic liquids," In *Ionic Liquids in Synthesis*; Wasserscheid, P.; Welton, T., Eds.; Wiley-VCH, Weinheim, 2003; pp 68-81.
526. Holbrey, J. D.; Visser, A. E. Spear, S. K.; Reichert, W. M.; Swatloski, R. P.; Broker, G. A.; Rogers, R. D. "Mercury(II) partitioning from aqueous solutions with a new, hydrophobic ethylene-glycol functionalized bis-imidazolium ionic liquid," *Green Chem.* **2003**, *5*, 129-135.
527. Huddleston, J. G.; Looney, T. K.; Broker, G. A.; Griffin, S. T.; Spear, S. K.; Rogers, R. D. "Comparative Behavior of Poly(ethylene glycol) Hydrogels and Poly(ethylene glycol) Aqueous Biphasic Systems," *Ind. Eng. Chem. Res.* **2003**, *42*, 6088-6095.
528. Huddleston, J. G.; Willauer, H. D.; Rogers, R. D. "Phase Diagram Data for Several PEG + Salt Aqueous Biphasic Systems at 25 ºC," *J. Chem. Eng. Data* **2003**, *48*, 1230-1236.
529. Park, G.; Przyborowska, A. M.; Ye, N.; Tsoupas, N. M.; Bauer, C. B.; Broker, G. A.; Rogers, R. D.; Brechbiel, M. W.; Planalp, R. P. "Steric effects caused by N-alkylation of the tripodal chelator N, N', N''-tris(2-pyridylmethyl)-*cis,cis*-1,3,5-triaminocyclohexane (tachpyr): structural and electronic properties of the Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes," *J. Chem. Soc., Dalton Trans.* **2003**, 318-324.
530. Rajagopal, D.; Lakshmikantham, M. V.; Cava, M. P.; Broker, M. P.; Rogers, R. D. "Synthesis and Transformations of Some New 2,4-Bismethylene-1,3-ditelluretanes," *Tetrahedron Lett.* **2003**, *44*, 2397-2400.
531. Rogers, R. D.; Seddon, K. R. "Ionic Liquids – Solvents of the Future?" *Science* **2003**, *302*, 792-793.
532. Shaughnessy, K. H.; Klingshirn, M. A.; P'Pool, S. J.; Holbrey, J. D.; Rogers, R. D. "Polar, Non-Coordinating Ionic Liquids as Solvents for Coordination Polymerization of Olefins," In *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical Society: Washington DC, 2003; pp 300-313.
533. Swatloski, R. P.; Holbrey, J. D.; Rogers, R. D. "Ionic liquids are not always green: hydrolysis of 1-butyl-3-methylimidazolium hexafluorophosphate," *Green Chem.* **2003**, *5*, 361-363.
534. Turner, M. B.; Spear, S. K.; Huddleston, J. G.; Holbrey, J. D.; Rogers, R. D. "Ionic Liquid-Induced Inactivation and Unfolding of Cellulase from *Trichoderma reesei*, *Green Chem.* **2003**, *5*, 443-447. (Also in *Chemical Biology Virtual Journal*, **2003**, Issue 15: http://www.rsc.org/cgi-shell/empower.exe?DB=rsc-cbvjournal&B=F22003&B=F415&ISSNO=15.)
535. Visser, A. E.; Jensen, M. P.; Laszak, I.; Nash, K. L.; Choppin, G. R.; Rogers, R. D. "Uranyl Coordination Environment in Hydrophobic Ionic Liquids: An in Situ Investigation," *Inorg. Chem.* **2003**, *42*, 2197-2199.
536. Visser, A. E.; Rogers, R. D. "Room Temperature Ionic Liquids: New Solvents for f-Element Separations and Associated Solution Chemistry," *J. Solid State Chem.* **2003**, *171*, 109-113.
537. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "Room Temperature Ionic Liquids as Replacements for Traditional Organic Solvents and Their Applications Towards "Green Chemistry" in Separation Processes," In *Green Industrial Applications of Ionic Liquids*, Rogers, R. D.; Seddon, K. R.; Volkov, S. (Eds.); Kluwer: Dordrecht, 2003; pp 137-156.
538. Burns, C. J.; Neu, M.; Boukhalfa, H.; Gutowski, K. E.; Bridges, N. J.; Rogers, R. D. "The Actinides," in *Comprehensive Coordination Chemistry-II From Biology to Nanotechnology*, McCleverty, J. A.; Meyer, T. J., Eds., Vol. 3 *Coordination Chemistry of the s, p, and f Metals*, Parkin, G. F. R. Ed.; Elsevier Pergamon: Amsterdam, 2004; pp 189-346.
539. Chen, J.; Spear, S. K.; Huddleston, J. G.; Holbrey, J. D.; Rogers, R. D. "Application of polyethylene glycol-based aqueous biphasic reactive extraction to the oxidation of olefins." *J. Chromatogr. B* **2004**, *807*, 145-149.
540. Chen, J.; Spear, S. K.; Huddleston, J. G.; Holbrey, J. D.; Swatloski, R. P.; Rogers, R. D. "Application of poly(ethylene glycol)-based aqueous biphasic systems as reaction and reactive extraction media," *Ind. Eng. Chem. Res.* **2004**, *43*, 5358-5364.
541. Gilbert, T. M.; Littrell, J. C.; Talley, C. E.; Vance, M. A.; Dallinger, R. F.; Rogers, R. D. "Experimental and Computational Studies of the Metal-Metal Stretching Vibration in $X_3M{\equiv}MX_3$ Compounds (X = Alkoxide, Alkyl, Amide)," *Inorg. Chem.* **2004**, *43*, 1762-1769.
542. Griffin, S. T.; Spear, S. K.; Rogers, R. D. "Effects of speciation on partitioning of iodine in aqueous biphasic systems and onto ABEC® resins," *J. Chromatogr. B* **2004**, *807*, 151-156.
543. Holbrey, J. D.; Reichert, W. M.; Rogers. R. D. "Crystal structures of imidazolium bis(trifluoromethanesulfonyl)imide 'ionic liquid' salts: The first organic salt with a cis-TFSI anion conformation," *J. Chem. Soc., Dalton Trans.* **2004**, 2267-2271.
544. Huddleston, J. G.; Willauer, H. D.; Burney, M. T.; Tate, L. J.; Carruth, A. D.; Rogers, R. D. "Comparison of an Empirical and a Theoretical Linear Solvation Energy Relationship Applied to the Characterization of Solute Distribution in a Poly(ethylene) Glycol-Salt Aqueous Biphasic System," *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 549-558.
545. Katritzky, A. R.; Tämm, K.; Kuanar, M.; Fara, D. C.; Oliferenko, A.; Oliferenko, P.; Huddleston, J. G.; Rogers, R. D. "Aqueous Biphasic Systems. Partitioning of Organic Molecules: a QSPR Treatment," *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 136-142.
546. Klingshirn, M. A.; Spear, S. K.; Subramanian, R.; Holbrey, J. D.; Huddleston, J. G.; Rogers, R. D. "Gellation of ionic liquids using a cross-linked poly(ethylene glycol) gel matrix," *Chem. Mater.* **2004**, *16*, 3091-3097.
547. Luo, H.; Dai, S.; Bonnesen, P. V.; Buchanan, A. C.; Holbrey, J. D.; Bridges, N. J.; Rogers, R. D. "Extraction of Cesium Ions from Aqueous Solutions Using Calix[4]arene-bis(tert-octylbenzo-crown-6) in Ionic Liquids," *Anal. Chem.* **2004**, 76, 3078-3083.
548. Oliferenko, A. A.; Oliferenko, P. V.; Huddleston, J. G.; Rogers, R. D.; Palyulin, V. A.; Zefirov, N. S.; Katritzky, A. R.

"Theoretical Scales of Hydrogen Bond Acidity and Basicity for Application in QSAR/QSPR Studies and Drug Design. Partitioning of Aliphatic Compounds," *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1042-1055.

549. Spear, S. K.; Holbrey, J. D.; Rogers, R. D. "Liquid Clathrates," In *Encyclopedia of Supramolecular Chemistry*, Atwood, J. L.; Steed, J. W. (Eds.); Marcel Dekker: New York, 2004; pp 804-808.
550. Swatloski, R. P.; Holbrey, J. D.; Memon, S. B.; Caldwell, G. A.; Caldwell, K. A.; Rogers, R. D. "Using *Caenorhabditis elegans* to probe toxicity of 1-alkyl-3-methylimidazolium chloride based ionic liquids," *Chem. Commun.* **2004**, 668-669.
551. Turner, M. B.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Production of bioactive cellulose films reconstituted from ionic liquids," *Biomacromolecules* **2004**, *5*, 1379-1384.
552. Wang, W.; Shen, G.; Swatloski, R. P.; Farag, R.; Broughton, Jr., R. M.; Rogers, R. D. "Cellulose Fibers Extruded from Ionic Liquids," In *Proceedings of the International Nonwovens Technical Conference, Toronto Canada, September 20-23, 2004*, INDA, Association of the Nonwoven Fabrics Industry: Cary, NC, 2004.
553. Ye, N.; Park, G.; Przyborowska, A. M.; Sloan, P. E.; Clifford, T.; Bauer, C. B.; Broker, G. A.; Rogers, R. D.; Ma, R.; Torti, S. V.; Brechbiel, M. W.; Planalp, R. P., "Nickel(II), copper(II) and zinc(II) binding properties and cytotoxicity of tripodal, hexadentate tris(ethylenediamine)– analogue chelators," *Dalton Trans.* **2004**, 1304-1311. (Among the Top Ten accessed papers for *Dalton Trans.* June 2004.)
554. Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. "Polyethylene glycol and solutions of polyethylene glycol as green reaction media," *Green Chem.* **2005**, *7*, 64-82. [This was the cover article for this issue of *Green Chemistry*. Reported to be the 10th most accessed article in *Green Chemistry* in 2006.]
555. Childers, M. L.; Su, F.; Przyborowska, A. M.; Bishwokarma, B.; Park, G.; Brechbiel, M. W.; Torti, S. V.; Torti, F. M.; Broker, G.; Alexander, J. S.; Rogers, R. D.; Ruhlandt-Senge, K.; Planalp, R. P. "Pyridine-ring alkylation of cytotoxic *N, N', N''*-tris(2-pyridylmethyl)-*cis,cis*-1,3,5-triaminocyclohexane chelators: Structural and electronic properties of the Mn^{II}, Fe^{II}, Ni^{II}, Cu^{II} and Zn^{II} complexes," *Eur. J. Inorg. Chem.* **2005**, *19*, 3971-3982.
556. Clapp, L. A.; Siddons, C. J.; Whitehead, J. R.; VanDerveer, D. J.; Rogers, R. D.; Griffin, S. T.; Jones, S. B.; Hancock, R. D. "Factors Controlling Metal-Ion Selectivity in the Binding Sites of Calcium-Binding Proteins. The Metal Binding Properties of Amide Donors. A Crystallographic and Thermodynamic Study," *Inorg. Chem.* **2005**, *44*, 8495-8502.
557. Cocalia, V. A.; Holbrey, J. D.; Gutowski, K. E.; Bridges, N. J.; Rogers; R. D. "Separations of Metal Ions Using Ionic Liquids: The Challenges of Multiple Mechanisms," In *Proceedings of the International Solvent Extraction Conference, Solvent Extraction for Sustainable Development (ISEC 2005) Beijing, China 19-23 September 2005*; China Academic Journal Electronic Publishing House; Beijing, 2005; pp 39-46.
558. Cocalia, V. A.; Jensen, M. P.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Identical Extraction Behavior and Coordination of Trivalent and Hexavalent f-Element Cations Using Ionic Liquid and Molecular Solvents," *Dalton Trans.* **2005**, 1966-1971.
559. DeVasher, R. B.; Spruell, J. M.; Dixon, D. A.; Broker, G. A.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H. "Experimental and Computational Study of Steric and Electrnic Effects n the Coordination of Bulky, Water-Soluble Alkylphosphines to Palladium under Reducing Conditions: Correlation to Catalytic Activity," *Organometallics* **2005**, *245*, 962-971.
560. Elshani, S.; Wai, C. M.; Shreeve, J. M.; Rogers, R. D.; Bartsch, R. A. "Synthesis of Proton-Ionizable Acyclic, Macrocyclic and Macrobicyclic Compounds Containing One or Two Triazole Groups," *J. Heterocyclic Chem.* **2005**, *42*, 621-629.
561. Fox, P. A.; Griffin, S. T.; Reichert, W. M.; Salter, E. A.; Smith, A. B.; Tickell, M. D.; Wicker, B. F.; Cioffi, E. A.; Davis, Jr. J. H.; Rogers, R. D.; Wierzbicki, A. "Exploiting isolobal relationships to create new ionic liquids: Novel room-temperature ionic liquids based upon (*N*-alkylimidazole)(amine)BH_2^+ "boronium" ions," *Chem. Commun.* **2005**, 3679-3681.
562. Gutowski, K. E.; Holbrey, J. D.; Rogers, R. D.; Dixon, D. A. "Prediction of the Formation and Stabilities of Energetic Salts and Ionic Liquids Based on ab Initio Electronic Structure Calculations," *J. Chem. Phys. B* **2005**, *109*, 23196-23208.
563. Gutowski, K. E.; Bridges, N. J.; Cocalia, V. A.; Spear, S. K.; Visser, A. E.; Holbrey, J. D.; Davis, Jr., J. H.; Rogers, R. D. "Ionic Liquid Technologies for Utilization in Nuclear-Based Separations," In *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities - Transformations and Processes*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington DC, 2005; pp 33-48.
564. Haque, A.; Daly, D. T.; Rogers, R. D.; Mobley, C.; Swatloski, R. P. "Effects of MAPP as Coupling Agent on the Performance of Cellulose/Polypropylene Laminated Composites," In *Proceedings of the 3rd International Conference on Eco-Composites*, Royal Institute of Technology, Stockholm, Sweden, June 20-21, 2005.
565. Holbrey, J. D.; Chen, J.; Turner, M. B.; Swatloski, R. P.; Spear, S. K.; Rogers, R. D., "Applying Ionic Liquids for Controlled Processing of Polymer Materials," In *Ionic Liquids in Polymer Systems: Solvents, Additives, and Novel Applications*, Brazel, C. S.; Rogers, R. D. (Eds.); ACS Symposium Series 913; American Chemical Society: Washington DC, 2005; pp 71-87.
566. Katritzky, A. R.; Singh, S.; Kirichenko, K.; Holbrey, J. D.; Smiglak, M.; Reichert, W. M.; Rogers, R. D. "1-Butyl-3-methylimidazolium 3,5-dinitro-1,2,4-triazolate: A novel ionic liquid containing a rigid, planar energetic anion," *Chem. Commun.* **2005**, 868-870. (Among the Top Five most accessed papers for *Chem. Commun.* February 2005.)
567. Klingshirn, M. A.; Rogers, R. D.; Shaughnessy, K. H., "Palladium-catalyzed hydroesterification of styrene derivatives in the presence of ionic liquids," *J. Organomet. Chem.* **2005**, *690*, 3620-3626.
568. Klingshirn, M. A.; Spear, S. K.; Holbrey, J. D.; Huddleston, J. G.; Rogers, R. D. "Synthesis, Characterization, and Application of Cross-Linked Poly(ethylene glycol) Networks Used for Gelation of Ionic Liquids," In *Ionic Liquids in Polymer Systems: Solvents, Additives, and Novel Applications*, Brazel, C. S.; Rogers, R. D. (Eds.); ACS Symposium Series 913; American Chemical Society: Washington DC, 2005; pp 149-162.
569. Klingshirn, M. A.; Spear, S. K.; Holbrey, J. D.; Rogers, R. D. "Ionic liquids as solvent and solvent additives for the synthesis of

sol-gel materials," *J. Mater. Chem.* **2005**, *15*, 5174-5180.
570. Mobley, C.; Ramasetty, A.; Haque, A.; Poplin, J. H.; Daly, D. T.; Rogers, R. D. "Affordable Bio-polymer Matrix Composites for Lightweight Automotive Components," In *Proceedings of the Sixth Annual Global Automotive Conference*, Western Kentucky University, Bowling Green, KY, April 6-8, 2005.
571. Moody, M. L.; Willauer, H. D.; Griffin, S. T.; Huddleston, J. G.; Rogers, R. D. "Solvent Property Characterization of Poly(ethylene glycol)/Dextran Aqueous Biphasic Systems Using the Free Energy of Transfer of a Methylene Group and a Linear Solvation Energy Relationship," *Ind. Eng. Chem. Res.* **2005**, *44*, 3749-3760.
572. Moulthrop, J. S.; Swatloski, R. P.; Moyna, G.; Rogers, R. D. "High-resolution ^{13}C NMR studies of cellulose and cellulose oligomers in ionic liquid solutions," *Chem. Commun.* **2005**, 1557-1559.
573. P'Pool, S. J.; Klingshirn, M. A.; Rogers, R. D.; Shaughnessy, K. H. "Kinetic Study of the Oxidative Addition of Methyl Iodide to Vaska's Complex in Ionic Liquids," *J. Organomet. Chem.* **2005**, *690*, 3522-3528.
574. Sliger, M. D.; Broker, G. A.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H. "Di-*t*-butyl(ferrocenylphosphine: Air-Stability, Structural Characterization, Coordination Chemistry, and Applications to Palladium-Catalyzed Cross-Coupling Reactions," *J. Organomet. Chem.* **2005**, *690*, 1478-1486.
575. Sliger, M. D.; P'Pool, S. J.; Traylor, R. K.; McNeill III, J.; Young, S. H.; Hoffman, N. W.; Klingshirn, M. A.; Rogers, R. D.; Shaughnessy, K. H. "Promoting Effect of Ionic Liquids on Ligand Substitution Reactions," *J. Organomet. Chem.* **2005**, *690*, 3540-3545.
576. Turner, M. B.; Holbrey, J. D; Spear, S. K.; Pusey, M. L.; Rogers, R. D. "Effects of Oxygen-Containing Functional Groups on Protein Stability in Ionic Liquid Solutions," In *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities - Transformations and Processes*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington DC, 2005; pp 233-243.
577. Turner, M. B.; Spear, S. K.; Holbrey, J. D.; Daly, D. T.; Rogers, R. D. "Ionic liquid-reconstituted cellulose composites as solid support matrices for biocatalyst immobilization," *Biomacromolecules* **2005**, *6*, 2497-2502.
578. Broughton, R.; Wang, W.; Shen, G.; Farag, R.; Swatloski, R. P.; Rogers, R. D. "Keynote Address: New Solvent for Cellulose Extrusion," In *Proceedings Beltwide Cotton Conferences,* National Cotton Council: Memphis, TN, 2005, pp 3291/1-3291/5 (ISSN: 1059-2644).
579. Cocalia, V. A.; Gutowski, K. E.; Rogers, R. D. **"**The coordination chemistry of actinides in ionic liquids: A review of experiment and simulation," *Coord. Chem. Rev.* **2006**, *250*, 755-764.
580. Cocalia, V. A.; Holbrey, J. D.; Gutowski, K. E.; Bridges, N. J.; Rogers; R. D. "Separations of Metal Ions Using Ionic Liquids: The Challenges of Multiple Mechanisms," *Tsinghua Sci. Technol.* **2006**, *11*, 188-193.
581. Cocalia, V. A.; Holbrey, J. D.; Spear, S. K.; Jensen, M. P.; Rogers, R. D. "Partitioning of Transuranic Metal Ions to Ionic Liquids Containing the Ionizable Complexant Cyanex-272," In *Molten Salts XIV: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2006; Vol. PV 2004-24; pp 779-789.
582. Drab, D. M.; Smiglak, M.; Rogers, R. D. "Should the Concepts of Green Chemistry be Restrictive or Prescriptive? The Greener Synthesis of High-Performance, Energetic Ionic Liquid Materials" *Chimica Oggi/CHEMISTRY TODAY* **2006**, *24*, 27-30.
583. Fort, D. A.; Swatloski, R. P.; Moyna, P.; Rogers, R. D.; Moyna, G. "Use of Ionic Liquids in the Study of Fruit Ripening by High-Resolution ^{13}C NMR Spectroscopy: 'Green' Solvents Meet Green Bananas," *Chem Commun.* **2006**, 714-716. (Highlighted as a Hot Article by *Chem. Commun.* January 16, 2006, URL: http://www.rsc.org/Publishing/Journals/cc/index.asp; last accessed January 19, 2006; Highlighted in Ritter, S. "Ionic liquids go bananas," *Chemical & Engineering News*, February 6, 2006, p. 48; Listed as a 'Top Ten' accessed article by *Chem. Commun.* for the month of January 2006 at http://www.rsc.org/chemcomm; Highlighted in Lavender, R. "Following the ripening of bananas," *Chemical Science* (an RSC web supplement) February 23, 2006 at URL: http://www.rsc.org/Publishing/ChemScience/Volume/2006/03/ripening_of_bananas.asp; last accessed April 17, 2006.)
584. Griffin, S. T.; Dilip, M.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. "The Opposite Effect of Temperature on Polyethylene Glycol-Based Aqueous Biphasic Systems versus Aqueous Biphasic Extraction Chromatographic Resins," *J. Chromatogr. B* **2006**, *844*, 23-31.
585. Gutowski, K. E.; Bridges, N. J.; Rogers, R. D. "Actinide Structural Chemistry," In *The Chemistry of the Actinide and Transactinide Elements*, 3rd Edition. Morss, L. R.; Edelstein, N.; Fuger, J.; Katz, J. K., Eds., Springer: Dordrecht, 2006; Vol. 4 pp 2380-2523.
586. Gutowski, K. E.; Rogers, R. D.; Dixon, D. A. "Accurate Thermochemical Properties for Energetic Materials Applications. I. Heats of Formation of Nitrogen-Containing Heterocycles and Energetic Precursor Molecules from Electronic Structure Theory," *J. Chem. Phys. A* **2006**, *110*, 11890-11897.
587. Haque, A.; Mobley, C.; Daly, D. T.; Rogers, R. D.; Swatloski, R. P.; Ramasetty, A. "Effects of MAPP as coupling agent on the performance of regenerated cellulose film reinforced polypropylene composites," *Proceedings of the American Society for Composites, Technical Conference* **2006**, *21st*, 272/1-272/15.
588. Hines, C. C.; Reichert, W. M.; Griffin, S. T.; Bond, A. H.; Snowwhite, P. E.; Rogers, R. D. "Exploring Control of Cadmium Halide Coordination Polymers via Control of Cadmium(II) Coordination Sites Utilizing Short Multidentate Ligands," *J. Mol. Struct.* **2006**, *796*, 76-85.
589. Holbrey, J. D.; Reichert, W. M.; Smiglak, M.; Spear, S. K.; Yang, H.; Manju, K.; Kirichenko, K.; Katritzky, A. R.; Thrasher, J. S.; Sun, L. Y.; Rogers, R. D. "Stability and Thermal Decomposition of Quaternary and Protonated Imidazolium Nitrate and

Picrate Salts," In *Molten Salts XIV: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2006; Vol. PV 2004-24; pp 396-406.

590. Holbrey, J. D.; Vigour, K. B.; Reichert, W. M.; Rogers, R. D. "The structure of $[Co(H\text{-}tptz)Cl_3]\cdot H_2O$ (tptz = 2,4,6-tri(2-pyridyl)-1,3,5-triazine) prepared by crystallization from the ionic liquid, *N*-butyl-*N*-methyl-pyrrolidinium *bis*(trifluoromethanesulfonyl)imide," *J. Chem. Crystallogr.* **2006**, *36*, 799-804.
591. Katritzky, A. R.; Yang, H.; Zhang, D.; Kirichenko, K.; Smiglak, M.; Holbrey, J. D.; Reichert, W. M.; Rogers, R. D. "Strategies Toward the Design of Energetic Ionic Liquids: Nitro- and Nitrile-substituted *N*,*N'*-Dialkylimidazolium Salts," *New. J. Chem.* **2006**, *30*, 349-358.
592. Katritzky, A. R.; Singh, S.; Kirichenko, K.; Smiglak, M.; Holbrey, J. D.; Reichert, W. M.; Spear, S. K.; Rogers, R. D. "In search of ionic liquids incorporating azolate anions," *Chem. Eur. J.* **2006**, *12*, 4630-4641.
593. Moore, L. R.; Cooks S. M.; Anderson, M. S.; Schanz, H.-J.; Griffin,S. T.; Rogers, R. D.; Kirk, M. C.; Shaughnessy, K. H. "Synthesis and Characterization of Water-Soluble Silver and Palladium Imidazol-2-ylidene Complexes with Noncoordinating Anionic Substituents," *Organometallics* **2006**, *25*, 5151-5158.
594. Parks, B. W.; Gilbertson, R. D.; Hutchison, J. E.; Rather Healey, E.; Weakley, T. J. R.; Rapko, B. M.; Hay, B. P.; Sinkov, S. I.; Broker, G. A.; Rogers, R. D. "Solution and Structural Investigations of Ligand Preorganization in Trivalent Lanthanide Complexes of Bicyclic Malonamides," *Inorg. Chem.* **2006**, *45*, 1498-1507.
595. Pernak, J.; Smiglak, M.; Griffin, S. T.; Hough, W. L.; Wilson, T. B.; Pernak, A.; Zabielska-Matejuk, J.; Fojutowski, A.; Kita, K.; Rogers, R. D. "Long alkyl chain quaternary ammonium-based ionic liquids and potential applications," *Green Chem.* **2006**, *8*, 798-806.
596. Reichert, W. M.; Holbrey, J. D.; Vigour, K. B.; Morgan, T. D.; Broker, G. A.; Rogers, R. D. "Approaches to Crystallization From Ionic Liquids: Complex Solvents-Complex Results, or, a Strategy for Controlled Formation of New Supramolecular Architectures?" *Chem Commun.* **2006**, 4767-4779 (Invited Feature Article).
597. Remsing, R. C.; Swatloski, R. P.; Rogers, R. D.; Moyna, G. "Mechanism of cellulose dissolution in the ionic liquid 1-n-butyl-3-methylimidazolium chloride: a ^{13}C and $^{35/37}Cl$ NMR relaxation study on model systems," *Chem. Commun.* **2006**, 1271-1273.
598. Smiglak, M.; Reichert, W. M.; Holbrey, J. D.; Wilkes, J. S.; Sun, L.; Thrasher, J. S.; Kirichenko, K.; Singh, S.; Katritzky, A. R.; Rogers, R. D. "Combustible Ionic Liquids by Design: Is Laboratory Safety Another Ionic Liquid Myth?" *Chem. Commun.* **2006**, 2554-2556. (Highlighted as a Hot Article by *Chem. Commun.* June 5, 2006, URL: http://www.rsc.org/Publishing/Journals/cc/index.asp; last accessed June 6, 2006); Highlighted in *Chemical Science* (an RSC web supplement), June 20, 2006, URL: http://www.rsc.org/Publishing/ChemScience/Volume/2006/07/ionic_combustible.asp; last accessed April 14, 2007.)
599. Swatloski, R. P.; Holbrey, J. D.; Weston, J. L.; Rogers, R. D. "Preparation of magnetic cellulosic composites using ionic liquids," *Chimica Oggi/CHEMISTRY TODAY* **2006**, *24*, 31-35.
600. Bridges, N. J.; Gutowski, K. E.; Rogers, R. D. "Investigation of aqueous biphasic systems formed from solutions of chaotropic salts with kosmotropic salts (salt-salt ABS)," *Green Chem.* **2007**, *9*,177-183.
601. Bridges, N. J.; Hines, C. C.; Smiglak, M.; Rogers, R. D. "An Intermediate for the Clean Synthesis of Ionic Liquids: Isolation and Crystal Structure of 1,3-Dimethylimidazolium Hydrogen Carbonate Monohydrate," *Chem. Eur. J.* **2007**,*13*, 5207-5212.
602. Cantorias, M. V.; Howell, R. C.; Todaro, L.; Cyr, J. E.; Berndorff, D.; Rogers, R. D.; Francesconi, L. C., "MO Tripeptide Diastereomers (M = $^{99/99m}Tc$, Re): Models to Identify the Structure of ^{99m}Tc Peptide Targeted Radiopharmaceuticals," *Inorg. Chem.* **2007**, *46*, 7326-7340.
603. Cocalia, V. A.; Rogers, R. D. "Ionic Liquid Impregnated Resins in Solid-Liquid Separations," *ECS Transactions* **2007**, *3*, 123-134.
604. Cordes, D. B.; Sharma, C. V. K.; Rogers, R. D. "Enantiomorphic Helical Coordination Polymers of $\{[M(pyrimidine)(OH_2)_4][SiF_6]\cdot H_2O\}_\infty$, (M = Co^{2+} , Cu^{2+}, Zn^{2+})," *Cryst. Growth Des.* **2007**, *7*, 1943-1945.
605. Fort, D. A.; Remsing, R. C.; Swatloski, R. P.; Moyna, P.; Moyna, G.; Rogers, R. D. "Can ionic liquids dissolve wood? Processing and analysis of lignocellulosic materials with 1-*n*-butyl-3-methylimidazolium chloride," *Green Chem.* **2007**, *9*, 63-69.
606. Gutowski, K. R.; Cocalia, V. A.; Griffin, S. T.; Bridges, N. J.; Dixon, D. A.; Rogers, R. D. "Interactions of 1-Methylimidazole with $UO_2(CH_3CO_2)_2$ and $UO_2(NO_3)_2$: Structural, Spectroscopic, and Theoretical Evidence for Imidazole Binding to the Uranyl Ion," *J. Am. Chem. Soc.* **2007** *129*, 526-536.
607. Gutowski, K. E.; Rogers, R. D.; Dixon, D. A. "Accurate Thermochemical Properties for Energetic Materials Applications. II. Heats of Formation of Imidazolium-, 1,2,4-Triazolium-, and Tetrazolium-Based Energetic Salts from Isodesmic and Lattice Energy Calculations" *J. Phys. Chem. B* , **2007**, *111*, 4788-4800.
608. Hines, C. C.; Bauer, C. B.; Rogers, R. D. "Lanthanide Polyether Complexation Chemistry: The Interaction of Hydrated Lanthanide(III) Nitrate Salts with an Acyclic 18-crown-6 Analog, Pentaethylene Glycol," *New J. Chem.* **2007**, *31*, 762-769.
609. Hough, W. L.; Rogers, R. D., "Ionic Liquids Then and Now: From Solvents to Materials to Active Pharmaceutical Ingredients," *Bull. Chem. Soc. Jpn*. **2007**, *80*, 2262-2269.
610. Hough, W. H.; Smiglak, M.; Rodríguez, H.; Swatloski, R. P.; Spear, S. K.; Daly, D. T.; Pernak, J.; Grisel, J. E.; Carliss, R. D.; Soutullo, M. D.; Davis, Jr., J. H.; Rogers, R. D. "The Third Evolution of Ionic Liquids: Active Pharmaceutical Ingredients," *New J. Chem.* **2007**, *31*, 1429-1436. (August Cover Article. Highlighted in Parker, D. "The Third Age of Ionic Liquids?" *Chemistry World*, August 2007, *4*, p 30 and *Chem. Sci.* **2007**, *4*, C59. Also in *Chemical Biology Virtual Journal*, **2007**, Issue 15: http://www.rsc.org/cgi-shell/empower.exe?DB=rsc-cbvjournal&B=F22003&B=F415&ISSNO=15.)

611. Pernak, J.; Feder-Kubis, J.; Cieniecka-Rosłonkiewicz, A.; Fischmeister, C.; Griffin, S. T.; Rogers, R. D. "Synthesis and Properties of Chiral Imidazolium Ionic Liquids with a (*1R,2S,5R*)-(–)-Menthoxymethyl Substituent," *New. J. Chem.* **2007**, *31*, 879-892. [Erratum: *New. J. Chem.* **2007**, *31*, 1022.]
612. Pernak, J.; Syguda, A.; Mirska, I.; Pernak, A.; Nawrot, J.; Prądzyńska, A.; Griffin, S. T.; Rogers, R. D. "Choline-Derivative-Based Ionic Liquids,"*Chem. Eur. J.* **2007**, *13*, 6817-6827.
613. Poplin, J. H.; Rudkevich, D. M.; Swatloski, R. P.; Rogers, R. D. "Development of Ionic Liquid Membranes for NO_x Gas Detection and Storage Utilizing Calix[4]Arenes," *ECS Transactions* **2007**, *3*, 105-108.
614. Poplin, J. H.; Swatloski, R. P.; Holbrey, J. D.; Spear, S. K.; Metlen, A.; Grätzel, M.; Nazeeruddin, M. K.; Rogers, R. D. "Sensor Technologies Based on a Cellulose Support," *Chem. Commun.* **2007**, 2025-2027.
615. Pusey, M. L.; Paley, M. S.; Turner, M. B.; Rogers, R. D. "Protein Crystallization Using Room Temperature Ionic Liquids," *Cryst. Growth Des.* **2007**, *7*, 787-793.
616. Reichert, W. M.; Holbrey, J. D.; Swatloski, R. P.; Gutowski, K. E.; Visser, A. E.; Nieuwenhuyzen, M.; Seddon, K. R.; Rogers, R. D. "Solid-state analysis of low-melting 1,3-dialkylimidazolium hexafluorophosphate salts (ionic liquids) by combined X-ray crystallographic and computational analyses," *Cryst. Growth Des.* **2007**, *7*, 1106-1114.
617. Rogers, R. D. "Reflections on Ionic Liquids," Nature **2007**, *447*, 917-918.
618. Smiglak, M.; Holbrey, J. D.; Griffin, S. T.; Reichert, W. M.; Swatloski, R. P.; Katritzky, A. R.; Yang, H.; Zhang, D.; Kirichenko, K.; Rogers, R. D. "Ionic Liquids *via* reaction of the zwitterionic 1,3-dimethylimidazolium-2-carboxylate with protic acids. Overcoming synthetic limitations and establishing new halide free protocols for the formation of ILs" *Green Chem.* **2007**, *9*, 90-98.
619. Smiglak, M.; Metlen, A.; Rogers, R. D. "The Second Evolution of Ionic Liquids: From Solvents and Separations to Advanced Materials - Energetic Examples from the Ionic Liquid Cookbook," *Acc. Chem. Res.* **2007**, *40*, 1182-1192.
620. Spear, S. K.; Griffin, S. T.; Granger, K. S.; Huddleston, J. G.; Rogers, R. D. "Renewable Plant-Based Soybean Oil Methyl Esters as Alternatives to Organic Solvents," *Green Chem.* **2007**, *9*, 1008–1015**.**
621. Sun, N.; Swatloski, R. P.; Maxim, M. L.; Broughton, Jr., R. M.; Spear, S. K.; Daly, D. T.; Haque, A.; Harland, A. G.; Rogers, R. D. "Cellulose Fibers Prepared from Direct Dissolution of Cellulose in Ionic Liquids," *Proceedings of the 4th International Conference of Textile Research Division NRC, Cairo, Egypt, April 14-17, 2007; Textile Processing : State of the Art & Future Developments* **2007**, *4*, 139-143.
622. Visser, A. E.; Huddleston, J. G.; Holbrey, J. D.; Reichert, W. M.; Swatloski, R. P.; Rogers, R. D. "Hydrophobic *n*-Alkyl-*N*-Isoquinolinium Salts: Ionic Liquids and Low melting Solids," In *Ionic Liquids IV Not Just Solvents Anymore*, Brennecke, J. F.; Rogers, R. D.; Seddon K. R. (Eds.); ACS Symposium Series 975; American Chemical Society: Washington DC, 2007; pp 362-380.
623. Whitcomb, D. R.; Swatloski, R. P.; Rogers, R. D. "Mode of complex formation between thiones and silver ion within a photothermographic formulation: The crystal and molecular structure of hexa-(silver-5-methyl-2-mercaptobenzimidazole THF)," *J. Imaging Sci. Technol.* **2007**, *51*, 547-551.
624. Bagheri, M.; Rodríguez, H.; Swatloski, R. P.; Spear S. K.; Daly, D. T.; Rogers, R. D. "Ionic liquid-based preparation of cellulose-dendrimer films as solid supports for enzyme immobilization," *Biomacromolecules* **2008**, *9*, 381-387.
625. Bailey, M. M.; Townsend, M. B.; Jernigan, P. L.; Sturdivant, J.; Hough-Troutman, W. L.; Rasco, J. F.; Swatloski, R. P.; Rogers, R. D.; Hood, R. D., "Developmental toxicity assessment of the ionic liquid 1-butyl-3-methylimidazolium chloride in CD-1 mice," *Green Chem.* **2008**, *10*, 1213-1217.
626. Bridges, N. J.; Rogers, R. D. "Can Kosmotropic Salt/Chaotropic Ionic Liquid (Salt/Salt Aqueous Biphasic Systems) be Used to Remove Pertechnetate from Complex Salt Waste?" *Sep. Sci. Technol.* **2008**, *43*, 1083-1090.
627. Cocalia, V. A.; Visser, A. E.; Rogers, R. D.; Holbrey, J. D. "Solubility and solvation in ionic liquids," In *Ionic Liquids in Synthesis, Second Edition*; Wasserscheid, P.; Welton, T., Eds.; Wiley-VCH, Weinheim, 2008; Vol. 1, pp 89-102.
628. Dilip, M.; Griffin, S. T.; Spear, S. K.; Rijksen, C.; Rodríguez, H.; Rogers, R. D. "Dual Nature of Polyethylene Glycol-Based Aqueous Biphasic Extraction Chromatographic (ABEC) Resins: Uptakes of Perchlorate versus Mercury(II)," *Ind. Eng. Chem. Res.* **2008**, *47*, 7390-7396.
629. Gurau, G.; Cocalia, V. A.; Rogers, R. D. "Separations, Coordination, And Solvation In Ionic Liquids; What Is There That Is Unique?" In *Solvent Extraction: Fundamentals to Industrial Applications - Proceedings of ISEC 2008 International Solvent Extraction Conference, (ISEC 2008)*, Moyer, B. A.; Baron, P.; Chagnes, A.; Cole, P. M.; Cote, G.; Dietz, M. L.; Hatton, T. A.; Horwitz, E. P.; de Ortiz, E. S. P.; Ritcey, G. M.; Robinson, D.; Rogers, R. D.; Sole, K. C.; Tasker, P. A.; Todd, T. A.; Virnig, M. J. (Eds.); Canadian Institute of Mining, Metallurgy and Petroleum: Montréal, 2008; Vol. 2; pp 1263-1270.
630. Hines, C. C.; Cocalia, V. A.; Rogers, R. D. "Using Ionic Liquids to Trap Unique Coordination Environments: Polymorphic Solvates of $ErCl_3(OH_2)_4 \cdot 2([C_2mim]Cl)$," *Chem. Commun.* **2008**, 226-228.
631. Hines, C. C.; Cordes, D. B.; Griffin, S. T.; Watts, S. I.; Cocalia, V. A.; Rogers, R. D. "Flexible Coordination Environments of Lanthanide Complexes Grown from Chloride-based Ionic Liquids," *New J. Chem.* **2008**, *32*, 872-877.
632. Hines, J. H.; Wanigasekara, E.; Rudkevich, D. M.; Rogers, R. D. "Calix[4]arenes immobilized in a cellulose-based platform for entrapment and detection of NO_x gases," *J. Mater. Chem.* **2008**, *18*, 4050-4055.
633. Holbrey, J. D.; Rogers, R. D. "Physicochemical properties of ionic liquids: Melting points and phase diagrams," In *Ionic Liquids in Synthesis, Second Edition*; Wasserscheid, P.; Welton, T., Eds.; Wiley-VCH, Weinheim, 2008; Vol. 1, pp 57-72.
634. Remsing, R. C.; Hernandez, G.; Swatloski, R. P.; Massefski, W. W.; Rogers, R. D.; Moyna, G. "Solvation of Carbohydrates in *N*,*N*'-Dialkylimidazolium Ionic Liquids: A Multinuclear NMR Spectroscopy Study," *J. Phys. Chem. B,* **2008**, *112*, 11071-11078.

635. Rodríguez, H.; Williams, M.; Wilkes, J. S.; Rogers, R. D. "Ionic Liquids for Liquid-in-Glass Thermometers", *Green Chem.*, **2008**, *10*, 501-507. (Highlighted in "Pegg, S. "Designer thermometers rise to new levels," *Chemical Technology* **2008** *5*; http://www.rsc.org/Publishing/ChemTech/Volume/2008/05/designer_thermometers.asp last accessed March 25, 2008.)
636. Rijksen, C.; Rogers, R. D. "A solventless route to 1-ethyl-3-methylimidazolium fluoride hydrofluoride, [C_2mim][F]·xHF," *J. Org. Chem.* **2008**, *73*, 5582-5584.
637. Smiglak, M.; Bridges, N. J.; Dilip, M.; Rogers, R. D. "Direct, atom efficient, and halide-free syntheses of azolium azolate energetic ionic liquids and their eutectic mixtures, and method for determining eutectic composition," *Chem. Eur. J.* **2008**, *14*, 11314-11319.
638. Sun, N.; Swatloski, R. P.; Maxim, M. L.; Rahman, M.; Harland, A. G.; Haque, A.; Spear, S. K.; Daly, D. T.; Rogers, R. D. "Magnetite-Embedded Cellulose Fibers Prepared from Ionic Liquid," *J. Mater. Chem.* **2008**, *18*, 283-290.
639. Cordes, D. B.; Smiglak, M.; Hines, C. C.; Bridges, N. J.; Dilip, M.; Srinivasan, G.; Metlen, A.; Rogers, R. D. "Ionic Liquid-Based Routes to Conversion or Reuse of Recycled Ammonium Perchlorate," *Chem. Eur. J.* **2009**, 15, 13441-13448.
640. Haque, R; Spear, S. K.; Daly, D. T.; Rogers R. D.; Vemuganti, S.; Haque, A. " Electrical and Mechanical Properties of Polypyrrole-Cellulose Fiber Composites Synthesized Via a Novel Chemical Processing Route," Technical Proceedings of the 17th International Conference on Composite Materials, Edinburgh, Scotland, 27-31 July, 2009.
641. Hough-Troutman, W. L.; Smiglak, M.; Griffin, S. T.; Reichert, W. M.; Mirska, I.; Jodynis-Liebert, J.; Adamska, T.; Nawrot, J.; Stasiewicz, M.; Rogers, R. D.; Pernak, J. "Ionic Liquids with Dual Biological Function: Sweet and Anti-microbial, Hydrophobic Quaternary Ammonium-based Salts," *New J. Chem.* **2009**, *33*, 26-33.
642. Rodríguez, H.; Francisco, M.; Rahman, M.; Sun, N.; Rogers, R. D. "Biphasic liquid mixtures of ionic liquids and polyethylene glycols," *Phys. Chem. Chem. Phys.* **2009**, *11*, 10916-10922.
643. Rodríguez, H.; Gurau, G.; Rogers, R. D. "Ionic liquids: growth of a field through the eyes of the I&EC division," In *Innovations in Industrial and Engineering Chemistry: A Century of Achievements and Prospects for the New Millenium*, Flank, W. H.; Abraham, M. A.; Matthews, M. A. (Eds.); ACS Symposium Series 1000; American Chemical Society: Washington DC, 2009; pp 389-400.
644. Shamery, T. L.; Huddleston, J. G.; Chen, J.; Spear, S. K.; Rogers, R. D. "Aqueous Biphasic Systems for Liquid-Liquid Separations," in *Experiments in Green and Sustainable Chemistry*, Roesky, H. W.; Kennepohl, D. K. (Eds.); Wiley-VCH: Weinheim, 2009; pp 92-96.
645. Sun, N.; Rahman, M.; Qin, Y.; Maxim, M. L.; Rodríguez, H.; Rogers, R. D. "Complete dissolution and partial delignification of wood in the ionic liquid 1-ethyl-3-methylimidazolium acetate," *Green Chem.* **2009**, *11*, 646-655.
646. Abai, M.; Holbrey, J. D.; Rogers, R. D.; Srinivasan, G. "Ionic liquid *S*-alkylthiouronium salts," *New J. Chem.* **2010**, *34*, 1981-1993.
647. Bailey, M.; Jernigan, P.; Henson, M. B.; Sturdivant, J.; Rasco, J.; Lovich, A. N.; Lockard, J. E.; Hough, W.; Di Bona, K. R.; Bearid, J.; Shernill, J.; Swatloski, R. P; Rogers, R. D.; Hood, R., "A Comparison of the Effects of Prenatal Exposure of CD-1 Mice to Three Imidazolium-Based Ionic Liquids," *Birth Def. Res. B Develop. Reprod. Tox.* **2010**, *89*, 233-238.
648. Bica, K.; Rijksen, C.; Nieuwenhuyzen, M.; Rogers, R. D. "In Search of Pure Liquid Salt Forms of Aspirin: Ionic Liquid Approaches with Acetylsalicylic Acid and Salicylic Acid," *Phys. Chem. Chem. Phys.* **2010**, *12*, 2011-2017. DOI: 10.1039/b923855g.
649. Bica, K.; Rogers, R. D. "Confused Ionic Liquid Ions – A "Liquification" and Dosage Strategy for Pharmaceutically Active Salts," *Chem. Commun.* **2010**, *46*, 1215-1217. DOI: 10.1039/b925147b. (Designated a *Chem. Commun.* Hot Article 02/18/10.)
650. Cocalia, V.; Smiglak, M.; Kelley, S. P.; Shamshina, J. L.; Gurau, G.; Rogers, R. D. "Crystallization of uranyl salts from dialkylimidazolium ionic liquids or their precursors," *Eur. J. Inorg. Chem.* **2010,** 2760-2767. DOI: 10.1002/ejic.201000162.
651. Dilip, M.; Griffin, S. T.; Spear, S. K.; Rodríguez, H.; Rijksen, C.; Rogers, R. D. "Comparison of Temperature Effects on the Salting-Out of Polyethylene Glycol versus Polyethylene Oxide-Polypropylene Oxide Random Copolymer," *Ind. Eng. Chem. Res.* **2010**, *49*, 2371-2379.
652. Drab, D. M.; Shamshina, J. L.; Smiglak, M.; Hines, C. C.; Cordes, D. B.; Rogers, R. D. "A general design platform for ionic liquid ions based on bridged multi-heterocycles with flexible symmetry and charge", *Chem. Commun.* **2010**, *46*, 3544-3546. DOI: 10.1039/c002861d.
653. Forton, M. S.; Sims, J. D.; Askins, R. E.; Stevenson, W. H.; Shamshina, J.; Smiglak, M.; Rogers, R. D.; Barrow, R. "An Ionic Liquid-Based Next Generation Double Base Propellant Stabilizer," In Proceedings of the 46th AIAA/ASME/SAE/ASEE Joint Propulsion Conference & Exhibit, 25-28 July 2010, Nashville, TN; American Institute of Aeronautics and Astronautics, Inc.: Reston, VA; AIAA 2010-6587; pp 1-8.
654. Hanes, Jr., R. E.; Ellingsworth, E. E.; Griffin, S. T.; Rogers, R. D.; Bartsch, R. A. "Polybenzocrown ethers: synthesis by cesium-assisted cyclization and solid-state structures," *ARKIVOC*, **2010**, *vii*, 217-237.
655. Hill, L. L.; Crowell, J. L.; Tutwiler, S. L.; Massie, N. L.; Hines, C. C.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H. "Synthesis and X-ray Structure Determination of Highly Active Pd(II), Pd(I), and Pd(0) Complexes of Di(*tert*-butyl)neopentylphosphine (DTBNpP) in the Arylation of Amines and Ketones," *J. Org. Chem.* **2010**, *75*, 6477-6488.
656. Holbrey, J. D.; Rogers, R. D.; Shukla, S. S.; Wilfred, C. D. "Optimised microwave-assisted synthesis of methylcarbonate salts: a convenient methodology to prepare intermediates for ionic liquid libraries," *Green Chem.* **2010**, *12*, 407-413.
657. Li, W.; Sun, N.; Rogers, R. D. "How can we improve the dissolution and recovery of biopolymers from biomass in ionic liquids specifically for biofuels applications?" In *Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry* **2010**, *55*, 103.

658. Maxim, M. L.; Sun, N.; Swatloski, R. P.; Rahman, M.; Harland, A. G.; Haque, A.; Spear, S. K.; Daly, D. T.; Rogers, R. D. "Properties of Cellulose/TiO_2 Fibers Processed from Ionic Liquids," In *Cellulose Solvents; For Analysis, Shaping and Chemical Modification*; Liebert, T. F.; Heinze, T. J.; Edgar, K. J., Eds.; ACS Symposium Series 1033, American Chemical Society: Washington, DC 2010; pp 261-274.
659. Nadeem, S.; Munawar, M. A.; Ahmad, S.; Smiglak, M.; Drab, D. M.; Malik, K. I.; Amjad, R.; Ashraf, C. M.; Rogers, R. D. "Solvent-free synthesis of benzothiazole-based quaternary ammonium salts: Precursors to Ionic Liquids," *ARKIVOC* **2010**, *vii*, 19-37.
660. Qin, Y.; Lu, X.; Sun, N.; Rogers, R. D. "Dissolution or Extraction of Crustacean Shells Using Ionic Liquids to Obtain High Molecular Weight Purified Chitin and Direct Production of Chitin Films and Fibers," *Green Chem.* **2010**, *12*, 968-971. **DOI:** 10.1039/c003583a
661. Rodríguez, H.; Rogers, R. D. "Liquid mixtures of ionic liquids and polymers as solvent systems," *Fluid Phase Equil.* **2010**, *294*, 7-14. DOI:10.1016/j.fluid.2009.12.036.
662. Rogers, R. D. "The fields of crystal engineering and ionic liquids are actually quite similar," *Aust. J. Chem.* **2010**, *63*, 533-534. DOI: 10.1071/CH10099
663. Shamshina, J. L.; Smiglak, M.; Drab, D. M.; Parker, T. G.; Dykes, Jr., H. W. H.; Di Salvo, R.; Reich, A. J.; Rogers, R. D. "Catalytic ignition of ionic liquids for propellant applications," *Chem. Commun.* **2010**, *46*, 8965-8967. DOI: 10.1039/C0CC02162H.
664. Smiglak, M.; Hines, C. C.; Rogers, R. D. "New hydrogen carbonate precursors for efficient and byproduct-free syntheses of ionic liquids based on 1,2,3-trimethylimidazolium and N,N-dimethylpyrrolidinium cores," *Green Chem.* **2010**, *12*, 491-501.
665. Smiglak, M.; Hines, C. C.; Wilson, T. B.; Singh, S.; Vincek, A. S.; Kirichenko, K.; Katritzky, A. R.; Rogers, R. D. "Ionic Liquids Based on Azolate Anions," *Chem. Eur. J.* **2010**, *16*, 1572-1584. (VIP designated paper)
666. Stoimenovski, J.; MacFarlane, D. R.; Bica, K.; Rogers, R. D. "Crystalline vs. Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper," *Pharm. Res.* **2010**, *27*, 521-526. DOI: 10.1007/s11095-009-0030-0
667. Sun, N.; Jiang, X.; Li, W.; Lu, X.; Rogers, R. D. "Wood Pulping Using Ionic Liquids," In *Research Progress in Paper Industry and Biorefinery - Proceedings of 4th International Symposium on Emerging Technologies of Pulping and Papermaking 2010 (4th ISETPP 2010)*, Sun, R.; Fu, S., Eds.; South China University of Technology Press, Guangzhou, 2010; pp 6-9.
668. Sun, N.; Jiang, X.; Maxim, M. L.; Rogers, R. D. "Wood Delignification Using Polyoxometalates in Ionic Liquid" In *Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry* 2010, *55*, 487-488.
669. Bica, K; Cooke, L. R.; Nugent, P.; Rijksen, C.; Rogers, R. D. "Toxic on Purpose: Ionic Liquid Fungicides as Combinatorial Crop Protecting Agents," *Green Chem.* **2011**, *13*, 2344-2346. DOI: 10.1039/C1GC15170C.
670. Bica, K.; Gaertner, P.; Rogers, R. D. "Ionic Liquids and Fragrances – Direct Isolation of Orange Essential Oil," *Green Chem.* **2011**, *13*, 1997-1999. DOI: 10.1039/c1gc15237h.
671. Bica, K.; Shamshina, J.; Hough. W. L.; MacFarlane, D. R.; Rogers, R. D. "Liquid Forms of Pharmaceutical Co-crystals: Exploring the Boundaries of Salt Formation," *Chem. Commun.* **2011**, *47*, 2267-2269. DOI: 10.1039/C0CC04485G
672. Choi, S. Y.; Rodríguez, H.; Mirjafari, A.; Gilpin, D. F.; McGrath, S.; Malcolm, K. R.; Tunney, M. M.; Rogers, R. D.; McNally, T. "Dual functional ionic liquids as plasticisers and antimicrobial agents for medical polymers," *Green Chem.* **2011**, *13*, 1527-1535. DOI: 10.1039/C1GC15132K.
673. Drab, D. M.; Smiglak, M.; Shamshina, J. L.; Kelley, S. P.; Schneider, S.; Hawkins, T. W.; Rogers, R. D. "Synthesis of *N*-cyanoalkyl-functionalized imidazolium nitrate and dicyanamide ionic liquids with a comparison of their thermal properties for energetic applications," *New J. Chem.* **2011**, *35*, 1701-1717. DOI:10.1039/C0NJ00889C
674. Gurau, G.; Rodríguez, H.; Kelley, S. P.; Janiczek, P.; Kalb, R. S.; Rogers, R. D. "Demonstration of Chemisorption of Carbon Dioxide in 1,3-Dialkylimidazolium Acetate Ionic Liquids," *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 12024-12026.
675. Li, W.; Sun, N.; Stoner, B.; Jiang, X.; Lu, X.; Rogers, R. D. "Rapid Dissolution of Lignocellulosic Biomass in Ionic Liquids Using Temperatures above the Glass Transition of Lignin," *Green Chem.* **2011**, *13*, 2038-2047. DOI: 10.1039/C1GC15522A.
676. Maiti, A.; Rogers, R. D. "A Correlation-Based Predictor for Pair-Association in Ionic Liquids," *Phys. Chem. Chem. Phys.* **2011,** *13*, 12138-12145. DOI: 10.1039/C1CP21018A.
677. Pogodina, N. V.; Metwalli, E.; Müller-Buschbaum, P.; Wendler, K.; Lungwitz, R.; Spange, S.; Shamshina, J. L.; Rogers, R. D.; Friedrich, Ch. "Peculiar Behavior of Azolium Azolate Energetic Ionic Liquids," *J. Phys. Chem. Lett.* **2011**, *2*, 2571-2576. DOI: 10.1021/jz201175v.
678. Rodríguez, H.; Gurau, G.; Holbrey, J. D.; Rogers, R. D. "Reaction of elemental chalcogens with imidazolium acetates to yield imidazole-2-chalcogenones: direct evidence for ionic liquids as proto-carbenes," *Chem. Commun.*, **2011**, *47*, 3222-3224. DOI: 10.1039/C0CC05223J.
679. Schoedel, A.; Wojtas, L.; Kelley, S. P.; Rogers, R. D.; Eddaoudi, M.; Zaworotko, M. J. "Network Diversity *via* Decoration of Trigonal Prismatic Nodes: Two-Step Crystal Engineering of Cationic Metal-Organic Materials," *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 11421-11424.
680. Sun, N.; Li, W.; Stoner, B.; Jiang, X.; Lu, X.; Rogers, R. D. "Composite Fibers Spun directly from Solutions of Raw Lignocellulosic Biomass Dissolved in Ionic Liquids," *Green Chem.* **2011**, *13*, 1158-1161. DOI: 10.1039/C1GC15033B.
681. Sun, N.; Jiang, X.; Maxim, M. L.; Metlen, A.; Rogers, R. D. "Use of Polyoxometalate Catalysts in Ionic Liquids to Enhance the Dissolution and Delignification of Woody Biomass," *ChemSusChem* **2011**, *4*, 65-73. DOI: 10.1002/cssc.201000272.
682. Sun, N.; Rodríguez, H.; Rahman, M.; Rogers, R. D. "Where are ionic liquid strategies most suited in the pursuit of chemicals and energy from lignocellulosic biomass?" *Chem. Commun.* **2011**, *47*, 1405-1421. DOI: 10.1039/C0CC03990J.

683. Zhang, X. W.; Maunder, G. H.; Gießmann, S.; MacDonald, R.; Ferguson, M. J.; Bond, A. H.; Rogers, R. D.; Sella, A.; Takats, J. "Stable heteroleptic complexes of divalent lanthanides with bulky pyrazolylborate ligands – iodides, hydrocarbyls and triethylborohydrides," *Dalton Trans.* **2011**, *40*, 195-210. DOI: 10.1039/C0DT00162G.
684. Aitipamula, S.; Banerjee, R.; Bansal, A. K.; Biradha, K.; Cheney, M. L.; Choudhury, A. R.; Desiraju, G. R.; Dikundwar, A. G.; Dubey, R.; Duggirala, N.; Ghogale, P. P; Ghosh, S.; Goswami, P. K.; Goud, N. R.; Jetti, R. R. K. R.; Karpinski, P.; Kaushik, P.; Kumar, D.; Kumar, V.; Moulton, B.; Mukherjee, A.; Mukherjee, G.; Myerson, A. S.; Puri, V.; Ramanan, A.; Rajamannar, T.; Reddy, C. M.: Rodriguez-Hornedo, N.; Rogers, R. D.; Guru Row, T. N.; Sanphui, P.; Shan, N.; Shete, G.; Singh, A.; Changquan, C. S.; Swift, J. A.; Thaimattam, R.; Thakur, T. S.; Thaper, R. K.; Thomas, S. P.; Tothadi, S.; Vangala, V. R.; Vishweshwar, P.; Weyna, D. R.; Zaworotko, M. J."Polymorphs, Salts, and Cocrystals: What's in a Name?" *Cryst. Growth Des.* **2012,** *12* 2147-2152. DOI: 10.1021/cg3002948. [Author List Correction Published *Cryst. Growth Des.* **2012**, *12*, 4290-4291. DOI: 10.1021/cg300704b.
685. Azubuike, C. P.; Rodríguez, H.; Okhamafe, A. O.; Rogers, R. D. "Physicochemical properties of maize cob cellulose powders reconstituted from ionic liquid solution," *Cellulose* **2012**, *19*, 425-433. DOI 10.1007/s10570-011-9631-y.
686. Barber, P. S.; Kelley, S. P.; Rogers, R. D. "Highly selective extraction of the uranyl ion with hydrophobic amidoximefunctionalized ionic liquids via η^2 coordination," *RSC Adv.* **2012**, *2*, 8526-8530. DOI: 10.1039/c2ra21344c.
687. Bica, K.; Rodríguez, H.; Gurau, G.; Cojocaru, O. A.; Riisager, A.; Fehrmann, R.; Rogers, R. D. "Pharmaceutically Active Ionic Liquids with Solids Handling, Enhanced Thermal Stability, and Fast Release," *Chem. Commun.* **2012**, *48*, 5422-5424. DOI: 10.1039/C2CC30959A
688. Drab, D. M.; Kelley, S. P.; Shamshina, J. L.; Smiglak, M.; Cojocaru, O. A.; Gurau, G.; Rogers, R. D. "Reactivity of *N*-cyanoalkyl-substituted imidazolium halide salts by simple elution through an azide anion exchange resin," *Sci. China Chem.* **2012**, *55*, 1683-1687. DOI: 10.1007/s11426-012-4664-0
689. Drab, D. M.; Shamshina, J. L.; Smiglak, M.; Cojocaru, O. A.; Kelley, S. P.; Rogers, R. D. "Zinc-assisted synthesis of imidazolium-tetrazolate bi-heterocyclic zwitterions with variable alkyl bridge length," *Sci. China Chem.* **2012**, *55*, 1620-1626. DOI: 10.1007/s11426-012-4676-9
690. Freire, M. G.; Pereira, J. F. B.; Francisco, M.; Rodríguez, H.; Rebelo, L. P. N.; Rogers, R. D.; Coutinho, J. A. P. "Insight into the Interactions that Control the Phase Behaviour of Novel Aqueous Biphasic Systems Composed of Polyethylene Glycol Polymers and Ionic Liquids," *Chem. Eur. J.* **2012**, *18*, 1831-1839. DOI: 10.1002/chem.201101780.
691. Gurau, G.; Wang, H.; Qiao, Y.; Lu, X.; Zhang, S.; Rogers, R. D. "Chlorine-free alternatives to the synthesis of ionic liquids for biomass processing" *Pure Appl. Chem.* **2012**, *84*, 745-754. DOI: 10.1351/PAC-CON-11-11-10.
692. Gurau, G.; Kelley, S. P.; Di Bona, K. R.; Smiglak, M.; Rogers, R. D. "Anhydrous Caffeine Hydrochloride and Its Hydration," *Cryst. Growth Des.* **2012**, *12*, 4658-4662. DOI: 10.1021/cg300878j.
693. McMahon, B. W.; Perez, J. P. L.; Schneider, S.; Boatz, J.; Hawkins, T.; McCrary, P. D.; Beasley, P. A.; Rogers, R. D.; Anderson, S. L. "Dual ligand passivation and homogeneous media ball milling: novel approaches for both the synthesis and capping of air-stable aluminum nanoparticles," In *Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry* **2012**, *57*, 965-967.
694. Maiti, A.; Kumar, A.; Rogers, R. D. "Water-clustering in hygroscopic ionic liquids-an implicit solvent analysis," *Phys. Chem. Chem. Phys.* **2012,** *14*, 5139-5146. DOI: 10.1039/c2cp00010e.
695. Mallick, B.; Metlen, A.; Nieuwenhuyzen, M.; Rogers, R. D.; Mudring, A.-V. "Mercuric Ionic Liquids: $[C_n mim][HgX_3]$, Where n = 3, 4 and X = Cl, Br," *Inorg. Chem.* **2012**, *52*, 193-200. DOI: 10.1021/ic201415d.
696. Maxim, M. L.; Sun, N.; Wang, H.; Sterner, J. R.; Haque, A.; Rogers, R. D. "Reinforced magnetic cellulose fiber from ionic liquid solution," *Nanomaterials and Energy* **2012**, *1*, 225-236. DOI: 10.1680/nme.12.00010.
697. Maxim, M. L.; White, J. F.; Block, L. E.; Gurau, G.; Rogers, R. D. "Advanced Biopolymer Composite Materials from Ionic Liquid Solutions," In *Ionic Liquids: Science and Applications*, Visser, A. E.; Bridges, N. J.; Rogers, R. D. (Eds.); ACS Symposium Series 1117; American Chemical Society: Washington, DC, 2012; pp 167-188.
698. McCrary, P. D.; Beasley, P. A.; Alaniz, S. A.; Griggs, C. S.; Frazier, R. M.; Rogers, R. D. "Graphene and Graphene Oxide Can 'Lubricate' Ionic Liquids based on Specific Surface Interactions Leading to Improved Low Temperature Hypergolic Performance," *Angew. Chem. Int. Ed.* **2012**, *51*, 9784-9787.
699. McCrary, P. D.; Beasley, P. A.; Cojocaru, O. A.; Schneider, S.; Hawkins, T. W.; Perez, J. P.; McMahon, B. W.; Pfeil, M.; Boatz, J. A.; Anderson, S. L.; Son, S. F.; Rogers, R. D. "Hypergolic Ionic Liquids to Mill, Suspend, and Ignite Boron Nanoparticles," *Chem. Commun.* **2012**, *48*, 4311-4313. DOI: 10.1039/C2CC30957B.
700. McCrary, P. D.; Beasley, P. A.; Kelley, S. P.; Schneider, S.; Hawkins, T. W.; Perez, J. P. L.; McMahon, B. W.; Pfeil, M.; Boatz, J. A.; Anderson, S. L.; Son, S. F.; Rogers, R. D. "Tuning azolium azolate ionic liquids to promote surface interactions with Titanium nanoparticles leading to increased passivation and colloidal stability," *Phys. Chem. Chem. Phys.* **2012**, *14*, 13194-13198. DOI: 10.1039/C2CP42510F.
701. Perez, J. Paulo L.; McMahon, B. W.; Schnieder, S.; Boatz, J.; Hawkins, T.; McCrary, P. D.; Beasley, P. A.; Rogers, R. D.; Son, S.; Anderson, S. L. "Synthesis of air-stable, unoxidized, boron nanoparticles using ball milling technique," In *Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry* **2012**, *57*, 955-956.
702. Smiglak, M.; Hines, C. C.; Reichert, W. M.; Vincek,A. S.; Katritzky, A. R.; Thrasher, J. S.; Sun, L. Y.; McCrary, P. D.; Beasley, P. A.; Kelley, S. P.; Rogers, R. D. "Synthesis, limitations, and thermal properties of energetically-substituted, protonated imidazolium picrate and nitrate salts and further comparison with their methylated analogs," *New J. Chem.* **2012**, *36*, 702-722. DOI: 10.1039/C1NJ20677J.

703. Trivedi, T. J.; Srivastava, D. N.; Rogers, R. D.; Kumar, A. "Agarose processing in protic and mixed protic–aprotic ionic liquids: dissolution, regeneration and high conductivity, high strength ionogels," *Green Chem.* **2012**, *14*, 2831-2839. DOI: 10.1039/C2GC35906E.
704. Wang, H.; Gurau, G.; Rogers, R. D. "Ionic liquid processing of cellulose," *Chem. Soc. Rev.* **2012**, *41*, 1519-1537. DOI: 10.1039/c2cs15311d.
705. Wang, H.; Zhou, X. S., Gurau, G.; Rogers, R. D. "The role of ionic liquids in the pharmaceutical manufacturing processes," in *Green Techniques for Organic Synthesis and Medicinal Chemistry*, Zhang, W.; Cue, B. W., Jr. (Eds.), Wiley-VCH: Weinheim, 2012; Ch. 17, pp 469-496. ISBN 9780470711514.
706. Zhao, Y.; Liu, X.; Lu, X.; Zhang, S.; Wang, J.; Wang, H.; Gurau, G.; Rogers, R. D.; Su, L.; Li, H. "The Behavior of Ionic Liquids under High Pressure: A Molecular Dynamics Simulation," *J. Phys. Chem. B*, **2012**, *116*, 10876-10884. DOI: 10.1021/jp3070568
707. Barber, P. S.; Griggs, C. S.; Bonner, J. R.; Rogers, R. D. "Electrospinning of chitin nanofibers directly from an ionic liquid extract of shrimp shells" *Green Chem.*, **2013**, *15*, 601-607. DOI: 10.1039/C2GC36582K.
708. Barber, P. S.; Griggs, C. S.; Gurau, G.; Liu, Z.; Li, S.; Li, Z.; Lu, X.; Zhang, S.; Rogers, R. D. "Coagulation of Chitin and Cellulose from 1-Ethyl-3-methylimidazolium Acetate Ionic-Liquid Solutions Using Carbon Dioxide," *Angew. Chem. Int. Ed.* **2013**, *52*, 12350-12353. DOI: 10.1002/anie.201304604.
709. Barber, P. S.; Shamshina, Julia L.; Rogers, R. D.; "A 'Green' Industrial Revolution: Using Chitin towards Transformative Technologies" *Pure Appl. Chem.* **2013**, *85*, 1693-1701. DOI: 10.1351/PAC-CON-12-10-14.
710. Cojocaru, O. A.; Bica, K.; Gurau, G.; Narita, A.; McCrary, P. D.; Shamshina, J. S.; Barber, P. S.; Rogers, R. D. "Prodrug ionic liquids: functionalizing neutral active pharmaceutical ingredients to take advantage of the ionic liquid form," *Med. Chem. Commun.* **2013**, *4*, 559-563. DOI: 10.1021/cg400686e.
711. Cojocaru, O. A.; Kelley, S. P.; Gurau, G.; Rogers, R. D. "Procainium acetate versus procainium acetate dihydrate: Irreversible crystallization of a room-temperature active pharmaceutical ingredient-ionic liquid upon hydration," *Cryst. Growth Des.* **2013**, *13*, 3290−3293. DOI: 10.1021/cg400686e.
712. Cojocaru, O. A.; Shamshina, J. L.; Gurau, G.; Syguda, A.; Praczyk, T.; Pernak, J.; Rogers, R. D. "Ionic liquid forms of the herbicide dicamba with reduced volatility and increased efficacy," *Green Chem.* **2013**, *15*, 2110-2120. DOI: 10.1039/C3GC37143C.
713. Cojocaru, O. A.; Shamshina, J. L.; Rogers, R. D. "Review/Preview: Prodrug ionic liquids," *Chimica Oggi/Chemistry Today*, **2013**, *31*, 24-29.
714. Freire, M. G.; Pereira, J. F. B.; Francisco, M.; Rodríguez, H. ; L. P. N.; Rogers, R. D.; Coutinho, J. A. P. "Insight into the Interactions That Control the Phase Behaviour of New Aqueous Biphasic Systems Composed of Polyethylene Glycol Polymers and Ionic Liquids," *Chem. Eur. J.* **2012**, *18*, 1831-1839.
715. Kelley, S. P.; Narita, A.; Holbrey, J. D.; Green, K. D.; Reichert, W. M.; Rogers, R. D. "Understanding the Effects of Ionicity in Salts, Solvates, Co-Crystals, Ionic Co-Crystals, and Ionic Liquids, Rather than Nomenclature, Is Critical to Understanding Their Behavior," *Cryst. Growth Des.* **2013**, *13*, 965-975. DOI: 10.1021/cg4000439.
716. Lu, W.; Barber, P. S.; Kelley, S. P.; Rogers, R. D. "Coordination and extraction of mercury(II) with an ionic liquid-based thione extractant," *Dalton Trans.* **2013**, *42*, 12908-12916. DOI: 10.1039/C3DT50410G.
717. Mateyawa, S.; Xie, D. F.; Truss, R. W.; Halley, P. J.; Nicholson, T. M.; Shamshina, J. L.; Rogers, R. D.; Boehm, M. W.; McNally, T. "Effect of the ionic liquid 1-ethyl-3-methylimidazolium acetate on the phase transition of starch: Dissolution or gelatinization?" *Carbohydrate Polymers* **2013**, *94*, 520-530. DOI: 10.1016/j.carbpol.2013.01.024.
718. McCrary, P. D.; Beasley, P. A.; Gurau, G.; Narita, A.; Barber, P. S.; Cojocaru, A.; Rogers, R. D. "Drug specific, tuning of an ionic liquid's hydrophilic–lipophilic balance to improve water solubility of poorly soluble active pharmaceutical ingredients," *New J. Chem.* **2013**, *37*, 2196-2202. DOI: 10.1039/c3nj00454f.
719. McCrary, P. D.; Rogers, R. D. "1-Ethyl-3-methylimidazolium Hexafluorophosphate: From Ionic Liquid Prototype to Antitype," *Chem. Commun.* **2013**, *49*, 6011-6014. DOI: 10.1039/C3CC42175A.
720. McNeil, S. K.; Kelley, S. P.; Beg, C.; Cook, H. Rogers, R. D.; Nikles, D. E. "Cocrystals of 10-methylphenthiazine and 1,3-dinitrobenzene: Implications for optical sensing of TNT-based explosives," *ACS Appl. Mater. Interfaces*, **2013**, *5*, 7647-7653. DOI: 10.1021/am401961s.
721. Metlen, A.; Mallick, B.; Murphy, R. W.; Mudring, A.-V.; Rogers, R. D. "Phosphonium Chloromercurate Room Temperature Ionic Liquids of Variable Composition," *Inorg. Chem.* **2013**, *52*, 13997-14009. DOI: 10.1021/ic401676r.
722. Pereira, J. F. B.; Rebelo, L. P. N.; Rogers, R. D.; Coutinho, J. A. P.; Freire, M. G. "Combining ionic liquids and polyethylene glycols to boost the hydrophobic-hydrophilic range of aqueous biphasic systems," *Phys. Chem. Chem. Phys.* **2013,** *15*, 19580-19583. DOI: 10.1039/C3CP53701C.
723. Pereira, J. F. B.; L. P. N.; Rogers, R. D.; Coutinho, J. A. P.; Freire, M. G. "Washing-out" Ionic Liquid from Polyethylene Glycol to form Aqueous Biphasic Systems," *Phys. Chem. Chem. Phys.* **2013**, *16*, 2271-2274. DOI: 10.1039/C3CP54047B.
724. Perez, J. P. P.; McMahon, B. W.; Schneider, S.; Boatz, J. A.; Hawkins, T. W.; McCrary, P. D.; Beasley, P. A.; Rogers, R. D.; Anderson, S. L. "Exploring the structure of nitrogen-rich ionic liquids and their binding to the surface of oxide-free boron nanoparticles," *J. Phys. Chem. C* **2013**, *117*, 5693-5707. DOI: 10.1021/jp3100409.
725. Raders, S. M.; Moore, J. N.; Parks, J. K.; Miller, A. D.; Leißing, T. M.; Kelley, S. P.; Rogers, R. D.; Shaughnessy, K. H. "Trineopentylphosphine: A Conformationally Flexible Ligand for the Coupling of Sterically Demanding Substrates in the Buchwald-Hartwig Amination and Suzuki-Miyaura Reaction." *J. Org. Chem.* **2013**, *78*, 4649-4664. DOI: 10.1021/jo400435z.

726. Shamshina, J. S.; Barber, P. S.; Rogers, R. D. "Ionic Liquids in Drug Delivery" *Expert Opin. Drug Deliv.* **2013**, *10*, 1367-1381. DOI: 10.1517/17425247.2013.808185.
727. Smiglak, M.; Hines, C. C.; Reichert, W. M.; Shamshina, J. L.; Beasley, P. A.; McCrary, P. D.; Kelley, S. P.; Rogers, R. D. "Azolium azolates from reactions of neutral azoles with 1,3-diemethyl-imidazolium-2-carboxylate, 1,2,3-trimethyl-imidazolium hydrogen carbonate, and N,N dimethyl-pyrrolidinium hydrogen carbonate," *New J. Chem.* **2013**, *37*, 1461-1469. DOI: 10.1039/C3NJ00147D.
728. Wang, H.; Gurau, G.; Kelley, S. P.; Myerson, A. S.; Rogers, R. D. "Hydrophobic *vs.* hydrophilic ionic liquid separations strategies in support of continuous pharmaceutical manufacturing" *RSC Advances*, **2013**, *3*, 10019-10026. DOI: 10.1039/C3RA41082J.
729. Wang, H.; Maxim, M. L.; Gurau, G.; Rogers, R. D. "Microwave-assisted dissolution and delignification of wood in 1-ethyl-3-methylimidazolium acetate" *Bioresour. Technol.* **2013**, *136*, 739-742. DOI: 10.1016/j.biortech.2013.03.064.
730. Barber, P. S.; Kelley, S. P.; Griggs, C. S.; Wallace, S.; Rogers, R. D. "Surface Modification of Ionic Liquid-Spun Chitin Fibers for the Extraction of Uranium from Seawater: Seeking the Strength of Chitin and the Chemical Functionality of Chitosan," *Green Chem.* **2014**, *16*, 1828-1836. DOI: 10.1039/c4gc00092g.
731. Chatel, G.; Pereira, J. F. B.; Debetti, V.; Wang, H.; Rogers, R. D. "Mixing Ionic Liquids – "Simple Mixtures" or "Double Salts"?" *Green Chem.* **2014**, *16*, 2051-2083. DOI: 10.1039/C3GC41389F.
732. Chatel, G.; Rogers, R. D. "Review: Oxidation of Lignin Using Ionic Liquids-An Innovative Strategy To Produce Renewable Chemicals," *ACS Sustainable Chem. Eng.* **2014**, *2*, 322–339. DOI: 10.1021/sc4004086.
733. Cheng, F.; Wang, H.; Chatel, G.; Gurau, G.; Rogers R. D. "Facile Pulping of Lignocellulosic Biomass Using Choline Acetate," *Bioresour. Technol.* **2014**, *164*, 394-401. DOI: 10.1016/j.biortech.2014.05.016.
734. Choi, S. Y.; Rodríguez, H.; Nimal Gunaratne, H. Q.; Puga, A. V.; Gilpin, D. ; McGrath, S.; Vyle, J. S.; Tunney, M. M.; Rogers, R. D.; McNally, T. "Dual functional ionic liquids as antimicrobials and plasticisers for medical grade PVCs," *RSC Adv.* **2014**, *4*, 8567-8581. DOI: 10.1039/c3ra46425c.
735. Cojocaru, O. A.; Siriwardana, A.; Gurau, G.; Rogers, R. D. "Pharmaceutically active supported ionic liquid phases," In *Supported Ionic Liquids – Fundamentals and Applications*, Fehrmann, R., Riisager, A., Haumann, M., Eds.; Wiley-VCH: Weinheim, Germany, 2014; Chapter 19; pp 387-406. ISBN: 978-3-527-32429-3.
736. Griggs, C. S.; Barber, P. S.; Kelley, S. P.; Moser, R. D.; Seiter, J. M.; Thomas, C. C.; Coleman, J. G.; Medina, V. F.; Rogers, R. D. "Biomimetic Mineralization of Uranium by Metabolically-Inactive Shrimp Shell." *Cryst. Growth. Des.* **2014**, *14*, 6172-6176. DOI: 10.1021/cg5015576.
737. Kelley, S. P.; Barber, P. S.; Mullins, P. H. K.; Rogers, R. D. "Structural clues to UO_2^{2+}/VO_2^{+}competition in seawater extraction using amidoxime-based extractants," *Chem. Commun.* **2014**, *50*, 12504-12507. DOI: 10.1039/c4cc06370h.
738. McCrary, P. D.; Barber, P. S.; Kelley, S. P.; Rogers, R. D. "Nonaborane and Decaborane Cluster Anions Can Enhance the Ignition Delay in Hypergolic Ionic Liquids and Induce Hypergolicity in Molecular Solvents," *Inorg. Chem.* **2014**, *53*, 4770-4776. DOI: 10.1021/ic500622f.
739. McCrary, P. D.; Chatel, G.; Alaniz, S. A.; Cojocaru, O. A.; Beasley, P. A.; Flores, L. A.; Kelley, S. P.; Barber, P. S.; Rogers, R. D. "Evaluating Ionic Liquids as Hypergolic Fuels: Determining Reactivity from Molecular Structure," *Energy Fuels* **2014**, *28*, 3460-3473. DOI: 10.1021/ef500264z.
740. Pereira, J. F. B.; Flores, L. A.; Wang, H.; Rogers, R. D. "Benzene Solubility in Ionic Liquids: Working Toward an Understanding of Liquid Clathrate Formation" *Chem. Eur. J.* **2014**, *20*, 15482-15492. DOI: 10.1002/chem.201404253.
741. Pereira, J. F. B.; Kurnia, K. A.; Cojocaru, O. A. ; Gurau, G.; Rebelo, L. P. N.; Rogers, R. D.; Freire, M. G.; Coutinho, J. A. P. "Molecular interactions in aqueous biphasic systems composed of polyethylene glycol and crystalline *vs.* liquid cholinium-based salts," *Phys. Chem. Chem. Phys.* **2014**, *16*, 5723-5731. DOI: 10.1039/C3CP54907K.
742. Perez, J. P. L.; McMahon, B. W.; Yu, J.; Schneider, S.; Boatz, J. A.; Hawkins, T. W.; McCrary, P. D.; Flores, L. A.; Rogers, R. D.; Anderson, S. L. "Boron Nanoparticles with High Hydrogen Loading: Mechanism for B-H Binding and Potential for Improved Combustibility and Specific Impulse," *ACS Appl. Mat. Interfaces* **2014**, *6*, 8513-8525. DOI: 10.1021/am501384m.
743. Pernak, J.; Niemczak, M.; Giszter, R.; Shamshina, J.; Gurau, G.; Cojocaru, O. A.; Praczyk, T.; Marcinkowska, K.; Rogers, R. D. Glyphosate-Based Herbicidal Ionic Liquids with Increased Efficacy. *ACS Sustainable Chem. Eng.* **2014**, *2*, 2845-2851. DOI: 10.1021/sc500612y.
744. Raders, S. M.; Jones, J. M.; Semmes, J. G.; Kelley, S. P; Rogers, R. D.; Shaughnessy, K. H. "Di-*tert*-butylneopentylphosphine (DTBNpP): An efficient ligand in the palladium-catalyzed α-arylation of ketones," *Eur. J. Org. Chem.* **2014**, 7395-7404. DOI: 10.1002/ejoc.201402474.
745. Shamshina, J. L.; Gurau, G.; Block, L. E.; Hansen, L, Dingee, C.; Walters, A.; Rogers, R. D. "Chitin-Calcium Alginate Composite Fibers for Wound Care Dressings Spun from Ionic Liquid Solution," *J. Mater. Chem. B* **2014**, *2*, 3924-3936. DOI: 10.1039/C4TB00329B.
746. Shamshina, J. L.; Rogers, R. D. "Overcoming the problems of solid state drug formulations with ionic liquids: When opinions crystallize is progress lost?" *Therapeutic Delivery* **2014**, *5*, 489-491. DOI: 10.4155/tde.14.28.
747. Smiglak, M.; Pringle, J. M.; Han, L.; Zhang, S.; Gao, H.; MacFarlane, D. R.; Rogers, R. D. "Ionic Liquids for energy, materials, and medicine," *Chem. Commun.* **2014**, *50* (66), 9228–9250. DOI: 10.1039/c4cc02021a.
748. Tome, L. I. N.; Pereira, J. F. B.; Rogers, R. D.; Freire, M. G.; Gomes, J. R. B.; Coutinho, J. A. P. "Evidence for the Interactions Occurring Between Ionic Liquids and Tetraethylene Glycol in Binary Mixtures and Aqueous Biphasic Systems," *J Phys. Chem. B* **2014**, *118*, 4615-4629. DOI: 10.1021/jp501718w.

749. Tome, L. I. N.; Pereira, J. F. B.; Rogers, R. D.; Freire, M. G.; Gomes, J. R. B.; Coutinho, J. A. P. "'Washing-out' ionic liquids from polyethylene glycol to form aqueous biphasic systems," *Phys.Chem.Chem.Phys.* **2014**, *16*, 2271-2274. DOI: 10.1039/c3cp54047b.
750. Wang, H.; Block, L. E.; Rogers, R. D. "Catalytic conversion of biomass in ionic liquids" in *Catalysis in Ionic Liquids: From Catalysts Synthesis to Application*; Hardacre, C.; Parvulescu, V. (Eds.) Series 15; Royal Society of Chemistry: Cambridge, 2014; pp 1-19.
751. Wang, H.; Gurau, G.; Pingali, S. V.; O'Neill, H. M.; Evans, B. R.; Urban, V. S.; Heller, W. T.; Rogers, R. D. "Physical insight into switchgrass dissolution in the ionic liquid 1-ethyl-3-methylimidazolium acetate" *ACS Sustainable Chem. Eng.* **2014**, *2*, 1264-1269. DOI: 10.1021/sc500088w
752. Wang, H.; Gurau, G.; Rogers, R. D. "Dissolution of biomass using ionic liquids," in *Structures and Interactions of Ionic Liquids*, Zhang, S.; Wang, l.; Lu X.; Zhou, Q., Eds., Springer-Verlag: Berlin Heidelberg, 2014; Ch. 3 pp 79-106; Structure and Bonding 151. DOI: 10.1007/978-3-642-38619-0_3.
753. Wang, H.; Gurau, G.; Shamshina, J. L.; Cojocaru, O. A.; Janikowski, J.; MacFarlane, D. R.; Davis, J. H. Jr.; Rogers, R. D "Simultaneous Membrane Transport of Two Active Pharmaceutical Ingredients by Charge Assisted Hydrogen Bond Complex Formation," *Chem. Sci.* **2014**, *5*, 3449-3456. DOI: 10.1039/c4sc01036a.
754. Wang, H.; Pereira, J. F. B.; Myerson, A. S.; Rogers, R. D. "Double Salt Ionic Liquids Prepared by Mixing Partially Miscible Ionic Liquids: Tuning the Solubility of Lipophilic Molecules," *ECS Trans.* **2014**, *64*, 33-44. DOI:10.1149/06404.0033ecst
755. Xie, F.; Flanagan, B.; Li, M.; Sangwan, P.; Truss, R.; Halley, P.; Strounina, E.; Whittaker, A.; Gidley, M.; Dean, K.; Shamshina, J.; Rogers, R. D. McNally, T. "Characteristics of starch-based films plasticised by glycerol and by the ionic liquid 1-ethyl-3-methylimidazolium acetate: a comparative study," *Carbohydrate Polymers* **2014**, *111*, 841–848. DOI: 10.1016/j.carbpol.2014.05.058.
756. Dilip, M.; Bridges, N. J.; Rodriguez, H.; Pereira, J. F. B.; Rogers, R. D. "Effect of Temperature on Salt-Salt Aqueous Biphasic Systems: Manifestations of Upper Critical Solution Temperature," *J. Solution Chem.* **2015**, *44*, 454-468. DOI: 10.1007/s10953-014-0278-9
757. Kelley, S. P.; Rogers, R. D. "A Practical Overview of Organic Synthesis in Ionic Liquids," *Aldrichim. Acta* **2015**, *48*, e1-e2; http://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Aldrich/Brochure/1/acta-48-1.pdf (Last accessed March 20, 2015).
758. Kelley, S. P.; Rogers, R. D. "Isolation of Uranyl Dicyanamide Complexes from N-Donor Ionic Liquids," *Inorg. Chem.* **2015**, *54*, 10323-10334. DOI: 10.1021/acs.inorgchem.5b01699.
759. Kelley, S. P.; Nuss, J. S.; Rogers, R. D. "Nonstoichiometric, Protic Azolium Azolate Ionic Liquids Provide Unique Environments for N-Donor Coordination Chemistry," *Chem.-Eur. J.* **2015**, *21*, 17196-17199. DOI: 10.1002/chem.201503914.
760. Ludwig, T.; Guo, L.; McCrary, P.; Zhang, Z.; Gordon, H.; Quan, H.; Stanton, M.; Frazier, R.; Rogers, R. D.; Wang, H.-T.; Turner, C. H. "Mechanism of Bismuth Telluride Exfoliation in an Ionic Liquid Solvent," *Langmuir* **2015**, *31*, 3644-3652. DOI: 10.1021/acs.langmuir.5b00239.
761. Meany, J. E., Kelley, S. P., Metzger, R. M., Rogers, R. D.; Woski, S. A. "4,4'-Dibromo-2',5'-dimethoxy-[1,1'-biphenyl]-2,5-dione (BrHBQBr)," *Acta Crystallogr. E* **2015**, *E71*, 1454-1456. DOI: 10.1107/S2056989015020472.
762. Moore, J. N.; Laskay, N. M.; Duque, K. S.; Kelley, S. P.; Rogers, R. D. "Synthesis of 4-sulfonatobenzylphosphines and their application in aqueous-phase palladium-catalyzed cross coupling." *J. Organomet. Chem.* **2015**, *777*, 16-24. DOI: 10.106/j.jorganchem.2014.11.011.
763. Pereira, J. F. B.; Kurnia, K. A.; Freire, M. G.; Coutinho, J. A. P.; Rogers, R. D. "Controlling the Formation of Ionic-Liquid-based Aqueous Biphasic Systems by Changing the Hydrogen Bonding Ability of Polyethylene Glycol End Groups," *ChemPhysChem* **2015**, *16*, 2219-2225. DOI: 10.1002/cphc.201500146.
764. Pernak, J.; Niemczak, M.; Shamshina, J.; Gurau, G.; Głowacki, G.; Praczyk, T.; Marcinkowska, K.; Rogers, R. D. "Metsulfuron-Methyl-Based Herbicidal Ionic Liquids," *J. Agric. Food Chem.* **2015**, *63*, 3357-3366. DOI: 10.1021/jf505782p.
765. Shadid, M.; Gurau, G.; Shamshina, J. L.; Chuang, B.-C.; Hailu, S.; Guan, E.; Chowdhury, S. K.; Wu, J.-T.; Rizvi, S. A. A.; Griffin, R. J.; Rogers, R. D. "Sulfasalazine in ionic liquid form with improved solubility and exposure," *MedChemComm* **2015**, *6*, 1837-1841. DOI: 10.1039/c5md00290g.
766. Shamshina, J. L.; Kelley, S. P.; Gurau, G.; Rogers, R. D. "Develop ionic liquid drugs," *Nature* **2015**, *528*, 188-189. DOI: 10.1038/528188a.
767. Tadros, A. M.; Rokyo, M. M.; Kelley, S. P.; Belmore, K.; Rogers, R. D.; Vincent, J. B. "Aminopyridine complexes of Cr(III) basic carboxylates as potential polymer precursors: Synthesis, characterization, and crystal structure of $[Cr_3O(propionate)_6(X\text{-aminopyridine})_3]^+$ (X = 3 or 4)," *Polyhedron* **2015**, *100*, 17-27. DOI: 10.1016/j.poly.2015.07.007.
768. Wang, H.; Kelley, S. P.; Brantley III, J. W.; Chatel, G.; Shamshina, J.; Pereira, J. F. B.; Debbeti, V.; Myerson, A. S.; Rogers, R. D. "Ionic fluids containing both strongly and weakly interacting ions of the same charge have unique ionic and chemical environments as a function of ion concentration," *ChemPhysChem* **2015**, *16*, 993-1002. DOI: 10.1002/cphc.201402894.
769. Weber, Cameron C.; Kulkarni, Samir A.; Kunov-Kruse, Andreas J.; Rogers, Robin D.; Myerson, Allan S. "The use of cooling crystallization in an ionic liquid system for the purification of pharmaceuticals," *Cryst. Growth Des.* **2015**, *15*, 4946-4951. DOI: 10.1021/acs.cgd.5b00855.
770. Weber, C. C.; Kunov-Kruse, A. J.; Rogers R. D.; Myerson, A. S. "Manipulation of ionic liquid anion-solute-antisolvent interactions for the purification of acetaminophen," *Chem. Commun.* **2015**, *51*, 4294-4297. DOI: 10.1039/C5CC00198F.

771. Xie, F.; Flanagan, B. M.; Li, M.; Truss, R. W.; Halley, P. J.; Gidley, M. J.; McNally, T.; Shamshina, J. L.; Rogers, R. D. "Characteristics of starch-based films with different amylose contents plasticised by 1-ethyl-3-methylimidazolium acetate," *Carbohydrate Polymers* **2015**, *122*, 160-168. DOI: 10.1016/j.carbpol.2014.12.072.
772. Yao, W.; Kelley, S. P.; Rogers, R. D.; Vaid, T. P. "Electrical conductivity in two mixed-valence liquids," *Phys. Chem. Chem. Phys.* **2015**, *17*, 14107-14114. DOI: 10.1039/C5CP01172H.
773. Zhang, B.; Chen, L.; Xie, F.; Li, X.; Truss, R. W.; Halley, P. J.; Shamshina, J. L.; Rogers, R. D.; McNally, T. "Understanding the structural disorganization of starch in water–ionic liquid solutions," *Phys. Chem. Chem. Phys.* **2015**, *17*, 13860-13871. DOI: 10.1039/C5CP01176K.
774. Berton, P.; Kelley, S. P.; Rogers, R. D. "Stripping uranium from seawater-loaded sorbents with the ionic liquid hydroxylammonium acetate in acetic acid for efficient reuse," *Ind. Eng. Chem. Res.* **2016**, *Advance Article*. DOI: 10.1021/acs.iecr.5b03996.
775. Kelley, S. P.; Nuss, J. S.; Rogers, R. D. "Using crystal structures of ionic compounds to explore complexation and extraction of rare earth elements in ionic liquids," in *Applications of Ionic Liquids on Rare Earth Green Separation and Utilization*; Chen, J., Ed.; Springer: Heidelberg, 2016; pp 21-42.
776. Meany, J. E.; Kelley, S. P.; Rogers, R. D.; Woski, S. A. "4'-Bromo-2,5-dihydoxy-2',5'-dimethoxy-[1,1'-biphenyl]-3,4-dicarbonitrile," *Acta Cryst. Sect. E: Struct. Commun.* **2016**, *submitted.*
777. Shen, X.; Shamshina, J. L.; Berton, P.; Bandomir, J.; Wang, H.; Gurau, G.; Rogers, R. D. "Comparison of hydrogels prepared with ionic-liquid-isolated vs commercial chitin and cellulose," *ACS Sustainable Chem. Eng.*, **2016**, 4, 471-480. DOI: 10.1021/acssuschemeng.5b01400.
778. Shen, X.; Shamshina, J. L.; Berton, P.; Gurau, G.; Rogers, R. D. "Hydrogels based on cellulose and chitin: fabrication, properties, and applications," *Green Chem.* **2016**, *18*, 53-75. DOI: 10.1039/C5GC02396C.
779. Zhang, B.; Xie, F.; Zhang, T.; Chen, L.; Li, X.; Truss, R. W.; Halley, P. J.; Shamshina, J. L.; McNally, T.; Rogers, R. D. "Different characteristic effects of ageing on starch-based films plasticised by 1-ethyl-3-methylimidazolium acetate and by glycerol," *Carbohydrate Polymers* **2016**, *146*, 67-79.

B. Non-Refereed Reviews, Reports, Articles, and Extended Abstracts:

1. Rogers, R. D. "Actinide Elements," In *The Encyclopedia of Physical Science and Technology*; 1st ed.; Meyers, R. A., Ed.; Academic Press: Orlando, FL, 1987; Vol. 1; 190-217.
2. Rogers, R. D. Book Review of "Studies in Surface Science and Catalysis. Volume 45. Transition Metal Oxides: Surface Chemistry and Catalysis," *J. Am. Chem. Soc.* **1990**, *112*, 6454.
3. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Year 1983," *J. Organomet. Chem.* **1990**, *380*, 51-76.
4. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Years 1984-1986," *J. Organomet. Chem.* **1991**, *416*, 201-290.
5. Rogers, R. D. "Actinide Elements," In *The Encyclopedia of Physical Science and Technology*; 2nd ed.; Meyer, R. A., Ed.; Academic Press: Orlando, FL, 1992; Vol. 1; pp 228-256.
6. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Years 1987-1989," *J. Organomet. Chem.* **1992**, *442*, 83-224.
7. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Year 1990," *J. Organomet. Chem.* **1992**, *442*, 225-269.
8. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Year 1991," *J. Organomet. Chem.* **1993**, *457*, 41-62.
9. Rogers, R. D.; Eiteman, M. A. "Preface," In *Aqueous Biphasic Separations: Biomolecules to Metal Ions*; Rogers, R. D.; Eiteman, M. A., Eds.; Plenum: New York, 1995; p v.
10. Rogers, R. D. "Crystal Engineering - ACA Transactions Symposium - July 1998," In *American Crystallographic Association Newsletter*, ACA: Buffalo, NY, Summer 1998.
11. Sharma, C. V. K.; Rogers, R. D. "Perspectives of Crystal Engineering," *Materials Today* **1998**, *1(3)*, 27-30.
12. Bond, A. H.; Dietz, M. L.; Rogers, R. D. "Preface," In *Metal-Ion Separation and Preconcentration, Progress and Opportunities*; Dietz, M. L.; Bond, A. H.; Rogers, R. D., Eds.; ACS Symposium Series 716, American Chemical Society: Washington, DC, 1999; pp XI-XII.
13. Huddleston, J. G.; Willauer, H. D.; Griffin, S. T.; Visser, A. E.; Rogers, R. D. "Green Separation Science & Technology: Using Environmentally Benign Polymers to Replace VOCs in Industrial Scale Liquid/Liquid Separations," In *Green Chemistry and Engineering Conference Proceedings: Implementing Vision 2020 for the Environment, (1997); Global Perspectives, (1998)*; American Chemical Society: Washington, DC, 1999; pp 225-228.
14. Rogers, R. D.; Griffin, S. T.; Willauer, H. D.; Nicol, J. A. "Clean Solvent Extraction Using Polyethylene Glycol-Based Aqueous Biphasic Systems," In *Green Chemistry and Engineering Conference Proceedings: Implementing Vision 2020 for the Environment, (1997); Global Perspectives, (1998)*; American Chemical Society: Washington, DC, 1999; pp 149-151.
15. Lumetta, G. J.; Rogers, R. D.; Gopalan, A. S. "Preface," In *Calixarenes for Separations*; Lumetta, G. J.; Rogers, R. D.; Gopalan, A. S., Eds.; ACS Symposium Series 757, American Chemical Society: Washington, DC, 2000; pp IX-X.
16. Rogers, R.D. "Preface," *J. Chromatogr., B: Biomed. Sci. Appl.* **2000**, *743*, 1.
17. Rogers, R. D. "Green Industrial Applications of Ionic Liquids – A NATO Advanced Research Workshop, Crete, Greece (12-16 April 2000)," *Green Chemistry* **2000**, *2*, G94-G96.
18. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "Chemical and Physical Characteristics of Room Temperature Ionic Liquids and the Associated Implications for their Use as Solvent Alternatives," In *Proceedings of GreenChem2000, 4th Annual Green Chemistry and Engineering Conference, Sustainable Technologies: From Research to Industrial Implementation,* American Chemical Society, Washington, DC, 2000; pp 50-52.
19. *Research Needs for High-Level Waste Stored in Tanks and Bins at U.S. Department of Energy Sites, Environmental Management Science Program*, Committee on Long-Term Research Needs for Radioactive High-Level Waste at Department of Energy Sites, Board on Radioactive Waste Management Division on Earth and Life Studies, National Research Council of the National Academies, National Academy Press, Washington, DC, 2001; 134 pp. (Written by Committee)
20. Rogers, R. D. "Editorial," *Cryst. Growth Des.* **2001**, *1*, 1-2.
21. Rogers, R. D. "Editorial," *Cryst. Growth Des.* **2002**, *2*, 1-2.
22. Rogers, R. D. "Editorial – Best New Journal," *Cryst. Growth Des.* **2002**, *2*, 161.
23. Huddleston, J. G.; Moody, M. L.; Willauer, H. D.; Broker, G. D.; Rogers, R. D. "Predicting the Performance of Alternative Solvents Through the Use of Free Energy Relationships," In *Proceedings of GreenChem2002, 6th Annual Green Chemistry and Engineering Conference, Meeting Global Challenges through Economics and Environmental Innovations,* American Chemical Society, Washington, DC, 2002; pp 59-62.
24. Holbrey, J. D.; Shaughnessy, K. H.; Rogers, R. D. "Polymerization and Polymers in Room Temperature Ionic Liquids," In *Proceedings of GreenChem2002, 6th Annual Green Chemistry and Engineering Conference, Meeting Global Challenges through Economics and Environmental Innovations,* American Chemical Society, Washington, DC, 2002; pp 62-64.
25. Rogers, R. D.; Holbrey, J. D.; Spear, S. K.; Swatloski, R. P. "Ionic Liquids: A Look at the Dissolution of Cellulose," In *Proceedings of GreenChem2002, 6th Annual Green Chemistry and Engineering Conference, Meeting Global Challenges through Economics and Environmental Innovations,* American Chemical Society, Washington, DC, 2002; pp 39-40.
26. Rogers, R. D.; Seddon, K. R. "Preface," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp XIII-XIV.

27. Swatloski, R. P.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Ionic Liquids as Green Solvents for Regeneration/Engineering of Cellulose Based Products," In *Proceedings of GreenChem2002, 6th Annual Green Chemistry and Engineering Conference, Meeting Global Challenges through Economics and Environmental Innovations,* American Chemical Society, Washington, DC, 2002; pp 151-152.
28. Rogers, R. D. "Editorial," *Cryst. Growth Des.* **2003**, *3*, 1-2.
29. Rogers, R. D. "Editorial: Introduction: Polymorphism in Crystals," *Cryst. Growth Des.* **2003**, *3*, 867.
30. Rogers, R. D.; Seddon, K. R. "Preface," In *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical Society: Washington DC, 2003; pp XIII-XVI.
31. Rogers, R. D.; Seddon, K. R.; Volkov, S. "Preface," In *Green Industrial Applications of Ionic Liquids*, Rogers, R. D.; Seddon, K. R.; Volkov, S. (Eds.); Kluwer: Dordrecht, 2003; pp XI-XVII.
32. Holbrey, J. D.; Chen, J.; Turner, M. B.; Swatloski, R. P.; Spear, S. K.; Rogers, R. D. "Applying ionic liquid solvent characteristics for controlled processing of polymer materials," *Polymer Preprints* (American Chemical Society, Division of Polymer Chemistry) **2004**, *45*, 297-298.
33. Klingshirn, M. A.; Spear, S. K.; Subramanian, R.; Holbrey, J. D.; Rogers, R. D. "Synthesis, characterization, and application of ionic liquid-poly(ethylene) glycol gel matrices," *Polymer Preprints* (American Chemical Society, Division of Polymer Chemistry) **2004**, *45*, 307-308.
34. Shaughnessy, K. H.; P'Pool, S. J.; Klingshirn, M. A.; Rogers, R. D. "Coordination polymerization of alkenes in ionic liquid solvents," *Polymer Preprints* (American Chemical Society, Division of Polymer Chemistry) **2004**, *45*, 317-318.
35. Rogers, R. D. "Editorial: *Crystal Growth & Design* on an Upward Track," *Cryst. Growth Des.* **2004**, *4*, 1.
36. Rogers, R. D. "Robin D. Rogers," *Green Chem.* **2004**, *6*, G17-G19.
37. Rogers, R. D.; Gutowski, K. E.; Griffin, S. T.; Holbrey, J. D. "Aqueous biphasic systems based on salting-out polyethylene glycol or ionic liquid solutions: strategies for actinide or fission product separations. Preprints of Extended Abstracts presented at the ACS National Meeting, American Chemical Society, Division of Environmental Chemistry **2004**, *44*, 403-407.
38. Rogers, R. D. "Editorial: Polymorphism in Crystals-A Special Issue of *Crystal Growth & Design*," *Cryst. Growth Des.* **2004**, *4*, 1085.
39. *Risk and Decisions About Disposition of Transuranic and High-Level Radioactive Waste*, Committee on Risk-Based Approaches for Disposition of Transuranic and High-Level Radioactive Waste, National Research Council of the National Academies, The National Academies Press, Washington, DC, 2005; 215 pp. (Written by Committee)
40. Rogers, R. D. "Editorial: *Crystal Growth & Design* on an Upward Track," *Cryst. Growth Des.* **2005**, *5*, 1.
41. Turner, M. B.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Ionic Liquids," In *2005 Yearbook of Science & Technology*, McGraw-Hill: New York, 2005; pp 158-160.
42. Rogers, R. D. "Editorial: *A Tribute to the Life and Career of J. Michael McBride*," *Cryst. Growth Des.* **2005**, *5*, 2021.
43. Rogers, R. D.; Seddon, K. R. "Preface," In *Ionic Liquids IIIA: Fundamentals, Progress, Challenges, and Opportunities – Properties and Structure*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington DC, 2005 pp xiii-xiv and In *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities - Transformations and Processes*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington DC, 2005 pp xiii-xiv.
44. Vlieg, E.; Rogers, D. R. "Polymorphism," (A report on the name microsymposium at the XX Congress and General Assembly of the IUCr (2005)), International Union of Crystallography Newsletter **2005**, *13*, 15 and 18.
45. Rogers, R. D. "Preface: China - A Growing Ionic Liquids Community," In *Ionic Liquids: From Fundamentals to Applications*, Zhang, S. (Ed.); ScienceP: Beijing, China, 2006.
46. Rogers, R. D. "Editorial: Authors Lead *Crystal Growth & Design* to Monthly Issues and Higher Impact!" *Cryst. Growth Des.* **2006**, *6*, 1.
47. Rogers, R. D. "First China-USA Green Chemistry Workshop," *Green Chem.* **2006**, *8*, 126-127.
48. Rogers, R. D.; Seddon, K. R. "A Response to an Old-Fashioned Thought Cop," *Anal. Chem.* **2006**, *78*, 3480-3481.
49. Rogers, R. D. "Editorial: Higher Impact, Higher Immediacy, Growth, and Outreach," *Cryst. Growth Des.* **2007**, *7*, 1.
50. Brennecke, J. F.; Rogers, R. D.; Seddon, K. R. "Preface," In *Ionic Liquids IV: Not Just Solvents Anymore*, Brennecke, J. F.; Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 975; American Chemical Society: Washington DC, 2007; pp xi-xiii.
51. Rogers, R. D.; Voth, G. A. "Guest Editorial: Ionic Liquids," *Acc. Chem. Res.* **2007**, *40*, 1077-1078.
52. Gurau, G.; Rogers, R. D. "Ionic Liquids: Green Solvents or Advanced Materials?" *Materials World* **2007**, *15*(12), 25-27.
53. Rogers, R. D., "Ionic Liquids: Green Miracles, Toxic Solvents, or New Drugs?," Center for Advanced Bioseparation Technology Newsletter, December 2007.
54. Rogers, R. D. "Editorial: Expanding Horizons," *Cryst. Growth Des.* **2008**, *8*, 1.
55. Rogers, R. D. "Is a Lower Risk 'Green' Industrial revolution in our Future?" *Risk Policy Report*; Inside EPA; Washington, DC; April 1, 2008, *15*, pp 11-12.
56. Kunle, O. O.; Fortunak, J.; Rogers, R. D. "Workshop in Green Chemistry Production of Essential Medicines in Developing Countries," *Green Chem.* **2008**, *10*, 823-824.
57. Rodríguez, H.; Bica, K.; Rogers, R. D. "(Editorial) Ionic Liquid Technology: A Potential New Platform for the Pharmaceutical Industry," *Trop. J. Pharm. Res.* **2008**, *7*, 1011-1012.
58. Rogers, R. D. "Journal Club: A Chemist Believes that an Ionic Liquid is the Place for a Noxious Gas," *Nature* **2008**, *454*, 555.

59. Rogers, R. D. "Editorial: *Crystal Growth & Design* in India," *Cryst. Growth Des.* **2009**, *9*, 1639.
60. *Advice on the Department of Energy's Cleanup Technology Roadmap: Gaps and Bridges*, Nuclear and Radiation Studies Board Division of Earth and Life Sciences Committee on Development and Implementation of a Cleanup Technology Roadmap, National Research Council of the National Academies, The National Academies Press, Washington, DC, 2009; 271 pp. (Written by Committee)
61. Rogers, R. D. "Editorial: *Crystal Growth & Design's* First Virtual Special Issue," *Cryst. Growth Des.* **2009**, *9*, 4207.
62. Rogers, R. D. "Preface," In *Ionic Liquids and Green Chemistry*, Zhang, S; Xu, C.; Lu, X.; Zhou, Q. (Eds.); Science Press: Beijing, China, 2009.
63. Rogers, R. D. "Preface, Twenty-Fifth Rare Earth Research Conference," *J. Alloys Comp.* **2009**, *488*, 491.
64. Plechkova, N. V.; Rogers, R. D.; Seddon K. R. "Preface" In *Ionic Liquids: From Knowledge to Application*, Plechkova, N. V.; Rogers, R. D.; Seddon K. R. (Eds.); ACS Symposium Series 1030; American Chemical Society: Washington, DC, 2009; pp xi-xii. DOI: 10.1021/bk-2009-1030.pr001.
65. Rogers, R. D. "10th Anniversary Anticipation," *Cryst. Growth Des.* **2010**, *10*, 1-2.
66. Rogers, R. D. "When Giants Cooperate instead of Collide," *Cryst. Growth Des.* **2010**, *10*, 4671.
67. Rogers, R. D. "A Look at Ionic Liquids," *Chemical & Engineering News*, November 29, 2010, pp 38-39.
68. Rogers, R. D. "Ten Years of Experience: How can we put it to good use?," *Cryst. Growth Des.* **2011**, *11*, 1-3.
69. Brennecke, J. F.; Schatz, G. C.; Rogers, R. D. "Ionic Liquids Virtual Special Issue," *Cryst. Growth Des.* **2011**, *11*, 625-626.
70. Rogers, R. D. "Halogen Bonding: Weak Interactions Result in Strong Opinions," *Cryst. Growth Des.* **2011**, *11*, 4721-4722.
71. Rogers, R. D. "*Crystal Growth & Design* Around the World in 2012," *Cryst. Growth Des.* **2012**, *12*, 1-2.
72. Chen, J.; Rodríguez, H.; Rogers, R. D. "Editorial: SS&T Special Issue on Ionic Liquids for Separations," *Sep. Sci. Technol.* **2012**, *47*, 167-168.
73. Rogers, R. D.; Zhang, S.; Wang, J. "Preface" An International Look at Ionic Liquids," *Sci. China Chem.* **2012**, *55*, 1475-1477. DOI: 10.1007/s11426-012-4718-3
74. Zhang, S.; Ng, F. T. T.; Rogers, R. D. "Preface," *Catalysis Today* **2013**, *200*, 1.
75. Visser, A. E.; Bridges, N. J.; Rogers, R. D. "Preface" In *Ionic Liquids: Science and Applications*, Visser, A. E.; Bridges, N. J.; Rogers, R. D. (Eds.); ACS Symposium Series 1117; American Chemical Society: Washington, DC, 2012; pp ix-x. DOI: 10.1021/bk-2012-1117.pr001.
76. Lind-Kovacs, C.; Rogers, R. D. "TR: The Transactions symposium: Crystallography for Sustainability," ACA Reflexions, ACA – Structure Matters; American Crystallographic Association: Buffalo, NY, 2015, No. 3 Fall; pp 20-21.
77. Rogers, R. D. "Eliminating the Need for Chemistry," *Chemical & Engineering News*, December 7/14, 2015, pp 42-43.
78. Rogers, R. D. "Recognizing, Catalyzing, and Embracing Change," *Cryst. Growth Des.* **2016**, *16*, 1-2. DOI: 10.1021/acs.cgd.5b01801.

C. Presentations before National and International Meetings and Workshops:

1. R. D. Rogers, W. E. Hunter, M. Zaworotko, and J. L. Atwood, "Structural Characterization of the Mo-C Sigma Bond in a Series of Related Organometallic Compounds," Presented by R. D. Rogers before the American Crystallographic Association Winter Meeting (1978), Norman, OK, Abstract E3.
2. J. L. Atwood, R. D. Rogers, and W. E. Hunter, "The Nature of the Cyclopentadienyl Ligand in $(C_5H_5)_4W(CO)_2$," Presented by J. L. Atwood before the American Crystallographic Association Winter Meeting (1978), Norman, OK, Abstract PA3.
3. J. L. Atwood, W. E. Hunter, R. D. Rogers, and R. V. Bynum, "A Comparison of Metal-Carbon Sigma and Pi Bonds in the Closely Related Series of Compounds CpZrRR'," Presented by J. L. Atwood before the 176th ACS National Meeting (1978), Miami Beach, FL, Abstract INOR 031.
4. R. D. Rogers and J. L. Atwood, "The Synthesis and Crystal Structure of $Cs[Al_2Me_6N_3]$•2 p-Xylene," Presented by R. D. Rogers before the 176th ACS National Meeting (1978), Miami Beach, FL, Abstract INOR 032.
5. R. D. Rogers, W. E. Hunter, M. J. Zaworotko, and J. L. Atwood, "Structural Characterization of Organometallic Compounds Containing a Novel Bulky Alkoxide Ligand," Presented by R. D. Rogers before the 177th ACS National Meeting (1979), Honolulu, HA, Abstract INOR 052.
6. J. L. Atwood, R. Shakir, M. J. Zaworotko, R. D. Rogers, and E. A. Lewis, "Synthesis, Crystal Structure, and Solution Behavior of $K[Al_2(CH_3)_6SCN]$," Presented by J. L. Atwood before the 177th ACS National Meeting (1979), Honolulu, HA, Abstract INOR 070.
7. R. D. Rogers, R. V. Bynum, and J. L. Atwood, "The Synthesis and Crystal Structure of $(\eta^5\text{-}C_5H_5)_3Gd$•$OC_4H_8$," Presented by R. D. Rogers before the American Crystallographic Association Winter Meeting (1979), Honolulu, HA, Abstract L7.
8. J. L. Atwood, R. V. Bynum, R. D. Rogers, and W. E. Hunter, "The Reaction of Dichlorodicyclopentadienylzirconium(IV) with Pyrrolylsodium: Synthesis and Structure of $(\eta^5\text{-}C_5H_5)_2Ti(\eta^1\text{-}NC_4H_4)_2$, $(\eta^5\text{-}C_5H_5)_2Zr(\eta^1\text{-}NC_4H_4)_2$, and $[Na(THF)_6]_2[Zr(\eta^1\text{-}NC_4H_4)_6]$," Presented by J. L. Atwood before the IXth International Conference on Organometallic Chemistry (1979), Dijon, France, Abstract C46.
9. E. A. Lewis, R. D. Rogers, and J. L. Atwood, "Heats of Solution and of Liquid Clathrate Formation for some Alkali Metal Tri-Alkyl Aluminum Azide Complexes," Presented by E. A. Lewis before the 34th Annual Calorimetry Conference (1979), Kent, OH, Abstract Program Booklet.
10. R. D. Rogers and J. L. Atwood, "Bonding Modes of the $N(SiMe_3)_2$ Ligands: The Crystal and Molecular Structure of $SnBr[N(SiMe_3)_2]_3$," Presented by R. D. Rogers before the American Crystallographic Association Summer Meeting (1979), Boston, MA, Abstract M10.
11. R. V. Bynum, R. D. Rogers, and J. L Atwood, "A Major Difference in the Structural Chemistry of Zirconium and Hafnium: The Crystal Structure of Tetra(cyclopentadienyl)hafnium," Presented by R. V. Bynum before the American Crystallographic Association Winter Meeting (1980), Eufala, AL, Abstract PB3.
12. R. D. Rogers and J. L. Atwood, "The Effect of the Pentamethylcyclopentadienyl Ligand on the Titanium-Carbonyl Bond in $(\eta^5\text{-}C_5Me_5)_2Ti(CO)_2$," Presented by R. D. Rogers before the American Crystallographic Association Winter Meeting (1980), Eufala, AL, Abstract I3.
13. R. D. Rogers, E. A. Lewis, and J. L. Atwood, "Calorimetric Investigations into Liquid Clathrate Behavior," Presented by R. D. Rogers before the 179th ACS National Meeting (1980), Houston, TX, Abstract PHYS 185.
14. R. D. Rogers, J. L. Atwood, and E. A. Lewis, "Thermodynamic Studies Into the Behavior of the First Air-Stable Liquid Clathrates," Presented by R. D. Rogers before the 35th Annual Calorimetry Conference (1980), Eufala, AL, Abstract page 40.
15. S. R. Stobart, A. D. McMaster, J. L. Atwood, and R. D. Rogers, "Tetra(Indenyl)Tin: A Stereochemically Significant Molecule," Presented by S. R. Stobart before the 3rd International Conference on the Organometallic and Coordination Chemistry of Germanium, Tin and Lead (1980), Dortmund, West Germany, Abstract.
16. J. L. Atwood and R. D. Rogers, "The Incorporation of Aromatic Molecules Into Solid-State Organoaluminum Structures," Presented by J. L. Atwood before the International Symposium on Clathrate Compounds and Molecular Inclusion Phenomena, (1980), Jachranka-Warsaw, Poland, Abstract page 51.
17. R. V. Bynum, R. D. Rogers, W. E. Hunter, and J. L. Atwood, "Novel Pyrrolyl Complexes of Group IVB Metals," Presented by R. D. Rogers before the Second Congress of the North American Continent (1980), Las Vegas, NV, Abstract INOR 139.
18. R. D. Rogers, L. G. Canada, and J. L. Atwood, "The Crystal and Molecular Structure of $Mn_2Br_2(CO)_6Te_2Ph_2$," Presented by R. D. Rogers before the American Crystallographic Association Winter Meeting (1981), College Station, TX, Abstract PA15.
19. R. D. Rogers and J. L. Atwood, "Structural Studies of Group IV-B Metallocence Carbonyl and Phosphine Complexes," Presented by R. D. Rogers before the 181st ACS National Meeting (1981), Atlanta, GA, Abstract INOR 063.
20. E. Carmona, J. Marin, M. L. Poveda, R. D. Rogers, and J. L. Atwood, "Synthesis and Crystal Structure of Molybdenum and Tungsten Dihaptoacyl and Related Compounds," Presented by E. Carmona before the Xth International Conference on Organometallic Chemistry (1981), Toronto, Canada, Abstract 2E37.
21. J. L. Atwood, R. D. Rogers, M. J. Zaworotko, W. E. Hunter, and D. C. Hrncir, "New Type of Electron-Deficient Bond in the Anion $[Me_3Al\text{-}H\text{-}AlMe_3]^-$," Presented by J. L. Atwood before the Xth International Conference on Organometallic Chemistry (1981), Toronto, Canada, Abstract 1B01.
22. R. D. Rogers, D. C. Hrncir, and J. L. Atwood, "Structural Investigations of Liquid Clathrate Parent Complexes: The Crystal and Molecular Structures of $K_2[Al_4Me_{16}SO_4]$, $K_2[Al_4Me_{12}SO_4]$•0.5 p-$Me_2C_6H_4$, and $K[Al_7O_6C_{16}H_{48}]$•C_6H_6," Presented by R. D.

Rogers before the XIIth International Congress and General Assembly of the International Union of Crystallography (1981), Ottawa, Canada, Abstract 09.3-01; *Acta Crystallogr., Sect. A*, A37, C217 (1981).

23. J. L. Atwood, R. D. Rogers, D. C. Hrncir, M. J. Zaworotko, and W. E. Hunter, "Classification Scheme for Aromatic 'Solvates' in Ionic Organometallic Compounds," Presented by J. L. Atwood before the XIIth International Congress and General Assembly of the International Union of Crystallography (1981), Ottawa, Canada, Abstract 04.1-09; *Acta Crystallogr., Sect. A*, A37, C83 (1981).
24. R. D. Rogers, R. Priester, D. C. Hrncir, and J. L. Atwood, "Synthesis and Structure of the $[Al_7O_6C_{16}H_{48}]^-$ Anion in $K[Al_7O_6C_{16}H_{48}]\bullet C_6H_6$ and $Cs[Al_7O_6C_{16}H_{48}]\bullet 3C_6H_5Me$," Presented by R. D. Rogers before the 182nd ACS National Meeting (1981), New York, NY, Abstract INOR 222.
25. R. D. Rogers, J. L. Atwood, D. F. Foust, and M. D. Rausch, "Formation and Structure of $Cp_2Y(C_6H_4\text{-}o\text{-}CH_2NMe_2)$," Presented by R. D. Rogers before the Sixteenth Rare Earth Research Conference (1983), Tallahassee, FL, Abstract A1; *J. Less-Comm. Metals*, 94, 402 (1983).
26. C. M. Means, N. C. Means, H.-M. Zhang, W. E. Hunter, R. D. Rogers, and J. L. Atwood, "New High-Oxygen Content Organoaluminum Compounds. Synthesis, Structure, and Decomposition Pathways," Presented by N. C. Means before the 187th ACS National Meeting (1984), St. Louis, MO, Abstract INOR 019.
27. R. D. Rogers, "Structural Characterization of New Pentamethylcyclopentadienyl Derivatives of Group IVB," Presented by R. D. Rogers before the 187th ACS National Meeting (1984), St. Louis, MO, Abstract INOR 271.
28. A. L. Wayda, J. L. Dye, and R. D. Rogers, "Divalent Lanthanoid Synthesis in Liquid Ammonia," Presented by A. L. Wayda before the XXIIIrd International Conference on Coordination Chemistry (1984), Boulder, CO, Abstract.
29. R. D. Rogers and A. L. Wayda, "X-ray Structural Investigations of Organolanthanoids," Presented by R. D. Rogers before the NATO Advanced Study Institute on Fundamental and Technological Aspects of Organo-f-Element Chemistry (1984), Acquafredda di Maratea, Italy, Abstract page P12.
30. L. K. Kurihara and R. D. Rogers, "Lanthanide Crown Ether Complexes," Presented by L. K. Kurihara before the 190th ACS National Meeting (1985), Chicago, IL, Abstract INOR 213.
31. M. M. Benning and R. D. Rogers, "Monosubstituted Cyclopentadienyl Ligands in f-Element Chemistry," Presented by M. M. Benning before the 190th ACS National Meeting (1985), Chicago, IL, Abstract INOR 212.
32. D. W. Macomber, M.-H. Hung and R. D. Rogers, "Preparation, Reactivity, and Structure of Mononuclear η^5-Cyclopentadienyl Cobalt Carbene Complexes," Presented by D. W. Macomber before the 190th ACS National Meeting (1985), Chicago, IL, Abstract INOR 137.
33. R. D. Rogers and D. W. Macomber, "Structural Chemistry of Cobalt and Rhodium Carbene Complexes," Presented by R. D. Rogers before the 190th ACS National Meeting (1985), Chicago, IL, Abstract INOR 214.
34. A. L. Wayda, R. D. Rogers, M. P. Andrews, I. Mukerji, S. H. Bertz and G. Dabbagh, "Lanthanoid Metals in Unusual Coordination Environments: Implications for Organic, Organometallic and Inorganic Chemistry," Presented by A. L. Wayda before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract G.3; *J. Less-Comm. Metals*, 126, 416 (1987).
35. R. D. Rogers, A. L. Wayda, I. Mukerji and J. L. Dye, "Divalent Lanthanoid Synthesis in Liquid Ammonia. 3. The Synthesis and X-ray Crystal Structure of $(C_8H_8)Yb(C_5H_5N)_3\bullet 1/2\ C_5H_5N$," Presented by R. D. Rogers before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract G.6; *J. Less-Comm. Metals*, 126, 418 (1987).
36. R. D. Rogers and L. K. Kurihara, "Solvent Interactions in f-Element/Crown Ether Complexation Chemistry: Synthesis and Structure of (Dibenzo-18-crown-6)$\bullet 2(CH_3CN)$," Presented by R. D. Rogers before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract C(III).5; *J. Less-Comm. Metals*, 127, 268 (1987).
37. L. K. Kurihara and R. D. Rogers, "Crown Ether Complexes of Hydrated f-Element Salts," Presented by L. K. Kurihara before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract C(III).6.
38. M. M. Benning, L. K. Kurihara and R. D. Rogers, "The Synthesis and Crystal Structure of $[UO_2Cl_4][(OH_3)$(Dibenzo-18-crown-6)$]_2\bullet 2CH_3OH$," Presented by M. M. Benning before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract C:(III).7; *J. Less-Comm. Metals*, 127, 269 (1987).
39. A. Verma, D. W. Macomber and R. D. Rogers, "Intermolecular [2+2+2] Cycloadditions of Alkynes and Alkenes Mediated by (η^5-Cyclopentadienyl)cobalt Complexes," Presented by A. Verma before the 192nd ACS National Meeting (1986), Anaheim, CA, Abstract INOR 266.
40. L. B. Kool, M. D. Rausch, and R. D. Rogers, "Dual Ring Phosphination of a Titanium Mixed-Sandwich: A New Route to Heterobimetallic Derivatives," Presented by L. B. Kool before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 250.
41. M. Liang, D. W. Macomber, and R. D. Rogers, "Synthesis and Reactivity of a,b-Unsaturated Tungsten Carbene Complexes: X-ray Crystal Structure of $(CO)_5W[C(OCH_3)(\eta^5\text{-}CH{=}CH_2)]W(CO)_5$," Presented by M. Liang before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 222.
42. E. J. Voss and R. D. Rogers, "Neutral Solvent/Crown Ether Interactions. Crystallization and Structural Characterization of Dibenzo-18-crown-6$\bullet 2(CH_3CN)$ and Dibenzo-18-crown-6$\bullet 2(CH_3NO_2)$, Assignment of Specific C-H···O Interactions," Presented by E. J. Voss before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 179.
43. M. M. Benning and R. D. Rogers, "f-Element/Crown Ether Complexes. Hydrogen Bonding in Actinide Complexes of Crown Ethers," Presented by M. M. Benning before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 180.

44. R. D. Rogers, "f-Element/Crown Ether Complexes. Synthetic and Structural Chemistry of Crown Ether Complexes of 4f and 5f Metal Chlorides," Presented by R. D. Rogers before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 316.
45. M. M. Benning and R. D. Rogers, "f-Element/Crown Ether Complexes. Crown Conformations in Hydrogen Bonded Complexes of Hydrated Actinide Salts," Presented by M. M. Benning before the XIVth International Congress and General Assembly of the International Union of Crystallography (1987), Perth, Australia, Abstract 09.4-13.
46. R. D. Rogers, "f-Element/Crown Ether Complexes. Structural Effects of Solvent and Water of Hydration Hydrogen Bonding," Presented by R. D. Rogers before the XIVth International Congress and General Assembly of the International Union of Crystallography (1987), Perth, Australia, Abstract 09.4-12.
47. L. Nunez, G. Crabtree, J. Z. Liu, A. Umazawa, H. Claus, and R. D. Rogers, "Structural and Magnetic Characterization of Single Crystals of $YBa_2Cu_3O_{7-\square}$," Presented by L. Nunez before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 152.
48. A. N. Rollins and R. D. Rogers, "f-Element/Crown Ether Complexes. Synthetic and Structural Survey of 12-crown-4 Complexes of Hydrated Lanthanide Chlorides," Presented by A. N. Rollins before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 155.
49. R. D. Etzenhouser and R. D. Rogers, "Precipitation and Structural Characterization of Tetraethylene Glycol Complexes of Hydrated Lanthanide Chlorides, Comparison with Triethylene Glycol," Presented by R. D. Etzenhouser before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 154.
50. M. M. Benning and R. D. Rogers, "f-Element/Crown Ether Complexes. Thia-Crown Ether Interactions with Actinide Chlorides, Comparison with Crown Ether Results," Presented by M. M. Benning before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 521.
51. R. D. Rogers, "f-Element/Crown Ether Complexes. The Role of Water in Complexing 12-Crown-4, 15-Crown-5, Benzo-15-Crown-5, 18-Crown-6, and Dibenzo-18-crown-6 to Hydrated Lanthanide Chlorides," Presented by R. D. Rogers before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 520.
52. R. F. Henry and R. D. Rogers, "Mixed Donor 18-Membered Macrocyclic Complexes of Hydrated f-Element Salts," Presented by R. F. Henry before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P4.45.
53. L. Nunez, R. D. Rogers, G. Crabtree, J. Z. Lui, and H. Claus, "Structure and Magnetic Characterization of Single Crystals of $YBa_2Cu_3O_{7-\square}$. Effects of Annealing," Presented by L. Nunez before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P6.9.
54. A. N. Rollins and R. D. Rogers, "f-Element/Crown Ether Complexes. Preparation and Structural Characterization of Mixed Anion (NO_3^-,Cl^-) Complexes of Lanthanum(III) and Crown Ethers," Presented by A. N. Rollins before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P4.43.
55. R. D. Etzenhouser and R. D. Rogers, "Precipitation and Structural Characterization of Pentaethylene Glycol and Hexaethylene Glycol Complexes of Hydrated Lanthanide Chlorides, Comparison with Tetraethylene Glycol," Presented by R. D. Etzenhouser before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P4.44.
56. R. D. Rogers, "f-Element/Crown Ether Complexation. Crown Ethers and Glycols as Variably Dentate Donors for Uranyl(VI) Chloride," Presented by R. D. Rogers before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P4.48.
57. R. Henry and R. D. Rogers, "Synthesis of an 18 Membered, Mixed Donor, Macrocyclic Lanthanide Complex," Presented by R. Henry at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (1988), Orange Beach, AL, Abstract D43.
58. A. N. Rollins and R. D. Rogers, "f-Element/Crown Ether Complexes: Effects of Anion Concentration on Complexation of Dibenzo-18-Crown-6, 18-Crown-6, 15-Crown-5, and 12-Crown-4 with Hydrated Lanthanide Chloride Salts," Presented by A. N. Rollins at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (1988), Orange Beach, AL, Abstract D44.
59. R. D. Etzenhouser and R. D. Rogers, "Tying Up the Ln(III) Coordination Sphere One Site at a Time: Tri-, Tetra-, Penta- and Hexaethylene Glycol Complexes of Hydrated Lanthanide Chloride Salts," Presented by R. D. Etzenhouser at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (1988), Orange Beach, AL, Abstract D45.
60. R. D. Rogers, "f-Element Crown Ether Complexes: Two Crystal Structures Containing Dicyclohexyl-24-Crown-8 Complexed to Na^+ and $H_5O_2^+$," Presented by R. D. Rogers at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (1988), Orange Beach, AL, Abstract D20.
61. D. W. Macomber, M. H. Hung, M. Liang, P. Madhukar, A. G. Verma and R. D. Rogers, "Synthesis, Reactivity, and Structures of (□-Bis(Carbene))Dimetallic Complexes of Chromium and Tungsten," Presented by D. W. Macomber before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 173.
62. A. H. Bond and R. D. Rogers, "f-Element/Crown Ether Complexes. The Reactions of Uranyl Sulfate with Crown Ethers in Sulfuric Acid," Presented by A. H. Bond before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 212.
63. W. G. Hipple and R. D. Rogers, "f-Element/Crown Ether Complexes. Higher Order Hydronium Ion Crown Ether Complexes Stabilized by $[UO_2Cl_4]^{2-}$ Anions. Crystal Structure of $[(H_5O_2)(H_9O_4)(\text{Benzo-15-Crown-5})_2][UO_2Cl_4]$," Presented by W. G. Hipple before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 210.

64. A. N. Rollins and R. D. Rogers, "f-Element/Crown Ether Complexes. A Comparison of the Crystal Structures of $La(NO_3)_3$(15-Crown-5), $Eu(NO_3)_3$(15-Crown-5)[1], and $La(NO_3)_3$(Monoaza-15-Crown-5)[2]," Presented by A. N. Rollins before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 211.
65. R. D. Etzenhouser and R. D. Rogers, "f-Element/Crown Ether Complexes. Supramolecular Structures of the Intricate Hydrogen Bonding Networks in Hydrated Lanthanide Chloride Polyethylene Glycol Complexes," Presented by R. D. Etzenhouser before the 197th ACS National Meeting (1989), Dallas, TX, Abstract CHED 113.
66. R. D. Rogers, "f-Element/Crown Ether Complexes. Supramolecular Structures of the Intricate Hydrogen Bonding Networks in Hydrated Lanthanide Chloride Crown Ether Complexes," Presented by R. D. Rogers before the 197th ACS National Meeting (1989), Dallas, TX, Abstract CHED 112.
67. M. A. Banks, O. T. Beachley, Jr., H. J. Gysling, H. R. Luss, J. D. Maloney, and R. D. Rogers, "Neopentylgallium Compounds which Incorporate Group 15 and Group 16 Lewis Bases," Presented by M. A. Banks before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 376.
68. C. W. Spangler, T. J. Hall, M. L. Saindon, R. D. Rogers, R. K. McCoy, R. R. Birge, P. A. Fleitz, and C.-F. Zhang, "The Relationship Between Structure and Nonlinear Optical Properties in Donor-Acceptor Polyenes," Presented by C. W. Spangler before the International Conference on Materials for Non-Linear and Electro-Optics (1989), Cambridge, United Kingdom, Abstract.
69. M. Ogasa, M. D. Rausch, and R. D. Rogers, "Synthesis of Ring-Phosphinated Titanium(II) Mixed Sandwich Compounds (η^5-$C_5H_4PR_2$)Ti(η^7-$C_7H_6PR_2$) (R=CH_3, C_6H_5) and Their Conversion to Heterobimetallic Compounds," Presented by M. Ogasa before the 198th ACS National Meeting (1989), Miami, FL, Abstract INOR 380.
70. D. N. Kevill, M.-G. Park, and R. D. Rogers, "Studies of the Reactions of Diarylimidoyl Chlorides with Diazomethyllithium," Presented by D. N. Kevill before the International Symposium on Nitrogen-Rings and -Chains (1990), Frankfurt, Federal Republic of Germany.
71. L. Nuñez, B. Veal, G. W. Crabtree, W. K. Kwok, H. Claus, R. R. Rogers, and A. P. Paulikas, "Powder X-ray Diffraction Study on $YBa_2(Cu_{3-x}Fe_x)O_{7-\square}$," Presented by L. Nuñez before the APS National Meeting (1989).
72. A. H. Bond and R. D. Rogers, "Macrocyclic Complexation Chemistry of the Environmentally Toxic Metals," Presented by A. H. Bond before the 199th ACS National Meeting (1990), Boston, MA, Abstract INOR 282.
73. L. Nuñez and R. D. Rogers, "Solution Precursors to New Materials Via Macrocyclic Complexation Chemistry," Presented by L. Nuñez before the 199th ACS National Meeting (1990), Boston, MA, Abstract INOR 281.
74. A. N. Rollins and R. D. Rogers, "Macrocyclic Chemistry of the Lanthanides and Actinides," Presented by A. N. Rollins before the 199th ACS National Meeting (1990), Boston, MA, Abstrct INOR 280.
75. R. D. Rogers, "Macrocyclic Complexation Chemistry: Uranyl Salts and Crown Ethers in Acidic Media," Presented by R. D. Rogers before the 199th ACS National Meeting (1990), Boston, MA, INOR 279.
76. W. M. Tsai, M. D. Rausch and R. D. Rogers, "Synthetic and Structural Studies on Pentabenzylcyclopentadienyliron Dicarbonyl Derivatives," Presented by W. M. Tsai before the 199th ACS National Meeting (1990), Boston, MA, Abstract INOR 291.
77. R. J. Strittmatter, B. E. Bursten, L. F. Rhodes, D. E. Morris, and R. D. Rogers, "Readily-Accessible Oxidation of d^0 Organozirconium Compounds: The Electronic Structure of (η^5-$C_5H_5)_3ZrX$ Compounds," Presented by R. J. Strittmatter before the 199th ACS National Meeting (1990), Boston, MA, Abstract INOR 313.
78. G. H. Robinson, B. Lee and R. D. Rogers, "The Interaction of Trimethylgallium with Macrocyclic Amines," Presented by G. H. Robinson before the 199th ACS National Meeting (1990), Boston, MA, Abstract INORG 152.
79. R. D. Rogers, "Macrocycle Complexation Chemistry of Lanthanide Chlorides. Can You Guess Structure from Elemental Data?" Presented by R. D. Rogers before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 617.
80. A. N. Rollins and R. D. Rogers, "Macrocycle Complexation Chemistry. Direct Comparison of Lanthanide Complexation with 18-Crown-6 and Pentaethylene Glycol," Presented by A. N. Rollins before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 631.
81. R. F. Henry and R. D. Rogers, "Macrocycle Complexation Chemistry of Lanthanides with Sulfur Donors," Presented by R. F. Henry before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 630.
82. A. H. Bond and R. D. Rogers, "Structural Comparison of Hard Donor Crown Ether and Polyethylene Glycol Complexes of Pb^{2+} and Bi^{3+}," Presented by A. H. Bond before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 632.
83. M. D. Rausch, W.-M. Tsai, and M. Ogasa, "Synthetic and Structural Studies on Pentabenzylcyclopentadienyl and Titanium-Containing Heterobimetallic Compounds," Presented by M. D. Rausch before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 607.
84. K. C. Sturge, R. D. Rogers, and M. J. Zaworotko, "Sterically Crowded Iron(II) Mixed Sandwich Complexes," Presented by K. C. Sturge before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 559.
85. N. Burford, B. W. Royan, R. E. V. H. Spence, T. S. Cameron, A. Linden, and R. D. Rogers, "Novel Acceptor Features for the Heavier Elements of Group 13 Allowing a Reclassification of the Coordinative Bonding Modes of Phosphine Chalcogenides," Presented by N. Burford before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 592.
86. S. Christie, M. J. Zaworotko and R. D. Rogers, "2-Oxybenzoate Aluminum Complexes," Presented by S. Christie before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 629.

87. N. Burford, R. E. V. H. Spence, T. S. Cameron, B. Borecka, R. D. Rogers, and J. F. Richardson, "The Reactions of Group 13 Acids with Diaminothiophosphoryl Chlorides," Presented by R. E. V. H. Spence before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 661.
88. J. R. Peterson, H. D. Do and R. D. Rogers, "Chemical and Biological Investigations of Anticancer Lignan Lactones," Presented by J. R. Peterson and H. D. Do before the 22nd National Medicinal Chemistry Symposium (1990), Austin, TX.
89. A. H. Bond and R. D. Rogers, "Polyethylene Glycols as Ionizable Complexing Agents of Bi^{3+}," Presented by A. H. Bond before the 201st ACS National Meeting (1991), Atlanta, GA, Abstract INOR 039.
90. L. Nunez, R. D. Rogers, G. W. Crabtree, U. Welp, A. Umezawa, K. Vandervoort, and Y. Fang, "Magnetic and Superconducting Properties of $YBa_2Cu_{3-x}Fe_xO_{7-\delta}$ Single Crystals," Presented by L. Nunez before the 201st ACS National Meeting (1991), Atlanta, GA, Abstract INOR 038.
91. A. N. Rollins and R. D. Rogers, "Electrocrystallization of Lanthanide Polyether Complexes," Presented by A. N. Rollins before the 201st ACS National Meeting (1991), Atlanta, GA, Abstract INOR 136.
92. R. D. Rogers, "Crown Ether vs. Polyethylene Glycol Complexation of $NdCl_3$. A Structural Study of Why the Chelate Effect is Greater than the Macrocyclic Effect in f-Element Extractions," Presented by R. D. Rogers before the 201st ACS National Meeting (1991), Atlanta, GA, Abstract INOR 135.
93. A. H. Bond and R. D. Rogers, "The Influence of Cd Halide Polymer Formation on Cd Polyether Structures," Presented by A. H. Bond before the American Crystallographic Association Meeting (1991), Toledo, OH, Abstract PJ06.
94. R. D. Rogers, "The Effect of Decreasing Ionic Size on the Primary Coordination Sphere of Hydrated Lanthanide Chloride Polyether Complexes," Presented by R. D. Rogers before the American Crystallographic Association Meeting (1991), Toledo, OH, Abstract C14.
95. E. P. Horwitz, M. L. Dietz, and R. Rogers, "A Combined Transuranic-Strontium-Technetium Extraction/Recovery Process," Presented by E. P. Horwitz before the 15th Actinide Separations Conference (1991), Charleston, SC, Abstract book page 27.
96. R. C. Gatrone, M. L. Dietz, A. H. Bond, R. D. Rogers, and E. P. Horwitz, "The Influence of Isomerization of Crown Ethers on the Extraction of Strontium and Potassium from Nitrate Media," Presented by R. C. Gatrone before the 7th Symposium on Separation Science and Technology for Energy Applications (1991), Knoxville, TN, Abstract book page 21.
97. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Aqueous Biphase Systems for Liquid/Liquid Extraction of f-Elements Utilizing Polyethylene and Polypropylene Glycols," Presented by R. D. Rogers before the 7th Symposium on Separation Science and Technology for Energy Applications (1991), Knoxville, TN, Abstract book page 60.
98. E. P. Horwitz, M. L. Dietz, R. Chiarizia, H. Diamond, and R. Rogers, "Recent Advances in Solvent Extraction and Extraction Chromatography for Processing Radioactive Waste," Presented by E. P. Horwitz before the 7th Symposium on Separation Science and Technology for Energy Applications (1991), Knoxville, TN, Abstract book page 95.
99. C. B. Bauer and R. D. Rogers, "Liquid/Liquid Extraction of the f-Elements Utilizing Aqueous Biphase Systems," Presented by C. B. Bauer before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract I&EC 10.
100. A. H. Bond and R. D. Rogers, "Extraction of Pb^{2+} Using Aqueous Polyethylene Glycol Biphasic Systems," Presented by A. H. Bond before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract I&EC 009.
101. A. N. Rollins and R. D. Rogers, "Comparison of the Crystal Structure and Molecular Models of CMPO," Presented by A. N. Rollins before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract I&EC 008.
102. A. H. Bond and R. D. Rogers, "Polyethylene Glycol Complexation of Pb^{2+}," Presented by A. H. Bond before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract INOR 528.
103. C. B. Bauer and R. D. Rogers, "A Structural Comparison Between the Complexes of Tetraethylene Glycol with Lanthanide(III) Chlorides and Nitrates," Presented by C. B. Bauer before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract INOR 527.
104. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Aqueous Biphasic Systems for Liquid/Liquid Extraction of Environmentally Toxic Heavy Metals," Presented by R. D. Rogers before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract I&EC 088. (Invited Symposium Presentation.)
105. T. M. Gilbert and R. D. Rogers, "Metathesis Chemistry of $Mo_2Cl_2(DME)_2$: Synthesis and X-ray Diffraction Studies of $Mo_2(OR_F)_6$ (Mo=Mo) Complexes," Presented by T. M. Gilbert before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract INOR 464.
106. T. M. Gilbert and R. D. Rogers, "Synthesis and Absorption Spectra of the "Dialkylidynes" $(RO)_3W/C\text{-}C/W(OR)_3$ (OR = $OCMe_3$, $OCMe_2CF_3$, $OCMe_2Et$): Excited State Transition Metal-Carbon p Conjugation," Presented by T. M. Gilbert before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract INOR 308.
107. R. D. Rogers, C. B. Bauer, and A. H. Bond, "Aqueous Biphasic Polyethylene Glycol/Salt Systems for Actinide Ion Separation and Extraction," Presented by R. D. Rogers before the 16th Annual Actinide Separations Conference (1992), Estes Park, CO, Abstract book page 32.
108. M. L. Dietz, E. P. Horwitz, and R. D. Rogers, "A Combined Transuranic-Strontium Extraction/Recovery Process," Presented by M. L. Dietz before the 16th Actinide Separations Conference (1992), Estes Park, CO, Abstract book page 33.
109. E. P. Horwitz, M. L. Dietz, and R. D. Rogers, "A Combined Transuranic-Strontium Extraction/Recovery Process," Presented by E. P. Horwitz before the 204th ACS National Meeting (1992), Washington, DC, Abstract I&EC 108.
110. A. H. Bond and R. D. Rogers, "Structural Analyses of Crown Ether and Polyethylene Glycol Complexes of Cd^{2+}, Hg^{2+}, and Pb^{2+}," Presented by A. H. Bond before the XVII International Symposium on Macrocyclic Chemistry (1992), Provo, UT, Abstract P13.

111. C. B. Bauer and R. D. Rogers, "Structural Analyses of Crown Ether and Polyethylene Glycol Complexes of Lanthanide(III) Ions," Presented by C. B. Bauer before the XVII International Symposium on Macrocyclic Chemistry (1992), Provo, UT, Abstract P7.
112. M. L. Dietz, E. P. Horwitz, R. C. Gatrone, A. H. Bond, and R. D. Rogers, "The Influence of Isomerization on the Extraction of Strontium and Potassium from Nitrate Media by Dicyclohexyl-18-Crown-6," Presented by M. L. Dietz before the XVII International Symposium on Macrocyclic Chemistry (1992), Provo, UT, Abstract P30.
113. R. D. Rogers, A. H. Bond, and C. B. Bauer, "The Crown Ether Extraction of Group 1 and 2 Cations in Polyethylene Glycol-Based Aqueous Biphasic Systems at High Alkalinity," Presented by R. D. Rogers before the XVII International Symposium on Macrocyclic Chemistry (1992), Provo, UT, Abstract IS19. (Invited Symposium Presentation.)
114. J. R. Peterson, J. K. Zjawiony, and R. D. Rogers, "A New Synthesis and Optical Resolution of the Taxol Side Chain," Presented by J. R. Peterson before the 2nd National Cancer Institute Workshop on Taxol and Taxus (1992), Alexandria, VA, Poster E-6.
115. A. N. Rollins and R. D. Rogers, "Conformation Analysis of 18-Crown-6 in Complexes with Hydrated Lanthanide Chlorides," Presented by A. N. Rollins before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 289.
116. A. H. Bond and R. D. Rogers, "Structural Studies of Aza-18-Crown-6 Complexes of $HgCl_2$, $HgBr_2$, and HgI_2," Presented by A. H. Bond before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 286.
117. C. B. Bauer and R. D. Rogers, "Inner Sphere Versus Outer Sphere Coordination of Hexaethylene Glycol in Complexes of Lanthanide(III) Chlorides and Nitrates," Presented by C. B. Bauer before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 069.
118. M. L. Jezl, T. S. Forbes, T. Amaro, and R. D. Rogers, "Polyethylene Glycol Complexes of $Sr(NO_3)_2$," Presented by M. L. Jezl before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 401.
119. T. M. Gilbert, F. J. Hadley, and R. D. Rogers, "Synthesis, Structure and Nonlinear Optical Properties of a,w-Diphenyl Polyenes Coordinated to Transition Metal Centers," Presented by T. M. Gilbert before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 588.
120. A. H. Bond and R. D. Rogers, "Partitioning of Cd^{2+} in Polyethylene Glycol Based Aqueous Biphasic Systems," Presented by A. H. Bond before the 205th ACS National Meeting (1993), Denver, CO, Abstract I&EC 025.
121. C. B. Bauer and R. D. Rogers, "The Extraction of Group 1 and 2 Cations in Aqueous Biphasic Systems," Presented by C. B. Bauer before the 205th ACS National Meeting (1993), Denver, CO, Abstract I&EC 026.
122. R. D. Rogers, A. H. Bond, C. B. Bauer, M. L. Jezl, and A. N. Rollins, "Is Metal Cation Recognition Possible with Acyclic Crown Ether Analogs? An Analysis of the Metal Directed Coordination Modes of Polyethylene Glycols," Presented by R. D. Rogers before the 205th ACS National Meeting (1993), Denver, CO, Abstract I&EC 108.
123. A. H. Bond and R. D. Rogers, "Crystallographic Challenges in the Structural Characterization of Aza-18-Crown-6 Versus 18-Crown-6 Metal Complexes," Presented by A. H. Bond before the American Crystallographic Association Meeting (1993), Albuquerque, NM, Abstract PE01.
124. C. B. Bauer and R. D. Rogers, "Supramolecular Structural Variations in Pentaethylene Glycol Complexes of Lanthanide(III) Nitrates Resulting from Variable Hydrogen Bonding Environments," Presented by C. B. Bauer before the American Crystallographic Association Meeting (1993), Albuquerque, NM, Abstract PD07.
125. R. D. Rogers, "Polyethylene Glycol Complexes of f-Element Salts: Structural Clues to Complexation Behavior," Presented by R. D. Rogers before the American Crystallographic Association Meeting (1993), Albuquerque, NM, Abstract Z003. (Invited Symposium Presentation.)
126. E. P. Horwitz, M. L. Dietz, H. Diamond, R. D. Rogers, and R. A. Leonard, "Advanced Chemical Separations in Support of the Clean Option Strategy," Presented by E. P. Horwitz before the 17th Actinide Separations Conference (1993), Pasco, WA, Abstract book page 52.
127. A. H. Bond and R. D. Rogers, "Crystallographic Investigation of 15-Crown-5 Complexes of CdX_2 (X = Cl, Br, I, NO_3)," Presented by A. H. Bond before the XVIth Congress and General Assembly of the International Union of Crystallography/IUCr XVI Meeting (1993), Beijing, China, Abstract PS-07.01.17.
128. R. D. Rogers, "How Metal Ion Character Controls the Coordination Mode of Polyethylene Glycol," Presented by R. D. Rogers before the XVIth Congress and General Assembly of the International Union of Crystallography/IUCr XVI Meeting (1993), Beijing, China, Abstract OPS-07.01.9.
129. D. M. Roden, A. H. Bond, and R. D. Rogers, "Structural Studies of Substituted Crown Ether Complexes of Bismuth(III) Halides," Presented by D. M. Roden before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 187.
130. Y. Song and R. D. Rogers, "Polyethylene Glycol-Based Aqueous Biphasic Systems for the Extraction of Transition Metal Ions," Presented by Y. Song before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 133.
131. C. B. Bauer and R. D. Rogers, "Anion Directed Coordination in Lanthanide(III) Complexes of Polyethylene Glycols," Presented by C. B. Bauer before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 110.
132. T. M. Gilbert and R. D. Rogers, "Spectroscopic and Structural Investigation of the Nature of the Frontier Orbitals in Hexa(alkoxy)- and Hexa(fluoroalkoxy)ditungsten Compounds $W_2[OCMe_x(CF_3)_{3-x}]$ (x = 1-3)," Presented by T. M. Gilbert before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 355.
133. T. M. Gilbert and R. D. Rogers, "Nonlinear Optical Properties of Substituted Stilbenes Coordinated to (Tricarbonyl)chromium Fragments," Presented by T. M. Gilbert before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 356.

134. E. P. Horwitz, M. L. Dietz, H. Diamond, R. D. Rogers, and R. A. Leonard, "Combined TRU-Sr Extraction/Recovery Process," Presented by M. L. Dietz. Proceedings International Solvent Extraction Conference/ISEC '93, York, England, Vol. 3, pp. 1805-1812, D. H. Logsdail and M. J. Slater (eds.), Elsevier, London (1993).
135. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Polyethylene Glycol-Based Aqueous Biphasic Systems for Liquid/Liquid Extraction of Environmentally Toxic Heavy Metals," Presented by R. D. Rogers. Proceedings International Solvent Extraction Conference/ISEC '93, York, England, Vol. 3, pp. 1641-1648, D. H. Logsdail and M. J. Slater (eds.), Elsevier, London (1993).
136. E. P. Horwitz, M. L. Dietz, H. Diamond, R. D. Rogers, and R. A. Leonard, "Advanced Chemical Separations in Support of the Clean Option Strategy," Presented by E. P. Horwitz before the Global '93 Conference on Future Nuclear Systems: Emerging Fuel Cycles and Waste Disposal Options (1993), Seattle, WA.
137. R. D. Rogers, C. B. Bauer, and A. H. Bond, "Crown Ethers as Actinide Extractants in Acidic Aqueous Biphasic Systems: Partitioning Behavior in Solution and Crystallographic Analyses of the Solid State," Presented by R. D. Rogers before the Actinides-93 International Conference (1993), Santa Fe, NM, Abstract 77. (Invited Symposium Presentation.)
138. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Novel Polyethylene Glycol-Based Aqueous Biphasic Systems for the Extraction of Strontium and Cesium," Presented by R. D. Rogers before the 8th Symposium on Separation Science and Technology for Energy Applications (1993), Gatlinburg, TN, Abstract book page 18.
139. L. Nunez, G. F. Vandegrift, and R. D. Rogers, "In Situ Magnetically Assisted Chemical Separation," Presented by L. Nunez before the 8th Symposium on Separation Science and Technology for Energy Applications (1993), Gatlinburg, TN, Abstract book page 40.
140. D. J. Chaiko and R. D. Rogers, "Aqueous Biphasic Systems for Radioactive Waste Pretreatment," Presented by D. J. Chaiko before the Efficient Separations and Processing Integrated Program (ESPIP) Technical Information Exchange Meeting (1994), Dallas, TX, Abstract book page 17.
141. E. P. Horwitz, M. L. Dietz, H. Diamond, R. D. Rogers, and R. A. Leonard, "Advanced Chemical Separations in Support of the Clean Option," Presented by P. Horwitz before the Efficient Separations and Processing Integrated Program (ESPIP) Technical Information Exchange Meeting (1994), Dallas, TX, Abstract book page 39.
142. F. E. Putnam, A. H. Bond, and R. D. Rogers, "Triethylene Glycol Dimethyl Ether Complexes of CdX_2 (X = C1, Br, I)," Presented by F. E. Putnam before the 207th ACS National Meeting (1994), San Diego, CA, Abstract INOR 347.
143. D. M. Roden, A. H. Bond, and R. D. Rogers, "Structural Studies of Tetra-, Penta- and Hexaethylene Glycol Complexes of Lead Nitrate," Presented by D. M. Roden before the 207th ACS National Meeting (1994), San Diego, CA, Abstract INOR 346.
144. C. B. Bauer and R. D. Rogers, "Structural Analyses of Group 2 Metal/Polyethylene Glycol Complexes," Presented by C. B. Bauer before the 207th ACS National Meeting (1994), San Diego, CA, Abstract INOR 472.
145. A. H. Bond and R. D. Rogers, "Crystallographic Analysis of the Stereochemically Active Lone Pair in Bismuth(III) Halide-Polyethylene Glycol Complexes," Presented by A. H. Bond before the 207th ACS National Meeting (1994), San Diego, CA, Abstract INOR 471.
146. D. M. Roden, Y. Song, M. L. Jezl, C. B. Bauer, A. H. Bond, and R. D. Rogers, "Pertechnetate Partitioning in Polyethylene Glycol-Based Aqueous Biphasic Systems: Applications from Nuclear Medicine to Nuclear Waste," Presented by D. M. Roden before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 052.
147. Y. Song and R. D. Rogers, "The Investigation of Polymer-Salt Based Aqueous Biphasic Systems for the Separation of Metal Ions," Presented by Y. Song before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 054.
148. A. H. Bond, D. M. Roden, F. E. Putnam, and R. D. Rogers, "Uptake of Metal Ions by DiphonixJ Resin From NaCl and $CaC1_2$ Solutions," Presented by A. H. Bond before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 037.
149. A. H. Bond and R. D. Rogers, "The Partitioning of Heavy Metal Halides in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by A. H. Bond before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 019.
150. C. B. Bauer and R. D. Rogers, "The Design of Metal Ion Specific Extractants for Use in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by C. B. Bauer before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 064.
151. R. D. Rogers, S. D. Rein, C. B. Bauer, J. Zhang, and A. H. Bond, "The Partitioning Behavior of TcO_4^- and I^- in Polyethylene Glycol-Based Aqueous Biphasic Systems Prepared from Simulated Liquid Radioactive Hanford Tank Wastes," Presented by R. D. Rogers before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 057.
152. R. D. Rogers, A. H. Bond, C. B. Bauer, and Y. Song, "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 003. (Invited Symposium Presentation.)
153. C. B. Bauer and R. D. Rogers, "Pseudo-Cyclic Behavior of Acyclic Polyether Ligands in Complexes with Lanthanide(III) Ions," Presented by C. B. Bauer before the XIX International Symposium on Macrocyclic Chemistry (1994), Lawrence, KS, Abstract A3.
154. A. H. Bond, D. M. Roden, and R. D. Rogers, "Mono- and Dicyclohexyl Substituted Crown Ether Complexes of Bismuth(III)," Presented by A. H. Bond before the XIX International Symposium on Macrocyclic Chemistry (1994), Lawrence, KS, Abstract A5.
155. R. D. Rogers and A. H. Bond, "Structural Analysis of cis-syn-cis-4,5'-Ditertbutyl-dicyclohexyl-18-crown-6 and cis-anti-cis-4,5'-Ditertbutyl-dicyclohexyl-18-crown-6•$2CH_3CN$: Comparison with Unsubstituted Dicyclohexyl-18-crown-6," Presented by R. D. Rogers before the XIX International Symposium on Macrocyclic Chemistry (1994), Lawrence, KS, Abstract ST7.

156. A. H. Bond, F. E. Putnam, and R. D. Rogers, "Structural Variations in Complexes of Cadmium Halides with Triethylene Glycol and its Dimethyl Ether Derivative," Presented by A. H. Bond before the American Crystallographic Meeting (1994), Atlanta, GA, Abstract PIC16.
157. C. B. Bauer and R. D. Rogers, "Structural Comparison of Lanthanide(III) Nitrate Complexes with Tetraethylene Glycol and Tetraethylene Glycol Dimethyl Ether Ligands," Presented by C. B. Bauer before the American Crystallographic Meeting (1994), Atlanta, GA, Abstract PIC17.
158. L. R. Morss and R. D. Rogers, "Synthesis and Crystal Structure of an f-Element Complex with Strong M-N Bonds," Presented by L. R. Morss before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 021.
159. A. H. Bond, R. D. Rogers, and F. E. Putnam, "Structural Characterization of Five Donor Cyclic and Acyclic Polyether Complexes of Cadmium Halides," Presented by A. H. Bond before the 208th ACS National Meeting (1994), Washington, DC, Abstract INOR 151.
160. C. B. Bauer and R. D. Rogers, "Structural Investigation of Lanthanide(III) Nitrates Complexed With Triethylene Glycol Ligands," Presented by C. B. Bauer before the 208th ACS National Meeting (1994), Washington, DC, Abstract INOR 150.
161. A. H. Bond and R. D. Rogers, "Bromide and Iodide Partitioning in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by A. H. Bond before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 016.
162. C. B. Bauer and R. D. Rogers, "Separation of Group 1 and 2 Cations in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by C. B. Bauer before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 015.
163. R. D. Rogers, A. H. Bond, C. B. Bauer, Y. Song, J. Zhang, and R. R. Chomko, "Polyethylene Glycol-Based Aqueous Biphasic Systems: Inexpensive, Nontoxic Alternatives for Hanford Tank Remediation," Presented by R. D. Rogers before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 017.
164. R. D. Rogers, "The Division of Industrial and Engineering Chemistry's Separation Science and Technology Subdivision: The Place for Separations Scientists," Presented by R. D. Rogers before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 010.
165. J. Zhang and R. D. Rogers, "Pertechnetate/Molybdate Separation Using Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 023.
166. C. B. Bauer and R. D. Rogers, "Cation and Anion Influence on the Partitioning of Group 1 and 2 Metals in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by C. B. Bauer before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 022.
167. A. H. Bond and R. D. Rogers, "Polyethylene Glycol-Based Aqueous Biphasic Partitioning Behavior of Monovalent Anions," Presented by A. H. Bond before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 021.
168. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Extraction and Recovery of Dyes and Metal/Dye Complexes with Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 020.
169. R. D. Rogers, "The Division of Industrial and Engineering Chemistry's Separation Science and Technology Subdivision: The Place for Separations Scientists," Presented by R. D. Rogers before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 019.
170. C. B. Bauer and R. D. Rogers, "Water Soluble Calixarenes as Possible Metal Ion Extractants in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by C. B. Bauer before the 6th Conference on Separation of Ionic Solutes/SIS'95 (1995), Piestany Spa, Slovakia, Abstract book page 41.
171. R. D. Rogers, "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 6th Conference on Separation of Ionic Solutes/SIS'95 (1995), Piestany Spa, Slovakia, Abstract book page 24. (Invited Symposium Presentation.)
172. J. Zhang and R. D. Rogers, "Effects of Increasing Polymer Hydrophobicity on Distribution Ratios of TcO_4^- in Polyethylene/Polypropylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 9th International Conference on Partitioning in Aqueous Two-Phase Systems: Advances in the Uses of Polymers in Cell Biology, Biotechnology and Environmental Sciences (1995), Zaragoza, Spain, Abstract book.
173. C. B. Bauer and R. D. Rogers, " Partitioning Behavior of Group 1 and 2 Cations in Aqueous Biphasic Systems: The Development of Predictive Models Based on Thermodynamic and System Composition Data," Presented by C. B. Bauer before the 9th International Conference on Partitioning in Aqueous Two-Phase Systems: Advances in the Uses of Polymers in Cell Biology, Biotechnology and Environmental Sciences (1995), Zaragoza, Spain, Abstract book.
174. R. D. Rogers, A. H. Bond, C. B. Bauer, and J. Zhang, "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems: Correlation of Partitioning Behavior with Available Thermodynamic Hydration Data," Presented by R. D. Rogers before the 9th International Conference on Partitioning in Aqueous Two-Phase Systems: Advances in the Uses of Polymers in Cell Biology, Biotechnology and Environmental Sciences (1995), Zaragoza, Spain, Abstract book. (Invited Symposium Presentation.)
175. R. D. Rogers, A. H. Bond, C. B. Bauer, J. Zhang, and S. T. Griffin, "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems: The Outlook for Commercial Applications," Presented by R. D. Rogers before the 9th International Conference on Partitioning in Aqueous Two-Phase Systems: Advances in the Uses of Polymers in Cell Biology, Biotechnology and Environmental Sciences (1995), Zaragoza, Spain, Abstract book. (Invited Symposium Presentation.)

176. T. M. Gilbert, A. H. Bond, C. B. Bauer, and R. D. Rogers, "Structural Aspects of Triply Bonded Homoleptic Hexa(tertiaryalkoxide)dimolybdenum and ditungsten Compounds," Presented by T. M. Gilbert before the 210th ACS National Meeting (1995), Chicago, IL, Abstract INOR 200.
177. T. M. Gilbert, M. D. Simmons, F. J. Hadley, C. B. Bauer, and R. D. Rogers, "Syntheses and Structures of Substituted a,w-Diphenylhexatrienes Coordinated to (Tricarbonyl)chromium Fragments," Presented by T. M. Gilbert before the 210th ACS National Meeting (1995), Chicago, IL, Abstract INOR 201.
178. R. D. Rogers, "The Division of Industrial and Engineering Chemistry's Separation Science and Technology Subdivision: The Place for Separations Scientists," Presented by R. D. Rogers before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 025.
179. J. Zhang and R. D. Rogers, "Structural Investigations of Lanthanum(III) Isothiocyanate Complexes with Polyethylene Glycol," Presented by J. Zhang before the 210th ACS National Meeting (1995), Chicago, IL, Abstract INOR 505.
180. J. Zhang and R. D. Rogers, "Structural Investigations of Lanthanide(III) Hydroxyethane-1,1-diphosphonic Acid (HEDPA) Complexes," Presented by J. Zhang before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 026.
181. J. Zhang and R. D. Rogers, "Predicting Distribution Ratios of Pertechnetate in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 027.
182. E. Wodziak, J. Zhang, and R. D. Rogers, "Investigation of the Salting-Out of Polyethylene Glycol-2000 in Aqueous Biphasic Systems," Presented by E. Wodziak before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 028.
183. H. McIlwraith, J. Zhang, and R. D. Rogers, "Structural Studies of Lanthanide(III) 1,2-Ethylene-diphosphonic Acid Complexes," Presented by H. McIlwraith before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 029.
184. J. Zhang, S. T. Griffin, and R. D. Rogers, "The Effects of Halide Anions on the Partitioning Behavior of Pertechnetate in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 9th Symposium on Separation Science and Technology for Energy Applications (1995), Gatlinburg, TN, Abstract book page 61.
185. R. D. Rogers, A. H. Bond, and E. P. Horwitz, "New Technetium-99m Generator Technologies Utilizing Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 9th Symposium on Separation Science and Technology for Energy Applications (1995), Gatlinburg, TN, Abstract book page 17.
186. R. D. Rogers, A. H. Bond, J. Zhang, and C. B. Bauer, "Polyethylene Glycol-Based Aqueous Biphasic Systems: A Potential ^{99m}Tc Generator Technology," Presented by R. D. Rogers before the International Chemical Congress of Pacific Basin Societies/Pacifichem'95 (1995) Honolulu, HA, Abstract INOR 1137.
187. M. T. Tran, R. P. Planalp, C. B. Bauer, and R. D. Rogers, "Titanium and Vanadium Complexes of Tripropoxideamine Derivative Ligand, $N(CH_2C(CH_3)_2O\text{-})_3$," Presented by R. P. Planalp before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract INOR 438.
188. N. M. Tsoupas, N. Ye, R. P. Planalp, C. B. Bauer, R. D. Rogers, and M. W. Brechbiel, "Metal Complexes of Novel Hexadentate Ligands Based on the cis-1,3,5-Triaminocyclohexane Framework: Synthesis, Structure and Stability under Biological Conditions", Presented by R. P. Planalp before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract INOR 559.
189. M. W. Brechbiel, N. M. Tsoupas, N. Ye, R. P. Planalp, C. B. Bauer, and R. D. Rogers, "Facile Synthesis of cis,cis-1,3,5-Triaminocyclohexane and Its use in Synthesis of Novel Hexadentate Chelating Agents as Radiopharmaceuticals," Presented by M. W. Brechbiel before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract ORGN 236.
190. J. Zhang, S. T. Griffin, and R. D. Rogers, "Partitioning Behavior of Iodide in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract I&EC 040.
191. S. T. Griffin, J. Zhang, and R. D. Rogers, "Partitioning Behavior of Iodide with Aqueous Biphasic Extraction Chromatographic (ABEC) Resins," Presented by S. T. Griffin before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract I&EC 041.
192. E. Wodziak, J. Zhang, and R. D. Rogers, "Modified Polyethylene Glycols (PEGs) as Potential Extractants for use in PEG-Based Aqueous Biphasic Systems," Presented by E. Wodziak before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract I&EC 042.
193. R. D. Rogers, S. T. Griffin, J. Zhang, E. P. Horwitz, M. J. Gula, and F. Chang, "Polyethylene Glycol-Based ABEC Resins for the Selective Removal of Technetium from Hanford Tank Wastes," Presented by R. D. Rogers before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract I&EC 184.
194. R. D. Rogers, A. H. Bond, C. B. Bauer, S. T. Griffin, and J. Zhang "Polyethylene Glycol-Based Aqueous Biphasic Systems for Extraction and Recovery of Dyes and Metal/Dye Complexes," Presented by R. D. Rogers before the International Solvent Extraction Conference/ISEC'96 (1996), Melbourne, Australia. *Value Adding through Solvent Extraction Proceedings of ISEC'96*; D. C. Shallcross, R. Paiman, and L. M. Prvcic, Eds.; The University of Melbourne: Parkville, Victoria, Australia, 1996; Vol. 2; pp 1537-1542.
195. D. R. Whitcomb, W. C. Frank, R. D. Rogers, B. P. Tolochkoc, S. V. Chernovc, S. G. Nikitenkod, "Silver Coordination Chemistry in Photothermographic Imaging Systems," Presented by D. R. Whitcomb before the Imaging Science and Technology Conference (1996), Minneapolis, MN, Abstract.
196. J. Zhang and R. D. Rogers, "Structural Investigation of Polyethylene Glycol/Neodymium(III) Isothiocyanate Complexes," Presented by J. Zhang before the Rare Earth Research Conference (1996), Duluth, MN, Abstract PC-7.
197. R. D. Rogers, J. Zhang, and C. B. Bauer, "The Affects of Choice of Anion ($X = Cl^-, Br^-, SCN^-, NO_3^-$) and Polyethylene Glycol Chain Length on the Local and Supramolecular Structures of LnX_3/PEG Complexes," Presented by R. D. Rogers before the Rare Earth Research Conference (1996), Duluth, MN, Abstract IC-5. (Invited Symposium Presentation.)

198. R. D. Rogers, "ABEC™ Resins for Removal of TcO_4^- from Hanford Tank Wastes," Presented by R. D. Rogers before the 20th Actinide Separation Conference (1996), Itasca, IL, no abstract.
199. R. D. Rogers, A. H. Bond, and C. B. Bauer, "New Separations Technologies for TcO_4^-: Applications from Nuclear Medicine to Nuclear Waste," Presented by R. D. Rogers, before the 212th ACS National Meeting (1996), Orlando, FL, Abstract I&EC 008.
200. R. D. Rogers, "Chemical Crystallography in Crystal Engineering," Presented by R. D. Rogers at the NATO ASI *Crystal Engineering: The Design and Application of Functional Solids* (1996), Digby, Nova Scotia, Canada. (Invited Lecture.)
201. L. M. Rogers and R. D. Rogers, "How the New CCD Area Detector for Small Molecule Crystallography will Advance Crystal Engineering," Presented by L. M. Rogers at the NATO ASI *Crystal Engineering: The Design and Application of Functional Solids* (1996), Digby, Nova Scotia, Canada.
202. J. He, L. C. Francesconi, S. Saluja, and R. Rogers, "Synthesis and Characterization of the Indium(III) Complex of a Novel Aminothiol (N_3S_2) Ligand, " Presented by L. C. Francesconi, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract INOR 027.
203. J. Bartis, L. C. Francesconi, M. Dankova, R. Rogers, and V. G. Young, Jr., "Stoichiometric and Structural Studies of Lanthanide Complexes of $[a\text{-}2\text{-}P_2W_{17}O_{61}]^{10-}$ Complexes," Presented by J. Bartis, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract INOR 839.
204. R. D. Rogers, M. L. Dietz, E. P. Horwitz, and A. H. Bond, "Ligand Design for Ion Separations: Crystal Structures of Substituted Dicyclohexyl-18-crown-6 Isomers," Presented by R. D. Rogers, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 004. (Invited Symposium Presentation.)
205. R. P. Swatloski, S. T. Griffin, L. M. Rogers, and R. D. Rogers, "4,4'-Dipyridyl as a Synthon for the Design and Synthesis of Porous Solids," Presented by R. P. Swatloski, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 053.
206. S. T. Griffin and R. D. Rogers, "A Direct Comparison of Metal Ion Partitioning in Liquid/Liquid PEG-Based ABS and Retention on ABEC™ Resin. How Good is the Analogy?," Presented by S. T. Griffin, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 054.
207. J. A. Nicol, H. D. Willauer, S. T. Griffin, and R. D. Rogers, "Partitioning of Dyes and Metal/Dye Complexes in Aqueous Biphasic Systems," Presented by H. D. Willauer, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 055.
208. R. D. Rogers, S. T. Griffin, E. P. Horwitz, A. H. Bond, M. J. Gula, and F. Chang, "ABEC™ Resins: From Aqueous Biphasic Novelties to Selective Aqueous Biphasic Extraction Chromatographic Resins for Metal Ions," Presented by R. D. Rogers, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 104. (Invited Symposium Presentation.)
209. A. H. Bond, M. J. Gula, F. Chang, R. D. Rogers, and E. P. Horwitz, "Eichrom's ABEC Resins: Alkaline Radioactive Waste Treatment, Radiopharmaceutical, and Potential Hydrometallurgical Applications," Presented by A. H. Bond, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 105.
210. R. D. Rogers and L. M. Rogers, "The SMART System at The University of Alabama: Experiences, Reflections, and Data," Presented by R. D. Rogers, before the Siemens Area Detector Users Group Meeting 'SADUG97' (1997), Athens, GA, Abstract book. (Invited Presentation.)
211. R. D. Rogers, S. T. Griffin, H. D. Willauer, and J. A. Nicol, "Clean Solvent Extraction Using Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 1997 Green Chemistry and Engineering Conference, 'Implementing Vision 2020 for the Environment' (1997), Washington, DC, Abstract book p. 23. (Invited Presentation.)
212. R. D. Rogers, S. T. Griffin, H. Willauer, J. Zhang, and J. G. Huddleston, "Utilization of Aqueous Polymers for 'Clean' Separations Technologies," Presented by R. D. Rogers before the Gordon Conference on Reactive Polymers, Ion Exchange, and Adsorption (1997), New England College, Henniker, NH.
213. J. G. Huddleston, H. Willauer, and R. D. Rogers, "Separations and Recovery of Food Coloring Dyes Using ABEC™ Resins," Presented by J. G. Huddleston before the 10th International Conference on Partitioning in Aqueous Two-Phase Systems (1997), Reading, United Kingdom, Abstract book.
214. S. T. Griffin and R. D. Rogers, "Partitioning of Mercury and Thallium in Aqueous Biphasic Systems and on ABEC™ Resins," Presented by S. T. Griffin before the 10th International Conference on Partitioning in Aqueous Two-Phase Systems (1997), Reading, United Kingdom, Abstract book.
215. H. D. Willauer, S. T. Griffin, and R. D. Rogers, "Partitioning of Small Organic Molecules in Aqueous Biphasic Systems," Presented by H. D. Willauer before the 10th International Conference on Partitioning in Aqueous Two-Phase Systems (1997), Reading, United Kingdom, Abstract book.
216. R. D. Rogers, "Potential Applications of Aqueous Biphasic Systems for the Reduction of Industrial Pollution," Presented by R. D. Rogers before the 10th International Conference on Partitioning in Aqueous Two-Phase Systems (1997), Reading, United Kingdom, Abstract book. (Invited Presentation.)
217. D. L. Clark, S. D. Conradson, D. W. Keogh, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait "Coordination Chemistry of Actinide Ions (U, Np, Pu) Under Highly Alkaline Conditions," Presented by D. L. Clark before the 1997 Plutonium Futures - The Science Conference (1997), Santa Fe, NM.
218. D. L. Clark, S. D. Conradson, D. W. Keogh, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait "Coordination Chemistry of Actinide Ions Under Highly Alkaline Conditions," Presented by D. L. Clark before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract GEOC 064.

219. E. J. Brandon, J. S. Miller, R. D. Rogers, and B. M. Burkhart "A New Bulk Magnet Based on the Semiquinone Anion: Structure and Ferrimagnetic Behavior of [MnTPP][Chloroanil]•PhMe," Presented by E. J. Brandon before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract INOR 276.
220. R. A. Bartsch, G. G. Talinova, H.-S. Hwang, V. S. Talanov, R. D. Rogers, and D. W. Purkiss "New Chromogenic Lariat Ethers for Selective Alkali Metal Cation Extraction," Presented by G. G. Talanova before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 035.
221. J. Zhang, J. G. Huddleston, and R. D. Rogers "Simple Methods for the Prediction of Pertechnetate Distribution in Aqueous Biphasic Systems Based on Polyethylene Glycol," Presented by J. G. Huddleston before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 009.
222. S. T. Griffin and R. D. Rogers "Partitioning of Mercury in Aqueous Biphasic Systems and Uptake on ABEC Resins," Presented by S. T. Griffin before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 008.
223. J. G. Huddleston, H. D. Willauer, K. R. Boaz, and R. D. Rogers "Extraction of Metal Complexed Dyes Utilizing Aqueous Biphasic Systems and Aqueous Biphasic Extraction Chromatography, " Presented by J. G. Huddleston before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 094.
224. R. D. Rogers, S. T. Griffin, J. Zhang, and J. G. Huddleston "New Technologies for Metal Ion Separations: Aqueous Biphasic Systems and Aqueous Biphasic Extraction Chromatographic Resins," Presented by R. D. Rogers before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 023. (Invited Symposium Presentation.)
225. R. D. Rogers, S. T. Griffin, J. Zhang, E. P. Horwitz, A. H. Bond, F. Chang, and M. J. Gula "Separation of Pertechnetate and Iodide from Alkaline Supernate Waste using ABEC™ Resins," Presented by R. D. Rogers before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 138.
226. G. Zucchi, P.-A. Pittet, J.-C. G. Bünzli, and R. D. Rogers, "Lanthanide Complexes with Functionalized Tetraaza Macrocyclic Ligands: Luminescence Studies and Structural Aspect," Presented by G. Zucchi before the International Conference on f Elements, ICFE3 (1997), Paris, France, Abstract.
227. F. Ihringer, J.-C. G. Bünzli, R. D. Rogers, P. Dumy, and C. Sager, "Solid State and Solution Structure of Dinuclear Lanthanide Complexes with Calix[8]arenes," Presented by F. Ihringer before the International Conference on f Elements, ICFE3 (1997), Paris, France, Abstract.
228. D. T. Campbell and R. D. Rogers, "Hydroxy-Crown Ether Complexes of Uranium and Thorium," Presented by D. T. Campbell before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract T3-P5.
229. S. T. Griffin and R. D. Rogers, "Separation of Actinides from Caustic Solution Using Aqueous Biphasic Systems," Presented by S. T. Griffin before the before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract TA-A4.
230. W. Runde, D. L. Clark, S. D. Conradson, D. W. Keogh, M. P. Neu, P. D. Palmer, B. L. Scott, S. D. Reilly, R. D. Rogers, and C. D. Tait " Coordination Chemistry of Actinyl Chloride Complexes in Aqueous Solutions," Presented by W. Runde before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract T3-P19.
231. D. L. Clark, S. D. Conradson, D. W. Keogh, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait "Coordination Chemistry of Actinide Ions (U, Np, Pu) Under Highly Alkaline Conditions," Presented by D. L. Clark before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract T3-A1.
232. R. D. Rogers, J. Zhang, and D. T. Campbell, "Structural Characterization of Crown Ether Complexes of $UO_2(NCS)_2$ and $Th(NCS)_4$," Presented by R. D. Rogers before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract T3-A6.
233. A. H. Bond, J. T. Harvey, M. J. Gula, F. Chang, J. M. Williamson, R. D. Rogers, and E. P. Horwitz, "Scale-up Synthesis and Performance Assessment of ABEC Resins for the Removal of Technetium and Iodine from Alkaline Radioactive Wastes," Presented by A. H. Bond before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 18.
234. R. P. Swatloski, S. T. Griffin, and R. D. Rogers, "Perrhenate/Tungstate Separations in Aqueous Biphasic Systems," Presented by R. P. Swatloski before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 50.
235. H. D. Willauer, S. T. Griffin, J. G. Huddleston, and R. D. Rogers, "Partitioning of Aromatic Molecules in Aqueous Biphasic Systems," Presented by H. D. Willauer before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 50.
236. S. T. Griffin, A. H. Bond, and R. D. Rogers, "Separation of Heavy Main Group Metal Ions from Sulfate Media Using Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by S. T. Griffin before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 80.
237. J. G. Huddleston and R. D. Rogers, "Partitioning Behavior of Porphyrins in Aqueous Biphasic Systems," Presented by J. G. Huddleston before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 49.
238. R. D. Rogers and S. T. Griffin, "Separation of Actinides from Caustic Solution Using Aqueous Biphasic Systems," Presented by R. D. Rogers before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 20. (Invited Symposium Presentation.)
239. L. M. Rogers, C. V. K. Sharma, and R. D. Rogers "One-Dimensional Polymers and Two-Dimensional Grids Formed by Lanthanide/Ethanediphosphonic Acid Complexation," Presented by L. M. Rogers before the Fifth Chemical Congress of North America (1997), Cancún, Mexico, Abstract 1090.

240. R. P. Swatloski, C. V. K. Sharma, and R. D. Rogers "The Design of Two-Dimensional Networks in Cadmium Halide Complexes," Presented by R. P. Swatloski before the Fifth Chemical Congress of North America (1997), Cancún, Mexico, Abstract 1091.
241. C. V. K. Sharma and R. D. Rogers "Crystal Engineering of Pyrimidine Metal Complexes," Presented by C. V. K. Sharma before the Fifth Chemical Congress of North America (1997), Cancún, Mexico, Abstract 1506.
242. R. D. Rogers, C. V. K. Sharma, R. P. Swatloski, and L. M. Rogers "Coordination Chemistry to Crystal Engineering," Presented by R. D. Rogers before the Fifth Chemical Congress of North America (1997), Cancún, Mexico, Abstract 163. (Invited Symposium Presentation.)
243. G. Broker, K. Sharma, and R. D. Rogers "Crystal Engineering: Synthesis and Characterization of Porphrine Metal Complexes," Presented by G. Broker before the 215th ACS National Meeting (1998), Dallas, TX, Abstract CHED 468.
244. L. M. Rogers and R. D. Rogers "Putting Lanthanide Ions in the Crystal Engineer's Tool Box," Presented by L. M. Rogers before the 215th ACS National Meeting (1998), Dallas, TX, Abstract INOR 302.
245. R. P. Swatloski, C. V. K. Sharma, and R. D. Rogers "Toward the Design of Porous Networks: Crystal Structures of Porphyrin-Metal Halide Complexes," Presented by R. P. Swatloski before the 215th ACS National Meeting (1998), Dallas, TX, Abstract INOR 303.
246. C. V. K. Sharma and R. D. Rogers "Crystal Engineering: Coordination and Hydrogen Bonding in Cocrystals of Lanthanide Complexes," Presented by C. V. K. Sharma before the 215th ACS National Meeting (1998), Dallas, TX, Abstract INOR 304.
247. A. E. Visser, S. T. Griffin, and R. D. Rogers "Sulfonic Acid Dyes as Radionuclide Complexants in Aqueous Biphasic Systems," Presented by A. E. Visser before the 215th ACS National Meeting (1998), Dallas, TX, Abstract I&EC 037.
248. H. D. Willauer, J. G. Huddleston, S. T. Griffin, A. D. Carruth, and R. D. Rogers "The Partitioning of Small Organic Molecules in Aqueous Biphasic Systems and on ABEC Resins," Presented by H. D. Willauer before the 215th ACS National Meeting (1998), Dallas, TX, Abstract I&EC 036.
249. J. G. Huddleston, H. D. Willauer, J. F. Herrington, A. D. Carruth, S. T. Griffin, and R. D. Rogers "Extraction of Organic Molecules Utilizing Aqueous Biphasic Systems and the Physicochemical Properties of the Phases," Presented by J. G. Huddleston before the 215th ACS National Meeting (1998), Dallas, TX, Abstract I&EC 035.
250. R. D. Rogers, J. G. Huddleston, S. T. Griffin. H. D. Willauer, and A. E. Visser "Utilizing Surfactants to Control Partitioning of Solutes in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 215th ACS National Meeting (1998), Dallas, TX, Abstract I&EC 016. (Invited Symposium Presentation.)
251. R. D. Rogers and D. E. Nikles, "The University of Alabama Center for Green Manufacturing," Presented by R. D. Rogers before the 2nd Annual Green Chemistry & Engineering Conference: Global Perspectives, (1998), Washington, DC, Abstract book page 11.
252. R. D. Rogers, J. G. Huddleston, H. D. Willauer, S. T. Griffin, and A. E. Visser, "Green Separation Science & Technology: Can Environmentally Benign Polymers Replace VOCs in Industrial Scale Liquid/Liquid Separations?," Presented by R. D. Rogers before the 2nd Annual Green Chemistry & Engineering Conference: Global Perspectives, (1998), Washington, DC, Abstract book page 20.
253. R. D. Rogers, "Crystal Engineering of Ordered Porphyrin Arrays," Presented by R. D. Rogers before the Fourth Department of Energy/Basic Energy Sciences Conference on Homogeneous Catalysis and Organometallic Chemistry (1998), Baltimore, MD, Abstract book p. 95.
254. R. D. Rogers, C. V. K. Sharma, G. A. Broker, R. P. Swatloski, and L. M. Rogers, "Crystal Engineering of Porous Solids using Coordination Polymers," Presented by R. D. Rogers before the American Crystallographic Association Annual Meeting (1998), Arlington, VA, Abstract TR.00.05. (Invited Transactions Symposium Presentation.)
255. L. M. Rogers, C. V. K. Sharma, and R. D. Rogers, "Lanthanide Ions as Part of the Crystal Engineer's Tool Box," Presented by L. M. Rogers before the American Crystallographic Association Annual Meeting (1998), Arlington, VA, Abstract P348.
256. G. G. Talanova, R. A. Bartsch, N. S. A. Elkarim, R. E. Haynes, Jr., V. S. Talanov, and R. D. Rogers, "Effect of the picrate anion on the selectivity of aromatic-containing crown ethers in alkali metal cation binding," Presented by G. G. Talanova before the 216th ACS National Meeting (1998), Boston, MA, Abstract INOR 008.
257. G. Park, R. D. Rogers, M. W. Brechbiel, and R. P. Planalp, "Structural and Steric Effect Study of Metal Complexes of Novel Hexadentate Ligands Derived from *cis*-1,3,5-Triaminocyclohexane Framework," Presented by G. Park before the 216th ACS National Meeting (1998), Boston, MA, Abstract INOR 645.
258. R. P. Swatloski, C. V. K. Sharma, G. A. Broker, L. M. Rogers, and R. D. Rogers, "The Crystal Engineer's Tool Box: Coordination Polymers for Design of Porous Solids," Presented by R. P. Swatloski before the 216th ACS National Meeting (1998), Boston, MA, Abstract INOR 500.
259. S. T. Griffin and R. D. Rogers, "Aqueous Biphasic Extraction Chromatographic Resins: New Technologies for Low Specific Activity-Molybdenum-99/Technetium-99m Separations," Presented by S. T. Griffin before the 216th ACS National Meeting (1998), Boston, MA, Abstract I&EC 006.
260. R. D. Rogers, R. P. Swatloski, and S. T. Griffin, "Aqueous Biphasic Extraction Chromatographic Resins for Separation of Rhenium-188 from Tungsten-188," Presented by R. D. Rogers before the 216th ACS National Meeting (1998), Boston, MA, Abstract I&EC 012. (Invited Symposium Presentation.)
261. R. D. Rogers, J. G. Huddleston, and S. T. Griffin, "Aqueous Biphasic Extraction Chromatographic Resins as Tunable Affinity Adsorbents: Definitions and Applications in Pollution Prevention," Presented by R. D. Rogers before the 1998 Annual Meeting of the American Institute of Chemical Engineers (1998), Miami Beach, FL, Abstract. (Invited Symposium Presentation.)

262. R. D. Rogers, C. V. K. Sharma, and G. A. Broker, "Crystal Engineering of Ordered Porphyrin Arrays," Presented by R. D. Rogers before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract INOR 046. (Invited Symposium Presentation.)
263. D. W. Keogh, D. L. Clark, S. D. Conradson, R. J. Donohoe, David E. Morris, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait, "Structure and Reactivity of Penta- and Hexa-Valent Actinide Ions (U, Np, Pu) Under Highly Alkaline Conditions," Presented by D. W. Keogh before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract NUCL 167.
264. B. M. Rapko, B. K. McNamara, G. J. Lumetta, B. P. Hay, R. D. Rogers, and G. Broker, "Coordination Chemistry of Tetraalkyldiamides with f-Block Metal Salts," Presented by B. M. Rapko before the 217th ACS National Meeting (1999), Anaheim, CA, Abstracts INOR 368.
265. D. L. Clark, D. W. Keogh, S. D. Conradson, R. J. Donohoe, D. E. Morris, M. P. Neu, P. D Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait, "Coordination Chemistry of Hexa- and Hepta-Valent Actinide Ions (U, Np, Pu) Under Alkaline Conditions," Presented by D. L. Clark before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract INOR 066.
266. D. L. Clark, D. W. Keogh, S. D. Conradson, L. A. Morales, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait, "Structural Trends in Actinyl(V, VI) Ions of U, Np, and Pu," Presented by D. L. Clark before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract NUCL 042.
267. J. M. Duffey, M. J. Gula, J. T. Harvey, E. P. Horwitz, A. H. Bond, S. T. Griffin, R. D. Rogers, and J. L. Collins, "A Flowsheet for the Separation, Concentration, and Immobilization of Pertechnetate Ion from Alkaline Wastes Using ABEC Resins," Presented by J. M. Duffey before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 044.
268. G. A. Broker, C. V. K. Sharma, B. T. Pyevich, J. A. Swenson, G. J. Szulczewski, and R. D. Rogers, "Hydrogen-Bonded Supramolecular Assembly of Tetrapyridylporphyrins on a Gold Surface," Presented by G. A. Broker before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract INOR 542.
269. G. A. Broker, C. V. K. Sharma, and R. D. Rogers, "Inclusion Properties of Crystal Engineered Tetrapyridylporphyrin Coordination Complexes," Presented by G. A. Broker before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract INOR 543.
270. A. E. Visser, R. P. Swatloski, J. G. Huddleston, and R. D. Rogers, "Room Temperature Ionic Liquids as Alternatives to Organic Solvents in Liquid/Liquid Extraction of Metal Ions," Presented by A. E. Visser before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 040.
271. A. E. Visser, D. H. Hartman, J. G. Huddleston, and R. D. Rogers, "Room Temperature Ionic Liquids for Liquid/Liquid Extraction of Dyes from Aqueous Media" Presented by A. E. Visser before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 041.
272. R. P. Swatloski, A. E. Visser, J. G. Huddleston, and R. D. Rogers, "Room Temperature Ionic Liquids as Alternatives to Organic Solvents in Liquid/Liquid Extraction of Dilute Organic Contaminants," Presented by R. P. Swatloski before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 042.
273. H. W. Willauer, J. G. Huddleston, and R. D. Rogers, "Modeling Partitioning Behavior in Aqueous Biphasic Systems," Presented by H. W. Willauer before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 043.
274. R. D. Rogers, A. E. Visser, R. P. Swatloski, D. H. Hartman, and S. T. Griffin, "Environmentally Benign Liquid/Liquid Extraction Media for Metal Ion Separations: Aqueous Biphasic Systems and Room Temperature Ionic Liquids," Presented by R. D. Rogers before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 109. (Invited Symposium Presentation.)
275. R. D. Rogers, S. T. Griffin, and A. E. Visser, "The Effects of Plutonium Speciation on Partitioning in Polyethylene Glycol-Based Aqueous Biphasic Systems and ABEC Resins," Presented by R. D. Rogers before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract NUCL 049. (Invited Symposium Presentation.)
276. A. E. Visser, D. H. Hartman, S. T. Griffin, and R. D. Rogers, "Calixarenes as Ligands in Environmentally-Benign Liquid/Liquid Extraction Media," Presented by R. D. Rogers before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 226. (Invited Symposium Presentation.)
277. Rogers, R. D. "Polymer-Based, Environmentally-Benign Liquid/Liquid Extraction Media for Separations," presented by R. D. Rogers before the Third DOE/BES Separations Workshop (1999), Savannah, GA, Abstract.
278. R. D. Rogers, A. E. Visser, and S. T. Griffin, "Using Environmentally Benign Liquid/Liquid Extraction Media for Metal Ion Separations: Aqueous Biphasic Systems and Room temperature Ionic Liquids," Presented by R. D. Rogers before the United Engineering Foundation, Inc. Conference *Metal Separation Technologies Beyond 2000: Integrating Novel Chemistry with Processing* (1999), Abstract.
279. A. E. Visser, R. P. Swatloski, D. H. Hartman, and R. D. Rogers, "Room Temperature Ionic Liquids as Replacements for Volatile Organic Solvents in Liquid/Liquid Separations," Presented by A. E. Visser before the United Engineering Foundation, Inc. Conference *Metal Separation Technologies Beyond 2000: Integrating Novel Chemistry with Processing* (1999), Abstract.
280. J. G. Huddleston, H. D. Willauer, S. K. Spear, K. D. Smith, and R. D. Rogers, "Polymer-Based Aqueous Biphasic Extraction Technology in the Paper Pulping Process," Presented by J. G. Huddleston before the 3rd Annual Green Chemistry and Engineering Conference: Moving Toward Industrial Ecology (1999), Washington, DC, Abstract book page 44.
281. R. D. Rogers, A. E. Visser, R. P. Swatloski, H. D. Willauer, and J. G. Huddleston, "Room Temperature Ionic Liquids As Alternatives To Organic Solvents In Liquid/Liquid Extraction," Presented by R. D. Rogers before the 3rd Annual Green Chemistry and Engineering Conference: Moving Toward Industrial Ecology (1999), Washington, DC, Abstract book page 5. (Invited Symposium Presentation.)

282. J. G. Huddleston, J. W. Baldwin, R. M. Metzger, and R. D. Rogers, "Solvatochromic Studies in Polyethylene Glycol/Salt Aqueous Biphasic Systems," Presented by J. G. Huddleston before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 1.
283. H. D. Willauer, J. G. Huddleston, and R. D. Rogers, "Modeling the Partitioning Behavior of Small Organic Molecules in Aqueous Biphasic Systems," Presented by H. D. Willauer before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 6.
284. A. D. Carruth, H. D. Willauer, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "The Use of Quantum Mechanical Models (AMSOL) to Predict the Distribution of Organic Molecules in Aqueous Biphasic Systems," Presented by A. D. Carruth before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 18.
285. K. D. Smith, S. K. Spear, and R. D. Rogers, "Aqueous Biphasic Systems: Influences of Polymer Molecular Weight on System Behavior," Presented by K. D. Smith before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 35.
286. H. D. Willauer, A. P. Kassangottuwar, J. G. Huddleston, J. M. Wiest, G. C. April, and R. D. Rogers, "Aqueous Biphasic Systems for the Separation of Lignins from Cellulose in the Paper Pulping Process," Presented by H. D. Willauer before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 55.
287. G. A. Broker, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Coordination vs. Hydration of Metal Ions with PEG Polymers as a Function of Polymer Length," Presented by G. A. Broker before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 62.
288. D. Boochee, L. Dunklin, R. Lee, J. G. Huddleston, H. D. Willauer, and R. D. Rogers, "Summer Undergraduate Research Program (SURP) at The University of Alabama: Synthesis and Characterization of Room Temperature Ionic Liquids and Phase Diagrams for Polyethylene Glycol/Salt Mixtures," Presented by L. Dunklin and R. Lee before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 64.
289. Rogers, R. D.; H. D. Willauer, S. T. Griffin, J. G. Huddleston, "Aqueous Polymeric Solutions as Environmentally-Benign Solvent Extraction Media," Presented by R. D. Rogers before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 86.
290. M. J. Gula, M. Langer, R. Rogers, and A. Bond, "Separation, Concentration and Immobilization of Technetium from Alkaline Supernate Waste with Eichrom's ABEC® resin," Presented by M. Langer before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 87.
291. S. T. Griffin, S. K. Spear, and R. D. Rogers, "Partitioning of Iodide in Aqueous Biphasic Systems and Uptake on ABEC® Resins," Presented by S. T. Griffin before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 88.
292. S. K. Spear, S. T. Griffin, and R. D. Rogers, "A New Rhenium-188 Generator Technology Using Polyethylene Glycol-Based Aqueous Biphasic Extraction Chromatographic Resins," Presented by S. K. Spear before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 89.
293. A. E. Visser, S. T. Griffin, D. H. Hartman, and R. D. Rogers, "Napthol and Resorcinol-Based Azo Dyes as Metal Ion Complexants in Aqueous Biphasic Systems," Presented by A. E. Visser before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 90.
294. M. Li, Z.-Q. Zhu, J. G. Huddleston, and R. D. Rogers, "Partitioning of Erythromycin by Temperature-Induced Aqueous Two-Phase System," Presented by M. Li before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 94.
295. L. M. Rogers, G. A. Broker, and R. D. Rogers, "Lanthanide Ions as Part of the Crystal Engineer's Tool Box," Presented by L. M. Rogers before the XVIIth International Union of Crystallography Congress & General Assembly (1999), Glasgow, Scotland, Abstract P11.OD.012.
296. R. D. Rogers, G. A. Broker, C. V. K. Sharma, B. T. Pyevich, J. A. Swenson, and G. J. Szulczewski, "Application of Crystal-Engineered Tetrapyridylporphyrin Complexes to Hydrogen-Bonded Supramolecular Assembly on a Gold Surface," Presented by R. D. Rogers before the XVIIth International Union of Crystallography Congress & General Assembly (1999), Glasgow, Scotland, Abstract P11.OD.005.
297. M. P. Neu, D. L. Clark, S. D. Conradson, R. J. Donohoe, J. C. Gordon, D. W. Keogh, D. E. Morris, R. D. Rogers, B. L. Scott, and C. D. Tait, "Structure and Stability of Actinides (U, Np, Pu) under Strongly Alkaline Radioactive Waste Tank Conditions," Presented by M. P. Neu before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract NUCL 088.
298. R. P. Planalp, G. Park, R. D. Rogers, and M. W. Brechbiel, "Synthesis and Characterization of Dicationic Metal Complexes of tachpyr and tach-6-mepyr Ligands Derived from the *cis*-1,3,5-Triaminocyclohexane Framework," Presented by G. Park before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract INOR 516.
299. D. R. Whitcomb and R. D. Rogers, "Taking Advantage of the Ag-O Supramolecular Synthon: Reprise of an Old Coordination Linkage," Presented by D. R. Whitcomb before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract INOR 508.
300. R. D. Rogers, G. A. Broker, C. V. K. Sharma, "Polymorphous One-Dimensional Tetrapyridylporphyrin-Coordination Polymers Structurally Mimic Aryl-Stacking Interactions," Presented by G. A. Broker before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract INOR 463.
301. S. J. Cooke, N. Jackson, and R. Rogers, "Why You Should be in the Division of Industrial & Engineering Chemistry," Presented by S. J. Cooke before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 010.

302. R. D. Rogers, A. D. Carruth H. D. Willauer, S. K. Spear, and J. G. Huddleston, "Quantum Mechanical Models (AMSOL) for the Prediction of the Distribution of Organic Molecules in Aqueous Biphasic Systems," Presented by K. D. Smith before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 016.
303. R. D. Rogers, K. D. Smith, and S. K. Spear, "Aqueous Biphasic Systems: Effect of Temperature on Partitioning," Presented by K. D. Smith before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 017.
304. R. D. Rogers, H. D. Willauer, and J. G. Huddleston, Effects of Temperature on the Partitioning of Solutes in PEG/Salt Aqueous Biphasic Systems," Presented by H. D. Willauer before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 018.
305. R. D. Rogers, J. G. Huddleston, H. D. Willauer, "Aqueous Polymers for the Extraction of Lignin During Alkaline Pulping," Presented by J. G. Huddleston before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 019.
306. R. D. Rogers, S. T. Griffin, and S. K. Spear, "Partitioning of Iodide in Aqueous Biphasic Systems and Uptake on ABEC Resins," Presented by S. T. Griffin before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 020.
307. R. D. Rogers, S. K. Spear, K. D. Smith, and J. G. Huddleston, "Aqueous Biphasic Systems Using Polyethylene Glycol/Ammonium Carbamate," Presented by S. K. Spear before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 021.
308. R. D. Rogers, R. P. Swatloski, and A. E. Visser, "Liquid-Liquid Extraction of Organics in Room-Temperature Ionic Liquids: Cationic Effects," Presented by R. P. Swatloski before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 022.
309. R. D. Rogers, A. E. Visser, R. P. Swatloski, and S. T. Griffin, "Anionic Extractants for Partitioning Metal Ions to Room-Temperature Ionic Liquids," Presented by A. E. Visser before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 023.
310. R. D. Rogers, G. A. Broker, and S. K. Spear, "Uptake of Metal Ions by Crystal-Engineered Tetrapyridylporphyrin Coordination Polymers," Presented by G. A. Broker before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 27.
311. R. D. Rogers, "Green/Sustainable Separation Science and Technology," Presented by R. D. Rogers at Industry Central, 218th ACS National Meeting (1999), New Orleans, LA (Invited Presentation, No Abstract).
312. R. D. Rogers, A. E. Visser, R. P. Swatloski, and J. G. Huddleston, "Room Temperature Ionic Liquids as Alternatives to Organic Solvents," Presented by R. D. Rogers to the Tenth Annual International Workshop on Solvent Substitution and the Elimination of Toxic Substances and Emissions (1999), Scottsdale, AZ. (Invited Presentation.)
313. K. D. Smith, S. K. Spear, and R. D. Rogers, "Aqueous Biphasic Systems: Polyethylene Glycol Compared with Polyethylene/Polypropylene Glycol Random Copolymer in Biphasic Systems," Presented by K. D. Smith before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 52.
314. S. K. Spear, K. D. Smith, J. G. Huddleston, and R. D. Rogers, "Polyethylene Glycol/Ammonium Carbamate Aqueous Biphasic Systems," Presented by S. K. Spear before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 53.
315. H. D. Willauer, J. G. Huddleston, S. Spear, and R. D. Rogers, "Modeling Partitioning Behavior of Organic Solutes in Aqueous Biphasic Systems," Presented by H. D. Willauer before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 58.
316. J. G. Huddleston, H. D. Willauer, S. K. Spear, K. D. Smith, and R. D. Rogers, "Polymer-Based Aqueous Biphasic Extraction Technology for Reaction Engineering of the Alkaline Paper Pulping Process," Presented by J. G. Huddleston before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 73.
317. A. E. Visser, R. P. Swatloski, H. D. Willauer, D. H. Hartman, J. G. Huddleston, and R. D. Rogers, "Room-Temperature Ionic Liquids as Solvents for Liquid/Liquid Extraction of Organic Molecules and Metal Ions," Presented by A. E. Visser before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 79.
318. S. T. Griffin, S. K. Spear, and R. D. Rogers, "Mercury Uptake from Solutions of Low Salt Concentration Using ABEC™ Resins," Presented by S. T. Griffin before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 82.
319. R. D. Rogers, A. E. Visser, R. P. Swatloski, H. D. Willauer, D. H. Hartman, and J. G. Huddleston, "Room-Temperature Ionic Liquids as Alternatives to Organic Solvents in Liquid/Liquid Extraction," Presented by R. D. Rogers before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 18.
320. R. D. Rogers, "Green Manufacturing: Changing the Way Students Think about Manufacturing Processes and the Environment," presented by R. D. Rogers before the 15th Annual NSF EPSCoR Conference (1999), Orange Beach, AL, No Abstract, Proceedings, page 6. (Invited Presentation.)
321. R. D. Rogers, "Ionic Liquids as Alternatives to Organic Solvents," presented by R. D. Rogers before the United Engineering Foundation, Inc. Conference *Clean Products and Processes II* (1999), Abstract. (Invited Presentation).
322. A. H. Bond, R. D. Rogers, M. J. Gula, E. P. Horwitz, J. T. Harvey, and J. L. Collins, "Flowsheet Development for the Separation and Immobilization of Pertechnetate from Alkaline Radioactive Wastes," presented by A. H. Bond before the Materials Research Society Fall Meeting (1999), Boston, MA, Abstract.
323. J. G. Huddleston, H. D. Willauer, S. K. Griffin, S. S. Spear, and R. D. Rogers, "Wholly Aqueous Solvent Extraction Systems: properties and Applications, Presented by J. G. Huddleston before the 2000 Spring AIChE National Meeting (2000), Atlanta,

GA, Paper 14b, Membrane and Extraction Science and Technologies for Environmental Applications Topical Conference Proceedings, D. Bhattacharyya and J. S. Kanel, Eds.; AIChE, New York, 2000; pp 192-196.

324. R. D. Rogers, A. E. Visser, R. P. Swatloski, H. D. Willauer, and J. G. Huddleston, Room Temperature Ionic Liquids as Alternatives to Organic Solvents in Liquid/Liquid Extraction, Presented by R. D. Rogers before the 2000 Spring AIChE National Meeting (2000), Atlanta, GA, Paper 14e, Membrane and Extraction Science and Technologies for Environmental Applications Topical Conference Proceedings, D. Bhattacharyya and J. S. Kanel, Eds.; AIChE, New York, 2000; pp 200-204.
325. R. D. Rogers, A. E. Visser, R. P. Swatloski, and D. H. Hartman "Room-Temperature Ionic Liquids as Alternatives to Volatile Organic Solvents in Liquid/Liquid Extraction," Presented by A. E. Visser before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 003.
326. A. Waterfeld, J. S. Thrasher, J. F. Sullivan, R. D. Rogers, and J. L. Howell "Synthesis, Structure, and Chemistry of the Bistrifluoromethylated Version of Meldrum's Acid," Presented by A. Waterfeld before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract FLUO 007.
327. R. D. Rogers, A. E. Visser, J. G. Huddleston, R. P. Swatloski, G. A. Broker, and H. D. Willauer, "Green Chemistry and Engineering in Separations Science," Presented by R. D. Rogers before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 025. (Invited Symposium Presentation.)
328. H. Luo, R. D. Rogers, and M. W. Brechbiel, "Synthesis of Difunctionalized Macrocyclic Chelates Based on Cyclam and Cyclen," Presented by H. Luo before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract INOR 175.
329. E. Blair, J. A. Nikles, D. E. Nikles, L. M. Rogers, R. D. Rogers, D. Stabler, and S. C. Street, "Molecular Structure of the Amine-Quinone Model Compound, 2,4-Bis(Dimethylamino)-1,4-Benzoquinone," Presented by E. Blair before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract POLY 192.
330. B. M. Rapko, G. J. Lumetta, B K. McNamara, B. P. Hay, R. D. Rogers, and G. Broker, "Coordination Chemistry of Tetraalkyldiamides with f-Block Metal Salts," Presented by B. M. Rapko before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 050.
331. R. D. Rogers, A. E. Visser, W. M. Reichert, and R. P. Swatloski, "Investigation of Room-Temperature Ionic Liquids via X-Ray Crystallographic Characterization of Low-Melting Analogs," Presented by R. P. Swatloski before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 084.
332. W. M. Reichert, A. E. Visser, R. P. Swatloski, and R. D. Rogers, "Synthesis and Characterization of Novel Room-Temperature Ionic Liquids," Presented by W. M. Reichert before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 085.
333. R. D. Rogers, A. E. Visser, R. P. Swatloski, and S. T. Griffin, "Crown Ethers as Extractants for Group 1 and 2 Metal Ions in Room-Temperature Ionic Liquids," Presented by A. E. Visser before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 086.
334. R. D. Rogers, "Development of ABEC resins: A Study of Academic/National Laboratory/Industry Cooperation," Presented by R. D. Rogers before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 164. (Invited Symposium Presentation.)
335. R. D. Rogers, and G. A. Broker, "Toward Understanding Weak Intermolecular Forces: Crystal Engineering of Porous Solids," Presented by R. D. Rogers before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 155. (Invited Symposium Presentation.)
336. R. D. Rogers, "Vision 2020: How Green Chemistry Can Shape the Future of the Sugar Processing Industry," Presented by R. D. Rogers Before the SPRI 2000 Conference on Sugar Processing Research (2000), Porto, Portugal, Abstract Book. (Invited Plenary Presentation).
337. R. D. Rogers, "Ionic Liquids as Solvent Replacements in Industrial-Scale Separations – Opportunities and Challenges," Presented by R. D. Rogers before the NATO Advanced Research Workshop, Green Industrial Applications of Ionic Liquids (2000), Crete, Greece, Abstract Book (Invited Presentation).
338. R. D. Rogers, A. Visser, W. M. Reichert, and R. P. Swatloski, "Investigation of Room-Temperature Ionic Liquids via X-ray Crystallographic Characterization of Low Melting Analogs," Presented by R. P. Swatloski before the NATO Advanced Research Workshop, Green Industrial Applications of Ionic Liquids (2000), Crete, Greece, Abstract Book.
339. A. E. Visser, R. P. Swatloski, S. T. Griffin, and R. D. Rogers, "Crown Ethers as Extractants for Group I and II Metal Ions in Room-Temperature Ionic Liquids," Presented by A. E. Visser before the NATO Advanced Research Workshop, Green Industrial Applications of Ionic Liquids (2000), Crete, Greece, Abstract Book.
340. J. G. Huddleston, H. D. Willauer, M. Li, and R. D. Rogers, "The Solution Properties of Aqueous Biphasic Systems," Presented by J. G. Huddleston before the Fourteenth Symposium on Thermophysical Properties (2000), Boulder, CO, Abstract book page 97.
341. R. D. Rogers, J. G. Huddleston, A. E. Visser, and R. P. Swatloski, "Linear Free Energy Relationships to Describe Solute Partitioning in Room Temperature Ionic Liquids," Presented by R. D. Rogers before the Fourteenth Symposium on Thermophysical Properties (2000), Boulder, CO, Abstract book page 97.
342. A. E. Visser, R. P. Swatloski, W. M. Reichert, R. D. Rogers, "Chemical and Physical Characteristics of Room-Temperature Ionic Liquids and the Associated Implications for Their Use as Solvent Alternatives," Presented by R. D. Rogers before the 4th Annual Green Chemistry and Engineering Conference: Sustainable Technologies: From Research to Industrial Implementation (2000), Washington, DC, Abstract book page 11.

343. H. D. Willauer, J. G. Huddleston, M. Li, and R. D. Rogers, "Aqueous Biphasic Systems as Green Alternatives to Chemical Pulping in the Alkaline Paper Pulping Process," Presented by H. D. Willauer before the 4th Annual Green Chemistry and Engineering Conference: Sustainable Technologies: From Research to Industrial Implementation (2000), Washington, DC, Abstract book page 38.
344. R. D. Rogers, "Ionic Liquids as Alternative Reaction Media: Challenges and Opportunities," Presented by R. D. Rogers before the Gordon Research Conference on Green Chemistry (2000), New London, CT (Invited Presentation).
345. R. D. Rogers, "Ionic Liquids as Alternatives to Organic Solvents for Liquid Extraction," Presented by R. D. Rogers before the Gordon Research Conference on Separation and Purification (2000), New London, NH (Invited Presentation).
346. A. E. Visser and R. D. Rogers, "Room Temperature Ionic Liquids as Solvents for Liquid/Liquid Extraction of Organic Molecules and Metal Ions," Presented by A. E. Visser before the Gordon Research Conference on Separation and Purification (2000), New London, NH.
347. H. W. Willauer and R. D. Rogers, "Development of Predictive Tools for Partitioning in Aqueous Biphasic Systems," Presented by H. W. Willauer before the Gordon Research Conference on Separation and Purification (2000), New London, NH.
348. H. Luo, N. Eberly, R. D. Rogers, and M. W. Brechbiel, "*cis,cis*-1,3,5-Triaminocyclohexane-*N,N'*,*N''*-Triacetic Acid (H_3tachta) and Its Metal Complexes," Presented by H. Luo before the 220th ACS National Meeting (2000), Washington, DC, Abstract INOR 387.
349. A. E. Visser, R. P. Swatloski, W. M. Reichert, and R. D. Rogers, "Chemical and Physical Characteristics of Room-Temperature Ionic Liquids and the Associated Implications for Their Use as Solvent Alternatives," Presented by A. E. Visser before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 014.
350. R. P. Swatloski, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Crystallographic Characterization of Solid-State Analogs of Room-Temperature Ionic Liquid Solvents," Presented by R. P. Swatloski before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 041.
351. W. M. Reichert, A. E. Visser, R. P. Swatloski, and R. D. Rogers, "Ionic Composition as a Variable to Fine Tune the Physical Properties of Room-Temperature Ionic Liquids," Presented by W. M. Reichert before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 042.
352. R. D. Rogers, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Liquid/Liquid Extraction of Actinides in Room-Temperature Ionic Liquids," Presented by A. E. Visser before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 043.
353. H. D. Willauer, J. G. Huddleston, M. Li, Z. Guo, G. C. April, R. D. Rogers, "Polymer-Based Aqueous Biphasic Systems for Reaction Engineering of the Kraft Pulping Process," Presented by H. D. Willauer before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 180.
354. R. D. Rogers, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Room-Temperature Ionic Liquids as Designer Solvents: Manipulation of Solvent Properties through Simple Variation in Ionic Composition," Presented by R. D. Rogers before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 018 (Invited Symposium Presentation).
355. R. D. Rogers, "University of Alabama's Center for Green Manufacturing," Presented by R.D. Rogers before the 22nd Annual Meeting of the Council for Chemical Research (2000), New Orleans, LA.
356. R. D. Rogers, "Alabama Institute of Manufacturing Excellence," Presented by R.D. Rogers before the 22nd Annual Meeting of the Council for Chemical Research (2000), New Orleans, LA
357. B. Wu, R. G. Reddy, and R. D. Rogers, "Aluminum Recycling via Room Temperature Electrolysis in Ionic Liquids," Presented by B. Wu before the TMS Fall Extraction & Process Metallurgy Meeting: New Technologies for the Next Millennium (2000), Pittsburgh, PA, Program booklet p 12.
358. Z. Guo, M. Li, H. D. Willauer, J. G. Huddleston, R. D. Rogers, and G. C. April, "Polymer-Based Aqueous Biphasic Systems as Improvement for Kraft Hardwood Pulping Process," Presented by Z. Guo before the 2000 Fall AIChE National Meeting (2000), Los Angeles, CA.
359. E. Dadachova, C. Park, H. Luo, N. Eberly, R. Rogers, C. Paik, and M. Brechbiel, "Characterization of $^{67}Ga^{3+}$ Complex with *cis, cis*-1,3,5-Triamino-Cyclohexane-*N,N',N''*-Triacetic Acid," Presented by E. Dadachova before the 2000 International Chemical Congress of Pacific Basin Societies, Pacifichem 2000 (2000), Honolulu, HI, Abstract MEDI 69.
360. R. D. Rogers, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Chemical and Physical Characteristics of Room-Temperature Ionic Liquids (and Solid-State Analogs): Implications for Their Use as Solvent Alternatives," Presented by R. D. Rogers before the 2000 International Chemical Congress of Pacific Basin Societies, Pacifichem 2000 (2000), Honolulu, HI, Abstract ANYL 281.
361. B. Wu, R. G. Reddy, and R. D. Rogers, "Aluminum Recycling via Room Temperature Electrolysis in Ionic Liquids," Presented by B. Wu before the 2001 TMS Annual Meeting (2001), New Orleans, LA, Abstract Program booklet.
362. R. D. Rogers, "Green Chemistry and Ionic Liquids: Synergies and Ironies," Presented by R. D. Rogers before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 001. (Invited Plenary Presentation)
363. W. M. Reichert, A. E. Visser, R. P. Swatloski, R. D. Rogers, and M. Koel, "Characterization of Solute-Solvent Properties in Ionic Liquids by Gas Chromatography," Presented by W. M. Reichert before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 024.
364. P. Scovazzo, A. E. Visser, J. H. Davis, Jr., R. D. Rogers, C. Koval, and R. D. Noble, "Supported Ionic Liquid Membranes and Facilitated Ionic Liquid Membranes," Presented by P. Scovazzo before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 028.

365. R. D. Rogers, A. E. Visser, W. M. Reichert, and R. P. Swatloski, "Comparative Study of the Chemical and Physical Properties of Hydrophobic vs. Hydrophilic Ionic Liquids," Presented by A. E. Visser before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 049.
366. R. P. Swatloski, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Characteristics of Room-Temperature Ionic Liquids in Various Water/Ethanol Solutions," Presented by R. P. Swatloski before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 050.
367. J. G. Huddleston, H. D. Willauer, and R. D. Rogers, "Free-Energy Relationships and Solvatochromic Properties of Aqueous Solvent Systems Based on Poly(Ethylene Glycol)," Presented by J. G. Huddleston before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 051.
368. W. M. Reichert, A. E. Visser, R. P. Swatloski, S. K. Spear, and R. D. Rogers, "Solubilization and Derivatization of Chitin In Room-Temperature Ionic Liquids," Presented by W. M. Reichert before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 052.
369. S. K. Spear, G. A. Broker, M. A. Klingshirn, L. Moens, M. A. Godshall, T. P. Johnson, and R. D. Rogers, "Solubility of Mono- and Disaccharides in Ionic Liquids," Presented by S. K. Spear before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 053.
370. P. Scovazzo, A. E. Visser, J. H. Davis, Jr., R. D. Rogers, C. Koval, and R. D. Noble, "Supported Ionic Liquid Membranes and Facilitated Ionic Liquid Membranes," Presented by P. Scovazzo before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 054.
371. R. D. Rogers, A. E. Visser, R. P. Swatloski, S. T. Griffin, and W. M. Reichert, "Applications of Room-Temperature Ionic Liquids: Actinide Separations," Presented by A. E. Visser before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 192.
372. B. Wu, R. G. Reddy, and R. D. Rogers, "Potential Applications of Ionic Liquids in Aluminum Industries," Presented by B. Wu before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 196.
373. J. G. Huddleston, G. A. Broker, H. D. Willauer, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Free-Energy Relationships and Solvatochromic Properties of Room-Temperature Ionic Liquids Based on Methylimidazolium Cations," Presented by J. G. Huddleston before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 278.
374. R. D. Rogers, M. A. Godshall, T. P. Johnson, L. Moens, and S. K. Spear, "Green Chemistry, the Carbohydrate Economy, and Ionic Liquids: Compatible Goals, Compatible Chemistries?" Presented by R. D. Rogers before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 347.
375. S. K. Spear, W. M. Reichert, R. P. Swatloski, and R. D. Rogers, "Ionic Liquids as Benign Solvents for Extraction Of Astaxanthin and Solubilitization of Chitin," Presented by S. K. Spear before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 412.
376. G. J. Lumetta, B. K. McNamara, B. M. Rapko, R. D. Rogers, G. A. Broker, and J. E. Hutchison, "Extraction of Uranium(VI) with Malonamides: What's Really Going On?" Presented by G. J. Lumetta before the 221st ACS National Meeting (2001), San Diego, CA, Abstract INOR 686.
377. J. G. Huddleston, H. D. Willauer, and R. D. Rogers, "Aqueous Biphasic Systems: Linear Free Energy Relationships and Solvatochromic Parameters," Presented by J. G. Huddleston before the DOE Office of Basic Energy Sciences Separations and Analysis Program Contractor's Meeting (2001), San Diego, CA, Abstract book.
378. J. G. Huddleston, H. D. Willauer, S. T. Griffin, and R. D. Rogers, "Aqueous Biphasic Systems: Solute Partitioning and the Physical Nature of the Phases," Presented by R. D. Rogers before the DOE Office of Basic Energy Sciences Separations and Analysis Program Contractor's Meeting (2001), San Diego, CA, Abstract book.
379. R. D. Rogers, J. G. Huddleston, S. K. Spear, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Green Chemistry and Ionic Liquids: Synergies and Ironies," Presented by R. D. Rogers before the 2001 Spring National Meeting of AIChE (2001), Houston, TX, Abstract 12b. (Invited Symposium Presentation)
380. Z. Guo, H. D. Willauer, J. G. Huddleston, R. D. Rogers, and G. C. April, "Polymer-Based Aqueous Biphasic Systems as Alternatives for Kraft Pulping Process," Presented by Z. Guo before the 2001 Spring National Meeting of AIChE (2001), Houston, TX, Abstract 99g.
381. Z. Guo, J. G. Huddleston, R. D. Rogers, and G. C. April, "Delignification of Hardwood in Aqueous Biphasic Systems with Metal Salts as Catalysts," Presented by Z. Guo before the 2001 Fall National Meeting of AIChE (2001), Reno, NV, Abstract.
382. B. Wu, R. G. Reddy, and R. D. Rogers, "Novel Ionic Liquid Thermal Storage for Solar Thermal Electric Power Systems," Presented by B. Wu before the Solar Forum 2001: Solar Energy: The Power to Choose (2001), Washington, DC, Abstract.
383. R. D. Rogers; S. K. Spear; R. P. Swatloski; W. M. Reichert; M. A. Godshall; T. P. Johnson; L. Moens "Non-Sugar Products from Sugarcane for the New Millennium: Green Pathways to a Carbohydrate Economy?" Presented by R. D. Rogers before the 60th Annual International Sugar Industry Technologists Meeting (2001), Taipei, Taiwan. (Invited Keynote Speaker)
384. R. D. Rogers, S. K. Spear, R. P. Swatloski, W. M. Reichert, M. A. Godshall, T. P. Johnson, and L. Moens, "Green Chemistry, the Carbohydrate Economy, and Ionic Liquids: Compatible Goals, Compatible Chemistries?" Presented by R. D. Rogers before IUPAC CHEMRAWN XIV World Conference, Toward Environmentally Benign Processes and Products (2001), Boulder, CO, Abstract Book.
385. R. D. Rogers, "Scientific journals, a conversation with top editors of science journals," Presented by R. D. Rogers as part of a Panel Discussion before the Image and Meaning Conference (2001), Cambridge, MA, no abstract (Invited Panel Participant).

386. J. G. Huddleston, M. Li, Z. Guo, H. D. Willauer, G. C. April, and R. D. Rogers, "Polymer-Based Aqueous Biphasic Systems Applied to the Alkaline Pulping Process," Presented by J. G. Huddleston before the 5th Annual Green Chemistry and Engineering Conference (2001), Washington, DC, Abstract Book p 3.
387. R. D. Rogers, S. K. Spear, M. A. Godshall, T. P. Johnson, and L. Moens, "Green Chemistry, the Carbohydrate Economy, and Ionic Liquids: Compatible Goals, Compatible Chemistries?" Presented by R. D. Rogers before the 5th Annual Green Chemistry and Engineering Conference (2001), Washington, DC, Abstract Book p 9.
388. A. E. Visser, R. P. Swatloski, W. M. Reichert, and R. D. Rogers, "Chemical and Physical Characteristics of Room Temperature Ionic Liquids and the Associated Implications for their Use as Solvent Alternatives," Presented by A. E. Visser before the 5th Annual Green Chemistry and Engineering Conference (2001), Washington, DC, Abstract Book p 38.
389. R. P. Swatloski, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Crystallographic Investigation of Room-Temperature Ionic Liquids via X-ray Crystallography – Characterization of Low-Melting Analogs," Presented by R. P. Swatloski before the 5th Annual Green Chemistry and Engineering Conference (2001), Washington, DC, Abstract Book p 39.
390. R. D. Rogers, A. E. Visser, and S. T. Griffin, "Extraction of complex metal anions in non-VOC solvents: Room-temperature ionic liquids and aqueous biphasic systems," Presented by R. D. Rogers before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 007.
391. R. D. Rogers, H. A. Betts, R. P. Swatloski, A. E. Visser, and W. M. Reichert, "Synthesis and characterization of 1-alkol-3-methylimidazolium bromide ionic liquids," Presented by H. A. Betts before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 020.
392. R. D. Rogers, M. A. Klingshirn, G. A. Broker, J. D. Holbrey, and K. H. Shaughnessy, "Palladium catalyzed CO/alkene copolymerization in room temperature ionic liquids," Presented by M. A. Klingshirn before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 021.
393. R. P. Swatloski, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Phase behavior of room-temperature ionic liquids in various water/alcohol solutions," Presented by R. P. Swatloski before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 022.
394. R. D. Rogers, G. A. Broker, M. A. Klingshirn, and J. D. Holbrey, "Solubility determination of organic and inorganic compounds in hydrophilic room-temperature ionic liquids," Presented by G. A. Broker before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 023.
395. R. D. Rogers and G. A. Broker, "Crystal engineering of coordination polymers containing molecular recognition sites," Presented by G. A. Broker before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 024.
396. W. M. Reichert, A. E. Visser, R. P. Swatloski, S. K. Spear, and R. D. Rogers, "Derivatization of chitin in room-temperature ionic liquids," Presented by W. M. Reichert before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 025.
397. A. E. Visser, R. P. Swatloski, W. M. Reichert, and R. D. Rogers, "Anionic extractants for metal ion partitioning in room-temperature ionic liquids," Presented by A. E. Visser before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 026.
398. R. D. Rogers, G. A. Broker, and M. A. Klingshirn, "Crystal Engineering Using Lanthanide Ions as Nodes in Coordination and Hydrogen Bonded Networks," Presented by R. D. Rogers before the Rare Earths' – 2001 Brazil Conference (2001), Campos do Jordão, Brazil, Abstract IL-12. (Invited Lecture Presentation)
399. G. A. Broker, J. G. Huddleston, J. D. Holbrey, and R. D. Rogers, "Biphasic Systems Formed by Water-Miscible Room-Temperature Ionic Liquids in the Presence of Aqueous Salt Solutions," Presented by G. A. Broker before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 37.
400. G. A. Broker, J. G. Huddleston, H. D. Willauer, and R. D. Rogers, "Solvatochromatic Properties and Linear Solvent Energy Relationships of Room-Temperature Ionic Liquids," Presented by G. A. Broker before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 38.
401. J. G. Huddleston, H. D. Willauer, Z. Guo, G. C. April, and R. D. Rogers, "Aqueous Biphasic Systems in High Temperature Reactive Extraction: Experiences with the Alkaline Pulping of Wood for Paper and Biomass Production," Presented by J. G. Huddleston before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 46.
402. M. A. Klingshirn, J. D. Holbrey, and R. D. Rogers, "The Use of Room Temperature Ionic Liquids for the Extraction of Metal Ions from Non-Aqueous Solvents," Presented by M. A. Klingshirn before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 48.
403. R. D. Rogers, J. D. Holbrey, J. G. Huddleston, G. A Broker, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Chemical and Physical Characteristics of Room-Temperature Ionic Liquids (and Solid-State Analogs): Implications for Their Use as 'Green' Solvent Alternatives," Presented by R. D. Rogers before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 61.
404. H. D. Willauer, J. G. Huddleston, and R. D. Rogers, "Solvent Properties of PEG-Salt Aqueous Biphasic Systems (ABS) Based on Linear Free Energy Relationships and Solvatochromic Parameters," Presented by H. D. Willauer before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 68.
405. S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Activity of Laccase Immobilized in a PEG Gel Matrix," Presented by S. K. Spear before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 79.

406. J. G. Huddleston, H. D. Willauer, S. T. Griffin, and R. D. Rogers, "Solute Partitioning and Phase Behavior in Aqueous Biphasic Systems," Presented by J. G. Huddleston before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 82.
407. A. E. Visser, R. P. Swatloski, W. M. Reichert, and R. D. Rogers, "Actinide Separations in Room-Temperature Ionic Liquids," Presented by A. E. Visser before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 88.
408. R. D. Rogers, J. D. Holbrey, R. P. Swatloski, and W. M. Reichert, "Reverse Crystal Engineering: Can We Use the Concepts Learned to Make New Room Temperature Ionic Liquids for Applications as Green Solvent Alternatives?" presented by R. D. Rogers before the 59th Pittsburgh Diffraction Conference (2001), Covington, KY, Abstract Book. (Invited Symposium Presentation)
409. M. G. Benton, M. P. Scott, J. D. Holbrey, R. D. Rogers, and C. S. Brazel "A New Class of Plasticizing Agents: Room Temperature Ionic Liquids in Poly (Methyl Methacrylate) and Polystyrene," Presented by C. S. Brazel before the 2001 Fall National Meeting of AIChE (2001), Reno, NV, Abstract 118b.
410. J. D. Holbrey, A. E. Visser, and R. D. Rogers, "A New Class of Solvents for TRU Dissolution and Separation: Ionic Liquids," Presented by J. D. Holbrey before the Department of Energy Environmental Management Science Program High Level Waste Kick-Off Meeting (November 7-9, 2001), Richland, WA, no abstract.
411. R. D. Rogers, A. E. Visser, and J. H. Davis, Jr., "Actinide Separations Utilizing Room Temperature Ionic Liquids," Presented by A. E. Visser at the Actinides-2001 International Conference (2001), Hayama, Japan, Abstract 4O10.
412. A. E. Visser, M. P. Jensen, K. L. Nash, and R. D. Rogers, "Investigation of Actinide Complexation and Solvation in Room Temperature Ionic Liquids," Presented by A. E. Visser at the Actinides-2001 International Conference (2001), Hayama, Japan, Abstract 2O15.
413. R. D. Rogers, A. E. Visser, J. H. Davis, Jr., C. Koval, D. L. DuBois, P. Scovazzo, and R. D. Noble, "Designing or Choosing Ionic Liquids for Utilization in Supported Ionic Liquid Membranes and Facilitated Ionic Liquid Membranes," Presented by R. D. Rogers before the 2002 Spring National Meeting of AIChE (2002), New Orleans, LA, Abstract 9e. (Invited Symposium Presentation)
414. S. K. Spear and R. D. Rogers, "Ionic Liquids: Green Solvents for Carbohydrate Studies," Presented by S. K. Spear before SPRI 2002, Conference on Sugar Processing Research (2002), New Orleans, LA, Abstract Book.
415. A. E. Visser, J. D. Holbrey, and R. D. Rogers, "Room temperature ionic liquids as alternatives to traditional organic solvents in solvent extraction," Presented by R. D. Rogers before the 16th International Solvent Extraction Conference, ISEC 2002 (2002), Cape Town, South Africa, Abstract Book p 11. (Invited Plenary Presentation)
416. R. P. Planalp, A. M. Przyborowska, G. Park, N. Ye, F. H. Lu, R. D. Rogers, G. A. Broker, S. V. Torti, and M. W. Brechbiel, "Novel cytotoxic chelators that bind iron(II) selectively over zinc(II) under aqueous aerobic conditions," Presented by R. P. Planalp before the Biometals 2002: 3rd International Biometals Symposium (2002), London, United Kingdom, Abstract S38.
417. R. P. Planalp, K. A. Deal, G. Park, J. Shao, F. H. Lu, N. D. Chasteen, R. D. Rogers, and M. W. Brechbiel, "Metal-promoted phosphate diester hydrolysis by novel Cu(II) complexes of tris(N-alkylated) *cis,cis*-1,3,5-triaminocyclohexane," Presented by R. P. Planalp before the Biometals 2002: 3rd International Biometals Symposium (2002), London, United Kingdom, Abstract E5.
418. R. P. Planalp, S. Lai, G. Lu, A. M. Przyborowska, G. Park, R. D. Rogers, G. A. Broker, M. W. Brechbiel, S. V. Torti, and R. Ma, "Structure, reactivity and cytotoxicity of tripodal chelators and complexes: the effects of heterocyclic donor groups and enforced coordination geometry on Fe(II) complexation by potential antitumor agents," Presented by R. P. Planalp before the Biometals 2002: 3rd International Biometals Symposium (2002), London, United Kingdom, Abstract E4.
419. R. P. Swatloski, A. E. Visser, J. H. Davis, Jr., and R. D. Rogers, "Actinides in room temperature ionic liquids; old elements - new solvents," Presented by R. P. Swatloski before the 223rd ACS National Meeting (2002), Orlando, FL, Abstract NUCL 132.
420. R. D. Rogers, A. E. Visser, J. H. Davis, Jr., C. Koval, D. L. DuBois, P. Scovazzo, and R. D. Noble, "Choosing ionic liquids for supported ionic liquid membranes," Presented by R. D. Rogers before the 223rd ACS National Meeting (2002), Orlando, FL, Abstract I&EC 128. (Invited Symposium Presentation)
421. Z. Guo, J. G. Huddleston, R. D. Rogers, and G. C. April, "Polyethylene glycol effects in aqueous biphasic systems delignification," Presented by Z. Guo before the 223rd ACS National Meeting (2002), Orlando, FL, Abstract CELL 062.
422. R. D. Rogers and J. D. Holbrey, "Challenges and Opportunities in the Use of Ionic Liquids: Focus on Separations and Recycle," Presented by R. D. Rogers before the Challenges of Novel Technologies in Molecular Chemistry Conference (2002), Rennes, France, Abstract Book. (Invited Keynote Presentation)
423. J. D. Holbrey, K. H. Shaughnessy, M. A. Klingshirn, G. A. Broker, and R. D. Rogers, "Transition Metal Catalyzed CO/Olefin Co-Polymerization in Room Temperature Ionic Liquids," Presented by J. D. Holbrey before the Thirteenth International Symposium on Molten Salts, part of the 201st National Meeting of the Electrochemical Society (2002), Philadelphia, PA, Abstract 1400.
424. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Ionic Liquids for the Dissolution and Regeneration of Cellulose," Presented by R. P. Swatloski before the Thirteenth International Symposium on Molten Salts, part of the 201st National Meeting of the Electrochemical Society (2002), Philadelphia, PA, Abstract 1394.
425. R. D. Rogers and A. E. Visser, "Actinide Chemistry in Novel Solvent Media: Room Temperature Ionic Liquids," Presented by R. D. Rogers before the Thirteenth International Symposium on Molten Salts, part of the 201st National Meeting of the Electrochemical Society (2002), Philadelphia, PA, Abstract 1446. (Invited Presentation)

426. R. D. Rogers and W. M. Reichert, "Polymorphic 1-butyl-3-methylimidazolium chloride: In search of clues to make ionic salts, ionic liquids," Presented by R. D. Rogers before the American Crystallographic Association Annual Meeting (2002), San Antonio, TX, Abstract 08.04.21. (Invited Presentation)
427. R. D. Rogers, J. D. Holbrey, S. K. Spear, and R. P., Swatloski, "Ionic Liquids—A Look at the Dissolution of Cellulose," Presented by R. D. Rogers before the 6th Annual Green Chemistry and Engineering Conference (2002), Washington, DC, Abstract Book p 17.
428. J. G. Huddleston, H. D. Willauer, G. D. Broker, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Predicting the Performance of Alternative Solvents Through the Use of Free Energy Relationships," Presented by J. G. Huddleston before the 6th Annual Green Chemistry and Engineering Conference (2002), Washington, DC, Abstract Book p 19.
429. J. D. Holbrey and R. D. Rogers, "Polymerization and Polymers in Room Temperature Ionic Liquids," Presented by J. D. Holbrey before the 6th Annual Green Chemistry and Engineering Conference (2002), Washington, DC, Abstract Book p 20.
430. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Ionic Liquids as Green Solvents for Regeneration/Engineering of Cellulose Based Products," Presented by R. P. Swatloski before the 6th Annual Green Chemistry and Engineering Conference (2002), Washington, DC, Abstract Book p 43.
431. R. D. Rogers and A. E. Visser, "Room Temperature Ionic Liquids: New Solvents for f-element Separations and Associated Solution Chemistry," Presented by R. D. Rogers before the 23rd Rare Earth Research Conference (2002), Davis, CA, Abstract OSE-1-05.
432. R. D. Rogers and J. D. Holbrey, "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers before the 57th Annual Calorimetry Conference CALCON 2002 (2002), New Brunswick, NJ, Abstract 47. (Invited Plenary Presentation)
433. J. D. Holbrey, W. M. Reichert, S. K. Spear, R. P. Swatloski, M. B. Turner, A. E. Visser, and R. D. Rogers, "Getting started with Ionic Liquids: An experience-based tutorial on synthesis and handling," Presented by J. D. Holbrey, W. M. Reichert, S. K. Spear, R. P. Swatloski, M. B. Turner, A. E. Visser, and R. D. Rogers before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 1.
434. J. D. Holbrey and R. D. Rogers, "Clean synthesis of 1,3-dialkylimidazolium ionic liquids," Presented by J. D. Holbrey before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 012.
435. J. D. Holbrey, W. M. Reichert, R. G. Reddy, and R. D. Rogers, "Specific heat capacities of common ionic liquids: an examination of the potential for using ionic liquids as thermal fluids," Presented by J. D. Holbrey before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 070.
436. R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Ionic Liquids: new solvents for non-derivitized cellulose dissolution," Presented by R. P. Swatloski before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 076.
437. W. M. Reichert, J. D. Holbrey, and R. D. Rogers, "Insight into the solvent properties of ionic liquids: a comparative study of solute partitioning in organic/ionic liquid biphasic systems," Presented by W. M. Reichert before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 087.
438. A. E. Visser, M. P. Jensen, K. L. Nash, and R. D. Rogers, "An investigation of actinide and fission product extraction in room temperature ionic liquids: Liquid/liquid separations and in-situ solution analysis," Presented by A. E. Visser before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 088.
439. S. K. Spear, W. M. Reichert, and R. D. Rogers, "Liquid-liquid extraction from ionic liquids using renewable plant-based soybean oil methyl ester as alternatives to organic solvents," Presented by S. K. Spear before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 091.
440. K. H. Shaughnessy, M. A. Klingshirn, S. J. P'Pool, J. D. Holbrey, and R. D. Rogers, "Metal-catalyzed olefin polymerization in polar, non-coordinating ionic liquids," Presented by K. H. Shaughnessy before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 121.
441. A. E. Visser, J. G. Huddleston, J. D. Holbrey, and R. D. Rogers, "Hydrophobic *n*-alkyl-isoquinolinium ionic liquids: characterization, solvent properties, and use in separations," Presented by A. E. Visser before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 021.
442. W. M. Reichert, J. D. Holbrey, and R. D. Rogers, "Comparative solid state analyses of polymorphic 1-butyl-3-methylimidazolium halide ionic liquids," Presented by W. M. Reichert before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 022.
443. M. B. Turner, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Cellulase activity in an ionic liquid," Presented by M. B. Turner before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 023.
444. K. Yamato, R. A. Bartsch, M. L. Dietz, and R. D. Rogers, "Stereospecific syntheses of the *trans-trans* and the *cis-trans*-isomers of dicyclohexano-18-crown-6," Presented by K. Yamato before the 224th ACS National Meeting (2002), Boston, MA, Abstract ORGN 032.
445. K. H. Shaughnessy, S. J. P'Pool, M. A. Klingshirn, J. D. Holbrey, and R. D. Rogers, "Polar noncoordinating ionic liquids as solvents for late transition metal-catalyzed olefin polymerization," Presented by K. H. Shaughnessy before the 224th ACS National Meeting (2002), Boston, MA, Abstract INOR 524.
446. H.-s. Chong, G. Bishwajit, G. A. Broker, R. D. Rogers, and M. W. Brechbeil, "Stereoselective and regioselective synthesis of azepane and azepine derivatives via piperidine ring expansion," Presented by H.-s. Chong before the 224th ACS National Meeting (2002), Boston, MA, Abstract ORGN 508.

447. M. G. Benton, J. D. Holbrey, R. D. Rogers, J. W. Mays, and C. S. Brazel, "Ionic Liquids as Environmentally-Benign Solvents for Synthesis of PMMA in [bmim][PF_6]: Kinetic, Thermal and Mechanical Analysis," Presented by C. S. Brazel before the 2002 AIChE Annual Meeting (2002), Indianapolis, IN, Abstract Book 233h.
448. R. D. Rogers, "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers before the 41st Eastern Analytical Symposium & Exposition (2002), Somerset, NJ, Abstract and Program Booklet page 21 (Invited Symposium Presentation).
449. J. D. Holbrey, W. M. Reichert, R. K. Reddy, and R. D. Rogers, "Specific Heat Capacities of Common Room Temperature Ionic Liquids: An Examination of the Potential for Using Ionic Liquids as Thermal Fluids," Presented by J. D. Holbrey before EUCHEM 2002, Molten Salts Conference (2002), Oxford, United Kingdom, Abstract K7. (Keynote Lecture)
450. R. D. Rogers and J. D. Holbrey, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by R. D. Rogers before EUCHEM 2002, Molten Salts Conference (2002), Oxford, United Kingdom, Abstract K15. (Keynote Lecture)
451. J. D. Holbrey and R. D. Rogers, "Clean Synthesis of Ionic Liquids," Presented by J. D. Holbrey before the Gordon Research Conference on Green Chemistry (2002), Oxford, United Kingdom, No abstract.
452. R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Green solvents for the dissolution and regeneration of cellulose--A look at ionic liquids," Presented by R. P. Swatloski before the Gordon Research Conference on Green Chemistry (2002), Oxford, United Kingdom, No abstract.
453. W. M. Reichert, J. D. Holbrey, J. G. Huddleston, and R. D. Rogers, "Insight into the Solvent Properties of Ionic Liquids: A Comparative Study of Organic Solute Partitioning in Liquid/Liquid Systems," Presented by W. M. Reichert before the Gordon Research Conference on Green Chemistry (2002), Oxford, United Kingdom, No abstract.
454. R. D. Rogers and J. D. Holbrey, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by J. D. Holbrey at Green Solvents for Catalysis - Environmentally Benign Reaction Media (2002), Bruchsal, Germany, Abstract Book p 17.
455. J. D. Holbrey, K. H. Shaughnessy, M. A. Klingshirn, G. A. Broker, and R. D. Rogers, "Transition Metal Catalysed CO/Olefin Co-polymerisation in Room Temperature Ionic Liquids," Presented by J. D. Holbrey at Green Solvents for Catalysis - Environmentally Benign Reaction Media (2002), Bruchsal, Germany, Abstract Book p 69.
456. R. D. Rogers, "Overview of State-of-the-Art in Ionic Liquids Research," Presented by R. D. Rogers at the Air Force Office of Scientific Research/Air Force Propulsion Laboratory Workshop on Energetic Ionic Liquids" (2002), Dulles, VA, No Abstract. (Invited Plenary Presentation)
457. R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Ionic liquids as green solvents for the dissolution and regeneration of cellulose," Presented by R. P. Swatloski before the 225th ACS National Meeting (2003), New Orleans, LA, Abstract CELL 131.
458. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Properties of regenerated cellulose from ionic liquids," Presented by R. P. Swatloski before the 225th ACS National Meeting (2003), New Orleans, LA, Abstract I&EC 167.
459. S. J. P'Pool, M. A. Klingshirn, J. D. Holbrey, R. D. Rogers, and K. H. Shaughnessy, "Polar, non-coordinating ionic liquids as solvents for coordination polymerization of olefins," Presented by S. J. P'Pool before the 225th ACS National Meeting (2003), New Orleans, LA, Abstract ORGN 057.
460. W. M. Reichert, J. D. Holbrey, M. Nieuwenhuyzen, O. Sheppard, C. Hardacre, and R. D. Rogers, "Liquid clathrate formation in ionic liquids and its effects on the solvent properties," Presented by W. M. Reichert before the 225th ACS National Meeting (2003), New Orleans, LA, Abstract I&EC 168.
461. R. D. Rogers, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by R. D. Rogers to Science in Industry, Fine Chemicals Group Meeting "Chemical Solutions with Ionic Liquids" (2003), London, United Kingdom. (Invited Presentation)
462. R. D. Rogers, "Fundamentals of Solute Partitioning in Aqueous Biphasic Systems," Presented by R. D. Rogers before the Department of Energy Basic Energy Sciences Heavy Elements and Separations Contractors Meeting (2003), Santa Fe, NM, Abstract P6-6.
463. R. D. Rogers, "Aqueous Biphasic Systems: Novel Delivery Systems and Novel Applications," Presented by R. D. Rogers before the Department of Energy Basic Energy Sciences Heavy Elements and Separations Contractors Meeting (2003), Santa Fe, NM, Abstract P6-7.
464. R. D. Rogers, "A New Class of Solvents for TRU Dissolution and Separation: Ionic Liquids," Presented by R. D. Rogers before the Department of Energy Environmental Management Sciences Program Principal Investigators Workshop (2003), Richland, WA, no abstract.
465. R. D. Rogers, J. D. Holbrey, S. K. Spear, K. E. Gutowski, N. J. Bridges, V. A. Cocalia, and R. P. Swatloski, "Application of Ionic Liquid Technologies to Nuclear Separations," Presented by R. D. Rogers before the 27th Actinide Separations Conference (2003), Lemont, IL, Abstract Book p 12.
466. V. A. Cocalia, N. J. Bridges, S. T. Griffin, S. K. Spear, and R. D. Rogers, "Uranyl Extraction using Cyanex-272 in 1-Decyl-3-methylimidazolium Bis(trifluoromethanesulfonyl)imide," Presented by V. A. Cocalia before the 27th Actinide Separations Conference (2003), Lemont, IL, Abstract Book p 36.
467. J. D. Holbrey, W. M. Reichert, M. B. Turner, K. Green, and R. D. Rogers, "Development of Ionic Liquids Containing Environmentally Acceptable and Sustainable Components," Presented by J. D. Holbrey before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 8.

468. R. P. Swatloski, J. D. Holbrey, S. K. Spear, R. B. Moore, and R. D. Rogers, "Greener Dissolution of Cellulose: Can Ionic Liquids Compete with *N*-Methyl-morpholine-*N*-oxide in the Lyocell Process?" Presented by R. P. Swatloski before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 10.
469. K. E. Gutowski, J. G. Huddleston, G. A. Broker, H. D. Willauer, R. P. Swatloski, and R. D. Rogers, "Controlling the Aqueous Miscibility of Hydrophilic Ionic Liquids by Addition of Water-Structuring Salts: Novel Aqueous Biphasic Systems for Separations and Recycle," Presented by K. E. Gutowski before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 32.
470. C. R. Lea, I. A. Miller, D. M. Brown, R. P. Swatloski, and R. D. Rogers, "X-ray Crystallography of Novel Ionic Liquids Based on *N*-Akylmorpholinium Salts," Presented by D. M. Brown before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 34.
471. M. B. Turner, S. K. Spear, R. P. Swatloski, J. D. Holbrey, and R. D. Rogers, "Entrapment and Activity of Biomolecules in Cellulose Films Regenerated from Ionic Liquids," Presented by M. B. Turner before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 40.
472. W. M. Reichert, J. D. Holbrey, J. G. Huddleston, and R. D. Rogers, "Solvent Properties and Liquid Clathrate Behavior of Ionic Liquids Determined by Partitioning Experiments and Linear Solvent Energy Relationships," Presented by W. M. Reichert before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 75.
473. M. A. Klingshirn, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Investigation of the Properties of Poly(ethylene Glycol) Hydrogels Doped with Ionic Liquids," Presented by M. A. Klingshirn before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 45.
474. J. G. Huddleston, S. K. Spear, and R. D. Rogers, "The Aqueous Solution Behavior of Poly(ethyleneglycol) Hydrogels," Presented by J. G. Huddleston before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 48.
475. S. K. Spear, M. B. Turner, J. G. Huddleston, and R. D. Rogers, "Poly(ethylene glycol) Hydrogel for Laccase Immobilization," Presented by S. K. Spear before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 51.
476. J. Chen, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Polyethylene Glycol Aqueous Solutions as Green Reaction Medium," Presented by J. Chen before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 52.
477. S. T. Griffin, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "A Comparison of the Effect of Temperature on the Uptake of TcO4- in PEG Based ABS and onto ABEC Resins," Presented by S. T. Griffin before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 52.
478. S. T. Griffin, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Partitioning of Iodide in Aqueous Biphasic Systems and onto ABEC® Resins," Presented by S. T. Griffin before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 59.
479. S. K. Spear, S. T. Griffin, J. G. Huddleston, and R. D. Rogers, "Partitioning Studies of Small Molecules in Ammonium Carbamate/Polyethylene Glycol Aqueous Biphasic Systems," Presented by S. K. Spear before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 59.
480. J. Chen, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Polyethylene Glycol Aqueous Solutions as Green Reaction Medium," Presented by J. Chen before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 60.
481. J. G. Huddleston, H. D. Willauer, S. T. Griffin, S. K. Spear, and R. D. Rogers, "Free Energy Relationships and Solvent Properties of PEG-Salt Aqueous Biphasic Systems," Presented by J. G. Huddleston before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 60.
482. J. G. Huddleston, Z. Guo, H. D. Willauer, M. Li, S. K. Spear, and R. D. Rogers, "Aqueous Biphasic Systems Applied to the Delignification of Cellulosics ? Experiences with the Paper Pulping Process," Presented by J. G. Huddleston before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 60.
483. S. T. Griffin, S. K. Spear, and R. D. Rogers, "Removal of Mercury from Tap Water and Groundwater Using Aqueous Biphasic Extraction Chromatographic Resin," Presented by S. T. Griffin before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 60.
484. M. A. Klingshirn, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Synthesis and Characterization of a Poly(ethylene Glycol) - Silica Sol Composite," Presented by M. A. Klingshirn before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 61.
485. M. L. Moody, H. D. Willauer, J. G. Huddleston, and R. D. Rogers, "Characterization studies of PEG/Dextran Aqueous Biphasic Systems Involving Linear Solvation Energy Relationship, pH, and Temperature," Presented by M. L. Moody before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 61.
486. M. L. Moody, J. G. Huddleston, and R. D. Rogers, "Use of Linear Solvation Energy Relationships in Studies of PEG/Organic Biphasic Systems," Presented by M. L. Moody before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 61.
487. R. D. Rogers, J. G. Huddleston, J. D. Holbrey, S. K. Spear, and M. B. Turner, "Ionic Liquids in Separations: What Are They? Are They Useful? and How Do They Compare to Aqueous Biphasic Systems?" Presented by R. D. Rogers before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 51.

488. R. D. Rogers, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Reactions, and the Choice of Ionic Liquid and/or Process," Presented by J. G. Huddleston before the 1st International Symposium on Process Intensification & Miniaturisation (PIM-1 2003), Newcastle upon Tyne, United Kingdom, Abstract Book. (Invited Keynote Lecture).
489. R. D. Rogers, "How to Talk to the Public About What You Do," Communications Clinic at the 226th ACS National Meeting (2003), New York, NY. (Invited Panel Participant).
490. R. D. Rogers, J. D. Holbrey, S. K. Spear, K. E. Gutowski, N. J. Bridges, V. A. Cocalia, and R. P. Swatloski, Application of ionic liquid technologies to nuclear separations," Presented by R. D. Rogers before the 226th ACS National Meeting (2003), New York, NY, Abstract NUCL 092. (Invited Presentation).
491. M. B. Turner, S. K. Spear, R. P. Swatloski, J. D. Holbrey, and R. D. Rogers "Cellulose films regenerated from ILs and their role as scaffolding for enzyme attachment via glutaraldehyde," Presented by M. B. Turner before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 190.
492. W. M. Reichert, J. D. Holbrey, and R. D. Rogers, "Relationships between solid-state ion-ion and hydrogen-bonding interactions and liquid properties in ionic liquid forming salts," Presented by W. M. Reichert before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 132.
493. K. E. Gutowski, G. A. Broker, N. J. Bridges, J. G. Huddleston, H. D. Willauer, J. D. Holbrey, and R. D. Rogers, "Formation of aqueous biphasic systems with hydrophilic ionic liquids via the addition of water-structuring salts: applications to nuclear tank wastes," Presented by K. E. Gutowski before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 131.
494. J. D. Holbrey, M. B. Turner, W. M. Reichert, and R. D. Rogers, "Synthesis, characterization, and applications of new hydroxyl-appended ionic liquids," Presented by J. D. Holbrey before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 130.
495. R. P. Swatloski, R. D. Rogers, C. R. Lea, I. A. Miller, and D. M. Brown, "X-Ray crystallography of novel ionic liquids based on N-alkylmorpholinium salts," Presented by R. P. Swatloski before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 129.
496. J. D. Holbrey, W. M. Reichert, M. B. Turner, K. Green, and R. D. Rogers, "Development of Ionic Liquids containing environmentally acceptable and sustainable components," Presented by J. D. Holbrey before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 128.
497. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Ionic liquids as green solvents: Engineering new bio-based materials," Presented by R. P. Swatloski before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 090.
498. W. M. Reichert, J. G. Huddleston, J. D. Holbrey, and R. D. Rogers, "Abraham solvent parameters for ionic liquid/organic two-phase systems," Presented by W. M. Reichert before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 070.
499. R. D. Rogers, J. D. Holbrey, S. K. Spear, K. E. Gutowski, and R. P. Swatloski, "CMPO-impregnated cellulosic materials from ionic liquids for f-element separations," Presented by R. D. Rogers before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 045. (Invited Presentation.)
500. J. D. Holbrey, R. P. Swatloski, W. M. Reichert, J. F. Brennecke, K. R. Seddon, U. Hakala, M. Deetlefs, M. Nieuwenhuyzen, T. Welton, P. Mawdsley, J. Vallance, O. Sheppard, R. D. Rogers," Getting started with Ionic Liquids: An experience-based tutorial," Presented by all authors before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 033.
501. A. M. Przyborowska, G. A. Broker, R. D. Rogers, M. W. Brechbiel, and R. P. Planalp, "Electronic properties and structures of novel Cu(II) complexes of hexadentate aminopyridyl ligands and their alkylated derivatives," Presented by A. M. Przyborowska before the 226th ACS National Meeting (2003), New York, NY, Abstract INOR 486.
502. R. P. Planalp, G. Lu, A. M. Przyborowska, M. W. Brechbiel, S-j. Lai, G. Park, G. A. Broker, R. D. Rogers, R. Ma, and S. V. Torti, "The metal-complexation properties of tripodal hexadentate chelators: Effects of heterocycle donor arms, tripod framework and imine formation on Fe(II) chelation and cytotoxicity," Presented by R. P. Planalp before the 226th ACS National Meeting (2003), New York, NY, Abstract INOR 058.
503. R. D. Rogers, "Utilizing Neoteric Solvent Systems to Explore New Decontamination Technologies," Presented by R. D. Rogers before the Radionuclide Decontamination Science and Technology Workshop (2003), Los Alamos, NM. (Invited Presentation).
504. K. E. Gutowski, N. J. Bridges, V. A. Cocalia, S. K. Spear, J. D. Holbrey, J. H. Davis, Jr., and R. D. Rogers, "Approaches to Nuclear Separations Using Room Temperature Ionic Liquids," Presented by K. E. Gutowski before Global 2003 "Atoms for Prosperity: Updating Eisenhower's Global Vision for Nuclear Energy," part of the 2003 ANS/ENS International Winter Meeting (2003), New Orleans, LA. (Invited Presentation).
505. R. D. Rogers, "Greener Industry: A Growing Trend," Panel Discussion and Invited Speaker before the Society of Women Engineers National Conference (2003), Birmingham, AL, Program Book, page 34 (Invited Presentation).
506. R. D. Rogers, "Alternative Separations in Support of DOE's Mission," Presented by R. D. Rogers before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 18. (Invited Plenary Presentation).
507. N. J. Bridges, V. A. Cocalia, A. E.Visser, J. H. Davis, Jr., J. Holbrey, and R. D. Rogers, "Task Specific Ionic Liquids for Recovery of Actinides from Aqueous Acid Media," Presented by N. J. Bridges before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 36-37.
508. K. E. Gutowski, S. K. Spear, and R. D. Rogers, "Use of Ionic Liquids in the Removal Actinides from Nitric Acid Media by HOPO-Type Extractants," Presented by K. E. Gutowski before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 43.

509. R. D. Rogers, J. D. Holbrey, S. K. Spear, K. E. Gutowski, and R. P. Swatloski, "CMPO-Impregnated Cellulosic Materials from Ionic Liquids for Actinide Separations," Presented by R. D. Rogers before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 52.
510. K. E. Gutowski, G. A. Broker, H. D. Willauer, J. G. Huddleston, R. P. Swatloski, J. D. Holbrey, and R. D. Rogers, "Controlling the Aqueous Miscibility of Hydrophilic Ionic Liquids via the Addition of Water-Structuring Salts," Presented by K. E. Gutowski before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 68.
511. N. J. Bridges and R. D. Rogers, "Comparative Studies of Cyanex-923® in Ionic Liquids Versus Traditional Organic Solvents," Presented by N. J. Bridges before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 79.
512. V. A. Cocalia, N. J. Bridges, S. T. Griffin, S. K. Spear, and R. D. Rogers, "Actinide Partitioning using the Traditional Extractant Cyanex-272 in a Room Temperature Ionic Liquid as a Novel Medium for Liquid/Liquid Extraction," Presented by V. A. Cocalia before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 80.
513. R. D. Rogers, "Alternative Solvents," Presented by R. D. Rogers before the Indo-US Science and Technology Forum Workshop on Green Chemistry (2003), Delhi, India. (Invited Delegate/Workshop Instructor).
514. J. D. Warner and R. D. Rogers, "Crystal Engineering and Non Covalent Derivatization," Presented by J. D. Warner and R. D. Rogers before the Indo-US Science and Technology Forum Workshop on Green Chemistry (2003), Delhi, India. (Invited Delegate/Workshop Instructor).
515. R. D. Rogers and D. L. Hjeresen, "International Issues," Presented by R. D. Rogers and D. L. Hjeresen before the Indo-US Science and Technology Forum Workshop on Green Chemistry (2003), Delhi, India. (Invited Delegate/Workshop Instructor).
516. R. D. Rogers, G. A. Broker, K. E. Gutowski, and N. J. Bridges, "Crystal Engineering Using Lanthanide Ions as Nodes," Presented by R. D. Rogers before the International Conference on Materials for Advanced Technologies (ICMAT 2003)/International Union of Materials Research Societies International Conference in Asia (ICA 2003), Singapore, Abstract D-4-1-I. (Invited Symposium Presentation).
517. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers before the LICP Discussions No. 1 Workshop - Ionic Liquids: Progress and Prospects (2004), Lanzhou China, Abstract book pp 9-19. (Invited Keynote Presentation).
518. R. D Rogers, J. D Holbrey, S. K Spear, W. M. Reichert, M. R Smiglac, H. Yang, K. Manju, and A. R Katritzky, "Energetic ionic liquids: Fundamental studies relating target structures and key physical properties," Presented by R. D. Rogers to the AFOSR Contractor's Review on Ionic Liquids Research (2004), Tampa, FL.
519. R. D. Rogers, "Green Chemistry," Presented by R. D. Rogers before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2004), Tuscaloosa, AL.
520. R. D. Rogers, "Liquid/Liquid Separations," Presented by R. D. Rogers before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2004), Tuscaloosa, AL.
521. M. A. Klingshirn, S. K. Spear, R. Subramanian, J. D. Holbrey, and R. D. Rogers, "Synthesis, characterization, and applications of ionic liquid-poly(ethylene) glycol gel matrices," Presented by M. A. Klingshirn before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract POLY 638.
522. J. D. Holbrey, J. Chen; M. B. Turner, R. P. Swatloski, S. K. Spear, and R. D. Rogers, "Applying ionic liquid solvent characteristics for controlled processing of polymer materials," Presented by J. D. Holbrey before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract POLY 607.
523. K. H. Shaughnessy, S. J. P'Pool, M. A. Klingshirn, and R. D. Rogers, "Coordination polymerization of alkenes in ionic liquid solvents," Presented by K. H. Shaughnessy before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract POLY 600.
524. M. A. Klingshirn, S. J. P'Pool, K. H. Shaughnessy, and R. D. Rogers, "Palladium-catalyzed hydroesterification of styrene in ionic liquids," Presented by M. A. Klingshirn before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract INOR 770.
525. R. P. Planalp, N. Ye, G. Park, A. M. Przyborowska, P. E. Sloan, T. Clifford, C. B. Bauer, G. A. Broker, R. D. Rogers, R. Ma, S. V. Torti, and M. W. Brechbiel, "Nickel(II), copper(II) and zinc(II) binding properties and cytotoxicity of tripodal, hexadentate tris(ethylenediamine)-analogue chelators," Presented by R. P. Planalp before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract INOR 107.
526. W. M. Reichert, J. D. Holbrey, S. T. Griffin, V. A. Cocalia, N. J. Bridges, J. Chambers, and R. D. Rogers, "Task specific ionic liquids that incorporate poly (ethylene glycols) functionality for the extraction of metal ions," Presented by W. M. Reichert before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract I&EC 228.
527. R. D. Rogers, N. J. Bridges, J. D. Holbrey, H. Luo, S. Dai, and P. V. Bonnesen, "The role of ion exchange vs. solvent extraction processes in metal ion partitioning in ionic liquid/aqueous systems: cesium extractions with calix[4]arene-bis(tert-octylbenzo-crown-6) in imidazolium bistrifylimide ionic liquids," Presented by R. D. Rogers before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract I&EC-227. (Invited Presentation)
528. G. J. Lumetta, B. K. McNamara, L. A. Snow, D. W. Wester, R. D. Rogers, and N. J. Bridges, "Characterization of the coordinative modes of alkyl-substituted Klaui ligand," Presented by G. J. Lumetta before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract I&EC 222.

529. R. D. Rogers, K. E. Gutowski, S. T. Griffin, and J. D. Holbrey, "Aqueous biphasic systems based on salting-out polyethylene glycol or ionic liquid solutions: Strategies for actinide or fission product separations," Presented by R. D. Rogers before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract ENVR 033. (Invited Presentation)
530. T. L. Shamery, S. K. Spear, and R. D. Rogers, "How the RET experience at The University of Alabama was incorporated into the high school teaching experience," Presented by T. L. Shamery before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract CHED 090.
531. R. D. Rogers, J. D. Holbrey, S. K. Spear, and M. B. Turner, "Ionic liquids as green solvents: Engineering bioactive cellulose materials," Presented by R. D. Rogers before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract CELL 198. (Invited Presentation)
532. R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Utilization of biorenewable resources: Bio-based materials from ionic liquids," Presented by R. P. Swatloski before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract CELL 046.
533. J. H. Poplin, R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Cellulose-supported colorimetric sensors for mercury ion detection," Presented by M. A. Klingshirn before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract CELL 024.
534. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Ionic Liquids Enabling Sustainable Technologies for New Advanced Materials," Presented by R. P. Swatloski before the Spring National AIChE Meeting (2004), New Orleans, LA. (Invited presentation)
535. R. D. Rogers, "Investigation of Ionic Liquids as Environmentally Benign Solvents," Presented by R. D. Rogers to the U. S. EPA National Center for Environmental Research EPA and NSF Technology for a Sustainable Environment (TSE) Grantees Meeting (2004), Arlington, VA. No Abstract.
536. R. D. Rogers, "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids?" Presented by R. D. Rogers before the Canada-US Joint Workshop on Innovative Chemistry in Clean Media (2004), Montreal, Quebec, Canada. (Invited presentation)
537. R. D. Rogers, "Toxicology of Nanoparticles and Analysis and Modeling of Nanoparticles Solution Properties for Physico-Chemical Characterization and Risk Assessment," Presented by R. D. Rogers before the Center for Nanoscale Materials Workshop for EPSCoR Faculty and Students (2004), Argonne, IL. (Invited presentation)
538. R. D. Rogers, "Prospective on the 2005 Conference 'Taking Measure of Green Progress: Opportunities to Meet Global Challenges,'" Presented by R. D. Rogers before the 8th Annual Green Chemistry and Engineering Conference: 'Green Chemistry and Engineering: The Business Imperative for Sustainability' (2004), Washington, DC, no abstract.
539. R. D. Rogers, S. T. Griffin, G. A. Broker, W. M. Reichert, J. H. Poplin, R. P. Swatloski, and J. D. Holbrey, "Supramolecular Chemistry in Alternative Solvents: Are Nonvolatile Ionic Liquids Effective Crystallization Solvents or Fodder for Co-Crystals?," Presented by R. D. Rogers before the American Crystallographic Association Annual Meeting (2004), Chicago, IL, Abstract TR.01.18. (Invited Presentation)
540. M. A. Klingshirn, R. D. Rogers, and K. H. Shaughnessy "Palladium-Catalyzed Hydroesterification of Styrene in the Presence of Ionic Liquids," Presented by M. Klingshirn before the ACS-PRF Summer School on Green Chemistry (2004), Pittsburgh, PA, Program Booklet 1-12.
541. M. B. Turner, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Entrapment of Biologically Active Macromolecules in Cellulosic Films Reconstituted from Ionic Liquids," Presented by M. Turner before the ACS-PRF Summer School on Green Chemistry (2004), Pittsburgh, PA, Program Booklet 1-20.
542. J. S. Moulthrop, R. P. Swatloski, R. D. Rogers, and G. Moyna "High-resolution ^{13}C NMR studies of amylose and cellulose oligomers in 1-butyl-3-methylimidazolium chloride solutions," Presented by J. S. Moulthrop before the 228th ACS National Meeting (2004), Philadelphia, PA, Abstract CARB 063.
543. R. D. Rogers, W. M. Reichert, and J. D. Holbrey "Ionic Liquids and Hydrogen Bonding: Understanding the Solvent Characteristics of Ionic Liquids through Study of Crystal Structures and Solvation Parameters," Presented by R. D. Rogers before the 228th ACS National Meeting (2004), Philadelphia, PA, Abstract ORGN 542. (Invited symposium presentation)
544. R. P. Planalp, N. Ye, G. Park, A. M. Przyborowska, P. E. Sloan, T. Clifford, C. B. Bauer, R. D. Rogers, R. Ma. S. V. Torti, and M. W. Brechbiel "Nickel(II), copper(II) and zinc(II) binding properties and cytotoxicity of tripodal, hexadentate tris(ethylenediamine)–analogue chelators," Presented by R. P. Planalp before the 228th ACS National Meeting (2004), Philadelphia, PA, Abstract INOR 424.
545. R. D. Rogers, W. M. Reichert, J. D. Holbrey, and G. A. Broker "Approaches to Crystallization: Techniques for Controlling the Formation of Materials and their Application to Industry," Presented by R. D. Rogers before the Crystallisation and Particle Science Workshop – Bridging the Gap between Research and Industrial Application (2004), Singapore, Abstract. (Invited Workshop Lecture)
546. S. V. Volkov and R. D. Rogers, ""Green" Route of Chemistry Development. Problems and Perspectives," Presented by S. Volkov before the XVIth Ukrainian Conference on Inorganic Chemistry (2004), Uzhhorod, Ukraine.
547. R. D. Rogers, "Supramolecular Chemistry in Alternative Solvents: Are Nonvolatile Ionic Liquids Effective Crystallization Solvents or Fodder for Co-Crystals?," Presented by R. D. Rogers before the Gordon Research Conference on Organic Structures & Properties (2004), Les Diablerets, Switzerland (Invited Presentation).
548. W. Wang, G. Shen, R. P. Swatloski, R. Farag, R. M. Broughton, Jr., and R. D. Rogers, "Cellulose Fibers Extruded from Ionic Liquids," Presented by R. M. Broughton, Jr. before the International Nonwovens Technical Conference (2004), Toronto Canada.

549. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Solvents: Enabling Sustainable Technologies for New Advanced Materials," Presented by R. D. Rogers before the Proctor & Gamble Ionic Liquids Symposium (2004), Proctor & Gamble, Cincinnati, OH on 11/10/04. (Invited Workshop Lecture)
550. R. D. Rogers, "A New Class of Solvents for TRU Dissolution and Separation: Ionic Liquids," Presented by R. D. Rogers before the DOE Environmental Management Science Program High Level Waste Workshop (2005), SREL Conference Center, Aiken, SC on 1/29/05; no abstract, Program Booklet.
551. H. Luo, S. Dai, P. V. Bonnesen, A. C. Buchanan, III, R. D. Rogers, J. D. Holbrey, and C. L. Hussey, "Novel Fission-Product Separations Based on Room Temperature Ionic Liquids," Presented by S. Dai before the DOE Environmental Management Science Program High Level Waste Workshop (2005), SREL Conference Center, Aiken, SC on 1/29/05; no abstract, Program Booklet.
552. W. Wang, G. Shen, R. P. Swatloski, R. Farag, R. M. Broughton, Jr., and R. D. Rogers "A New Solvent for Cellulose Extrusion," Presented by R. M. Broughton, Jr. before the Cotton Beltwide Conferences (2005), New Orleans, LA.
553. R. D. Rogers, "Solvent Strength of Ionic Liquids," Presented by R. D. Rogers before the Council for Chemical Research 10th NIChE Conference: Ionic Liquids – Background, State-of-the-Art, and Applications (2005), February 21-22, 2005, University of Notre Dame, South Bend, IN; no abstract. (Invited Workshop Lecturer)
554. R. D. Rogers, "Liquid-Liquid Separations with Ionic Liquids," Presented by R. D. Rogers before the Council for Chemical Research 10th NIChE Conference: Ionic Liquids – Background, State-of-the-Art, and Applications (2005), February 21-22, 2005, University of Notre Dame, South Bend, IN; no abstract. (Invited Workshop Lecturer)
555. R. D. Rogers, "Polymer Chemistry of Ionic Liquids," Presented by R. D. Rogers before the Council for Chemical Research 10th NIChE Conference: Ionic Liquids – Background, State-of-the-Art, and Applications (2005), February 21-22, 2005, University of Notre Dame, South Bend, IN; no abstract. (Invited Workshop Lecturer)
556. R. D. Rogers, "Advanced Materials Utilizing ILs as Enabling Solvents," Presented by R. D. Rogers before the Council for Chemical Research 10th NIChE Conference: *Ionic Liquids – Background, State-of-the-Art, and Applications* (2005), February 21-22, 2005, University of Notre Dame, South Bend, IN; no abstract. (Invited Workshop Lecturer)
557. R. P. Planalp, M. Childers, D. P. Kennedy, A. Lindell, G. Broker, R. D. Rogers, M. W. Brechbiel, R. Ma, F. M. Torti, and S. V. Torti, "Polyamino-heterocycle chelating agents with cytotoxic activity in tumor cells: Structure-activity relationship of imidazole, thiazole and pyridyl donor groups," Presented by R. P. Planalp before the 229th ACS National Meeting (2005), San Diego, CA, Abstract MEDI-501.
558. R. D. Rogers, "DE-FG02-96ER14673 - Alternative (Potentially Green) Separations Media: Aqueous Biphasic and Related Systems - Extending the Frontier," Presented by R. D. Rogers before the Department of Energy Basic Energy Sciences Separations Program, Heavy Elements Program Contractor's Meeting (2005), Rockville, MD; Abstract O6-1.
559. C. Mobley, A. Ramasetty, A. Haque, J. H. Poplin, D. T. Daly, and R. D. Rogers, "Affordable Bio-polymer Matrix Composites for Lightweight Automotive Components," Presented by A. Haque at the Sixth Annual Global Automotive Conference (2005), Western Kentucky University, Bowling Green, KY.
560. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers at the NSF Joint China-USA Workshop *Determining the Grand Challenges of Green Chemistry Development and Implementation* (2005), May 27-31, 2005, Beijing, China; Abstract Book (Co-Organizer).
561. R. D. Rogers, V. A. Cocalia, K. E. Gutowski, N. J. Bridges, J. D. Holbrey, "Separations Using Ionic Liquids: The Challenges of Multiple Mechanisms," Presented by R. D. Rogers at the 1st International Congress on Ionic Liquids (COIL) (2005), Salzburg, Austria; Abstract Book p 28. (Plenary Lecture).
562. J. G. Huddleston, J. Chen, S. K. Spear, R. D. Rogers, "The Role of PEG-based Solvents in Green Chemistry," Presented by J. G. Huddleston before the International Conference on Biopartitioning and Purification, BPP 2005 (2005), The Netherlands, Abstract Book p 7.
563. R. P. Planalp, D. P. Kennedy, M. L. Childers, M. W. Brechbiel, R. Ma, G. A. Broker, R. D. Rogers, F. M. Torti, and S. V. Torti, "Polyamino-heterocycle chelating agents with cytotoxic activity in tumor cells: structure-activity relationship of metal-binding geometry and metal donor groups," Presented by R. P. Planalp before the First Congress of the International BioIron Society (2005), Prague, Czech Republic, Paper P281.
564. R. D. Rogers, D. T. Daly, J. D. Holbrey, J. G. Huddleston, J. H. Poplin, S. K. Spear, R. P. Swatloski, M. B. Turner, and R. L. Wells, "A Platform Strategy Using Ionic Liquids to Dissolve and Process Cellulose for Advanced New Materials," Presented by R. D. Rogers before the joint meeting of the 2nd International Conference on Green and Sustainable Chemistry and the 9th Annual Green Chemistry and Engineering Conference – Taking Measure of Green Progress: Opportunities to Meet Global Challenges (2005), Washington, DC; Abstract 1. (Presidential Green Chemistry Challenge Award Presentation)
565. S. T. Griffin, M. Dilip, S. K. Spear, and R. D. Rogers, "Comparison of the Effect of Temperature in Aqueous Biphasic Systems (ABS) and Aqueous Biphasic Extraction Chromatographic Resins (ABEC®)," Presented by M. Dilip before the joint meeting of the 2nd International Conference on Green and Sustainable Chemistry and the 9th Annual Green Chemistry and Engineering Conference – Taking Measure of Green Progress: Opportunities to Meet Global Challenges (2005), Washington, DC; Abstract 81.
566. M. Dilip, S. T. Griffin, S. K. Spear, and R. D. Rogers, "Towards Greener Environmental Remediation: Use of Aqueous Biphasic Extraction Chromatographic Resins (ABEC®) for Perchlorate Removal," Presented by M. Dilip before the joint meeting of the 2nd International Conference on Green and Sustainable Chemistry and the 9th Annual Green Chemistry and Engineering

Conference – Taking Measure of Green Progress: Opportunities to Meet Global Challenges (2005), Washington, DC; Abstract 82.

567. R. P. Swatloski, J. H. Poplin, D. T. Daly, A. Haque, C. Mobley, and R. D. Rogers, "Functional Bio-polymer Matrix Composites via Ionic Liquid Solution Routes," Presented by R. P. Swatloski before the joint meeting of the 2nd International Conference on Green and Sustainable Chemistry and the 9th Annual Green Chemistry and Engineering Conference – Taking Measure of Green Progress: Opportunities to Meet Global Challenges (2005), Washington, DC; Abstract 264.
568. V. A. Cocalia, M. P. Jensen, J. D. Holbrey, and R. D. Rogers, "The Challenges of Using Ionic Liquids as a New Media for Metal Ion Separations," Presented by V. A. Cocalia before the 24th Rare Earth Research Conference (2005), Keystone, CO; Abstract D-5, p 27.
569. D. A. Dixon, K. Gutowski, R. Rogers, S. Li, N. Shah, P. Keenum, W. deJong, T. L. Windus, and A. Felmy, "Computational Approaches to Lanthanide and Actinide Chemistry for Environmental Remediation," Presented by D. A. Dixon before the 24th Rare Earth Research Conference (2005), Keystone, CO; Abstract F-5, p 37.
570. N. J. Bridges, K. E. Gutowski, S. K. Spear, and R. D. Rogers, "Partitioning Studies of Pertechnetate Salts in Aqueous Biphasic Systems Formed by Contact of Ionic Liquids Solutions with Solutions of Kosmotropic Salts," Presented by N. J. Bridges before the 24th Rare Earth Research Conference (2005), Keystone, CO; Abstract P3-01, p 118.
571. A. Haque, D. T. Daly, R. D. Rogers, C. Mobley, and R. P. Swatloski, "Effects of MAPP as Coupling Agent on the Performance of Cellulose/Polypropylene Laminated Composites," Presented by A. Haque at the 3rd International Conference on Eco-Composites (2005), Royal Institute of Technology, Stockholm, Sweden.
572. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers at the Japan IL workshop July 15, 2005; Abstract. (Invited Presentation).
573. R. D. Rogers and V. Cocalia, "Separations Using Ionic Liquids: Multiple Uses/Multiple Mechanisms," Presented by R. D. Rogers at the 7th International Symposium on Molten Salts Chemistry & Technology (2005), Toulouse, France; Abstract - Proceedings Vol. II, p 1003.
574. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers at the 7th International Symposium on Molten Salts Chemistry & Technology (2005), Toulouse, France; Abstract - Proceedings Vol. I, p 59. (Invited Plenary Presentation)
575. R. D. Rogers, J. D. Holbrey, and S. K. Spear, "Green Chemistry and Applications of Ionic Liquids: Enabling Sustainable Technologies for Advanced New Materials," Presented by R. D. Rogers before the European Congress on Advanced Materials and Processes, EUROMAT 2005 (2005), Prague, Czech Republic; Abstract Symposium D52. (Keynote Lecture)
576. V. A. Cocalia, J. D. Holbrey, K. E. Gutowski, N. J. Bridges, and R. D. Rogers, "Separations of Metal Ions Using Ionic Liquids: The Challenges of Multiple Mechanisms," Presented by R. D. Rogers before the International Solvent Extraction Conference "Solvent Extraction for Sustainable Development" ISEC 2005 (2005), Beijing, China; Abstract A111. (Keynote Lecture)
577. R. D. Rogers, "Applications of Green Chemistry in a Recycling Economy," Presented by R. D. Rogers before the 7th World Congress on Recovery, Recycling and Re-integration (2005), Beijing, China; Abstract Book Page II. (Plenary Lecture)
578. R. D. Rogers, N. J. Bridges, J. G. Huddleston, K. E. Gutowski, and S. K. Spear, "Salt/Salt Aqueous Biphasic Systems Formed by Solutions of Ionic Liquids and Kosmotropic Salts," Presented by R. D. Rogers before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 37. (Invited Presentation).
579. N. J. Bridges, J. G. Huddleston, S. K. Spear, and R. D. Rogers, "Utilization of Salt/Salt Aqueous Biphasic Systems Formed by Solutions of Ionic Liquids and Kosmotropic Salts for the Extraction of Fission Products," Presented by N. J. Bridges before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 15.
580. V. A. Cocalia, S. K. Spear, and R. D. Rogers, "$^{99}TcO_4^-$ Extraction from Aqueous Media by XAD-7 Resin Coated with CYPHOS IL101 and CYPHOS IL104 Ionic Liquids," Presented by V. A. Cocalia before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 16.
581. K. E. Gutowski, R. D. Rogers, and D. A. Dixon, "DFT Studies of the Complexation Behavior of Phosphates and Silicates with Actinide and Fission Product Cations," Presented by K. E. Gutowski before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 20.
582. S. T. Griffin, S. K. Spear, W. M. Reichert, and R. D. Rogers, "Liquid-Liquid Extractions Using Renewable Plant-Based Soybean Oil as Alternatives to Organic Solvents," Presented by S. T. Griffin before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 31.
583. J. H. Davis, Jr., R. D. Rogers, S. Griffin, M. Tickell, and P. Fox, "Task-Specific Ionic Liquids (TSIL) for Separations Applications," Presented J. H. Davis, Jr. before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 39.
584. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers before the 6th Inha ERC International Symposium "Application of Ionic Liquids in Chemical Engineering" (2005), Incheon, Korea, Abstract book p 6. (Invited Keynote Speaker).
585. R. D. Rogers, "Green (or Not) Ionic Liquids to Access Biorenewable Polymer Materials," Presented by R. D. Rogers before the Joint US-Japan Workshop on Sustainable Chemical Synthesis (2005), Honolulu, HI (Invited Speaker).
586. R. D. Rogers, C. Mobely, R. P. Swatloski, J. H. Poplin, D. T. Daly, and A. Haque, "Cellulose-based composites prepared from ionic liquids: Affordable materials for industrial applications," Presented by R. D. Rogers before the 2005 International

Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract AGRO 391. (Invited Presentation)

587. R. M. Broughton, G. Shen, J. Lee, U. Cho, R. Swatloski, and R. D. Rogers, "Extrusion of composite fibers and films," Presented by R. M. Broughton before the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract ENVR 883. (Invited Presentation)
588. R. D. Rogers, R. P. Swatloski, S. K. Spear, and D. T. Daly, "Designer ionic liquids enabling sustainable technologies," Presented by R. D. Rogers before the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract ENVR 894. (Invited Presentation)
589. R. D. Rogers, R. P. Swatloski, J. H. Poplin, V. A. Cocalia, and N. J. Bridges, "Cellulosic materials containing lanthanide complexes: ionic liquid routes to new materials," Presented by R. D. Rogers before the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract INOR 803. (Invited Presentation)
590. A. Wierzbicki, J. Davis, R. D. Rogers, E. A. Salter, M. Reichert, S. Griffin, E. A. Cioffi, P. A. Fox, B. Wicker, A. Smith, M. Tickell, "Boron, but not boring: Boronium ions and their use in ionic liquids," Presented by A. Wierzbicki before the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract ENVI 769.
591. R. D. Rogers, M. Smiglak, D. W. Drab, W. M. Reichert, K. E. Gutowski, T. Wilson, A Vincek, D. Zhang, H. Fang, K. Kirischenko, S. Singh, and A. R. Katritzky, "Energetic Ionic Liquids: Fundamental Studies Relating Target Structures and Key Physical Properties," Presented by R. D. Rogers before Air Force Office of Scientific Research Ionic Liquids Research Workshop (2006), Tuscaloosa, AL.
592. A Vincek, D. Zhang, H. Fang, K. Kirischenko, S. Singh, A. R. Katritzky, J. D. Holbrey, , M. Smiglak, W. M. Reichert, S. K. Spear, and R. D. Rogers, "In search of Energetic Ionic Liquids," Presented by K. Kirischenko before Air Force Office of Scientific Research Ionic Liquids Research Workshop (2006), Tuscaloosa, AL.
593. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers, before the Chemical Engineering Students Society VII International Chemical Engineering Congress (2006), Monterrey, Mexico. (Invited Plenary Presentation)
594. C. C. Hines, W. M. Reichert, S. T. Griffin, T. Morgan, and R. D. Rogers, "Ionic liquids as solvents for metal-ligand complexation," Presented by C. C. Hines before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
595. M. Dilip, N. J. Bridges, and R. D. Rogers, "Influence of Temperature on Phase Diagrams and Partitioning of Alcohols in Salt/Salt ABS," Presented by M. Dilip before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
596. J. H. Poplin, R. Swatloski, J. Holbrey, S. Spear, and R. Rogers, "Development of Cellulose Based Dip-and-Read Test Strips for Hg^{2+} Detection," Presented by J. H. Poplin before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
597. M. Smiglak, D. M. Drab, T. Wilson, W. M. Reichert, R. D. Rogers, H. Yang, D. Zhang, K. Kirichenko, and A. R. Katritzky, "Strategies Toward the Design of Energetic Ionic Liquids: Nitro- and Nitrile Substituted Imidazolium Salts," Presented by M. Smiglak before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
598. M. Smiglak, D. M. Drab, T. Wilson, W. M. Reichert, R. D. Rogers, H. Yang, D. Zhang, K. Kirichenko, and A. R. Katritzky, "Strategies Toward the Design of Energetic Ionic Liquids: Azolate-Based Salts," Presented by M. Smiglak before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
599. M. Smiglak, W. M. Reichert, S. T. Griffin, J. D. Holbrey, R. D. Rogers, K. Kirichenko, D. Zhang, and A. R. Katritzky, "Ionic liquids via reaction of the zwitterion 1,3-dimethylimidazolium-2-carboxylate with protic acids," Presented by M. Smiglak before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
600. M. Smiglak, W. M. Reichert, J. D. Holbrey, L. Sun, J. S. Thrasher, R. D. Rogers, and J. S. Wilkes, "Combustible ionic liquids by design: Destroying another ionic liquid myth," Presented by M. Smiglak before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
601. K. E. Gutowski, J. D. Holbrey, D. A. Dixon, and R. D. Rogers, "Prediction of the Formation and Stabilities of Energetic Salts and Ionic Liquids Based on Ab Initio Electronic Structure Calculations," Presented by K. E. Gutowski before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
602. N. J. Bridges and R. D. Rogers, "Fundamental Studies of Chaotropic Salts (e.g., Ionic Liquids) and Kosmotropic Salts in the Formation of Salt/Salt Aqueous Biphasic Systems," Presented by N. J. Bridges before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
603. V. A. Cocalia, S. T. Griffin, and R. D. Rogers, "Ionic Liquids in Actinide Chemistry," Presented by V. A. Cocalia before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
604. W. L. Hough, T. Wilson, M. Smiglak, J. Pernak, S. K. Spear, J. H. Davis, Jr., and R. D. Rogers, "Ionic Liquids: The Next Generation of Sweeteners," Presented by W. L. Hough before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
605. R. D. Rogers, "ILs as Technical Materials, Literature, and Choice," Presented before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL. (Organizer).
606. R. D. Rogers, "Separations and Energetic Materials," Presented before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL. (Organizer).

607. M. Smiglak, W. M. Reichert, J. D. Holbrey, J. S. Wilkes, L. Sun, J. S. Thrasher, and R. D. Rogers, "Combustible ionic liquids by design: Destroying another ionic liquid myth," Presented by M. Smiglak before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 103.
608. M. Smiglak, W. M. Reichert, S. T. Griffin, J. D. Holbrey, R. D. Rogers**,** K. Kirichenko, D. Zhang, and A. R. Katritzky, "Ionic liquids via reaction of the zwitterion 1,3-dimethylimidazolium-2-carboxylate with protic acids," Presented by M. Smiglak before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 104.
609. C. C. Hines, W. M. Reichert, S. T. Griffin, and R. D. Rogers**,** "Ionic liquid mediated metal-ligand complexation," Presented by C. C. Hines before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 105.
610. W. Hough, T. Wilson, M. Smiglak, J. Pernak, S. K. Spear, J. H. Davis Jr., and R. D. Rogers**,** "Ionic liquids: The next generation of sweeteners," Presented by W. Hough before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 106.
611. R. C. Remsing, D. A. Fort, R. P. Swatloski, P. Moyna, R. D. Rogers**,** and G. Moyna, "Use of ionic liquids for the processing and analysis of lignocellulosic materials," Presented by G. Moyna before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 151.
612. R. P. Swatloski, R. M. Broughton, G. Moyna, D. T. Daly, S. K. Spear, and R. D. Rogers, "How understanding the ionic liquid/cellulose dissolution mechanism can guide the generation of advanced cellulose-based materials," Presented by R. P. Swatloski before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 204.
613. J. H. Davis Jr., A. Smith, M. Tickell, R. D. Rogers, W. M. Reichert, S. T. Griffin, A. Wierzbicki, and E. A. Salter, "Boronium ion based ionic liquids: Surprises abound," Presented by J. H. Davis, Jr. before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 220.
614. R. C. Remsing, D. A. Fort, R. P. Swatloski, P. Moyna, R. D. Rogers, and G. Moyna, "Green solvents gone bananas: Use of ionic liquids for the processing and analysis of biomass," Presented by G. Moyna before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 244.
615. J. H. Davis Jr., M. Tickell, R. D. Rogers, W. M. Reichert, and S. T. Griffin, "New task-specific ionic liquids incorporating amine groups and their use for reactive capture," Presented by J. H. Davis, Jr. before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 280.
616. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers before the 2nd Australian Symposium on Ionic Liquids (2006), Melbourne, Australia, Abstract Book. (Invited Plenary Speaker).
617. R. D. Rogers and W. M. Reichert, "Approaches to crystallization from ionic liquids: complex solvents-complex results – or – A strategy for controlled formation of new supramolecular architectures?" Presented by R. D. Rogers before the 89th Canadian Chemical Congress (2006), Halifax, Nova Scotia, Canada, Abstract 0338. (Invited Symposium Presentation)
618. J. Fortunak, F. Ohwoavworhua, O. Kunle, R. P. Swatloski, and R. D. Rogers, "Valuable products from Nigerian elephant sawgrass," Presented by J. Fortunak before the 10th Annual Green Chemistry and Engineering Conference (2006), Washington, D.C.
619. D. G. Whitten, L. V. Interrante, P. V. Kamat, and R. D. Rogers, "The Peer Review Process," Panel Presentation at the Institute of Chemistry of the Chinese Academy of Science Workshop on the Frontiers of Molecular Sciences & Symposium on Scholarly Publishing for Celebrating the 50th Anniversary of the Foundation of ICCAS (2006), Beijing, China, Abstract. (Invited Presentation)
620. R. D. Rogers, L. V. Interrante, P. V. Kamat, and D. G. Whitten, "Getting Involved in the Scientific Publishing Process; What Does it Take?," Panel Presentation (Led by R. D. Rogers) at the Institute of Chemistry of the Chinese Academy of Science Workshop on the Frontiers of Molecular Sciences & Symposium on Scholarly Publishing for Celebrating the 50th Anniversary of the Foundation of ICCAS (2006), Beijing, China, Abstract. (Invited Presentation)
621. L. V. Interrante, P. V. Kamat, R. D. Rogers, and D. G. Whitten, "What Constitutes Publishable Science," Panel Presentation at the Institute of Chemistry of the Chinese Academy of Science Workshop on the Frontiers of Molecular Sciences & Symposium on Scholarly Publishing for Celebrating the 50th Anniversary of the Foundation of ICCAS (2006), Beijing, China, Abstract. (Invited Presentation)
622. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Crystallization Solvents: Complex Solvents-Complex Results – or – A Strategy for Controlled Formation of New Supramolecular Architectures?," Presented by R. D. Rogers before the Institute of Chemistry of the Chinese Academy of Science Workshop on the Frontiers of Molecular Sciences & Symposium on Scholarly Publishing for Celebrating the 50th Anniversary of the Foundation of ICCAS (2006), Beijing, China, Abstract. (Invited Presentation)
623. D. G. Whitten, L. V. Interrante, P. V. Kamat, and R. D. Rogers, "The Peer Review Process," Panel Presentation at the 25th Chinese Chemical Society Congress (2006), Changchun, China, Abstract 20-I-002. (Invited Presentation)
624. R. D. Rogers, L. V. Interrante, P. V. Kamat, and D. G. Whitten, "Getting Involved in the Scientific Publishing Process; What Does it Take?," Panel Presentation (Lead by R. D. Rogers) at the Panel Presentation at the 25th Chinese Chemical Society Congress (2006), Changchun, China, Abstract 20-I-001. (Invited Presentation)
625. L. V. Interrante, P. V. Kamat, R. D. Rogers, and D. G. Whitten, "What Constitutes Publishable Science," Panel Presentation at the Panel Presentation at the 25th Chinese Chemical Society Congress (2006), Changchun, China, Abstract 20-I-003. (Invited Presentation)
626. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Crystallization Solvents: Complex Solvents-Complex Results – or – A Strategy for Controlled Formation of New Supramolecular Architectures?," Presented by R. D. Rogers before the 25th Chinese Chemical Society Congress (2006), Changchun, China, Abstract 01-I-004. (Invited Presentation)

627. A. Haque, C. Mobeley, D. T. Daly, R. D. Rogers, R. P. Swatloski, and A. Ramasetty, "Effects of MAPP as Coupling Agent on the performance of Regenerated Cellulose Film Reinforced Polypropylene Composites," Presented by A. Haque before the American Society for Composites 21st Annual Technical Conference (2006), Dearborn, MI.
628. J. Fortunak, F. Ohwoavworhua, O. Kunle, and R. D. Rogers, "Valuable products from Nigerian elephant sawgrass," Presented by J. Fortunak before the 10th Annual Green Chemistry & Engineering Conference 'Designing for a Sustainable Future' (2006), Washington, DC, Abstract 145.
629. C. C. Hines, M. Smiglak, W. M. Reichert, S. T. Griffin, and R. D. Rogers, "Crystal engineering utilizing ionic liquids," Presented by C. C. Hines before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 552.
630. R. P. Planalp, G. Lu, D. P. Kennedy, M. W. Brechbiel, R. D. Rogers, R. Ma, F. M. Torti, and S. V. Torti, "The metal-complexation properties of cytotoxic tripodal hexadentate chelators: Effects of heterocycle donor arms on Fe(II) chelation and fibroblast IC50 value," Presented by R. P. Planalp before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract MEDI 260.
631. M. Smiglak, C. C. Hines, T. Wilson, W. M. Reichert, S. T. Griffin, R. D. Rogers, K. Kirichenko, S. Singh, and A. Vincek, "Ionic liquids based on azole anions," Presented by M. Smiglak before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 555.
632. M. Smiglak, D. M. Drab., C. C. Hines, W. M. Reichert, R. D. Rogers, K. Kirichenko, and A. Vincek, "Halide free synthesis of energetic azolium azolate salts," Presented by M. Smiglak before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 522.
633. W. M. Reichert, J. D. Holbrey, K. B. Vigour, T. D. Morgan, G. A. Broker, S. T. Griffin, C. C. Hines, and R. D. Rogers, "Stepping stones and stumbling blocks for the utilization of ionic liquids as crystallization solvents," Presented by W. M. Reichert before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 098.
634. N. J. Bridges, and R. D. Rogers "Investigation into ion-pairing of 1-butyl-3-methylimidazolium chloride in aqueous media," Presented by N. J. Bridges before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 059.
635. N. J. Bridges, M. Smiglak, and R.D. Rogers "Synthesis of hydrogen carbonate ionic liquids through the Krapcho reaction," Presented by N. J. Bridges before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract I&EC 082.
636. R. D. Rogers and W. M. Reichert, "Approaches To Crystallization From Ionic Liquids: Complex Solvents-Complex Results – Or – A Strategy For Controlled Formation Of New Supramolecular Architectures," Presented by R. D. Rogers before the EUCHEM Conferences on Molten Salts and Ionic Liquids (2006), Hammamet, Tunisia, Abstract Book p 82.
637. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Solvents: Enabling Sustainable Technologies for New Advanced Materials," Presented by R. D. Rogers before XVI Congresso Brasileiro de Engenharia Química - COBEQ (2006), Santos, Brazil, Abstract Book p 12. (Invited Plenary Presentation)
638. R. D. Rogers, V. A. Cocalia, L. Nunez "Crystallization of Actinide Complexes from Ionic Liquids", Presented by R. D. Rogers before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 1989.
639. C. C. Hines, W. M. Reichert, S. T. Griffin, and R. D. Rogers, "Crystallization of new and interesting crystal structures in ionic liquids: Complex systems with complex results," Presented by C. C. Hines before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 2021.
640. M. Smiglak, M. Dilip, N. J. Bridges, W. M. Reichert, and R. D. Rogers, "Formation of ionic liquid eutectic mixtures as a tool for melting point depression." Poster presented by M. Smiglak before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 70 and 2022.
641. J. H. Poplin, D. Rudkevich, R. P. Swatloski, and R. D. Rogers, "Development of Liquid Membranes for NO_x Gas Detection and Storage Utilizing Calix[4]Arenes in Ionic Liquids," Presented by J. H. Poplin before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 83.
642. R. P. Swatloski, R. P. Broughton, N. Sun, M. Maxim, D. T. Daly, S. K. Spear, and R. D. Rogers, "A Look at Ionic Liquid Generated Cellulose and Modified Cellulose Fibers," Presented by R. P. Swatloski before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 1970.
643. R. D. Rogers, "What are Ionic Liquids," Presented by R. D. Rogers before the Intertech Pira Conference *Ionic Liquids: Technical Innovations, Emerging Markets and Applications* (2006), Orlando, FL, Abstract Book. (Co-Chair of the meeting)
644. R. D. Rogers, "Have You Considered the Unique Potential of Ionic Liquids as Crystallization Solvents?" Presented by R. D. Rogers before the ACS ProSpectives Series: *Crystallization Process Development: Case Studies & Research* (2007), Boston, MA.
645. R.D. Rogers and M. A. Abraham, "A 'Green' Industrial Revolution is in Our Future," Presented by R. D. Rogers and M. A. Abraham before the 233rd ACS National Meeting (2007), Chicago, IL, Abstract I&EC 046. (Invited Presentation)
646. J. H. Poplin, D. M. Rudkevich, and R. D. Rogers, "New Platforms for Immobilization of Calixarenes for Gas-Sensing and Trapping," Presented by R. D. Rogers before the 233rd ACS National Meeting (2007), Chicago, IL, Abstract I&EC 042. (Invited Presentation)

647. R.D. Rogers, N. J. Bridges, V. A. Cocalia, and K. E. Gutowski, "Separations, coordination, and solvation of f-elements in ionic liquids," Presented by R. D. Rogers before the 233rd ACS National Meeting (2007), Chicago, IL, Abstract NUCL 066. (Invited Presentation)
648. Sun, N.; Swatloski, R. P.; Maxim, M. L.; Broughton, Jr., R. M.; Spear, S. K.; Daly, D. T.; Haque, A.; Harland, A. G.; Rogers, R. D. "Cellulose Fibers Prepared from Direct Dissolution of Cellulose in Ionic Liquids," 4th International Conference of Textile Research Division National Research Centre, Cairo, Egypt; Textile Processing: State of the Art & Future Developments (2007), Abstract Page 16. Invited presentation, not presented due to illness.
649. R. D. Rogers, "The Evolution of Ionic Liquids: From Solvents to Materials to??? (and the New Business Opportunities that Follow)," Presented by R. D. Rogers before the Queen's University Ionic Liquid Laboratory 'Ionic Liquid Week' (2007), Belfast, Northern Ireland. (Invited Presentation)
650. R. D. Rogers, D. M. Drab, and M. Smiglak, "Ionic Liquids as a Unique and Versitile Platform for the Synthesis and Delivery of Energetic Materials," Presented by R. D. Rogers before the 54th Joint Army-Navy-NASA_Air Force (JANNAF) Propulsion Meeting (2007), Denver, CO, Program Booklet page 62.
651. R. D. Rogers "A Green Industrial Revolution is in Our Future," Presented by R. D. Rogers before the Licensing Executives Society Spring Meeting (2007), Atlanta, GA.
652. R. D. Rogers, "A 'Green' Industrial Revolution is in Our Future: Are Ionic Liquids Pointing the Way?," Presented by R. D. Rogers before the 11th Annual Green Chemistry and Engineering Conference: "From Small Steps to Giant Leaps – Breakthrough Innovations for Sustainability" (2007), Washington, DC; Abstract 15. (Invited Plenary Presentation)
653. R. D. Rogers, "Task-Specific Ionic Liquids: What Does this Term Really Mean," Presented by R. D. Rogers before the International Symposium on Task-Specific Ionic Liquids (2007), Keio University, Yokohama, Japan, Abstract p 2. (Invited Presentation)
654. S. Schneider, T. Hawkins, M. Rosander, R. Rogers, D. Drab, M. Smiglak, and A. Vij "From Halides to Azides – Novel Ionic Liquid Azides as Energetic Materials," Presented by S. Schneider before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 2P03-43.
655. C. Rijksen, M. Rahman, Y. Qin, N. Sun, M. Maxim, and R. D. Rogers, "Biomass: Dissolution, Separation, and Applications Enabled by Ionic Liquids," Presented by C. Rijksen before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 1P04-055.
656. M. Smiglak, C. C. Hines, N. J. Bridges, D. M. Drab, and R. D. Rogers, "New Precursors for the Halide Free Synthesis of Ionic Liquids Utilizing the Chemistry of Dimethylcarbonate," Presented by M. Smiglak before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 1P03-047.
657. M. Smiglak, C. C. Hines, D. M. Drab, and R. D. Rogers "Novel Energetic Ionic Liquid Materials Composed Solely of C, H, N, and O," Presented by M. Smiglak before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 2P06-066.
658. A. Metlen, C. Rijksen, W. L. Hough, M. Smiglak, H. Rodríguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis, Jr., and R. D. Rogers, "Ionic Liquids as Active Pharmaceutical Ingredients Exemplified by Lidocaine Docusate," Presented by A. Metlen before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 1P09-094.
659. D. R. MacFarlane, P. M. Dean, J. Turanjanin, J. L. Scott, W. L. Hough, M. Smiglak, H. Rodríguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis, Jr., and R. D. Rogers, "'Drug'" Ionic Liquids - A New Phase for the Pharmaceutical World," Presented by D. R. MacFarlane before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract PL9.
660. R. D. Rogers, M. Smiglak, W. L. Hough, A. Metlen, H. Rodríguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis, Jr., J. L. Scott, D. R. MacFarlane, "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials to Pharmaceuticals: Energetic and API Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract LMA1. (Invited Lecture)
661. R. D. Rogers, "The Third Evolution of Ionic Liquids: Physical to Chemical to Biological Properties," Presented by R. D. Rogers before the International Symposium on Ionic Liquids and Life Sciences (2007), Yokohama, Japan. (Invited Keynote Lecture)
662. R. D. Rogers, M. Rahman, N. Sun, M. L. Maxim, G. Moyna, and P. Moyna, "Utilizing Ionic Liquids for Access to and Modification of Bio-renewable Polymers," Presented by A. Metlen (R. Rogers was delayed by air travel difficulties) before Europacat VIII (2007), Turku, Finland, Abstract K12-2. (Invited (Rogers) Keynote Address)
663. R. D. Rogers, "What are Ionic Liquids (ILs)?," Presented by R. D. Rogers before the Intertech Pira Conference *Ionic Liquids: Technical Innovations, Emerging Markets and Applications* (2007), Prague, Czech Republic, Abstract Book. (Invited Talk and Chair of the meeting)
664. R. D. Rogers, "Approaches to Crystallization From Ionic Liquids: Complex Solvents-Complex Results – or – A Strategy for Controlled Formation of New Supramolecular Architectures?" Presented before the 5th Chinese National Symposium on Structural Chemistry and Symposium on Chinese Strategy of *Crystal Growth & Design* (2007), Fuzhou, China, Abstract PL-03. (Invite Plenary Presentation)
665. R. D. Rogers, "Getting Involved in the Scientific Publishing Process with *Crystal Growth & Design*: What Does It Take?" Presented before the 5th Chinese National Symposium on Structural Chemistry and Symposium on Chinese Strategy of *Crystal Growth & Design* (2007), Fuzhou, China, Abstract PL-10. (Invite Plenary Presentation)

666. R. D. Rogers, "Separations, coordination, and solvation of f-elements in ionic liquids," Presented by R. D. Rogers before the 59th Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy (2008), New Orleans, LA, Abstract 300-3. (Invited Symposium Presentation)
667. R. D. Rogers, "Green Chemistry and the New Transformational Platform Technologies Needed to Meet the Goals of Sustainability," Presented by R. D. Rogers before the Workshop in Green Chemistry Production of Essential Medicines in Developing Countries (2008), Abuja, Nigeria, No Abstract. (Invited Presentation)
668. R. D. Rogers, "Cracking Hydrocarbons: Direct Dissolution and Processing of Cellulosic and Related Biomass with Ionic Liquids Leading to New Materials," Presented by R. D. Rogers before the Workshop in Green Chemistry Production of Essential Medicines in Developing Countries (2008), Abuja, Nigeria, No Abstract. (Invited Presentation.
669. R. D. Rogers, M. Rahman, Y. Qin, N. Sun, M. L. Maxim, S. K. Spear, S. K. Mroczynski, and D. T. Daly, "New or Enhanced Materials from Biomass Utilizing the Unique Property Sets of Ionic Liquids," Presented by R. D. Rogers before the Materials Research Society Spring Meeting (2008), San Francisco, CA, Abstract Q1.1. (Invited Presentation)
670. N. Sun, R. P. Swatloski, M. L. Maxim, M. Rahman, A. G. Harland, A. Haque, S. K. Spear, D. T. Daly, and R. D. Rogers, "Cellulose Composite Fibers Prepared from Ionic Liquid-Based Solution," Presented by N. Sun before the 235th ACS meeting (2008), New Orleans, LA, Abstract CELL 285.
671. R. D. Rogers, M. Dilip, N. J. Bridges, M. Smiglak, D. B. Cordes, and K. Materna, "Utilization of hydrophilic ionic liquids in separations: Understanding and taming complexity," Presented by R. D. Rogers before the 235th ACS meeting (2008), New Orleans, LA, Abstract I&EC 078 (Invited Presentation).
672. R. D. Rogers, M. Rahman, Y. Qin, N. Sun, and M. L. Maxim, "Dissolution and processing of cellulosic and related biomass with ionic liquids: Fundamentals and applications," Presented by R. D. Rogers before the 235th ACS meeting (2008), New Orleans, LA, Abstract CELL 164 (Invited Presentation).
673. R. D. Rogers, "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers before Current Status of Ionic Liquid Technology in Chemical Engineering Symposium; part of the Spring National Meeting of the Korean Institute of Chemical Engineering (2008), Jeju Island, Korea, Abstract C-2 p 82. (Invited presentation)
674. R. D. Rogers, "Ionic Liquids Beyond Solvents: Unprecedented Opportunities to Fine Tune Physical, Chemical, and Biological Properties," Presented by R. D. Rogers before the Gordon Research Conference on Organic Structures & Properties: Molecular Design & Supramolecular Assemblies (2008), Lucca (Barga), Italy, no abstract. (Invited Presentation)
675. R. D. Rogers, "The Nature of Ionic Liquids: Are they Green Solvent Replacements or Tunable Crystallization Agents for Proteins?" Presented by R. D. Rogers before the 12th International Conference on the Crystallization of Biological Macromolecules (2008), Cancun, Mexico, Abstract Book Page 23. (Invited Keynote Lecture)
676. R. M. Frazier, W. L. Hough-Troutman, D. T. Daly, and Robin D. Rogers, "Microencapsulation of Active Nutraceutical Ingredients for Controlled Delivery," Presented by R. M. Frazier before Particles 2008, Particle Synthesis, Characterization, and Particle-Based Advanced Materials (2008), Orlando, Florida. Abstract B1.18.
677. R. D. Rogers, "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook, Presented by R. D. Rogers before the 3rd Australian Symposium on Ionic Liquids (2008), Melbourne, Australia, Abstract Book. (Invited presentation)
678. M. Smiglak and R. D. Rogers, "Protocols for halide free synthesis of ionic liquids via hydrogen carbonate precursors: Design of Ionic Liquid Energetic Materials," Presented by M. Smiglak before the 3rd Australian Symposium on Ionic Liquids (2008), Melbourne, Australia, Abstract Book.
679. W. Hough-Troutman, M. Smiglak, J. Pernak, D. T. Daly, and R. D. Rogers, "Ionic Liquids for Application in the Food Industry," Presented by W. L. Hough-Troutman before the 3rd Australian Symposium on Ionic Liquids (2008), Melbourne, Australia, Abstract Book.
680. R. D. Rogers, "The Evolution of Ionic Liquids – From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers before the Danish Chemical Society Kemisk Forenings Årsmøde (2008), Odense, Denmark, Abstract. (Invited Plenary Presentation)
681. R. D. Rogers, "Separation & Bioprocessing with Ionic Liquids," Presented by R. D. Rogers at the 1st Ionic Liquid Workshop "Ionic Liquid: The Future Solvent for Oil and Gas Industries" (2008), Glenmarie, Malaysia. (Invited Keynote Lecture)
682. R. D. Rogers, "Ionic Liquid Patents and Technology Development," Presented by R. D. Rogers at the 1st Ionic Liquid Workshop "Ionic Liquid: The Future Solvent for Oil and Gas Industries" (2008), Glenmarie, Malaysia. (Invited Keynote Lecture)
683. R. D. Rogers, Marcin Smiglak, and David M. Drab "A Modular 'Ionic Liquid' Platform for the Custom Design of Energetic Materials," Presented by R. D. Rogers at the Energetic Ionic Liquids Workshop (2008), Colorado Springs, CO; no abstract. (Invited Presentation)
684. R. D. Rogers, "Approaches to the Understanding and Utilization of Unique Ionic Liquid Properties: Physical (Solvents), Chemical (Energetic Materials), and Biological (Pharmaceuticals)," Presented by R. D. Rogers before the 20th International Conference on Chemical Thermodynamics (2008), Warsaw, Poland, Abstract IL-In-1, p 181. (Invited Lecture)
685. R. D. Rogers, "How I&EC supports innovative technologies for a sustainable future and those who will develop them," Presented by R. D. Rogers before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract PRES 005. (Invited Presentation)
686. R. D. Rogers, "Ionic liquids: Growth of a field through the eyes of the I&EC division," Presented by R. D. Rogers before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 079. (Invited Presentation)

687. D. R. MacFarlane, J. L. Scott, and R. D. Rogers, "Drug" ionic liquids: A new phase for the pharmaceutical world," Presented D. R. MacFarlane before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract ORGN 302.
688. M. Smiglak and R. D. Rogers, "Protocols for halide free synthesis of ionic liquids via hydrogen carbonate precursors," Presented by M. Smiglak before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 200.
689. R. D. Rogers, "From crystalline salts to ionic liquids and back again: In the hunt for novel separations," Presented by R. D. Rogers before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 003. (Invited Presentation)
690. W. L. Hough-Troutman, M. Smiglak, J. Pernak, D. T. Daly, and R. D. Rogers, "Sweetener and antibacterial ionic liquids," Presented by W. L. Hough-Troutman before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 183.
691. J. L. Scott, D. R. MacFarlane, P. Dean, J. Turanjanin, and R. D. Rogers, "An anticrystal engineering approach to functional ionic liquids," Presented by J. L. Scott before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 178.
692. G. Gurau, K. Rogers, and R. D. Rogers, "Caffeine ionic liquids – dream or reality?" Presented by G. Gurau before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 111.
693. R. D. Rogers, "What are Ionic Liquids?" Presented by R. D. Rogers at the Intensive Seminar of the Crystallization Technical Group of the Association of Powder Process Industry and Engineering (APPIE) (2008), Tokyo, Japan, Abstract Booklet. (Invited Plenary Lecture)
694. G. Gurau, V. Cocalia, and R. D. Rogers, "Separations, Coordination, and Solvation in Ionic Liquids: What is There That is Unique? Presented by R. D. Rogers at the International Solvent Extraction Conference: Solvent Extraction - Fundamentals to Industrial Applications (2008), Tucson, AZ, Abstract 266. (Invited Keynote Presentation)
695. R. D. Rogers, "Ionic Liquids and Solvent Extraction," Presented by R. D. Rogers in the Solvent Extraction Short Course at the International Solvent Extraction Conference: Solvent Extraction - Fundamentals to Industrial Applications (2008), Tucson, AZ. (Invited Instructor)
696. R. D. Rogers, J. Chen, H. L. Yang, and D. Q. Li, "Preliminary Investigation of the Kinetics of the Separation of Yttrium(III) Using Cyanex 923 and Ionic Liquids," Presented by R. D. Rogers at the International Solvent Extraction Conference: Solvent Extraction - Fundamentals to Industrial Applications (2008), Tucson, AZ, Abstract 87.
697. R. D. Rogers, "Ionic liquids for the dissolution of biomass: Where can this lead?" Presented by R. D. Rogers before the Green Solvents – Progress in Science and Application conference (2008), Friedrichshafen, Germany, Abstract Book, p 25 (Invited Keynote Presentation)
698. M. Dilip, S. T. Griffin, S. K. Spear, H. Rodríguez, and R. D. Rogers, "Aqueous biphasic extraction chromatographic (ABEC) resins based on polyethylene glycol as an alternative for the removal of perchlorate from aqueous media" Presented by H. Rodríguez before the Green Solvents – Progress in Science and Application conference (2008), Friedrichshafen, Germany, Abstract Book, p 109.
699. M. Francisco, H. Rodríguez, M. Rahman, and R. D. Rogers, "Liquid-liquid equilibria of mixtures of polyethylene glycol and ionic liquid: biphasic systems for high temperature applications" Presented by H. Rodríguez before the Green Solvents – Progress in Science and Application conference (2008), Friedrichshafen, Germany, Abstract Book, p 112.
700. R. D. Rogers, Invited Panelist at the Royal Institution of Great Britain Event "The Best President for Science" (2008), London, United Kingdom. (Invited Lecture).
701. R. D. Rogers, "Approaches to the Understanding and Utilization of Unique Ionic Liquid Properties: Physical (Solvents), Chemical (Energetic Materials), and Biological (Pharmaceuticals)," Presented by R. D. Rogers before the International Bunsen Discussion Meeting "Influence of Ionic Liquids on chemical and physicochemical reactions" (2008), Clausthal, Germany, Abstract Book p 63. (Invited Plenary).
702. R. D. Rogers, "At the Intersection of Cocrystals and Ionic Liquids," Presented by R. D. Rogers before the Indo-US Bilateral Workshop on Pharmaceutical Co-Crystals and Polymorphs (2009), Mysore, India, Abstract Book p 22. (Invited Lecture).
703. R. D. Rogers, "Getting Involved in the Scientific Publishing Process with *Crystal Growth & Design*: What Does it Take?," Presented by R. D. Rogers) at the 38th National Seminar on Crystallography (2009), Mysore, India, Abstract-Supplement to Abstract Book. (Invited Special Presentation)
704. R. D. Rogers, K. R. Seddon, M. Smiglak, and D. F. Wassell, "Ionic Liquids: Tailoring Unique, Multiply Redundant Liquids for Space Applications," Presented by R. D. Rogers before the Space, Propulsion & Energy Sciences International Forum (SPESIF-2009), Huntsville, AL Abstract Book Section W4.1.1.2.
705. R. D. Rogers, "From Green Chemistry to a 'Green' Industrial Revolution: Are Ionic Liquids Pointing the Way?," Presented by R. D. Rogers before the 237th ACS National Meeting (2009), Salt Lake City, UT, Abstract YCC 011. (Invited Presentation)
706. R. D. Rogers, S. Mroczynski, S. K. Spear, M. Rahman, N. Sun, and D. T. Daly "Utilizing the Unique Properties of Ionic Liquids to Prepare Advanced Composite Fibers," Presented by R. D. Rogers before the 6th International Conference of Textile Research Division National Research Centre, Cairo, Egypt; Textile Processing : State of the Art & Future Developments (2009), Cairo, Egypt, Abstract Book Page 9 (4/5/09). (Invited Plenary Presentation)
707. R. D. Rogers, "Ionic Liquids as Active Pharmaceutical Ingredients," Presented by R. D. Rogers before Molecules, Materials, Medicines (M3-2009) an International Conference on the Role of Materials Science and Engineering in Drug Development (2009), Santa Barbara, CA. (Invited Presentation)
708. R. D. Rogers, K. Bica, G. Gurau, M. Smiglak, H. Rodríguez, and J. Shamshina, "Ionic Liquids at the Intersections," Presented by R. D. Rogers before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Oral 41. (Invited Plenary Presentation)
709. K. Bica and R. D. Rogers, "Confused Ions in Ionic Liquids Pharmaceutically Active Ionic Liquids composed of Oligomers,"

Presented by K. Bica before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 52.

710. H. Rodríguez, M. Francisco, and R. D. Rogers, "Polymer/Ionic Liquid Aqueous Biphasic Systems," Presented by H. Rodríguez before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 158.
711. H. Rodríguez, and R. D. Rogers, "Biphasic, Non-Volatile, Liquid Mixtures of Polyethylene Glycols or Polypropylene Glycols with Hydrophilic Imidazolium Ionic Liquids," Presented by H. Rodríguez before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 157.
712. M. F. Taha, G. Srinivasan, J. D. Holbrey, and R. D. Rogers, "Standard reduction potentials ionic liquids containing polyhalide anions ($[XY_2]^-$, where X and Y are Cl, Br, I)," Presented by M. F. Taha before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 100.
713. G. Gurau and R. D. Rogers, "At the Intersection of Cocrystals and Ionic Liquids", Presented by G. Gurau before the 3rd Congress on Ionic Liquid (COIL-3) (2009), Cairns, Australia, Abstract Poster 211.
714. M. Abai, G. Srinivasan, Y. Zou, J. D. Holbrey, R. D. Rogers, "Ionic Liquid Thiouronium Salts," Presented by M. Abai before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 323.
715. C. D. Wilfred, S. Shukla, J. D. Holbrey, R. D. Rogers, "Microwave optimized synthesis of N-butyl-N-methylpyrrolidinium methylcarbonate; a functional precursor to the diversity synthesis of ionic liquids," Presented by J. D. Holbrey before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 324.
716. W. L. Hough-Troutman, J. Shamshina, M. Smiglak, and R. D. Rogers, "The Synthesis and Characterization of Caine Ionic Liquids," Presented by W. L. Hough-Troutman before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 325.
717. M. Huszár, A. Varga, A. Metlen, A. Horváth, T. Vántus, H. Rodríguez, M. Idei, G. Kéri, and R. D. Rogers, "Analytical and biological study of a new hydroxiquinoline-based library," Presented by M. Huszár and A. Varga before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 326.
718. A. Metlen, R. D. Rogers, "Syntheses and characterization of dithiocarbamate salts and ionic liquids," Presented by A. Metlen before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 340.
719. A.-F. Ngomisk and R. D. Rogers, "From ferrofluids to magnetic ionic liquids: New smart fluids in separation process," Presented by A.-F. Ngomisk before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 343.
720. R. D. Rogers, "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers before the joint 9º Encontro Nacional de Química Física/1st Iberian Meeting on Ionic Liquids (2009), Aveiro, Portugal, Abstract Book p 4. (Invited Plenary Presentation)
721. R. D. Rogers, "Separations using Ionic Liquids; What is there that is unique?," Presented by R. D. Rogers before the 15th International Conference on Biopartitioning and Purification (2009), Uxbridge, UK, Abstract K-8. (Invited Keynote Presentation)
722. A. N. Lovich, J. E. Lockhard, R. L. White, M. M. Bailey, J. F. Rasco, M. B. Henson, P. L. Jernigan, J. Sturdivant, R. P. Swatloski, R. D. Rogers, and R. D. Hood, "A Comparison of the Effects of Prenatal Exposure of CD-1 Mice to Three Imidazolium-based Ionic Liquids," Teratology Society, Presented by M. M. Bailey before the 49th Annual Meeting of the Teratology Society (2009), Rio Grande, Puerto Rico, Abstract P31 (*Birth Defects Research (Part A)* **2009**, *85*, 431.
723. W. L. Hough-Troutman, C. Troutman, M. Smiglak, J. Shamshina, D. Daly, and R. Rogers, "PDH Technologies, Inc. experience in raising funds in a university environment," Presented by W. L. Hough-Troutman before the before the 238th ACS National Meeting (2009), Washington, DC, Abstract BMGT 010.
724. R. D. Rogers and N. Sun, "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers before the Joint Conference: The 4th International Conference on Green and Sustainable Chemistry (GSC-4) & the 2nd Asian-Oceanian Conference on Green and Sustainable Chemistry (AOC-2) (2009), Beijing, China, Abstract PL-8; p. 9. (Invited Plenary Speaker)
725. R. D. Rogers, "Aspects of the Application of Ionic Liquids in the Separations of f-Elements: Coordination and Solvation," Presented by R. D. Rogers before the 7th International Conference on f-Elements ,ICfE-7 (2009), Cologne, Germany, Abstract P12. (Invited Plenary Speaker)
726. R. D. Rogers and N. Sun, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers before the Sixteenth Symposium on Separation Science and Technology for Energy Applications (2009), Gatlinburg, TN, Abstract Book p. 30. (Invited Speaker)
727. H. Rodríguez, M. Francisco, M. Rahman, and R. D. Rogers, "Biphasic liquid mixtures of imidazolium-based chloride ionic liquids and polyethylene glycols," Presented by H. Rodríguez before the 24th European Symposium on Applied Thermodynamics (ESAT-24) (2009), Santiago de Compostela, Spain, Abstract Book, p. 144.
728. R. D. Rogers, "The Hidden Commercial Opportunities for Ionic Liquids" Presented by R. D. Rogers before the Intertech Pira Conference *Ionic Liquids* (2009), Miami Beach, FL, Abstract on cd. (Invited Talk and Co-Chair of the meeting)
729. R. D. Rogers and N. Sun, "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers before Society of Environmental Toxicology and Chemistry (SETAC) North America 30th Annual Meeting (2009), New Orleans, LA, Abstract 431; p. 100. (Invited Speaker)
730. P. E. Clark, R. Boyle, J. Ku, B. Beaman, R. D. Rogers, M. Smiglak, S. Nagihara, G. Knowles, M. Bradley, M. B. Milam, "Geothermal System Designs for Lunar Surface Environment Science Activities," Presented by P. E. Clark before the Annual Meeting of the Lunar Exploration Analysis Group (LEAG 2009) (2009), Houston, TX.

731. R. D. Rogers, "What are the greatest challenges for increasing the contribution of green chemistry to the larger scientific community, i.e. what is holding green chemistry back?" Panel Presentation by R. D. Rogers at the National Academies/National Research Council Green Chemistry and Sustainability Project Initiation Meeting (2009), Washington, DC, No Abstract.
732. R. D. Rogers, "Crystallization Process in Ionic Liquids," Presented by R. D. Rogers before the Symposium on Green Process for Particle Production (2010), Kyoto, Japan; Abstract Book pp 7-11. (Invited Keynote Lecture)
733. M. Smiglak, G. T. Parker, R. D. Rogers, "Thermal conductivities of ionic liquid-regolith mixtures: Improving heat transfer for innovative thermal and power systems at the Lunar surface," Presented by M. Smiglak before SPESIF-2010 Space, Propulsion & Energy Sciences International Forum, Johns Hopkins University Applied Physics Laboratory, Laurel, MD, February 23-26, 2010, Abstract 068.
734. R. D. Rogers, "Ionic Liquids: Are the applications of ionic liquids as materials more important than the use of ionic liquids as solvents?" Presented by R. D. Rogers before EUCHEM 2010 Conference on Molten Salts and Ionic Liquids (2010), Bamberg, Germany, Abstract Book p 89. (Invited Keynote Lecture)
735. K. Bica, P. Gaertner, and R. D. Rogers, "Ionic Liquids and Fragrances: Isolation of Essential Oils from Biomass," Presented by K. Bica before EUCHEM 2010 Conference on Molten Salts and Ionic Liquids (2010), Bamberg, Germany, Abstract LMP 47, Abstract Book p 343.
736. B. Stoner, N. Sun, and R. D. Rogers, "Dissolution and regeneration of wood in [C_2mim]OAc and formation of wood composite fibers," Presented by B. Stoner before the 239th ACS National Meeting (2010), San Francisco, CA, Abstract CHED 725.
737. N. Sun, X. Jiang, M. L. Maxim, R. D. Rogers, "Wood delignification using polyoxometalates in ionic liquid," Presented by R. D. Rogers before the 239th ACS National Meeting (2010), San Francisco, CA, Abstract FUEL 014. (Invited Speaker)
738. M. Smiglak, G. Gurau, D. M. Drab, J. L. Shamshina, S. P. Kelley, V. Cocalia, S. T. Griffin, A.-V. Mudring, and R. D. Rogers, "Crystallization of actinides from ionic liquids," Presented by R. D. Rogers before the 239th ACS National Meeting (2010), San Francisco, CA, Abstract NUCL 016. (Invited Speaker)
739. G. Gurau and R. D. Rogers, "Importance of benchmarking Green Chemistry," Presented by R. D. Rogers before the 239th ACS National Meeting (2010), San Francisco, CA, Abstract CINF 026. (Invited Speaker)
740. R. D. Rogers, "Ionic Liquids Laboratory to Commercialization," Presented by R. D. Rogers before the Home for Foreign Experts – Meeting of the Chinese Academy of Sciences Senior International Scientists and Young Fellows (2010), Beijing, China; No Abstract. (Invited Plenary presentation).
741. B. J. Herring, A. L. Logsdon, A. N. Lovich, J. E. Lockard, E. R. Janzen, J. F. Rasco, K. R. Di Bona, R. D. Hood, R. P. Swatloski, R. D. Rogers, and M. M. Bailey, "Anion Influence on the Toxicity of Short-Chain Imidazolium-Based Ionic Liquids in CD-1 Mice," Presented by B. J. Herring before the 50th Annual Meeting of the Teratology Society (2010), Louisville, KY, Abstract P41 (*Birth Defects Research (Part A)* **2010**, *88*, 392).
742. W. Li, N. Sun, B. Stoner, X. Lu, and R. D. Rogers, "How can we improve the dissolution and recovery of biopolymers from biomass in ionic liquids specifically for biofuels applications?" Presented by R. D. Rogers before the 240th ACS National Meeting (2010), Boston, MA, Abstract FUEL 061. (Invited Plenary Speaker)
743. R. D. Rogers, G. Gurau, and D. T. Daly, "Open innovation and the faculty entrepreneur: opportunities and perils," Presented by R. D. Rogers before the 240th ACS National Meeting (2010), Boston, MA, Abstract BMGT 037. (Invited Speaker)
744. R. D. Rogers and Ning Sun, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers before the 2nd Asia Pacific Conference on Ionic Liquids and Green Processes (2010) (APCIL-2), Dalian, China, Abstract Book page 27. (Invited Plenary Presentation)
745. R. D. Rogers, "Developing Ionic Liquid Know-How for the Design of Modular Functionality, Versatile Platforms, and New Synthetic Methodologies for Energetic Materials, Presented by R. D. Rogers before the AFOSR Review for Organic Materials Chemistry and Molecular Design and Synthesis (2010), National Harbor, MD, Abstract.
746. *R. D. Rogers, "How can we improve the dissolution and recovery of biopolymers from biomass in ionic liquids specifically for biofuels applications?" Presented by R. D. Rogers before Frontiers in Biorefining: Biobased Products from Renewable Carbon (2010), St. Simons Island, GA, Abstract Book p 11. (Invited Speaker)*
747. N. Sun, X. Jiang, W. Li, X. Lu, and R. D. Rogers, "Wood Pulping Using Ionic Liquids," Presented by G. Gurau substituting for R. D. Rogers before the 4th International Symposium on Emerging Technologies of Pulping and Papermaking, 4th ISETPP (2010), Guangzhou, China, Abstract. (Invited Plenary Lecture)
748. R. D. Rogers, N. Sun, and Y. Qin, "The unique ability of ionic liquids to dissolve raw biopolymers such as cellulose and chitin, provides an opportunity to develop analytical techniques for molecular weight determination," Presented by R. D. Rogers before the 2010 International Chemical Congress of Pacific Basin Societies, Pacifichem 2010 (2010), Honolulu, HI, Abstract ANYL 870. (Invited Presentation)
749. R. D. Rogers, M. Smiglak, and J. Shamshina, "Azolium azolate ionic liquids from reactions of neutral azoles with 1,3-diemthylimidazolium-2-carboxylate, 1,2,3-trimethylimidazolium hydrogen carbonate, and *N,N*-dimethylpyrrolidinium hydrogen carbonate," Presented by R. D. Rogers before the 2010 International Chemical Congress of Pacific Basin Societies, Pacifichem 2010 (2010), Honolulu, HI, Abstract ENVI 237. (Invited Presentation)
750. R. D. Rogers, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers to the 1st Japanese Symposium on Ionic Liquids (2011), Tottori, Japan, Abstract Book PL-01 pp 1-2. (Invited Plenary Presentation)

751. R. D. Rogers, "Where are ionic liquids strategies most suited in the pursuit of chemicals and energy from lignocellulosic biomass?" Presented by R. D. Rogers before the 2nd Annual Next Generation Bio-Based Chemicals Summit, Bringing Together the Value Chain for Drop-In and New Chemicals (2011), San Diego, CA, Published Presentation. (Invited Keynote Presentation)
752. N. Pogodina, E. Metwalli, P. Müller-Buschbaum, J. Shamshina, R. D. Rogers, and C. Friedrich, "Structure and Dynamics of Azolium-Azolate Ionic Liquids," Presented by N. Pogodina before the DFG-SPP 1191 Priority Program Spring 2011 meeting (Potsdam, Germany); Abstract.
753. S. P. Kelley, T. G. Parker, and R. D. Rogers, "Actinide chemistry in ionic liquids," Presented by Steven Kelley before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 029.
754. S. P. Kelley, T. G. Parker, and R. D. Rogers, "Actinide complexes with *N*-donors from ionic liquids," Presented by Steven Kelley before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract NUCL 057.
755. P. D. McCrary, M. Smiglak, S. K. Spear, N. S. Bates, D. T. Daly, and R. D. Rogers, "Release of Ionic Liquid-Active Pharmaceutical Ingredients from Biopolymeric Beads," Presented by P. D. McCrary before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 106.
756. G. Gurau and R. D. Rogers, "Ionic liquids as active pharmaceutical ingredients (IL-APIs) – the challenges of commercialization," Presented by G. Gurau before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 119.
757. J. Shamshina, M. Smiglak, D. M. Drab, and R. D. Rogers, "Energetic Ionic Liquids," Presented by J. Shamshina before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 107.
758. D. Daly, R. Rogers, and Y. Qin, "Amine-CO_2: Tunable Approach for Ionic Liquid Supported Biomass Production and IL Recovery," Presented by D. Daly before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 117.
759. J. R. Canada, P. D. McCrary, G. Gurau, and R. D. Rogers, "Building a Career in Chemistry: The Importance of Undergraduate Research," Presented by J. R. Canada before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 120.
760. C. Sharma, C. Hines, and R. D. Rogers, "Temperature Controlled Release of Nicotine from its Metal Complexes," Presented by C. Sharma before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 028.
761. H. Rodríguez, S. Lago, M. Francisco, M. J. Earle, J. H. Holbrey, K. R. Seddon, R. D. Rogers, A. Soto, and A. Acre, "Ionic Liquids for Improved Liquid-Liquid Extraction Processes," Presented by H. Rodríguez before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 101.
762. M. Francisco, H. Rodríguez, N. Sun, M. Rahman, J. F. Pereira, M. G. Freire, L. P. Rebelo, J. A. Coutinho, and R. D. Rogers, "Biphasic Liquid-Liquid Systems Based on Ionic Liquids and Polyethylene Glycols," Presented by M. Francisco before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 103.
763. R. D. Rogers, "Award Address (ACS Award in Separations Science & Technology): Ionic Liquids form There to Here," Presented by R. D. Rogers before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 148. (Invited Award Address)
764. R. D. Rogers, "An Editor's Perspective on Contentious Issues Arising During Peer Review," Presented by R. D. Rogers before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract CHED 1236. (Invited Presentation)
765. P. D. McCrary, P. A. Beasley, R. D. Rogers, T. W. Hawkins, S. Schneider, J. P. Perez, B. W. McMahon, S. L. Anderson, and S. Son "Loading Metal Nanoparticles in Energetic Ionic Liquids," Presented by P. D. McCrary before the Air Force Office of Scientific Research Molecular Dynamics Contractors Meeting (May 15-17, 2011), Pasadena, CA, Abstract.
766. R. D. Rogers, "Developing Ionic Liquid Know-How for the Design of Modular Functionality, Versatile Platforms, and New Synthetic Methodologies for Energetic Materials," Presented by R. D. Rogers before the Air Force Office of Scientific Research Molecular Dynamics Contractors Meeting (May 15-17, 2011), Pasadena, CA, Abstract.
767. R. D. Rogers, "Crystallographic Publication in the American Chemical Society Journal *Crystal Growth & Design*: An Editor's Perspective (*so pay attention!*)," Presented by R. D. Rogers before the American Crystallographic Association 2011 Annual Meeting (May 28 – June 2, 2011), New Orleans, LA Abstract 08.04.6. (Invited presentation)
768. J. F. B. Pereira, M. G. Freire, M. Francisco, H. Rodríguez, L. P. N. Rebelo, R. D. Rogers, and J. A. P. Coutinho, "Aqueous Biphasic Systems Composed of Polyethylene Glycols and Ionic Liquids and their Ability to Extract Biomolecules," Presented by M. G. Freire before the **2nd Iberian Meeting on Ionic Liquids** (2nd IMIL) (2011), Santiago de Compostela and A Coruña, Galicia, Spain, Abstract.
769. H. Wang, G. Gurau, M. L. Maxim and R. D. Rogers, "Microwave-assisted dissolution and delignification of wood using 1-ethyl-3-methylimidazolium acetate ([emim]OAc)", Presented by H. Wang before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, DC, Abstract 368.
770. A. Narita, Parker D McCrary, John R Canada and R. D. Rogers, "Synthesis of ionic liquids consisting of FDA approved compounds", Presented by A. Narita before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, DC, Abstract 256.
771. G. Gurau, H. Rodríguez, S. P. Kelley, and R. D. Rogers, "Looking at the reactivity of 1-ethyl-3-methylimidazolium acetate with CO_2 and biomass from crystal structures: Will chemistry explain the controversies?", Presented by G. Gurau before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, DC, Abstract 310.
772. S. P. Kelley, E. S. Stoner, T. G. Parker, R. D. Rogers, "Ionic Liquids and Actinides: Unique Environments for f-Element Chemistry", Presented by S. P. Kelley before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D.C., Abstract 86.

773. P. D. McCrary, P. A. Beasley, T. W. Hawkins, S. Schneider, J. Paulo Perez, B. W. McMahon, S. L. Anderson, S. Son and R. D. Rogers, "Loading Metal Nanoparticles in Energetic Ionic Liquids", Presented by P. D. McCrary before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 213.
774. E. Stoner, S. Kelley, and R.D. Rogers, "Role of ionic liquids in the future of the thorium based nuclear fuel cycle", Presented by E. Stoner before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington DC, Abstract 333.
775. P. A. Beasley, P. D. McCrary, and R. D. Rogers, "New Generation of Energetic Materials based on Novel Asymmetric Multi-heterocyclic Architectures", Presented by P. A. Beasley before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, DC, Abstract 93.
776. J. R. Canada, P. D. McCrary, P. A. Beasley, A. Narita, R. D. Rogers, "Ionic Liquids Comprised of Biologically Active Amines", Presented by J. R. Canada before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 75.
777. J. Shamshina, H. W. H. Dykes, A. J. Reich, R. DiSalvo, M. Smiglak, and R. D. Rogers, "Catalytic ignition of ionic liquids for propellant applications," Presented by J. Shamshina before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 11.
778. M. G. Freire, J. F. B. Pereira, M. Francisco, H. Rodríguez, L. P. N. Rebelo, R. D. Rogers, and J. A. P. Coutinho, "Novel aqueous biphasic systems composed of ionic liquids and polyethylene glycols: Phase diagrams and extraction ability," Presented by M. G. Freire before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 17.
779. S. Y. Choi, H. Rodríguez, A. Mirjafari, D. F Gilpin, S. McGrath, K. R Malcolm, M. M Tunney, R. D Rogers, and Tony McNally, "Dual functional ionic liquids as plasticisers and antimicrobial agents for medical polymers, Presented by H. Rodríguez before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 201.
780. R. M. Frazier, D. T. Daly, W. L. Hough, S. K. Spear, and R. D. Rogers, "New Ionic Liquids for Active Layers in Photovoltaics," Presented by R. M. Frazier before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 436.
781. N. V Pogodina, E. Metwalli, P. Müller-Buschbaum, G. Dlubek, J. Shamshina, R. D Rogers, and C. Friedrich, "Molecular structure and dynamics of Azolium-Azolate ionic liquids," Presented by N. V. Pogodina before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 54.
782. C. P Azubuike, H. Rodríguez, A. O Okhamafe, and Robin D Rogers, "Physicochemical properties of maize cob cellulose powders reconstituted from ionic liquid solution," Presented by H. Rodríguez before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 71.
783. O. A. Cojocaru, J. L. Shamshina, J. P. Edgeworth, G. Gurau, R. S. Ruoff, and R. D. Rogers, "Improved Electrical Energy Storage with Electrochemical Double Layer Capacitance Basedon Novel Carbon Electrodes," Presented by O. A. Cojocaru before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 160.
784. R. D. Rogers, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers to the Joint Bioenergy Institute/Energy Biosciences Institute Workshop Lignin, Characterization, Extraction, & Adding Value (July 18-19, 2011), Emeryville, CA, No Abstract. (Invited Presentation)
785. R. D. Rogers, "Crystallographic Publication in the American Chemical Society Journal *Crystal Growth & Design* and Contentious Issues arising During Peer Review: An Editor's Perspective," Presented by R. D. Rogers before the 8th National Conference on Inorganic Chemistry (July 26-28, 2011), Harbin, China, Abstract 26M-PL-003. (Invited Plenary Presentation).
786. R. D. Rogers, "Crystallographic Publication in the American Chemical Society Journal *Crystal Growth & Design* and Contentious Issues arising During Peer Review: An Editor's Perspective (*so pay attention!*)," Presented by R. D. Rogers before the IUCr 2011 Satellite Workshop Categorizing Halogen Bonding and other Noncovalent Interactions Involving Halogen Atoms (Aug. 20-21, 2011), Sigüenza, Spain, Abstract Book p 49. (Invited Plenary). (http://www.iucr2011madrid.es/images/stories/pdf/Book_of_abstracts.pdf).
787. D. T. Daly, R. D. Rogers, and G. Gurau, "Disruptive technology for biomass processing using ionic liquids," Presented by D. T. Daly before the 242nd ACS National Meeting (Aug. 28 – Sept. 1, 2011), Denver, CO, Abstract BMGT 015.
788. J. F. B. Pereira, M. G. Freire, M. Francisco, H. Rodríguez, L. P. N. Rebelo, R. D. Rogers, and J. A. P. Coutinho, "Biomolecules Separation using Aqueous Biphasic Systems Composed of Polyethylene Glycols and Ionic Liquids," Presented by J. F. B. Pereira before IL SEPT (Sept. 4-7, 2011), Sitges, Spain, Abstract K09.
789. R. D. Rogers "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers before the 6th Asian Pacific Chemical Engineering Symposium, APCRE11 (Sept. 18-21, 2011), Beijing, China, Abstract Book p 1. (Invited Plenary Speaker)
790. P. S. Barber, S. P. Kelley, and R. D. Rogers, "Design and Coordination of f-elements with Amidoxime-Functionalized Ionic Liquids," Presented by P. S. Barber before the 17th Symposium on Separation Science and Technology for Energy Applications (Oct. 23–27, 2011), Gatlinburg, TN, Abstract 621.
791. S. P. Kelley, E. L. Stoner, and R. D. Rogers, "N-Donor Ionic Liquids as Unique Environments for f-Element Chemistry," Presented by S. P. Kelley before the 17th Symposium on Separation Science and Technology for Energy Applications (Oct. 23–27, 2011), Gatlinburg, TN, Abstract 617.
792. C. S. Griggs, S. L. Larson, J. H. Ballard, P. S. Barber, and R. D. Rogers, "Optimization and Evaluation of Uranium Sorptive Bio-materials," Presented by C. S. Griggs before the 17th Symposium on Separation Science and Technology for Energy Applications (Oct. 23–27, 2011), Gatlinburg, TN, Abstract 113.

793. E. L. Stoner, S. P. Kelley, and R. D. Rogers, "Application of Ionic Liquids for Separations in the Thorium Nuclear Fuel Cycle," Presented by E. L. Stoner before the 17th Symposium on Separation Science and Technology for Energy Applications (Oct. 23–27, 2011), Gatlinburg, TN, Abstract 618.
794. J. F. B. Pereira, M. G. Freire, H. Rodríguez, L. P. N. Rebelo, R. D. Rogers, and J. A. P. Coutinho "Insights into the Interactions that Control the Phase Behaviour of Novel Aqueous Biphasic Systems Composed of Polyethylene Glycols and Ionic Liquids," Presented by J. F. B. Pereira before MicroBiotec'11 (December 1-3, 2011), Braga, Portugal.
795. R. D. Rogers, "Preparation of High Purity, High Molecular Weight Chitin Nanofibers from Direct Extraction from Shrimp Shells with ILs for Use as an Adsorbate for Uranium from Seawater," Presented by R. D. Rogers before the DOE-NE Fuel Resources FY 12 Working Group Meeting (January 5–6, 2012), Oak Ridge, TN (No Abstract).
796. R. D. Rogers, "How an Understanding of Solid State Interactions can be Used to Prevent Solidification; the Case for Pure Pharmaceutical Liquid Salts and Cocrystals," Indo-US Bilateral Meeting on the Evolving Role of Solid State Chemistry in the Pharmaceutical Science (February 2-4, 2012), Manesar, India, Abstract Book pp 38-39. (not presented due to illness)
797. R. D. Rogers, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers before the Indo-US Workshop on Green Chemistry for Environments and Sustainable Development (March 11-13, 2012), Dehradun, India, Abstract PL-2 p 7. (Plenary Speaker)
798. D. T. Daly, R. M. Frazier, Y. Qin, S. K. Spear, W. L. Hough, and R. D. Rogers, "Ionic liquids: A platform for innovation," Presented by R. M. Frazier before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 261.
799. R. D. Rogers, O. A. Cojocaru, A. Siriwardana, H. Holding, K. Bica, H. Rodriguez, G. Gurau, A. Riisager, and R. Fehrmann, "Ionic liquid active pharmaceutical ingredients loaded on silica: Solids handling for liquid pharmaceutical forms," Presented by R. D. Rogers before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 093. (Invited Award Presentation)
800. G. Gurau and R. D. Rogers, "Ionic liquids and shrimp shell waste – emerging technologies for the manufacture of nanochitin materials," Presented by G. Gurau before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 117.
801. H. Wang, G. Gurau, and R. D. Rogers, "Membrane transport of active pharmaceutical ingredient-based ionic liquids," Presented by H. Wang before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 292.
802. O. A. Cojocaru, G. Gurau, D. T. Daly, J. Pernak, and R. D. Rogers, "Improved Efficacy and Delivery of Herbicides in Ionic Liquid Form," Presented by O. A. Cojocaru before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 324.
803. P. A. Beasley, O. A. Cojocaru, P. D. McCrary, and R. D. Rogers, "Energetic Ionic Liquid 'Liquid Clathrates'," Presented by P. A. Beasley before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 008.
804. P. D. McCrary, P. A. Beasley, O. A. Cojocaru, T. W. Hawkins, S. Schneider, J. Paulo Perez, B. W. McMahon, S. L. Anderson, S. F. Son, and R. D. Rogers, "Nanoparticles in Hypergolic and Energetic Ionic Liquids," Presented by P. D. McCrary before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 007.
805. G. W. Drake, P. D. McCrary, P. A. Beasley, and R. D. Rogers, "Evaluating Energetic Ionic Liquids as Hypergolic Fuels," Presented by P. D. McCrary and Preston A. Beasley before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 003.
806. J. R. Canada, O. A. Cojocaru, Gabriela Gurau, Juliusz Pernak, and R. D. Rogers, "Using Herbicidal Ionic Liquids to Reduce the Impact on the Environment," Presented by O. A. Cojocaru before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 325.
807. J. R. Canada, R. Rogers, K. E. Peterman, G. P. Foy, "COP 17: Spreading the Word," Presented by K. E. Peterman before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract SOCED 006.
808. G. Gurau, D. T. Daly, and R. D. Rogers, "Ionic liquid (IL) base drugs for the $1.2B pain management sector: New disruptive directions in pain management," Presented by G. Gurau before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract COMSCI 008.
809. B. W. McMahon, J. L. Perez, S, L. Anderson, S, Schneider, J. Boatz, T. Hawkins, P. D. McCray, P. A. Beasley, R. D. Rogers, and S. Son, "Dual ligand passivation and homogeneous media ball milling: Novel approaches for both the synthesis and capping of air-stable aluminum nanoparticles," Presented by B. W. McMahon before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract FUEL 367.
810. J. L. Perez, B. W. McMahon, S, L. Anderson, S, Schneider, J. Boatz, T. Hawkins, P. D. McCray, P. A. Beasley, and R. D. Rogers "Synthesis of air-stable, unoxidized boron nanoparticles using ball milling technique," Presented by J. L. Perez before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract FUEL 369.
811. R. D. Rogers, P. S. Barber, C. S. Griggs, E. L. Stoner, and S. P. Kelley, "Ionic Liquids for Extraction and Functionalization of Uranium Selective Chitin Sorbents," Presented by G. Gurau before the 2012 Materials Research Society Spring Meeting & Exhibit (April 9-13, 2012), San Francisco, CA, Abstract BBB 6.3. (Invited Speaker)
812. H. Wang, A. Kumar, G. Gurau, and R. D. Rogers, "Extraction of Sandalwood Oil from Sandalwood using Ionic Liquids," Presented by H. Wang before the 2012 Materials Research Society Spring Meeting & Exhibit (April 9-13, 2012), San Francisco, CA, Abstract BBB 4.8. (Invited Speaker)
813. G. Gurau and R. D. Rogers, "Nanochitin Materials from Shrimp Shell Waste – Manufacturing Challenges in an Ionic Liquid Process," Presented by G. Gurau before the 2012 Materials Research Society Spring Meeting & Exhibit (April 9-13, 2012), San Francisco, CA, Abstract BBB 3.6. (Invited Speaker)

814. R. D. Rogers, "Do you really understand all there is to know about Ionic Liquids?" Presented by R. D. Rogers before M3 Molecules Materials Medicines: An International Conference on the Role of Materials Science and Engineering in Drug Development (May 19-22, 2012), Banff, Alberta, Canada, Abstract. (Invited Keynote Address)
815. P. D. McCrary, P. A. Beasley, O. A. Cojocaru, S. P. Kelley, S. A. Alaniz, T. W. Hawkins, S. Schneider, J. A. Boatz, J. P. L. Perez, B. W. McMahon, S. L. Anderson, M. Pfeil, S. F. Son, and R. D. Rogers. "Controlling the Properties of Energetic Ionic Liquids (EILs) by Stabilizing Reactive Nanomaterials," Presented by P. D. McCrary before the AFOSR Contractors' Meeting (May 22-24, 2012), Arlington, VA, Abstract.
816. P. A. Beasley, P. D. McCrary, O. A. Cojocaru, T. W. Hawkins, S. Schneider, and R. D. Rogers, "Energetic Ionic Liquid "Liquid Clathrates"," Presented by P. A. Beasley before the AFOSR Contractors' Meeting (May 22-24, 2012), Arlington, VA, Abstract.
817. G. Gurau, H. Wang, and R. D. Rogers, "Polymorphs, Salts, and Cocrystals of Active Pharmaceutical Ingredients and the FDA Proposed Classifications: What will they think of Ionic Liquid Forms?," Presented by G. Gurau before the Gordon Research Conference on Crystal Engineering (June 10-15, 2012), Waterville Valley Resort, NH, Abstract 34.
818. S. P. Kelley, A. Narita, H. Wang, O. A. Cojocaru, G. Gurau, and R. D. Rogers "Ionic Liquids, Ionic Cocrystals, and Salts: Structural Consequences of Proton Sharing via Strong Hydrogen Bonds," Presented by S. P. Kelley before the Gordon Research Conference on Crystal Engineering (June 10-15, 2012), Waterville Valley Resort, NH, Abstract 41.
819. R. D. Rogers, "Science, service, and the ACS: Becoming an ACS Fellow from the I&EC Division," Presented by R. D. Rogers before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 043. (Invited Presentation)
820. C. S. Griggs, P. S. Barber, S. P. Kelley, G. Gurau, and R. D. Rogers, "Electrospun chitin nanofibers for uranyl absorbant materials," Presented by C. S. Griggs before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 058.
821. P. S. Barber, S. P. Kelley, C. S. Griggs, and R. D. Rogers, "Amidoxime functionalized materials for the selective extraction of the uranium," Presented by P. S. Barber before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 054.
822. R. D. Rogers, P. S. Barber, C. S. Griggs, S. P. Kelley, and G. Gurau, "Extraction of uranium with regenerated chitin from the dissolution of shrimp shells in ionic liquid," Presented by R. D. Rogers before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 106.
823. S. P. Kelley and R. D. Rogers, "Application of Unusual Metal Speciation in ILs to f-Element Separations," Presented by S. P. Kelley before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 105.
824. R. D. Rogers, "Ionic liquids and strategic metals: Challenges and opportunities," Presented by R. D. Rogers before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract ANYL 189. (Invited Presentation)
825. J. F. B. Pereira, Teresa Mourão, O. A. Cojocaru, G. Gurau, L. P. N. Rebelo, R. D. Rogers, J. A. P. Coutinho, and M. G. Freire, "Biodegradable and biocompatible aqueous biphasic systems composed of polymers and choline-based ionic liquids," Presented by J. F. B. Pereira before the 4th International IUPAC Conference on Green Chemistry (August 25-29, 2012), Foz do Iguaçu/PR, Brazil, Abstract Book p 74.
826. R. D. Rogers, "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin," Presented by R. D. Rogers before the 4th International IUPAC Conference on Green Chemistry (August 25-29, 2012), Foz do Iguaçu/PR, Brazil, Abstract Book p 11. (Invited Plenary Speaker).
827. R. D. Rogers, "Solvents, Separations, and Renewables," A Short Course presented by R. D. Rogers before the 4th International IUPAC Conference on Green Chemistry (August 25-29, 2012), Foz do Iguaçu/PR, Brazil, Abstract Book p xi. (Invited Course Instructor).
828. H. Wang, A. Myerson, and R. D. Rogers, "Separations utilizing hydrophobic vs. hydrophilic ionic liquids in support of continuous pharmaceutical manufacturing," Presented by H. Wang before the 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12 (Sept. 17-19, 2012), Beijing, China, Abstract E-12, p. 128.
829. G. Gurau, C. S. Griggs, P. S. Barber, and R. D. Rogers, "Shell Fish and Ionic Liquids – Turning Waste into Advance Materials," Presented by G. Gurau before the 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12 (Sept. 17-19, 2012), Beijing, China, Abstract G-13, p. 176.
830. P. D. McCrary, P. A. Beasley, and R. D. Rogers, "Ionic Liquids as 'Practical' Energetic Materials," Presented by P. D. McCrary before the 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12 (Sept. 17-19, 2012), Beijing, China, Abstract G-03, p. 166.
831. R. D. Rogers and G. Gurau, "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin," Presented by R. D. Rogers before the 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12 (Sept. 17-19, 2012), Beijing, China, Abstract P-01, p. 1. (Invited Plenary Speaker).
832. R. D. Rogers and G. Gurau, "Extraction and Manufacturing of Nanochitin Materials from Shrimp Shell Waste Using Ionic Liquids," 15th International Biotechnology Symposium and Exposition (IBS 2012), "Innovative Biotechnology for a Green World and Beyond" (Sept. 16-21, 2012), Daegu, South Korea, Abstract cd O-S8-0086. (Invited Speaker).
833. S. Mateyawa, P. Halley, R. Truss, F. Xie, T. Nicholson, T. McNally, and R. Rogers, Starch polymer nanocomposite systems: use of ionic liquids and nanofillers," Presented by S. Mateyawa before the 13th International Symposium on Biopolymers (ISBP 2012, October 7-10, 2012), Cairns, Australia, Abstract http://isbp2012.com.au/symposium-abstracts/.
834. R. D. Rogers, "What can ionic liquids, the antithesis of solid crystalline materials, teach us about controlling the form of active pharmaceutical ingredients? Crystals, cocrystals, and salts," Presented by R. D. Rogers before the Indian Institute of Technology Bombay – American Chemical Society Symposium (Oct. 1-2, 2012), Mumbai, India, Abstract. (Invited Lecture)

835. R. D. Rogers, "What can ionic liquids, the antithesis of solid crystalline materials, teach us about controlling the form of active pharmaceutical ingredients? Crystals, cocrystals, and salts," Presented by R. D. Rogers before the National Chemical Laboratory - American Chemical Society On Campus Symposium (Oct. 10, 2012), Pune, India, Abstract. (Invited Lecture)
836. R. D. Rogers, "What can ionic liquids, the antithesis of solid crystalline materials, teach us about controlling the form of active pharmaceutical ingredients? Crystals, cocrystals, and salts," Presented by R. D. Rogers before the Indian Association for the Cultivation of Science - American Chemical Society On Campus Symposium (Oct. 12, 2012), Calcutta, India, Abstract. (Invited Lecture)
837. R. D. Rogers, "How can the liquid state help us master the solid state? A study of Ionic Liquids in the pharmaceutical sector," Presented by R. D. Rogers before the 6th National Symposium on Structural Chemistry (6th NSSC; Oct. 22-25, 2012), Suzhou, China, Abstract KL-01. (Invited Keynote Lecture)
838. R. D. Rogers, "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin" Presented by R. D. Rogers before the CSIRO Cutting Edge 2012 Symposium on Biological and Chemical Conversion of Renewables to Fuels and Chemicals (Nov. 13-15, 2012), Parkville, Australia, Abstract D2. (Invited Lecture).
839. R. D. Rogers, "Developing Ionic Liquid Know-How for the Design of Modular Functionality, Versatile Platforms, and New Synthetic Methodologies for Energetic Materials," Presented by R. D. Rogers before the Air Force Office of Scientific Research Molecular Dynamics Contractors Meeting (December 3-4, 2012), Pasadena, CA, Abstract .
840. R. D. Rogers and P. D. McCrary, "The Development of Advanced Liquid Composite Materials by Controlling Stabilization of Nanoparticles in Ionic Liquids," Presented by R. D. Rogers before the 2013 Materials Research Society Spring Meeting & Exhibit (April 1-5, 2013), San Francisco, CA, Abstract VV2.07.
841. P. D. McCrary, G. P. Foy, K. E. Peterman, and R. D. Rogers, "Youth Involvement at the 18th Conference of Parties and the Need for Climate Science Literacy," Presented by P. D. McCrary before the 245th ACS National Meeting (April 7-11, 2013), New Orleans, LA, Abstract CHED 506.
842. P. D. McCrary, S. A. Alaniz, and R. D. Rogers. "Controlling the Properties of Energetic Ionic Liquids through the Incorporation of Reactive Nanomaterials," Presented by P. D. McCrary before the 245th ACS National Meeting (April 7-11, 2013), New Orleans, LA, Abstract I&EC 116.
843. S. K. McNeil, S. P. Kelley, C. Beg, H. W. Cook, R. D. Rogers, and D. E. Nikles. "Co-crystals of 1,3-dinitrobenzene and 10-methylphonothiazine: Implications for detecting explosives," Presented by S. K. McNeil before the 245th ACS National Meeting (April 7-11, 2013), New Orleans, LA, Abstract I&EC 133.
844. R. D. Rogers, "What happens when co-crystals don't crystallize?" Presented by R. D. Rogers before the CPI Conference CRYSTALLIZATION (April 16-17, 2013), Mumbai, India. (Invited Lecture)
845. O. A. Cojocaru, J. Shamshina, K. Bica, G. Gurau, A. Narita, P. D. McCrary, P. S. Barber, and R. D. Rogers, "Prodrug ionic liquids: functionalizing neutral active pharmaceutical ingredients to take advantage of the ionic liquid form," Presented by J. Shamshina before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P342. Poster
846. K. R. Di Bona, D. Yancey, S. Rizvi, M. Gray, G. Gurau, J. L. Shamshina, J. F. Rasco, and R. D. Rogers, "Transdermal Pharmacokinetic Studies of Ionic Liquids Composed Entirely of Active Pharmaceutical Ingredients," Presented by K. R. Di Bona before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P339.
847. G. Gurau, L. E. Block, J. Shamshina, and R. D. Rogers, "Wound dressings through an ionic liquid process – filling a gap in the wound care sector" Presented by G. Gurau before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract OP3.
848. P. D. McCrary, P. A. Beasley, G. Gurau, P. S. Barber, and R. D. Rogers, "Drug specific, tuning of an ionic liquid's hydrophilic-lipophilic balance to improve water solubility of poorly soluble pharmaceutical ingredients," Presented by P. D. McCrary before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P104.
849. P. D. McCrary, G. P. Foy, K. E. Peterman, and R. D. Rogers, "Youth Involvement at the 18th Conference of Parties and the Need for Climate Science Literacy," Presented by P. D. McCrary before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P105.
850. P. D. McCrary, S. A. Alaniz, and R. D. Rogers, "Controlling the Properties of Energetic Ionic Liquids through the Incorporation of Reactive Nanomaterials," Presented by P. D. McCrary before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract F36/P291.
851. P. S. Barber, C. S. Griggs, S. P. Kelley, S. Wallace, R. D. Rogers, "Using an Ionic Liquid Platform for the Development of Materials for the Extraction of Uranium from Seawater," Presented by P. S. Barber before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract F43/P81.
852. J. F. B. Pereira, L. P. N. Rebelo, R. D. Rogers, J. A. P. Coutinho, and M. G. Freire, "Combining ionic liquids and polyethylene glycols to boost the hydrophobic-hydrophilic range of aqueous biphasic systems," Presented by J. F. B. Pereira before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P65
853. J. Shamshina, P. D. McCrary, O. A. Cojocaru, G. Gurau, and R. D. Rogers, "Formation of pure liquid salt forms from active pharmaceutical ingredients to establish new drug delivery systems with superior properties," Presented by J. Shamshina before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P85.
854. R. D. Rogers and S. P. Kelley, Liquid Engineering to Crystal Engineering: How Ionic Liquids Can Help Us Master the Pharmaceutical Solid State," Abstract Only no Presentation to Past, Present, and Future of Crystallography@Politecnico di

Milano, from Small Molecules to Macromolecules and Supramolecular Structures (June 6-7, 2013), Milan, Italy, Abstract Book p 11. (Invited)

855. R. D. Rogers, "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin," Presented by R. D. Rogers before INORG2013 Conference (June 30 – July 4, 2013), Durban, South Africa, Abstract GS3, http://www.ic2013.ukzn.ac.za/. (Invited Plenary Speaker).
856. R. D. Rogers, "Basics of Scholarly Publishing: Peer Review - What It Is, How It Works, and Why It Matters!" Presented by R. D. Rogers before the University of KwaZulu-Natal - American Chemical Society On Campus Symposium (July 5, 2013), Durban, South Africa. (Invited).
857. R. D. Rogers, "Basics of Scholarly Publishing: Peer Review - What It Is, How It Works, and Why It Matters!" Presented by R. D. Rogers before the Wits University - American Chemical Society On Campus Symposium (July 8, 2013), Johannesburg, South Africa. (Invited).
858. R. D. Rogers, "Past, Present, and Future Ghosts in Submission, Review, and Archiving of Crystallographic Data in the American Chemical Society Journal *Crystal Growth & Design*," Presented by R. D. Rogers before the American Crystallographic Annual Meeting (July 20-24, 2013), Honolulu, HI, Abstract 13.10.04. (Invited)
859. O. A. Cojocaru and R. D. Rogers, "Ionic liquid forms of active pharmaceutical ingredients in drug delivery," Presented by O. A. Cojocaru before the 246th ACS National Meeting (September 8-12, 2013), Indianapolis, IN, Abstract AEI 066.
860. R. D. Rogers and G. Gurau, "Novel chitin fibers for wound care," Presented by D. T. Daly before the 246th ACS National Meeting (September 8-12, 2013), Indianapolis, IN, Abstract SCHB 019.
861. Z. Tywabi, B. Sithole, N. Deenadayalu, and R. D. Rogers, Structural changes in South African eucalyptus bleached dissolving pulp after dissolution in ionic liquid and co-solvent mixtures evidenced by FTIR and P'XRD, presented by Z. Tywabi before the Technical Association of the Pulp and Paper Industry of South Africa (TAPPSA) National Conference & Exhibition (October 22-23, 2013), Durban, South Africa.
862. M. Shadid, G. Gurau, B.-C. Chuang, M. Liao, S. Chowdhury, J.-T. Wu, S. A. A. Rizvi, R. D. Rogers, and R. J. Griffin, "Investigating the ADME properties of an ionic liquid salt form of sulfasalzine, a novel approach to improve drug exposure," Presented by M. Shadid before the 10th International Meeting of the International Society for the Study of Xenobiotics (September 30 – October 3, 2013), Toronto, Ontario, Canada, Abstract P127.
863. R. D. Rogers, "Advanced Materials from Renewable Polymers: Why Are We Still Using Synthetics?" Presented by R. D. Rogers before the 2013 CAS – TWAS Symposium on Green Technology (SGT2013; October 20–23, 2013; http://www.sgt2013.com/dct/page/1), Beijing, China, P-01, no abstract. (Plenary Speaker)
864. R. D. Rogers, (Walden Award Lecture) "Liquid Engineering to Crystal Engineering: How Ionic Liquids Can Help Us Master the Pharmaceutical Solid State," Presented by R. D. Rogers to COST Meeting, EXIL – Exchange on Ionic Liquids (November 24-26, 2013), Dresden, Germany, Abstract. (Invited Award Lecture)
865. R. D. Rogers, "Advanced Materials from Renewable Polymers: Why Are We Still Using Synthetics?" Presented by R. D. Rogers to the 65th Detmold Starch Convention, Detmold, Germany, Abstract 4.11. (Invited)
866. J. P. L. Perez, B. W. McMahon, J. Yu, S. Schneider, J. A. Boatz, T. W. Hawkins, P. D. McCrary, L. A. Flores, R. D. Rogers, and S. L. Anderson, "Synthesis and characterization of surface-functionalized aluminum and boron nanoparticles in hypergolic ionic liquid propellants," presented by S. L. Anderson before the Air Force Molecular Dynamics meeting (May 19-21, 2014), Arlington, VA.
867. R. D. Rogers, "Ideality vs. Reality of Green Chemistry in the Development of Advanced Materials from Renewable Polymers," Presented by R. D. Rogers before the 2014 CAS - TWAS Symposium on Advanced Engineering Science for Sustainable Development (AES 2014; May 28-30, 2014), Beijing, China, Abstract P-01. (Plenary Speaker)
868. R. D. Rogers, "Crystal Engineering to Liquid Engineering: Salts, cocrystals, deep eutectics, crystals, liquids…It's about the interactions and effects!" Presented by R. D. Rogers before the International Union of Pure and Applied Chemistry/International Council for Science Workshop on Crystal Engineering at the 1st International Symposium on Halogen Bonding (ISXB-1; June 18-22, 2014), Porto Cesareo, Italy, Abstract CE2. (Plenary Speaker)
869. H. Wang and R. D. Rogers, "Double salt ionic liquids: Expanding the range and tuneability of separations media," Presented by R. D. Rogers before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract PL2 (Plenary Presentation).
870. C. C. Weber, A. J. Kunov-Kruse1, R. D. Rogers, and A. S. Myerson, "Manipulating hydrogen bond complexes in ionic liquids to facilitate the purification of pharmaceuticals," Presented by C. C. Weber before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract O02.4.
871. M. G. Freire, A. M. Ferreira, A. M. Fernandes, R. D. Rogers, and J. A. P. Coutinho, "pH-triggered reversible aqueous biphasic systems composed of ionic liquids," Presented by M. G. Freire before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract O13.1.
872. J. F. B. Pereira, K. A. Kurnia, O. A. Cojocaru, G. Gurau, L. P. N. Rebelo, M. G. Freire, J. A. P. Coutinho, and R. D. Rogers, "Are crystalline cholinium salts really different from liquid cholinium salts in the formation of aqueous biphasic systems with polyethylene glycol?" Presented by J. F. B. Pereira before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract O15.1.
873. S. Nemser, P. R. Campos, D. Campos, S. Majumdar, R. D. Rogers, G. Gurau, B. A. Simmons, S. Singh, and J. Sun, "Dehydration of ionic liquids by pervaporation with perfluorinated membranes," Presented by S. Nemser before the 2nd

International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract O17.1.

874. J. A. P. Coutinho, L. I. N. Tomé, M. G. Freire, J. R. Gomes, J. F. B. Pereira, and R. D. Rogers, "'Washing-out' polyethylene glycol-ionic liquid mixtures to form aqueous biphasic systems," Presented by J. A. P. Coutinho before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract P010.
875. F. A. e Silva, J. F. B. Pereira, R. D. Rogers, A. M. S. Silva, J. A. P. Coutinho, and M. G. Freire, "When do quaternary ammonium halides behave as ionic liquids in the formation of aqueous biphasic systems?" Presented by J. F. B. Pereira before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract PO44.
876. J. F. B. Pereira, L. A. Flores, H. Wang, and R. D. Rogers, "Ionic liquid-benzene mixtures: The key to understanding liquid clathrate formation," Presented by J. F. B. Pereira before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract P074.
877. R. D. Rogers, "Processing of Lignocellulosic Biomass Using Ionic Liquids," Presented by R. D. Rogers before the Hybrid Processing for Biorenewable Fuels & Chemicals Production Symposium (July 10-11, 2014), Denver, CO, No Abstract (Invited Speaker).
878. R. D. Rogers, "Using Ionic Liquids for the Development of Renewable Biopolymer-Based Adsorbents for the Extraction of Uranium from Seawater and Testing Under Marine Conditions," Presented by R. D. Rogers before the DOE-NE Fuel Resources FY 14 Working Group Meeting (July 28-29, 2014), Sequim, WA (No Abstract).
879. G. Gurau, J. L. Shamshina, and R. D. Rogers, "High Throughput Electrospinning of Uranium Selective Chitin Adsorbents – A Sustainable Ionic Liquid Technology," Presented by G. Gurau before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 23.
880. J. L. Shamshina, G. Gurau, L. E. Block, L. K. Hansen, C. Dingee, A. Walters, and R. D. Rogers, "Chitin-Calcium Alginate Composite Fibers for Wound Care Dressings Spun from an Ionic Liquid," presented by J. L. Shamshina before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 48.
881. S. Yerkimbekova, J. L.Shamshina, G. Gurau, A. Zazybin, V. Yu1, and R. D. Rogers, "Ionic Liquids as Electrolytes," Presented by S. Yerkimbekova before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 64.
882. F. Cheng, H. Wang, and R. D. Rogers, "Enhancement of Dissolution and Delignification of Woody Biomass in Ionic Liquids in the Presence of Polyoxometalate and Oxygen," Presented by F. Cheng before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 10.
883. O. A. Cojocaru, J. Shamshina, J. Pernak, and R. D. Rogers, "Herbicidal Ionic Liquids with Reduced Volatility and Increased Efficacy," Presented by J. Shamshina before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 70.
884. H. Wang, A. S. Myerson, and R. D. Rogers, "Finely Tunable Solvent Properties of Ionic Fluids Containing More Than Two Ions," Presented by H. Wang before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 60.
885. S. P. Kelley, J. S. Nuss, and R. D. Rogers, "Forcing unusual Coordination with ionic Liquids designed for f-Element Coordination Chemistry," Presented by S. P. Kelley before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 28.
886. L. Flores, J. Pereira, H. Wang, P. McCrary, and R. D. Rogers, "Ionic Liquid Mixtures with benzene: A Greater Understanding of Liquid Clathrates," Presented by L. Flores before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines? (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 15.
887. H. Wang, J. Pereira, A. Myerson, and R. D. Rogers, "Double Salt Ionic Liquids Prepared by Mixing Partially Miscible Ionic Liquids: Tuning the Solubility of Lipophilic Molecules," Presented by R. D. Rogers before the 19th International Symposium on Molten Salts part of the 2014 ECS and SMEQ Joint International Meeting of the 226th Meeting of the Electrochemical Society Meeting and the XXIX Congreso de la Sociedad Mexicana de Electroquímica (October 5-9, 2014), Cancun, Mexico, Abstract H6.1419. (Invited Keynote Presentation)
888. R. D. Rogers and K. Boykin, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers before the Joint 31st Latin American Chemistry Congress (Congreso Latinoamericano de Química; CLAQ-2014) and XXVII Peruvian Chemistry Congress (October 14-17, 2014), Lima, Peru, Abstract. (Invited Plenary Presentation)
889. S. Nemser, D. Campos, P. R. Campos, J. Bowser, S. Majumdar, B. A. Simmons, S. Singh, J. Sun, J. Shi, R. D. Rogers, G. Gurau, and F. Cheng, "Perfluorinated Membranes for the Dehydration of Ionic Liquids for Processing Biomass," Presented by S. Nemser before the 2014 AIChE Annual Meeting (November 16-21, 2014), Atlanta, GA, Abstract 637b.
890. R. D. Rogers, "Ideality vs. Reality of Green Chemistry in the Development of Advanced Materials from Renewable Polymers," Presented by R. D. Rogers before the Semi-Annual Meeting of the Innovative Green Wood Fibre Products Network (Nov. 18-20, 2014), Esterel, QC, Canada, Abstract book. (Keynote Speaker)

891. R. D. Rogers, "Using Ionic Liquids for the Development of Renewable Biopolymer-Based Adsorbents for the Extraction of Uranium from Seawater and Testing Under Marine Conditions," Presented by R. D. Rogers before the DOE-NE Fuel Resources FY 15 Working Group Meeting (January 12-13, 2015), Oak Ridge, TN (No Abstract).
892. R. D. Rogers, H. Wang, and S. P. Kelley, "Double salt ionic liquids with unique chemical environments for separations." Presented by R. D. Rogers before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 1.
893. J. L. Shamshina, G. Gurau, S. P. Kelley, and R. D. Rogers, "Uranium-from-seawater sorbents from fishing industry waste – cost reduction through solvent recycle." Presented by J. L. Shamshina before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 50.
894. G. Gurau, J. L. Shamshina, S. P. Kelley, and R. D. Rogers, "Uranium-from-seawater sorbents from industry waste – from batch to continuous production." Presented by G. Gurau before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 30.
895. S. P. Kelley, J. L. Shamshina, G. Gurau, and R. D. Rogers, "Dual functional sorbents for coextraction of aqueous copper and uranium." Presented by S. P. Kelley before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 48.
896. R. D. Rogers, S. P. Kelley, G. Gurau, G., and J. L. Shamshina, "Nanofiber chitin mats for coextraction of value added metals from seawater: Improving the economics of uranium recovery." Presented by R. D. Rogers before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 15.
897. J. Bandomir, S. P. Kelley, J. L. Shamshina, G. Gurau, and R. D. Rogers, "Homogeneous blending of chitin with biopolymers for advanced biodegradable sorbents for uranium extraction from seawater." Presented by J. Bandomir before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 47.
898. R. D. Rogers and S. P. Kelley, "A practical overview of organic synthesis in ionic liquids." Presented by R. D. Rogers before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract ORGN 307.
899. R. D. Rogers, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers before the 5th Annual Meeting of the Canada Excellence Research Chairs (April 13-14, 2015), Waterloo, ON, Canada.
900. R. D. Rogers, "Innovation is the Gateway to the Biomass Biorefinery and Ultimately A sustainable Bio-based Economy," Presented by R. D. Rogers before the L'Oréal Satellite Symposium at the 3rd International Symposium on Green Chemistry (ISGC 2015), May 3-7, 2015, La Rochelle France (Invited).
901. R. D. Rogers, "Are Alternative Solvent Systems such as Ionic Liquids Green or not Based on Toxicity, Chemical or Energy Use, or Utilization? (Hint: It Depends)," Presented by R. D. Rogers before the 3rd International Symposium on Green Chemistry (ISGC 2015), May 3-7, 2015, La Rochelle, France, Abstract PL9. (Invited Plenary Presentation)
902. R. D. Rogers, and H. Wang, "Ionic Fluids Containing Both Strongly and Weakly Interacting Ions of the Same Charge Have Unique Ionic and Thus Chemical Environments As a Function of Ion Concentration," Presented by R. D. Rogers before the 227th ECS Meeting (May 24-28, 2015), Chicago, IL, Abstract M04-2158. (Invited Keynote presentation)
903. R. D. Rogers, "Green chemistry and advanced materials from renewable polymers: education, research, and entrepreneurship to motivate the next generation of scientists," Presented by R. D. Rogers before the 98th Canadian Chemistry Conference and Exhibition (June 13-17, 2015), Ottawa, ON, Abstract 1177 PL2. (Invited Plenary Presentation).
904. R. D. Rogers, "Is 'Sustainability' a new paradigm for the future chemical industry? Cross border perspectives and what we need to train the next generation to face," Presented by R. D. Rogers before the 98th Canadian Chemistry Conference and Exhibition (June 13-17, 2015) CIC Chair's Event: CIC/CGCEN Business Innovation Session, Ottawa, ON, Abstract. (Invited Presentation).
905. H. Passos, T. B. V. Dinis, A. M. Fernandes, R. D. Rogers, M. G. Freire, and J. A. P. Coutinho, "Ionic liquids as phase-forming components of aqueous multiphasic systems," Presented by H. Passos before the 6th International Congress on Ionic Liquids (COIL-6; Jun. 16-20, 2015), Jeju City, South Korea, Abstract S28.
906. M. Ferreira, R. D. Rogers, M. G. Freire, and J. A. P. Coutinho, "pH reversible aqueous biphasic systems," presented by A. M. Ferreira before the 6th International Congress on Ionic Liquids (COIL-6; Jun. 16-20, 2015), Jeju City, South Korea, Abstract S42.
907. M. Ferreira, R. D. Rogers, M. G. Freire, and J. A. P. Coutinho, "pH-Driven Reversible Aqueous Biphasic Systems Composed of Ionic Liquids," Presented by J. A. P. Coutinho before the Nineteenth Symposium on Thermophysical Properties (June 21-26, 2015), Boulder, CO, Abstract 2385.
908. F. B. Pereira, V. C. Santos-Ebinuma, A. Pessoa, R. D. Rogers, S. P. M. Ventura, M. G. Freire, and J. A. P. Coutinho, "Facing the Complexity of Bioproducts' Purification using PEG-IL-based Aqueous Biphasic Systems: From Antibiotics to L-Asparaginase," Presented by J. F. B. Pereira before the Iberoamerican Meeting on Ionic Liquids - IMIL 2015 (July 2-3 July, 2015), Madrid, Spain, Abstract P13.
909. R. D. Rogers, "Using Ionic Liquids for the Development of Renewable Biopolymer-Based Adsorbents for the Extraction of Uranium from Seawater and Testing Under Marine Conditions," Presented by R. D. Rogers before the DOE-NE Fuel Resources Summer 2015 Working Group Meeting (August 6-7, 2015), College Park, MD (No Abstract).
910. R. M. Hanes, J. L. Shamshina, G. Gurau, T. Di Nardo, P. Berton, S. P. Kelley, and R. D. Rogers, "Uranium-from-Seawater Sorbents from Fishing Industry Waste – Pilot Testing and Financial Analysis," Presented by R. M. Hanes before the DOE-NE Fuel Resources Summer 2015 Working Group Meeting (August 6-7, 2015), College Park, MD (No Abstract).

911. R. D. Rogers and S. P. Kelley, "Covalent, Supramolecular…. Ionic? Using Ionic Liquids to Demonstrate Manipulation of the Ionic Bond; an Underutilized Tool in Crystal Engineering," Presented by R. D. Rogers before the 2nd International Council for Science/International Union of Pure and Applied Chemistry Workshop on Crystal Engineering, (August 30-September 1, 2015), Como, Italy, Abstract Book p. 43. (Invited Expert)
912. R. D. Rogers, "Does the Nature of the Bonding in Double Salt Ionic Liquids "Prove" A Difference Between Ionic Liquids and Molecular Liquids?" Presented by R. D. Rogers before the Joint European Molecular Liquids Group/Japanese Molecular Liquids Group Annual Meeting "Molecular Liquids Meet Ionic Liquids, From Fundamentals to Applications," (Sept. 6-10, 2015), Rostock, Germany, Abstract Book OL p. 16. (Invited Opening Lecture)
913. R. D. Rogers, "Basics of Scholarly Publishing: Peer Review - What It Is, How It Works, and Why It Matters!" Presented by R. D. Rogers to the American Chemical Society On Campus Symposium at the University of Toronto (September 24, 2015), Toronto, ON, Canada, No Abstract (Invited).
914. R. D. Rogers, "Basics of Scholarly Publishing: Peer Review - What It Is, How It Works, and Why It Matters!" Presented by R. D. Rogers to the American Chemical Society On Campus Symposium at York University (September 25, 2015), Toronto, ON, Canada, No Abstract (Invited).
915. R. D. Rogers, "Green Chemistry and Sustainable Technology through Innovation," Presented by R. D. Rogers before the Seminar on Exploitation of Residue Generated by Agribusiness Activity Organized by The Centre of Piscicultural Technological Development at Surcolombiano-Acuapez and Corporación Universitaria del Huila-CORHUILA (November 30, 2015), Neiva, Colombia, No Abstract (Invited Opening Lecture – presented via Skype).
916. R. D. Rogers, "ACS *Crystal Growth & Design*: Founding a journal in the cusp of electronic publishing and open access," Presented by R. D. Rogers before the 2015 International Chemical Congress of Pacific Basin Societies, Pacifichem 2015 (Dec. 15-20, 2015), Honolulu, HI, Abstract SCTY 063. (Invited Presentation)
917. G. Gurau, J. L. Shamshina, N. Abdul Faruk Khan, S. P. Kelley, P. Berton, and R. D. Rogers, "Sustainable materials for energy harvesting – how shrimp shell waste and ionic liquids can make an impact on today's society," Presented by G. Gurau before the 2015 International Chemical Congress of Pacific Basin Societies, Pacifichem 2015 (Dec. 15-20, 2015), Honolulu, HI, Abstract SCTY 335.
918. R. D. Rogers, "Green chemistry and advanced materials from renewable polymers: Education, research, and entrepreneurship to motivate the next generation of scientists," Presented by R. D. Rogers before the 2015 International Chemical Congress of Pacific Basin Societies, Pacifichem 2015 (Dec. 15-20, 2015), Honolulu, HI, Abstract SCTY 385. (Invited Presentation)
919. R. D. Rogers, "Using Ionic Liquids for the Development of Renewable Biopolymer-Based Adsorbents for the Extraction of Uranium from Seawater and Testing Under Marine Conditions," Presented by R. D. Rogers before the DOE-NE Fuel Resources Winter 2016 Working Group Meeting (January 14-15, 2016), Oak Ridge National Lab, TN (No Abstract).
920. R. D. Rogers, "Understanding the Interactions of Seawater Ions with Amidoxime through X-Ray Crystallography," Presented by R. D. Rogers before the DOE-NE Fuel Resources Winter 2016 Working Group Meeting (January 14-15, 2016), Oak Ridge National Lab, TN (No Abstract).
921. R. M. Hanes, J. L. Shamshina, Ezinne Achinivu, and R. D. Rogers, "Uranium-from-Seawater Sorbents from Fishing Industry Waste – Pilot Testing and Financial Analysis," Presented by R. M. Hanes before the DOE-NE Fuel Resources Winter 2016 Working Group Meeting (January 14-15, 2016), Oak Ridge National Lab, TN (No Abstract).
922. R. D. Rogers, "What is an Appropriate Academic Business Model to Drive Commercialization of Sustainable Ionic Liquids-Based Technologies?" Presented by R. D. Rogers before the International Symposium on Ionic Liquids (ISOIL_2016; Jan. 21-22, 2016), Mumbai, India, Abstract. (Invited Keynote Presentation)
923. R. D. Rogers, "Why is the Sugar Industry letting 'Big Corn' Drive the Biorefinery? Innovation is the Gateway to the Biomass Biorefinery and Ultimately A sustainable Bio-based Economy," Presented by R. D. Rogers Before the Sugar Processing Research Institute 2016 Conference on The Science and Technology of a Sustainable Sugar Industry (Feb. 21-25, 2016), Walnut Creek, CA, Abstract Book. (Invited Plenary Presentation).
924. S. P. Kelley, G. P. Rachiero, J. Wang, and R. D. Rogers, "Imidazole-2-thiones as liquid sorbents of Hg(0): Thermal behavior, redox chemistry, and loading on solid supports," Presented by R. D. Rogers before the 251st National Meeting of the American Chemical Society (March 13-17, 2016), San Diego, CA, Abstract ENVR 093.
925. J. L. Shamshina, G. Gurau, and R. D. Rogers, "Translational research: From academia to industry. Following the pathway of George Washington Carver," Presented by R. D. Rogers before the 251st National Meeting of the American Chemical Society (March 13-17, 2016), San Diego, CA, Abstract I&EC 054.
926. P. Berton, G. Gurau, J. L. Shamshina, and R. D. Rogers, "In search of green chemistry and sustainability: Polymeric materials based on renewable polymers," Presented by R. D. Rogers before the 251st National Meeting of the American Chemical Society (March 13-17, 2016), San Diego, CA, Abstract I&EC 109.
927. T. Di Nardo, and R. D. Rogers, "Unlocking the true power of ionic liquids: highly functional, environmentally compatible biopolymer platform," Presented by R. D. Rogers before the 1st Middle-Eastern Materials Science Conference (March 22-23, 2016), Abu Dhabi, United Arab Emirates, Abstract. (Invited)
928. R. D. Rogers, "What is an Appropriate Academic Business Model to Drive Commercialization of Sustainable Technology?" Presented by R. D. Rogers before the CIC/SCI Canada Green, Clean and Sustainable Chemistry Seminar: Innovation Through Collaboration (April 7, 2016), Toronto, ON, Canada. (Invited)
929. R. D. Rogers, "Green Quest: Resourceful Approaches to Resources," Presented by R. D. Rogers before the 6th Annual Meeting of the Canada Excellence Research Chairs (April 11-12, 2016), Ottawa, ON, Canada.

930. R. D. Rogers, “What is an Appropriate Academic Business Model to Drive Commercialization of Sustainable Technology?” Presented by R. D. Rogers before GreenWin’s International Conference on Green Chemistry and White Biotechnology (May 12-13, 2016), Gembloux, Belgium, Abstract. (Invited Plenary)
931. R. D. Rogers, “Green chemistry and advanced materials from renewable polymers: Education, research, and entrepreneurship to motivate the next generation of scientists,” Presented by video by R. D. Rogers before the (May 18-20, 2016), Buenos Aires, Argentina, Abstract. (Invited Plenary Presentation)
932. P. Berton and R. D. Rogers, “Millions of new ionic liquids are hiding in plain sight: Understanding the nature of the bonding in double salt ionic liquids (aka ionic liquid mixtures),” Presented by R. D. Rogers before the Pacific Rim Meeting on Electrochemical and Solid-State Science (October 2-7, 2016), Honolulu, HI, Abstract. (Invited)
933. R. D. Rogers, “Innovation is the Gateway to the Biomass Biorefinery and Ultimately A sustainable Bio-based Economy," Presented by R. D. Rogers before the Workshop on Insights and Strategies Towards a Bio-Based Economy (November 22-25, 2016), Montevideo, Uruguay.

D. Presentations before Regional Meetings:

1. R. D. Rogers and J. L. Atwood, "The Crystal Structure of $Cu[P(C_6H_5)_2CH_3]_3BH_4$," Presented by R. D. Rogers before the Southeast Regional American Chemical Society Student Affiliate Meeting (1977), University, AL, Abstract 20.
2. R. D. Rogers, W. E. Hunter, and J. L. Atwood, "The Crystal and Molecular Structure of $Mo[CH_2Si(CH_3)_3]_3[P(CH_3)_3]Cl$," Presented by R. D. Rogers before the 29th Southeast Regional ACS Meeting (1977), Tampa, FL, Abstract 348.
3. W. E. Hunter, R. D. Rogers, and J. L. Atwood, "The Lanthanide-Carbon Sigma Bond in $Li[Yb\{CH(SiMe_3)_3\}_3C1]$," Presented by W. E. Hunter before the 29th Southeast Regional ACS Meeting (1977), Tampa, FL, Abstract 350.
4. R. D. Rogers, J. L. Atwood, and R. Gruning, "Synthesis and X-ray Structure Determination of N-Lithiohexamethyldisilazane - Bulky Ligand Effects," Presented by R. D. Rogers before the Annual Meeting of the Alabama Academy of Science (1978), Montgomery, AL, Abstract.
5. P. A. Grutsch, C. Kutal, J. L. Atwood, and R. D. Rogers, "Structure of a Copper(I) Compound Containing the Tetrahydroborate Group," Presented by P. A. Grutsch before the 30th Southeast Regional ACS Meeting (1978), Savannah, GA, Abstract 139.
6. R. D. Rogers, W. J. Cook, and J. L. Atwood, "The Synthesis and Crystal Structure of $(\eta^5\text{-}C_5H_5)Fe[\eta^5\text{-}C_5H_4Al_2(CH_3)_4Cl]$," Presented by R. D. Rogers before the 30th Southeast Regional ACS Meeting (1978), Savannah, GA, Abstract 171.
7. R. D. Rogers, W. E. Hunter, and J. L Atwood, "Crystallographic Examination of the Zirconium-Carbonyl Bond in $(\eta^5\text{-}C_5H_5)_2Zr(CO)_2$," Presented by R. D. Rogers before the 31st Southeast Regional ACS Meeting (1979), Roanoke, VA, Abstract 185.
8. M. S. Dalton, R. D. Rogers, and J. L. Atwood, "X-ray Crystal Structure of $ReBr(CO)_3(Me_2NH)_2$," Presented by M. S. Dalton before the 31st Southeast Regional ACS Meeting (1979), Roanoke, VA, Abstract 188.
9. E. A. Lewis, R. Rogers, and J. L. Atwood, "Thermodynamic Studies of Liquid Clathrate Formation and Coal Liquefaction with Liquid Clathrates," Presented by E. A. Lewis before the 31st Southeast Regional ACS Meeting (1979), Roanoke, VA, Abstract 331.
10. M. S. Dalton, R. D. Rogers, L. D. Kispert, and J. L. Atwood, "The Crystal and Molecular Structure of Bromoflouroacetic Acid, A Chiral Hydrogen Bonded Dimer," Presented by M. S. Dalton before the Annual Meeting of the Alabama Academy of Science (1980), Birmingham, AL, Abstract *Journal of the Alabama Academy of Science*, 51(3), 199 (1980).
11. L. G. Canada, R. D. Rogers, and J. L. Atwood, "The Application of X-ray Crystallography to the Pesticide Aldrin and Related Compounds," Presented by L. G. Canada before the Annual Meeting of the Alabama Academy of Science (1980), Birmingham, AL, Abstract *Journal of the Alabama Academy of Science*, 51(3), 196 (1980).
12. R. D. Rogers and J. L. Atwood, "A Comparison of Mo-Ligand (η^2-) Bonding in $MoCl(\eta^2\text{-}COCH_2SiMe_3)(CO)(PMe_3)_3$ and $Mo(\eta^2\text{-}C_2H_4)_2(PMe_3)_4$," Presented by R. D. Rogers before the 28th Southeast/32nd Southwest Regional ACS Meeting (1980), New Orleans, LA, Abstract 232.
13. F. R. Anderson, R. D. Rogers, and J. L. Atwood, "Crystal and Molecular Structure of 7-Aminothiozolo[5,4-d]pyrimidine-6-oxide," Presented by F. R. Anderson before the 32nd Southeast/28th Southwest Regional ACS Meeting (1980), New Orleans, LA, Abstract 303.
14. L. G. Canada, R. D. Rogers, and J. L. Atwood, "Crystal and Molecular Structure of $Mn_2(CO)_6Br_2Te_2Ph_2$," Presented by L. G. Canada before the Annual Meeting of the Alabama Academy of Science (1981), Auburn, AL, Abstract.
15. R. D. Rogers, C. R. Kerr, M. J. Zaworotko, and J. L. Atwood, "Decomposition of High-Oxygen Content Organoaluminum Compounds: Identification and Characterization of Products," Presented by R. D. Rogers before the 37th Southwest Regional ACS Meeting (1981), San Antonio, TX, Abstract 96.
16. L. G. Canada, R. Priester, R. D. Rogers, and J. L. Atwood, "Complexes of Crown Ethers with Aluminum Alkyls," Presented by L. G. Canada before the 34th Southeast Regional ACS Meeting (1982), Birmingham, AL, Abstract 280.
17. R. D. Rogers, "Crystal and Molecular Structures of Formyl-, Cyano-, and Amino-Cyclopentadienyldicarbonylnitrosylchromium," Presented by R. D. Rogers before the 3rd Joint Great Lakes and Central Regional ACS Meeting (1984), Kalamazoo, MI, Abstract 208.
18. L. K. Kurihara and R. D. Rogers, "Crown Ether Complexation of f-Elements," Presented by L. K. Kurihara before the 19th Great Lakes Regional ACS Meeting (1985), Lafayette, IN, Abstract 191.
19. M. M. Benning and R. D. Rogers, "Crystal and Molecular Structures of (η^5-Pentamethylcyclopentadienyl)(η^5-cyclopentadienyl)dichlorotitanium, -zirconium and -hafnium," Presented by M. M. Benning before the 19th Great Lakes Regional ACS Meeting (1985), Lafayette, IN, Abstract 193.
20. R. D. Rogers, "Structural Chemistry of Mixed Sandwich Compounds: $(\eta^5\text{-}C_5Me_5)(\eta^8\text{-}C_8H_8)Ti$ and $(\eta^5\text{-}C_5Me_5)(\eta^7\text{-}C_7H_7)Ti$," Presented by R. D. Rogers before the 19th Great Lakes Regional ACS Meeting (1985), Lafayette, IN, Abstract 192.
21. E. J. Voss and R. D. Rogers, "X-ray Structure of $(\eta^5, \eta^5\text{-}C_{10}H_8)[Rh(CO)_2]_2$," Presented by E. J. Voss before the Thirty-Seventh Annual Undergraduate Research Symposium (1986), Abbott Park, IL, Abstract.
22. R. D. Rogers and L. K. Kurihara, "f-Element/Crown Ether Complexation-Structural Effects of Hydrogen Bonding," Presented by R. D. Rogers before the 20th Great Lakes Regional ACS Meeting (1986), Milwaukee, WI, Abstract 201.
23. L. K. Kurihara and R. D. Rogers, "f-Element/Crown Ether Complexation- Synthesis and Structures," Presented by L. K. Kurihara before the 20th Great Lakes Regional ACS Meeting (1986), Milwaukee, WI, Abstract 200.
24. M. M. Benning and R. D. Rogers, "Crystal Structures of $(\eta^5\text{-}C_5Me_5)M(\eta^7\text{-}C_7H_7)$ (M=Zr, Hf) and $(\eta^5\text{-}C_5Me_5)Zr(\eta^8\text{-}C_8H_8)$," Presented by M. M. Benning before the 20th Great Lakes Regional ACS Meeting (1986), Milwaukee, WI, Abstract 199.

25. E. J. Voss and R. D. Rogers, "f-Element/Crown Ether Complexes. The Exclusion of H_2O from the Metal Ion's Coordination Sphere," Presented by E. J. Voss before the 21st Great Lakes Regional ACS Meeting; Thirty-Eighth Annual Undergraduate Research Symposium (1987), Chicago, IL, Abstract.
26. M. M. Benning and R. D. Rogers, "f-Element/Crown Ether Complexes. Synthetic and Structural Survey of UCl_4 Complexes of Common Crown Ethers," Presented by M. M. Benning before the 21st Great Lakes Regional ACS Meeting (1987), Chicago, IL, Abstract 215.
27. R. D. Rogers, "f-Element/Crown Ether Complexes. Structural Effects of Anion Concentration," Presented by R. D. Rogers before the 21st Great Lakes Regional ACS Meeting (1987), Chicago, IL, Abstract 216.
28. A. H. Bond and R. D. Rogers, "Macrocycle Complexation Chemistry. Complexation and Structural Characterization of Biochemically Toxic Metals," Presented by A. H. Bond before the 22nd Great Lakes Regional ACS Meeting (1989), Duluth, MN, Abstract 031.
29. L. Nunez and R. D. Rogers, "Macrocycle Complexation Chemistry. The Crystal Structure of A Cu(I) Thiacrown Polymer, $[CuCl(18\text{-thiacrown-}6)]_n$," Presented by L. Nunez before the 22nd Great Lakes Regional ACS Meeting (1989), Duluth, MN, Abstract 054.
30. R. F. Henry and R. D. Rogers, "Acyclic Mixed Donor Crown Ether Analogs. Synthesis and Characterization of Lanthanide Complexes of Polyethylene Glycols Containing Sulfur," Presented by R. F. Henry before the 22nd Great Lakes Regional ACS Meeting (1989), Duluth, MN, Abstract 053.
31. R. D. Rogers, "The Effects of Anion Concentration on Crystallization of Lanthanide Chloride Polyethylene Glycol Complexes," Presented by R. D. Rogers before the 22nd Great Lakes Regional ACS Meeting (1989), Duluth, MN, Abstract 052.
32. A. H. Bond and R. D. Rogers, "Macrocycle Complexation Chemistry. 12-crown-4, 15-crown-5, and 18-crown-6 Complexes of Biochemically Toxic Metals," Presented by A. H. Bond before the 40th Annual Undergraduate Symposium (1989, Chicago Section ACS), Libertyville, IL, Abstract.
33. M. M. Witt and R. D. Rogers, "Macrocycle Complexation Chemistry. Six Donor (Pentaethylene Glycol) and Seven Donor (Hexaethylene Glycol) Acyclic Crown Ether Analogs as Dehydrating Agents for Lanthanoid Salts?" Presented by M. M. Witt before the 40th Annual Undergraduate Symposium (1989, Chicago Section ACS), Libertyville, IL, Abstract.
34. H. D. Do, J. R. Peterson, and R. D. Rogers, "Synthetic Approaches Toward Anticancer Lignan Lactones," Presented by H. D. Do before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 185.
35. T. J. Smillie, J. R. Peterson, R. D. Rogers, and T. P. Conway, "Lignan Derivatives as Potential Platelet Activating Factor Antagonists," Presented by T. J. Smillie before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 244.
36. A. N. Rollins and R. D. Rogers, "Macrocycle Complexation Chemistry. Structural Effects of Changing Anion and Anion Concentration in Complexes of Lanthanide(III) Ions and Crown Ethers," Presented by A. N. Rollins before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 139.
37. L. Nunez and R. D. Rogers, "Modification of the Lanthanide Ion Coordination Sphere Via Electrocrystallization of Hydrated Lanthanide Chloride Complexes of 12-Crown-4," Presented by L. Nunez before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 122.
38. R. F. Henry and R. D. Rogers, "Wrapping the Lanthanide Ion Coordination Sphere. A Study of Polyethylene Glycol Complexes with Four to Eight Donor Atoms," Presented by R. F. Henry before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 130.
39. A. H. Bond and R. D. Rogers, "Crystallographic Studies of Potential Macrocyclic Extractants for Cd," Presented by A. H. Bond before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 138.
40. J. Wolff, A. H. Bond, and R. D. Rogers, "Macrocyclic Complexation Chemistry. Four, Five, Six and Seven Donor Polyethylene Glycols as Acyclic Crown Ether-Like Complexing Agents of Mercury," Presented by J. Wolff before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 236.
41. K. C. Sturge, R. D. Rogers, and M. J. Zaworotko, "Reactivity of Iron(II) Mixed Sandwich Complexes Towards Nucleophiles," Presented by K. C. Sturge before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 110.
42. S. Christie, M. J. Zaworotko, and R. D. Rogers, "Synthesis and Characterization of Oxybenzoate Metal Complexes," Presented by S. Christie before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 235.
43. T. J. Smillie, J. R. Peterson, R. D. Rogers, and T. P. Conway, "Lignan Derivatives as Potential Platelet Activating Factor Antagonists," Presented by T. J. Smillie before the 17th MALTO Medicinal Chemistry-Pharmacognosy Meeting (1990), Oklahoma City, OK.
44. A. H. Bond and R. D. Rogers, "Macrocyclic Complexation Chemistry of the Environmentally Toxic Metals," Presented by A. H. Bond before the 13th Mid-West Environmental Chemistry Workshop (1990), Urbana, IL, Abstract 21.
45. R. D. Rogers, "Investigation of Macrocyclic and Polyfunctional Acyclic Chelating Agents in the Development of Improved f-Element Extractants," Presented by R. D. Rogers before the 13th Mid-West Environmental Chemistry Workshop (1990), Urbana, IL, Abstract 20.
46. A. H. Bond and R. D. Rogers, "Synthetic and Crystallographic Studies of Novel Crown Ether and Polyethylene Glycol Complexes of Bi^{3+}," Presented by Andrew H. Bond before the Argonne Undergraduate Symposium (1990), Argonne, IL, Abstract 91.
47. S. E. Huggins, A. H. Bond, A. N. Rollins, and R. D. Rogers, "Crystallographic Investigations of Polymer Crown-Ether Model Compounds," Presented by S. E. Huggins before the 23rd Central/24th Great Lakes Joint Regional ACS Meeting (1991), Indianapolis, IN, Abstract 301.

48. A. H. Bond and R. D. Rogers, "Crystallographic Investigations of Crown Ether and Polyethylene Glycol Complexes of Pb^{2+}," Presented by A. H. Bond before the 23rd Central/24th Great Lakes Joint Regional ACS Meeting (1991) Indianapolis, IN, Abstract 302.
49. A. N. Rollins and R. D. Rogers, "Complexation of Mixtures of Hydrated Lanthanum Chloride with Other Hydrated Lanthanide Chloride Salts and 18-Crown-6," Presented by A. N. Rollins before the 23rd Central/24th Great Lakes Joint Regional ACS Meeting (1991), Indianapolis, IN, Abstract 303.
50. R. D. Rogers and A. H. Bond, "Evidence of a Stereochemically Active Lone Pair in the Complexation Chemistry of Bismuth(III) Halides with Crown Ethers and Polyethylene Glycols," Presented by R. D. Rogers before the 23rd Central/24th Great Lakes Joint Regional ACS Meeting (1991), Indianapolis, IN, Abstract 304.
51. A. H. Bond and R. D. Rogers, "Extraction of Bi^{+3} Using Polyethylene Glycol Based Aqueous Biphase Systems," Presented by A. H. Bond before the Amoco/University Poster Session (1991), Naperville, IL.
52. C. B. Bauer, R. D. Rogers, and A. H. Bond, "Aqueous Biphasic Systems for Liquid/Liquid Extraction of Americium, Plutonium, Thorium, and Uranium from Sulfate and Carbonate Media," Presented by C. B. Bauer before the Amoco/University Poster Session (1991), Naperville, IL.
53. Y. Song and R. D. Rogers, "The Investigation of Polyethylene Glycol-Based Aqueous Biphasic Systems for the Extraction of Transition Metal Ions," Presented by Y. Song before the Amoco/University Poster Session (1993), Naperville, IL, Abstract C68.
54. M. W. Brechbiel, O. A. Gansow, C. G. Pippin, R. P. Planalp, and R. D. Rogers, "Synthesis of Polyamino Carboxylate Chelating Agents and X-ray Structural Analysis of Metal Complexes," Presented by R. P. Planalp before the 29th ACS Middle Atlantic Regional Meeting (1995), Washington, DC, Abstract 191.
55. A. H. Bond, C. M. Tomasek, M. J. Gula, F. Chang, E. P. Horwitz, and R. D. Rogers "Concentration, Purification, and Recycle of Dyes from Salt Solutions," Presented by A. H. Bond before the American Association of Textile and Color Chemists/Northern Textile Association 33rd New England Regional Technical Conference (1997), Danvers, MA.
56. B. M. Rapko, B. K. McNamara, and R. D. Rogers, "Coordination Chemistry of Lanthanide Salts with *N,N,N′,N′*-Tetramethylsuccinamide and *N,N,N′,N′*-Tetrahexylsuccinamide," Presented by B. M. Rapko before the 53rd ACS Northwest Regional Meeting (NORM '98) (1998), Pasco, WA, Abstract 065.
57. R. D. Rogers, K. D. Smith, and S. K. Spear, "Aqueous Biphasic Systems: Polyethylene Glycol versus Polyethylene/Polypropylene Glycol Random Copolymer Phase Formation," Presented by K. D. Smith before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 092.
58. R. D. Rogers, S. T. Griffin, and S. K. Spear, "Partitioning of Mercury using ABEC™ Resins," Presented by S. T. Griffin before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 214.
59. R. D. Rogers, H. D. Willauer, and J. G. Huddleston, "Polymer-Based Aqueous Biphasic Extraction of Lignin During Alkaline Pulping," Presented by H. D. Willauer before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 217.
60. R. D. Rogers, A. E. Visser, R. P. Swatloski, and D. H. Hartman, "Liquid/Liquid Extraction of Metal Ions in Room Temperature Ionic Liquids: Cation Effects," Presented by A. E. Visser before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 595.
61. R. D. Rogers, G. A. Broker, C. V. K. Sharma, and G. J. Szulczewski, "Engineering Tetrapyridylporphyrin Coordination Complexes for Metal Ion Recognition in Crystalline Materials or on Surfaces," Presented by R. D. Rogers before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 589.
62. R. D. Rogers, "Center for Green Manufacturing," presented by R. D. Rogers before the Green Chemistry Workshop, University of Regina, Energy Research Unit (1999), Regina, Saskatchewan, Canada (Invited Plenary).
63. R. D. Rogers, "Green Chemistry – International Definitions," Presented by R. D. Rogers before the Industries of the Future Alabama Symposium: Sustainable Industry through Green Chemistry and Engineering (2000), Mobile, AL.
64. R. D. Rogers, "R&D in UA's Center for Green Manufacturing," Presented by R. D. Rogers before the Industries of the Future Alabama Symposium: Sustainable Industry through Green Chemistry and Engineering (2000), Mobile, AL.
65. A. E. Visser, R. P. Swatloski, W. M. Reichert, R. D. Rogers, R. Mayton, S. Sheff, A. Wierzbicki, and J. H. Davis, Jr., "Task Specific Ionic Liquids: Urea Thiourea, and Thioether-Derivatized Imidazolium Cations for Hg^{2+} and Cd^{2+} Extraction in Liquid/Liquid Separations, Presented by A. E. Visser before the 52nd Southeast/56th Southwest Combined Regional Meeting of the ACS (2000), New Orleans, LA, Abstract 286.
66. W. M. Reichert, A. E. Visser, R. P. Swatloski, and R. D. Rogers, "Synthesis and Characterization of Novel Environmentally-Benign Solvents: Room Temperature Ionic Liquids," presented by W. M. Reichert before the 52nd Southeast/56th Southwest Combined Regional Meeting of the ACS (2000), New Orleans, LA, Abstract 285.
67. R. D. Rogers, R. P. Swatloski, A. E. Visser, and W. M. Reichert, "Reverse Crystal Engineering: Can We Use the Concepts Learned to Make New Room Temperature Ionic Liquids for Applications as Green Solvent Alternatives?" presented by R. D. Rogers before the 52nd Southeast/56th Southwest Combined Regional Meeting of the ACS (2000), New Orleans, LA, Abstract 203 (Invited Symposium Presentation).
68. R. D. Rogers, "Non-Sugar Products from Sugarcane for the New Millennium: Green Pathways to a Carbohydrate Economy?" Presented by R. D. Rogers to the Louisiana Division of the American Society of Sugar Cane Technologists, Baton Rouge, LA, on 2/6/01.
69. R. D. Rogers, "Innovations in the Sugar Industry," Presented by R. D. Rogers before the 32nd Annual Meeting of the American Society of Sugar Cane Technologists, Florida Division (2001), Belle Glade, FL, no abstract (Invited Keynote Presentation).

70. R. D. Rogers, "From Liquid Clathrates to Ionic Liquids," Presented by R. D. Rogers before the New Directions in Chemistry Symposium (2002), Columbia, MO (Invited Symposium Presentation).
71. R. D. Rogers and J. D. Holbrey, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by R. D. Rogers before the 37th Midwest Regional ACS Meeting (2002), Lawrence, KS, Abstract 070 (Invited Symposium Presentation).
72. R. D. Rogers, G. A. Broker, K. E. Gutowski, and N. J. Bridges, "Crystal Engineering Using Lanthanide Ions as Nodes in Coordination Polymers," Presented by R. D. Rogers before the 54th Southeast Regional ACS Meeting (2002), Charleston, SC, Abstract 118 (Invited Symposium Presentation).
73. S. J. P'Pool, M. A. Klingshirn, J. D. Holbrey, R. D. Rogers, and K. H. Shaughnessy, "Polar, Non-Coordinating Ionic Liquids as Novel Solvents for Coordination Polymerization of Olefins," Presented by S. J. P'Pool before the 54th Southeast Regional ACS Meeting (2002), Charleston, SC, Abstract 275.
74. R. D. Rogers, J. D. Holbrey, and A. E. Visser, "Application of Task Specific Ionic Liquids to the Extraction of Hg^{2+} and Actinides," Presented by R. D. Rogers before the 54th Southeast Regional ACS Meeting (2002), Charleston, SC, Abstract 575 (Invited Symposium Presentation).
75. R. D. Rogers, J. D. Holbrey, and W. M. Reichert, "Polymorphism in 'Ionic Liquids'," Presented by R. D. Rogers before the 38th Midwest Regional ACS Meeting (2003), Columbia, MO, Abstract 364. (Invited Symposium Presentation).
76. S. Spear, J. Holbrey, and R. Rogers, "Ionic liquids as solvents in green chemistry: from fundamental studies to applied implementation," Presented by S. Spear before the 55th Southeast Regional ACS Meeting (2003), Atlanta, GA, Abstract 890.
77. V. A. Cocalia, M. P. Jensen, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Coordination of Trivalent *f*-elements and Uranyl Ions with Cyanex-272® in the Hydrophobic Ionic Liquid, 1-Decyl-3-methylimidazolium Bis(trifluoro-methanesulfonyl)imide", Presented by V. A. Cocalia at Alabama Actinide Day (2004), Auburn, AL.
78. N. J. Bridges and R. D. Rogers "Actinide Extractions from Nitric Acid using Cyanex 923 in $[C_{10}mim][Tf_2N]$," Presented by N. J. Bridges at Alabama Actinide Day (2004), Auburn, AL.
79. K. E. Gutowski, G. A. Broker, H. D. Willauer, S. K. Spear, and R. D. Rogers "Ionic Liquids in Nuclear Processing and Waste Remediation Applications," Presented by K. E. Gutowski at Alabama Actinide Day (2004), Auburn, AL.
80. S. Memon, K. Caldwell, G. Caldwell, and R. D. Rogers, "Using Caenorhabditis Elegans to Probe the Toxicity of Ionic Liquids," Presented by S. Memon to The University of Alabama College of Arts & Sciences Undergraduate Research and Creative Activity Presentations Competition (2004), Tuscaloosa, AL. (First Place Natural Sciences Division Award)
81. J. H. Poplin, R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Cellulose-Supported Colorimetric Sensors for Mercury Ion Detection," Presented by J. H. Poplin to The University of Alabama College of Arts & Sciences Undergraduate Research and Creative Activity Presentations Competition (2004), Tuscaloosa, AL. (Third Place Natural Sciences Division Award)
82. J. S. Moulthrop, R. P. Swatloski, R. D. Rogers, and G. Moyna, "High-Resolution ^{13}C NMR Studies of Amylose and Cellulose Oligomers in 1-Butyl-3-methylimidazolium Chloride Solutions," Presented by J. S. Moulthrop to the local Sigma Xi Chapter (2004), Philadelphia, PA.
83. R. D. Rogers, S. K. Spear, and J. D. Holbrey, "Ionic Liquids: Fundamental Studies to Technological Applications in Support of Green Chemistry," Presented by R. D. Rogers before the 60th Southwest Regional ACS Meeting (2004), Ft. Worth, TX, Abstract 265. (Invited Presentation)
84. R. D. Rogers, "Radiochemistry at The University of Alabama," Presented by R. D. Rogers before the Alabama Actinide Day Conference (2005), Tuscaloosa, AL.
85. K. E. Gutowski, D. A. Dixon, and R. D. Rogers "Probing Gas-phase Uranyl-Orthophosphate Structure with Density Functional Theory," Presented by K. E. Gutowski before the Alabama Actinide Day Conference (2005), Tuscaloosa, AL.
86. V. A. Cocalia and R. D. Rogers, "Ionic Liquids and Actinides", Presented by V. A. Cocalia before the Alabama Actinide Day Conference (2005), Tuscaloosa, AL.
87. N. J. Bridges and R. D. Rogers "Aqueous Biphasic Systems (ABS) for the Removal and Recovery of Tc(VI) from High Salt Solutions," Presented by N. J. Bridges before the Alabama Actinide Day Conference (2005), Tuscaloosa, AL.
88. S. B. Memon, G. Caldwell, K. Caldwell, and R. Rogers, "Using *Caenorhabditis elegans* to probe the toxicity of ionic liquids," Presented by S. B. Memon, before the Fourth Annual University of Alabama System Honors Research Day (2005), Birmingham, AL, Abstract A4.
89. W. L. Hough and R. D. Rogers, "Ionic Liquids: The Next Generation of Sweeteners," Presented by W. L. Hough before the Second Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2005), Tuscaloosa, AL, Abstract.
90. T. B. Wilson and R. D. Rogers, "Thermal Studies of Dual Functional Ionic Liquids," Presented by T. B. Wilson before the Second Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2005), Tuscaloosa, AL, Abstract.
91. J. H. Poplin and R. D. Rogers, "Utilizing Potentially Green Ionic Liquids: Development of Cellulose Based Magnetic Materials," Presented by J. H. Poplin before the Second Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2005), Tuscaloosa, AL, Abstract.
92. M. B. Townsend, P. L. Jernigan, M. M. Bailey, S. R. Smith, J. F. Rasco, R. P. Swatloski, R. D. Rogers, and R. D. Hood "Effects of 1-Butyl-3-Methylimidazolium Chloride on Developmental Toxicity in Mice," Presented by M. B. Townsend before the Howard Hughes Poster Session (2005), Tuscaloosa, AL.

93. P. L. Jernigan, M. B. Townsend, M. M. Bailey, S. R. Smith, J. F. Rasco, R. P. Swatloski, R. D. Rogers, and R. D. Hood, "Effects of 1-Decyl-3-Methylimidazolium Chloride on Fetal Development of Mice," Presented by P. L. Jernigan before the Howard Hughes Poster Session (2005), Tuscaloosa, AL.
94. M. L. Moody, J. G. Huddleston, S. T. Griffin, and R. D. Rogers, "Aqueous Influence on the Solvent Properties of Polyethylene Glycol," Presented by M. L. moody before the 57th Southeast/61st Southwest Joint Regional ACS Meeting (2005), Memphis, TN, Abstract Nov 04-098.
95. D. T. Daly and R. D. Rogers, "Multi-Functional Ionic Liquid Compositions Improved Properties for Active Pharmaceutical, Biological, and Nutritional Ingredients," Presented by D. T. Daly before the Biotechnology Association of Alabama Annual Meeting (2006), Birmingham, AL.
96. R. D. Rogers, "Green Chemistry: An Overview," Presented by R. D. Rogers before the Alabama Health and Safety Conference (2006), Tuscaloosa, AL (Keynote Speaker).
97. W. L. Hough and R. D. Rogers, "Dual Function Ionic Liquids," Presented by W. L. Hough before the Third Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2006), Tuscaloosa, AL, Abstract 16A.
98. M. B. Suggs and R. D. Rogers, "Regeneration of Cellulose Membranes with Ionic Liquids," Presented by M. B. Suggs before the Third Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2006), Tuscaloosa, AL, Abstract 28A.
99. S. K. Spear, S.T. Griffin, W. M. Reichert, and R. D. Rogers, "Applications of Bio-Solvents to the Nuclear Power Industry," Presented by S. K. Spear before the 5th Southern Bioproducts and Renewable Energy Conference (2006), Choctaw, MS.
100. R. D. Rogers, "Green Chemistry: Can Society and the Chemical Industry Co-Exist?" Presented by R. D. Rogers before the 29th Annual Area Collegiate Chemistry Meeting in conjunction with the Industry-Academe Interaction for Green Chemistry Meeting (2006), Martin, TN. (Invited Panel Participant)
101. R. D. Rogers, R. P. Swatloski, G. Moyna, D. A. Fort, and P. Moyna, "Use of ionic liquids in the study of fruit ripening by high-resolution 13C NMR spectroscopy: 'Green' solvents meet green bananas," by R. D. Rogers before the 37th Great Lakes Regional ACS Meeting (2006), Milwaukee, WI, Abstract 068. (Invited Presentation)
102. R. D. Rogers, "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented to the Queen's University of Belfast QUILL Ionic Liquids Week (2008), Belfast, NI. No Abstract. (Invited Presentation)
103. R. D. Rogers, "Ionic Liquids," The University of Alabama IP Forum (2008), Tuscaloosa, AL.
104. S. Watts, D. Daly, R. Frazier, R. Rogers, and W. Hough-Troutman, "Slow Release of an Active Ingredient from Ionic Liquid Regenerated Cellulose Beads," Presented by S. Watts before The University of Alabama First Annual Undergraduate Research and Creative Activity Conference (2008), Tuscaloosa, AL; Abstract Book. (Second Place Poster)
105. S. Mroczynski, D. Daly, S. Spear, and R. D. Rogers, "Strength from the Sea," Presented by S. Mroczynski before The University of Alabama First Annual Undergraduate Research and Creative Activity Conference (2008), Tuscaloosa, AL.
106. N. Sun, M. Rahman, Y. Qin, M. L. Maxim, and R. D. Rogers, "Dissolution and Separation of Biomass Utilizing Ionic Liquids" Presented by N. Sun before the 60th Southeast Regional Meeting of the American Chemical Society (SERMACS) (2008), Nashville, TN, Abstract 250.
107. N. J. Bridges, T. M. Adams, A. E. Visser, M. J. Williamson, and R. D. Rogers, "Ionic Liquids from Phase Modifier to Solvent for Future Nuclear Fuel Processing," Presented by N. J. Bridges before the 60th Southeast Regional Meeting of the American Chemical Society (SERMACS) (2008), Nashville, TN, Abstract 647.
108. J. Sherrill, J. Beaird, J. F. Rasco, J. M. Sturdivant, M. B. Townsend, P. L. Jernigan, R. D. Hood, R. P. Swatloski, R. D. Rogers, and M. M. Bailey, "Developmental Toxicity of Ionic Liquids," Presented by J. Sherrill before the 86th Annual Meeting of the Alabama Academy of Science (2009), Livingston, AL, Abstract: *J. Alabama Acad. Sci.* **2009**, *80*, 117-118.
109. A. Metlen and R. D. Rogers, "Dithiocarbamate Salts and Ionic Liquids," Poster presented by A. Metlen at the QUILL 10th Anniversary Meeting (March-April 2009), Belfast, Northern Ireland, UK.
110. Y. Zou, J. D. Holbrey, and R. D. Rogers, "Ionic Liquids for Aromatic and Aliphatic Hydrocarbon Separation," Poster presented by Y. Zou at the QUILL 10th Anniversary Meeting (March-April 2009), Belfast, Northern Ireland, UK.
111. R. D. Rogers "Ionic Liquids: At the Intersections," Presented by R. D. Rogers at the QUILL 10th Anniversary Meeting (March-April 2009), Belfast, Northern Ireland, UK.
112. D. M. Drab, J. L. Shamshina, S. Smiglak, C. C. Hines, D. B. Cordes, and R. D. Rogers, "Establishing a flexible synthetic design platform for multi-heterocyclic ionic liquids: Introduction of concept and initial demonstration," Presented by D. M. Drab at the 13th Annual Graduate Student Association Research and Thesis Conference (2010), The University of Alabama, Tuscaloosa, AL, Abstract Book.
113. S. Kyle Lee, W. Hough-Troutman, R. D. Rogers, K. A. Caldwell, and G. A. Caldwell, "Searching for Ionic Liquid Partners That Will Enhance the Neuroprotective Role of Lidocaine," Presented by S. Kyle Lee before the UA Undergraduate Research Competition (2010), Tuscaloosa, AL.
114. R. D. Rogers, "Green Chemistry, Technology, & Innovation," Presented by R. D. Rogers at the Crimson In Green: An Energy Forum (February 17, 2012), Tuscaloosa, AL, No Abstract (Invited Speaker).
115. R. D. Rogers, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin" Presented by R. D. Rogers before the Inaugural SEC Symposium: Impact of the Southeast in the World's Renewable Energy Future (Feb. 10-12, 2013), Atlanta, GA, Abstract Book p 34. (Invited Presenter).

116. P. D. McCrary, L. A. Flores, G. Chatel, and R. D. Rogers, "Evaluating Ionic Liquids as Hypergolic Fuels: From Reactive Nanomaterials to Trigger Additives," Presented by P. D. McCrary before the Energetic Ionic Liquid Mini-Symposium (May 21-22, 2013), Air Force Research Laboratory, Edwards Air Force Base, CA, No Abstract.
117. L. A. Flores, P. D. McCrary, G. Chatel, O. Andreea Cojocaru, and R. D. Rogers, "Molecular Characteristics and Interactions Leading to Liquid Clathrate Behavior," Presented by L. A. Flores before the Energetic Ionic Liquid Mini-Symposium (May 21-22, 2013), Air Force Research Laboratory, Edwards Air Force Base, CA, No Abstract.
118. R. D. Rogers and S. P. Kelley, "Supramolecular chemistry in the liquid state: What can halogen bonding offer ionic liquids?" Presented by R. D. Rogers before the 49th Midwest Regional Meeting of the American Chemical Society (November 12-15, 2014), Columbia, MO, Abstract 384.
119. R. D. Rogers, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers before the 3rd Annual *Sustainable Innovation through Green Chemistry* Workshop and Case Competition Schedule (January 16-17, 2015), McGill University, Montreal, QC, Canada, No Abstract (Invited Keynote).
120. R. D. Rogers, "Innovation is the Gateway to the Biomass Biorefinery and Ultimately A Sustainable Bio-based Economy," Presented by R. D. Rogers before the Quebec-Ontario Biotech Meeting (May 21-22, 2015), McGill University, Montreal, QC, Canada, No Abstract (Invited Keynote).
121. R. D. Rogers, "What is an Appropriate Academic Business Model to Drive Commercialization of Sustainable Technology?" Presented by R. D. Rogers before the Science for a Sustainable Society Symposium (January 26-27, 2016), McGill University, Montreal, QC, Canada, No Abstract (Invited Keynote).

E. Seminars:

1. "C_1 Chemistry in Group IVB - Some Structural Aspects," Presented by R. D. Rogers at Bell Laboratories, Murray Hill, NJ, on 8/15/83.
2. "Structural Investigations of New Pentamethylcyclopentadienyl Derivatives of Group IVB," Presented by R. D. Rogers at Northwestern University, Evanston, IL on 2/3/84.
3. "Early Transition Metal Chemistry: A Structural Point of View," Presented by R. D. Rogers at the Instituto Venezolano de Investigaciones Cientifica, Caracas, Venezuela on 8/15/84.
4. "Structural Organometallic Chemistry of the Early Transition Metals," Presented by R. D. Rogers at Fisk University, Nashville, TN on 3/18/85.
5. "Structural Organometallic Chemistry of the Early Transition Metals," Presented by R. D. Rogers at Tuskeegee Institute, Tuskeegee, AL on 3/20/85.
6. "Structural Organometallic Chemistry of the Early Transition Metals," Presented by R. D. Rogers at The University of Alabama, Tuscaloosa, AL on 3/21/85.
7. "Crown Ether Coordination in the f-Element Series," Presented by R. D. Rogers at the University of Illinois at Chicago, Chicago, IL on 2/18/86.
8. "Early Transition Metal Chemistry - A Structural Point of View," Presented by R. D. Rogers at Marquette University, Milwaukee, WI on 3/21/86.
9. "f-Element/Crown Ether Complexes, Structural Effects of Solvent and Water of Hydration Hydrogen Bonding," Presented by R. D. Rogers at Victoria University, Wellington, New Zealand on 7/24/87.
10. "f-Element/Crown Ether Complexes," Presented by R. D. Rogers at the University of Hawaii, Honolulu, HA on 8/26/87.
11. "f-Element/Crown Ether Complexes," Presented by R. D. Rogers at the University of Toledo, Toledo, OH on 10/14/87.
12. "Hydrogen Bonding in f-Element Complexes of Crown Ethers," Presented by R. D. Rogers at Ripon College, Ripon, WI, on 11/22/88.
13. "Crown Ether Complexation Chemistry of the Lanthanides," Presented by R. D. Rogers at Albany State College, Albany, GA, on 2/10/89.
14. "Crown Ether Complexation Chemistry of the Lanthanides," Presented by R. D. Rogers at Tuskeegee University, Tuskeegee, AL, on 2/13/89.
15. "f-Element/Crown Ether Complex Chemistry," Presented by R. D. Rogers at The University of Alabama, Tuscaloosa, AL, on 2/14/89.
16. "Crown Ether Chemistry of the Lanthanides," Presented by R. D. Rogers at Saint Mary's University, Halifax, Canada on 3/3/89.
17. "Coordination versus Hydrogen Bonding in Crown Ether Complexes of Hydrated f-Element Salts," Presented by R. D. Rogers at Dalhousie University, Halifax, Canada, on 3/3/89.
18. "Macrocycle Complexation Chemistry: The Toxic Metals (Cd, Hg, Tl, Pb, Bi) and Their Removal from the Environment," Presented by R. D. Rogers at Western Michigan University, Kalamazoo, MI, on 10/23/89.
19. "Macrocycle Complexation Chemistry: The Toxic Metals (Cd, Hg, Tl, Pb, Bi) and Their Removal from the Environment," Presented by R. D. Rogers at Rockford College, Rockford, IL, on 3/27/90.
20. "Structural Characterization of Light Atom Structures via X-ray Crystallography," Presented by R. D. Rogers at The University of Mississippi, Oxford, MS, on 4/10/90.
21. "The Toxic Metals and Their Removal from the Environment," Presented by R. D. Rogers at Illinois Benedictine College, Lisle, IL, on 4/19/90.
22. "Crown Ether vs. Polyethylene Glycol Complexation of Lanthanide Chlorides," Presented by R. D. Rogers at Indiana University, Bloomington, IN, on 2/28/91.
23. "Polyethylene Glycols as Ionizable Complexing Agents of Bi^{+3}," Presented by R. D. Rogers at Indiana University, Bloomington, IN, on 3/1/91.
24. "Investigations of Polyethylene Glycols as Complexing Agents and Liquid/Liquid Extraction Diluents for Bismuth," Presented by R. D. Rogers at Loyola University of Chicago, Chicago, IL, on 9/19/91.
25. "Polyethylene Glycols and Metal Ions: Structural Chemistry to Aqueous Biphasic Extraction," Presented by R. D. Rogers at the Universität Bayreuth, Bayreuth, Germany, on 6/23/92.
26. "Polyethylene Glycols: From Coordination Chemistry of Metal Cations to Unique Systems for Dissolved Metal Ion Separations," Presented by R. D. Rogers at the University of Groningen, Groningen, The Netherlands, on 7/2/92.
27. "Macrocycle Complexation Chemistry: Toxic Metals and Their Removal from the Environment," Presented by R. D. Rogers at Elmhurst College, Elmhurst, IL, on 11/18/92.
28. "Aqueous Biphasic Systems: New Systems for Metal Ion Extraction," Presented by R. D. Rogers at Los Alamos National Laboratory, Los Alamos, NM, on 5/26/93.
29. "Polyethylene Glycol-Based Aqueous Biphasic Systems: New Systems for Novel Metal Ion Separations," Presented by R. D. Rogers at the University of New Mexico, Albuquerque, NM, on 9/24/93.
30. "Structural Investigation of Cyclic and Acyclic Polyether Complexes - Cation Control of Coordination," Presented by R. D. Rogers at Valparaiso University, Valparaiso, IN, on 12/10/93.
31. "Polyethylene Glycol-Based Aqueous Biphasic Systems: New Systems for Novel Metal Ion Separations," Presented by R. D. Rogers at Loyola University of Chicago, Chicago, IL, on 4/14/94.

32. "The Effects of Polyethylene Glycol on the Coordination Sphere of Strontium: Are PEGs Useful in Sr^{2+} Extraction Technologies?" Presented by R. D. Rogers at Oak Ridge National Laboratory, Oak Ridge, TN, on 5/16/94.
33. "Polyethylene Glycol-Based Aqueous Biphasic Systems: New Systems for Novel Metal Ion Separations," Presented by R. D. Rogers at Union Carbide Corporation, South Charleston, WV, on 6/3/94.
34. "The Effects of Polyethylene Glycol on the Coordination Sphere of Strontium: Are PEGS Useful in Sr^{2+} Extraction Technologies?" Presented by R. D. Rogers at The University of Alabama, Tuscaloosa, AL, on 6/22/94.
35. "Polyethylene Glycol-Based Aqueous Biphasic Systems: New Ways to Separate Metal Ions," Presented by R. D. Rogers at Western Michigan University, Kalamazoo, MI, on 10/10/94.
36. "Polyethylene Glycol-Based Aqueous Biphasic Systems: New Ways to Separate Metal Ions," Presented by R. D. Rogers at the University of Wisconsin-Oshkosh, Oshkosh, WI, on 11/10/94
37. "Polyethylene Glycols: Coordination Chemistry of Metal Cations to Unique Systems for Metal Ion Separations," Presented by R. D. Rogers at the University of Sevilla, Sevilla, Spain, on 6/16/95.
38. "Polyethylene Glycols: Coordination Chemistry of Metal Cations to Unique Systems for Metal Ion Separations," Presented by R. D. Rogers at The University of Alabama, Tuscaloosa, AL, on 7/12/95.
39. "Polyethylene Glycols: Coordination Chemistry of Metal Cations to Unique Systems for Metal Ion Separations," Presented by R. D. Rogers at The University of Iowa, Iowa City, IA, on 9/13/95.
40. "Polyethylene Glycols: Coordination Chemistry of Metal Cations to Unique Systems for Metal Ion Separations," Presented by R. D. Rogers at The University of Wisconsin at Milwaukee, Milwaukee, WI, on 10/9/95.
41. "Polyethylene Glycol-Based Aqueous Biphasic Systems: New Technologies for Metal Ion Separations," Presented by R. D. Rogers at Argonne National Laboratory, Argonne, IL, on 1/29/96.
42. "Polyethylene Glycol-Based Aqueous Biphasic Systems: New Technologies for Metal Ion Separations," Presented by R. D. Rogers at Monash University, Clayton, Victoria, Australia, on 3/19/96.
43. "ABEC Resins: From Aqueous Biphasic Novelties to Selective Aqueous Biphasic Extraction Chromatography Resins for Metal Ions," Presented by R. D. Rogers at Mississippi State University, Starkville, MS, on 1/24/97.
44. "Green Chemistry in Separation Science," Presented by R. D. Rogers at the March meeting of the Alabama Section of The American Chemical Society, Birmingham, AL, on 3/20/97.
45. "ABEC Resins: From Aqueous Biphasic Novelties to Selective Aqueous Biphasic Extraction Chromatography Resins for Metal Ions," Presented by R. D. Rogers at the University of Alabama at Huntsville, Huntsville, AL, on 3/28/97.
46. "The SMART System at The University of Alabama: Experiences, Reflections, and Data," Presented by R. D. Rogers at the Siemens Area Detector Users Group Meeting (SADUG97), Athens, GA, on 4/19/97.
47. "Coordination Chemistry and Separations of Actinides," Presented by R. D. Rogers at Florida State University, Tallahassee, FL, on 4/24/97.
48. "Polyethylene Glycol-Based Aqueous Biphasic Systems and ABEC Resins for the Selective Removal and Recovery of Metal Ions," Presented by R. D. Rogers at the University of Birmingham, Birmingham, England, UK, on 5/21/97.
49. "Polyethylene Glycol-Based ABEC Resins for the Selective Removal of Technetium from Hanford Tank Wastes," Presented by R. D. Rogers at British Nuclear Fuels, Ltd., Preston, England, UK, on 5/22/97.
50. "Aqueous Biphasic Systems: New Technologies for Metal Ion Separations," Presented by R. D. Rogers at Queen's University, Belfast, Northern Ireland, UK, on 5/27/97.
51. "Clean Separation Technologies," Presented by R. D. Rogers at the University of New Hampshire, Durham, NH, on 7/24/97.
52. Clean Separation Technologies," Presented by R. D. Rogers at the University of Marburg, Marburg, Germany, on 9/26/97.
53. "Green Separation Science: Traditional Polymeric Supports to Crystal Engineered Inorganic Polymers," Presented by R. D. Rogers at Clemson University, Clemson, SC, on 10/1/97.
54. "Utilization of Polyethylene Glycol in Industrially and Environmentally Important Separations," Presented by R. D. Rogers at Union Carbide, South Charleston, WV, on 10/3/97.
55. "Clean Separation Technologies," Presented by R. D. Rogers at The University of Alabama (Chemical Engineering Department), Tuscaloosa, AL, on 10/9/97.
56. "Polyethylene Glycol-Based Aqueous Biphasic Systems and ABEC Resins for the Selective Removal and Recovery of Metal Ions," Presented by R. D. Rogers at the University of Tennessee at Knoxville, Knoxville, TN, on 2/5/98.
57. "Green Separation Science: Traditional Polymeric Supports to Crystal Engineered Inorganic Polymers," Presented by R. D. Rogers at Oak Ridge National Laboratory, Oak Ridge, TN, on 2/6/98.
58. "Green Separation Science: Traditional Polymeric Supports to Crystal Engineered Inorganic Polymers," Presented by R. D. Rogers at Tennessee Technological University, Cookeville, TN, on 2/19/98.
59. "Coordination Chemistry to Crystal Engineering," Presented by R. D. Rogers at the University of Puerto Rico, San Jaun, PR, on 4/6/98.
60. "Clean Separations Using Non-Toxic Aqueous Polymers: In Support of Vision 2020," Presented by R. D. Rogers in the J. Clarence Karcher Lecture series at the University of Oklahoma, Norman, OK, on 4/23/98.
61. "Environmentally Benign Liquid/Liquid Extraction Media for Metal Ion Separations: Aqueous Biphasic Systems and Room Temperature Ionic Liquids," Presented by R. D. Rogers at the University of Mississippi, Oxford, MS, on 12/4/98.
62. "Green Separation Science and technology: Using Environmentally Benign Liquid/Liquid Extraction Media for Metal Ion Separations: Aqueous Biphasic Systems and Room temperature Ionic Liquids," Presented by R. D. Rogers at the Exxon Research and Development Laboratories, Baton Rouge, LA, on 5/7/00.

63. "Green Separation Science and Technology: Using Environmentally Benign Liquid/Liquid Extraction Media, Aqueous Biphasic Systems and Room Temperature Ionic Liquids," Presented by R. D. Rogers at the University of South Alabama, Mobile, AL, on 5/21/99.
64. "Environmentally Benign Liquid/Liquid Extraction Media: Aqueous Biphasic Systems and Room Temperature Ionic Liquids," Presented by R. D. Rogers at Pacific Northwest National Laboratory, Richland, WA, on 10/7/99.
65. "Environmentally Benign Liquid/Liquid Extraction Media: Aqueous Biphasic Systems and Room Temperature Ionic Liquids," Presented by R. D. Rogers at Washington State University, Pullman, WA, on 10/8/99.
66. "A Toolbox Approach to Green Separations Science & Technology: Crystal Engineering, Aqueous Biphasic Systems, and Room Temperature Ionic Liquids," Presented by R. D. Rogers at The University of Kentucky, Lexington, KY, on 10/28/99.
67. "Room Temperature Ionic Liquids as VOC Solvent Replacements," Presented by R. D. Rogers at Mercer University, Macon, GA, on 11/9/99.
68. "Ionic Liquids in Separations," Presented by R. D. Rogers at Queen's University, Belfast, Northern Ireland, UK, during Ionic Liquid Week, 1/31/00-2/4/00.
69. "Green Chemistry and Ionic Liquids: Sustainable Industrial Development from Academic Challenges," Presented by R. D. Rogers at Birmingham Southern College, Birmingham, AL, on 2/29/00.
70. "Ionic Liquids in Separations," Presented by R. D. Rogers as the 2nd Queen's University Ionic Liquid Laboratory Lecture, Queen's University, Belfast, Northern Ireland, UK on 4/3/00.
71. "Ionic versus Molecular Solvents: Challenges in Adopting Ionic Liquids as Alternative Reaction Media," Presented by R. D. Rogers at the University of Florida, Gainesville, FL on 5/3/00.
72. "The Role of the Sugar Industry in the New Green Chemistry & Engineering Paradigm of Sustainable Industry," Presented by R. D. Rogers at the Sugar Cane Growers Cooperative of Florida, Belle Glade, Fl on 5/4/00.
73. "Ionic Liquids & Their Application to Separation Processes," Presented by R. D. Rogers at Union Carbide, South Charleston, WV on 5/9/00.
74. "Crystal Engineering of Coordination Polymers," Presented by R. D. Rogers at Université Louis Pasteur, Strasbourg, France on 6/7/00 (Visiting Professor Lecture).
75. "Green Chemistry and Applications of Ionic Liquids as Solvents," Presented by R. D. Rogers at Université Louis Pasteur, Strasbourg, France on 6/16/00 (Visiting Professor Lecture).
76. "How Green Chemistry can Shape the Future of the Chemical Industry," Presented by R. D. Rogers at the Green Chemical Processes –Issue, Challenges, Innovations, Technical Symposium, BP Amoco Chemicals Central Technology, Naperville, IL on 7/11/00.
77. "Engineering Tetrapyridylporphyrin Coordination Complexes for Metal Ion Recognition in Crystalline Materials or on Surfaces," Presented by R. D. Rogers at Emory University on 9/28/00.
78. "Ionic Liquids as Alternatives to Organic Solvents" Presented by R. D. Rogers at North Carolina State University, Raleigh, NC on 10/5/00.
79. "Ionic Liquids as Alternatives to Organic Solvents" Presented by R. D. Rogers at Kennedy Space Center, Cape Canaveral, FL on 10/6/00.
80. "Ionic Liquids as 'Green' Alternatives to Organic Solvents," Presented by R. D. Rogers at Dow Agrosciences LLC, Indianapolis, IN on 10/30/00.
81. "Ionic Liquids," Presented by R. D. Rogers at University of Massachusetts at Boston, Boston, MA on 11/28/00.
82. "Room Temperature Ionic Liquids as Alternative Reaction Media," Presented by R. D. Rogers at Tulane University, New Orleans, LA on 12/5/00.
83. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers at Louisiana State University, Baton Rouge, LA on 1/31/01.
84. "Ionic Liquids as 'Green' Alternatives to Organic Solvents," Presented by R. D. Rogers at Dow Corning, Midland, MI on 2/5/01.
85. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers at University of South Florida, Tampa, FL on 4/19/01."Ionic Liquids as 'Green' Alternatives to Organic Solvents," Presented by R. D. Rogers at Cognis Corporation, Cincinnati, OH on 5/16/01.
87. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers at the U.S. Environmental Protection Agency, Washington, DC on 5/23/01.
88. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers at Tennessee State University, Nashville, TN on 10/18/01.
89. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers at the University of Illinois at Urbana-Champaign, Urbana, IL on 2/12/02.
90. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers at Wesleyan University, Middletown, CT on 2/15/02.
91. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers at Kansas State University, Manhattan, KS on 2/22/02.
92. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers to Stellenbosch University, Stellenbosch, South Africa on 3/20/02.
93. "Non-Sugar Products from Sugarcane for the New Millennium: Green Pathways to a Carbohydrate Economy?" Presented by R.

D. Rogers to the Sugar Milling Research Institute, Durban, South Africa on 3/26/02.

94. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers to Monsanto Company, St. Louis, MO on 6/6/02.
95. "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers to The Dow Chemical Company, Midland, MI on 6/19/02.
96. "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers to The Lubrizol Corporation, Cleveland, OH on 7/24/02.
97. "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers to Honeywell Corporation, Buffalo, NY on 8/14/02.
98. "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers to Eastman Corporation, Kingsport, TN on 10/28/02.
99. "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers to Savannah River Technical Center, SC on 11/13/02.
100. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers to Auburn University, Auburn, AL on 1/16/03.
101. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers to GE Global Research Center, Schenectady, NY on 2/3/03.
102. "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by R. D. Rogers to AstraZeneca, Loughborough, United Kingdom on 3/28/03.
103. "Green Chemistry" in Pursuit of Traditional Chemical Research, Education, and Service: A Path Forward for the University of Massachusetts- Boston?" Presented by R. D. Rogers to the University of Massachusetts-Boston, Boston, MA on 5/5/03.
104. "Radiochemistry in the Rogers Group at The University of Alabama," Presented by R. D. Rogers at The University of Alabama, Tuscaloosa, AL on 8/28/03.
105. "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by R. D. Rogers to Los Alamos National Laboratory, Los Alamos, NM on 9/18/03.
106. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers to Mississippi State University, Starkville, MS on 10/17/03.
107. "Ionic Liquids as Green Solvents: Engineering New Bio-Based Materials," Presented by R. D. Rogers at the University of Alabama at Huntsville, Huntsville, AL on 1/16/04.
108. "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers to Sun Yat-Sen University, Guangzhou, China on 2/23/04.
109. "A Burnum Legacy: Red Chemistry, Green Chemistry, and My Road from Alabama to Alabama" Presented by R. D. Rogers to The University of Alabama (Burnum Award Address), Tuscaloosa, AL on 4/6/04.
110. "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids for Extreme Environments (i.e. NASA)?" Presented by R. D. Rogers to Marshall Space Flight Center, Huntsville, AL on 4/8/04.
111. "Green Chemistry" in Pursuit of Traditional Chemical Research, Education, and Service: A Path Forward for the University of Central Florida?" Presented by R. D. Rogers to the University of Central Florida, Orlando, FL on 4/14/04.
112. "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids?" Presented by R. D. Rogers to BASF Corporation, Ludwigshafen, Germany on 4/26/04.
113. "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids?" Presented by R. D. Rogers to Merck KGaA, Darmstadt, Germany on 4/27/04.
114. "Advanced Materials from Direct Dissolution of Cellulose," Presented to by R. D. Rogers to Gulf States Paper Corporation, Tuscaloosa, AL on 6/7/04.
115. "Applications of Ionic Liquid Technologies to f-Element Separations," Presented by R. D. Rogers to the E. O. Lawrence Berkeley Laboratory, Berkeley, CA on 6/16/04.
116. "Ionic Liquids: An Overview," Presented by R. D. Rogers to Stepan Company, Northfield, IL on 8/20/04.
117. "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids?" Presented by R. D. Rogers to the U. S. Environmental Protection Agency, National Risk Management Research Laboratory, Cincinnati, OH on 9/1/04.
118. "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids?" Presented by R. D. Rogers to Davidson College, Davidson, NC on 9/2/04.
119. "Ionic Liquids: An Overview," Presented by R. D. Rogers to The Proctor & Gamble Company, Cincinnati, OH on 11/10/04.
120. "Green Chemistry and Applications of Ionic Liquids as Solvents: Enabling Sustainable Technologies for New Advanced Materials," Presented by R. D. Rogers to the Swiss Federal Institute of Technology at Lausanne, Switzerland, on 10/13/04.
121. "Ionic Liquid Processing of Cellulose," Presented by R. D. Rogers to Lenzing AG, Lenzing, Austria, on 10/18/04.
122. "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids?" Presented by R. D. Rogers to the University of South Dakota, Vermillion, SD on 11/1/04.
123. "Green Chemistry and Applications of Ionic Liquids as Solvents: Enabling Sustainable Technologies for New Advanced Materials," Presented by R. D. Rogers to the Naval Research Laboratory, Washington, DC on 11/9/04.
124. "Green Chemistry, Ionic Liquids, Advanced Materials, and Everything in Between" Presented by R. D. Rogers to the University of Missouri, Columbia, MO on 11/11/04.
125. "Green Chemistry, Ionic Liquids, Advanced Materials, and Everything in Between" Presented by R. D. Rogers to Howard

University, Washington, DC on 12/3/04.

126. "Green Chemistry, Ionic Liquids, Advanced Materials, and Everything in Between" Presented by R. D. Rogers to the University of Bucharest, Bucharest, Romania on 12/13/04.
127. "Green Chemistry, Ionic Liquids, Advanced Materials, and Everything in Between" Presented by R. D. Rogers to Wake Forest University, Winston, NC on 1/12/05.
128. "Supramolecular Chemistry in Alternative Solvents: Are Nonvolatile Ionic Liquids Effective Crystallization Solvents or Fodder for Co-Crystals?" Presented by R. D. Rogers to the University of Bucharest, Bucharest, Romania on 3/16/05.
129. "Green Chemistry – An Overview," Presented by R. D. Rogers to the University of Bucharest, Bucharest, Romania on 3/17/05.
130. "Ionic Liquids: Solvents for Cellulose," Presented by R. D. Rogers to the U.S. Bureau of Engraving and Printing, Washington, DC on 4/29/05.
131. "Ionic Liquids: Applications are Coming; Get Ready Now!," Presented by R. D. Rogers to NIEHS, Raleigh, NC, on 5/4/05.
132. "Green Chemistry, Ionic Liquids, Advanced Materials, and Everything in Between" Presented by R. D. Rogers to the Institute of Process Engineering, Chinese Academy of Sciences, Beijing, China on 5/26/05.
133. "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids? (R&D, Trends, and Practical Application)," Presented by R. D. Rogers to Merck KGaA, Darmstadt, Germany on 6/16/05.
134. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents for Crystal Engineering to Advanced New Materials," Presented by R. D. Rogers to The University of Tokyo, Tokyo, Japan on 7/20/05.
135. "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers to Tokyo University of Agricultural and Technology, Tokyo, Japan on 7/21/05.
136. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents for Crystal Engineering to Advanced New Materials," Presented by R. D. Rogers to Kyoto University, Kyoto, Japan on 7/22/05.
137. "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers to Eastman Kodak Company, Rochester, NY on 8/9/05.
138. "Energetic Ionic Liquids: Fundamental Studies Relating Target Structures and Key Physical Properties," Presented by R. D. Rogers to the Air Force Research Laboratory, Edwards Air Force Base, CA on 8/11/05.
139. "A Platform Strategy Using Ionic Liquids to Dissolve and Process Cellulose for Advanced New Materials," Presented by R. D. Rogers to FMC BioPolymer, Princeton, NJ on 9/13/05.
140. "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers to the Changchung Institute of Applied Chemistry, Chinese Academy of Sciences, Changchung, China on 9/27/05.
141. "Energetic Ionic Liquids: Fundamental Studies Relating Target Structures and Key Physical Properties," Presented by R. D. Rogers to the American Pacific/Georgia Tech. Roundtable, Atlanta, GA on 10/6/05; (also Panel Member for the Energetic Materials Panel Discussion).
142. "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers to the University of South Carolina, Columbia, SC on 11/18/05.
143. "Green Chemistry and Applications of Ionic Liquids as Solvents: Enabling Sustainable Technologies for New Advanced Materials," Presented by R. D. Rogers to the University of Southern Mississippi, Hattiesburg, MS on 12/2/05.
144. "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers to the DuPont 2005 Discovery Chemistry Seminar Series, DuPont Central Research and Development, Wilmington, DE on 12/7/05.
145. "Green Chemistry and Applications of Ionic Liquids as Solvents," Presented by R. D. Rogers to Jackson State University, Jackson, MS on 1/27/06.
146. "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers to Millennium Chemical/Lyondell, Baltimore, MD on 2/28/06.
147. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers as the Arnold C. Ott Lectureship in Chemistry (research presentation), Grand Valley State University, Allendale, MI on 4/5/06.
148. "Green Chemistry: Can Society and the Chemical Industry Co-Exist?" Presented by R. D. Rogers as the Arnold C. Ott Lectureship in Chemistry (public lecture), Grand Valley State University, Grand Rapids, MI on 4/5/06.
149. "Ionic Liquids," Presented by R. D. Rogers to Albion College, Albion, MI on 4/7/06.
150. "How the Center for Green Manufacturing Can Impact Alabama," Presented by R. D. Rogers to the Tuscaloosa League of Women Voters, Tuscaloosa, AL on 4/20/06.
151. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers at the 7th Annual Science Symposium *The Science of Sustainability, A Balance for the Future*, St. Olaf College, Northfield, MN on 5/5/06. (Invited Keynote Lecture)
152. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers at the University of Cologne, Cologne, Germany on 5/16/06.
153. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers at IReS Chimie Nucleaire Strasbourg, France on 6/14/06.
154. "Green Chemistry, Ionic Liquids, Advanced Materials, and Everything in Between," Presented by R. D. Rogers at the Institute Le Bel, Université Louis Pasteur, Strasbourg, France on 6/15/06 (Visiting Professor Lecture).
155. "Strategies Toward the Design of Energetic Materials," Presented by R. D. Rogers at the Institute Le Bel, Université Louis Pasteur, Strasbourg, France on 6/16/06 (Visiting Professor Lecture).

156. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers at the Stamford Seminar Series, Cytec Industries, Inc., Stamford, CT on 10/18/06.
157. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers at the University of Texas San Antonio, San Antonio, TX on 10/20/06.
158. "Green Chemistry and Applications of Ionic Liquids as Solvents: Enabling Sustainable Technologies For New Advanced Materials," Presented by R. D. Rogers at the University of Texas Arlington, Arlington, TX on 11/10/06.
159. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers at the University of Toledo, Toledo, OH on 1/17/07.
160. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers to Lyondell Chemical Co., Newton Square, PA on 2/13/07.
161. "The Past, Present, and Future of Ionic Liquids: From Designer Solvents to Advanced New Materials," Presented by R. D. Rogers to Colgate-Palmolive, Piscataway, NJ on 9/10/07.
162. "Applications and The Third Evolution of Ionic Liquids: Physical to Chemical to Biological Properties," Presented by R. D. Rogers to Colgate-Palmolive, Piscataway, NJ on 9/10/07.
163. **"**The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers to Technische Universiteit Eindhoven, Eindhoven, The Netherlands on 9/24/07.
164. "Ionic Liquids as Transformational Technologies," Presented by R. D. Rogers to Nippon Chemical Industrial Company, Tokyo, Japan, on 4/21/08.
165. "The Evolution of Ionic Liquids – From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers at the Danish Technical University (2008), Copenhagen, Denmark, on 6/16/08.
166. "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers to Brookhaven National Laboratory, Upton, NY on 7/14/08.
167. "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers to Abbott, Waukegan, IL on 8/14/08.
168. "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers to the University of Alabama at Birmingham, Birmingham, AL on 9/8/08.
169. "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers to AMGEN, South San Francisco, CA on 9/10/08.
170. "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples for the Fragrance Industries," Presented by R. D. Rogers to Givaudan, Ashford, United Kingdom on 10/01/08.
171. "Green Chemistry and the Industrial Revolution," Presented by R. D. Rogers to the Royal Institution of Great Britain as an invited Friday Evening Discourse, London, United Kingdom on 11/14/08. (Invited)
172. "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers to The U.S. Army Research Office/U.S. Army Research Laboratory Ionic Liquids in Eletroactive Devices MURI Annual Review, Philadelphia, PA on 12/16/08. (Invited Guest Speaker)
173. "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers to Rutgers University, New Brunswick, NJ on 1/20/09. (Invited Colloquium Speaker)
174. "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers to Abbott, Waukegan, IL on 2/20/09. (Invited Abbott Seminar Series)
175. "Ionic Liquids and the Green Industrial Revolution," Presented by R. D. Rogers to The Queen's University of Belfast, Belfast, United Kingdom on 3/2/09. (Inaugural Lecture)
176. "The 'Ionic Liquid Talk'," Webinar presented by R. D. Rogers to the American Chemical Society Publications Division from Belfast, Northern Ireland to Washington, DC on 4/24/09.
177. "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers to the Institute of Process Engineering, Chinese Academy of Sciences, Beijing, China on 8/22/09.
178. "From Green Chemistry to a 'Green' Industrial Revolution: Are Ionic Liquids Pointing the Way?" Presented by R. D. Rogers to the Foster Colloquium University of Buffalo, Buffalo, NY on 10/30/09. (Invited Colloquium Speaker)
179. "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers to Tuskegee Institute, Tuskegee, AL, on 11/30/09.
180. "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers to The Westerveld Company, Tuscaloosa, AL, on 12/16/09.
181. "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers to The University of Colorado, Boulder, CO, on 1/12/10.
182. "Ionic Liquid Advances and Retreats as Solvents and Materials," Presented by R. D. Rogers to Colgate-Palmolive, Piscataway, NJ on 1/27/10.
183. "Ionic Liquids with or without Biological Activity for use in Personal Care Products," Presented by R. D. Rogers to Colgate-Palmolive, Piscataway, NJ on 1/27/10.

184. “Crystallization Process in Ionic Liquids,” Presented by R. D. Rogers to Nippon Chemical Industrial, Tokyo, Japan on 2/8/10.
185. “Ionic Liquids Laboratory to Commercialization,” Presented by R. D. Rogers to the Institute of Process Engineering, Chinese Academy of Sciences, Beijing, China on 04/28/10.
186. “Ionic Liquids: Introduction, Brief History, Evolution, and Potential Applicability to Your Projects,” Presented by R. D. Rogers to the Massachusetts Institute of Technology, Cambridge, MA on 06/10/10.
187. “Ionic Liquids: Introduction, Brief History, Evolution, and Potential Applicability to Your Projects,” Presented by R. D. Rogers to the Arch Chemicals Inc., Innovation Committee, Atlanta, GA on 09/15/10.
188. “Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to the Joint Bioenergy Research Institute, Lawrence Berkeley National Laboratory, Emeryville, CA on 10/05/10.
189. “Ionic Liquids: Laboratory to Commercialization Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to Lanzhou University, Lanzhou, China on 10/28/10.
190. “Ionic Liquids: Laboratory to Commercialization,” Presented by R. D. Rogers to The Chinese Academy of Sciences Institute of Chemical Physics, Lanzhou, China on 10/29/10.
191. “Ionic Liquids: Laboratory to Commercialization Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to Jiaotong University, Xi’an, China on 11/01/10.
192. “Ionic Liquids: Laboratory to Commercialization Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to Northwest University, Xi’an, China on 11/01/10.
193. “Ionic Liquids: Introduction, Brief History, Evolution, and Potential Applicability to Your Projects,” Presented by R. D. Rogers to Monsanto, St. Louis, MO on 11/11/10.
194. “Ionic Liquids: Introduction, Brief History, Evolution, and Potential Applicability to Your Projects,” Presented by R. D. Rogers to Frontier Scientific and Echelon, Logan, UT on 12/09/10.
195. “Vignettes of Ionic Liquids Strategies in the Rogers Group,” Presented by R. D. Rogers to Tokyo University of Agricultural and Technology, Tokyo, Japan on 1/13/11.
196. “Vignettes of Ionic Liquids Strategies in the Rogers Group,” Presented by R. D. Rogers to Nippon Chemical Industrial Company, Tokyo, Japan, on 1/14/11.
197. “Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to University of Guelph on 1/24/11.
198. “Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to Tennessee Technological University, Cookeville, TN on 2/8/11.
199. “Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to Oak Ridge National Laboratory, Oak Ridge, TN on 2/9/11.
200. “An Editor’s Perspective on Contentious Issues Arising During the Peer Review Process,” Presented by R. D. Rogers to the National Chemical Laboratory, Pune, India, on 6/24/11.
201. “An Editor’s Perspective on Contentious Issues Arising During the Peer Review Process,” Presented by R. D. Rogers to the Indian Institute of Science, Bangalore, India, on 6/27/11.
202. “Ionic Liquids: Unique Environments for f-Element Chemistry,” Presented by R. D. Rogers to the Changchung Institute of Applied Chemistry, Chinese Academy of Sciences, Changchung, China on 07/26/11.
203. “The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook,” Presented by R. D. Rogers to Merck, Summit, NJ on 09/09/11.
204. “Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to Loyola University, New Orleans, LA on 11/21/11.
205. “The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook,” Presented by R. D. Rogers to Ruhr Universität Bochum, Bochum, Germany on 12/01/11.
206. “Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to the Fraunhofer Institute for Wood Research Wilhelm Klauditz Institute, Braunschweig, Germany on 12/05/11.
207. “Ionic Liquids: Solvents and Materials,” Presented by R. D. Rogers to Reliance Industries Limited, Mumbai, India on 03/09/12.
208. “Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to the Central Salt & Marine Chemicals Research Institute, Bhavnagar, Gujarat, India on 03/15/12.
209. “Ionic Liquids in Support of the Pharmaceutical Industries,” Presented by R. D. Rogers to Novartis, Basel, Switzerland on 05/07/12.
210. “Green Chemistry, Technology, & Innovation (on the road to ‘Shrimp Bandages’),” Presented by R. D. Rogers to the Mobile Kiwanis Club, Mobile, AL on 6/27/12.
211. “Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose,” Presented by R. D. Rogers to the University of Mississippi, Oxford, MS on 11/01/12.

212. "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin" Presented by R. D. Rogers to the U.S. Army ERDC Environmental Laboratory, Vicksburg, MS on 11/02/12.
213. "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers to McGill University, Montreal, Quebec, Canada on 11/06/12.
214. "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers to The University of Tennessee at Martin, Martin, TN on 02/18/13.
215. "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers to The University of Aveiro, Averio, Portugal on 04/29/13.
216. "A study of Ionic Liquids in the pharmaceutical sector - How can the liquid state help us master the solid state?" Presented by R. D. Rogers to Instituto de Technologia Quimica e Biologica (ITQB), Lisbon, Portugal on 04/30/13.
217. "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers to the Sugar Milling Research Institute, Council for Scientific and Industrial Research Forestry and Forest Products Research Centre, University of KwaZulu-Natal Chemical Engineering Department, and Durban University of Technology, Durban, South Africa on 07/03/13.
218. "A study of Ionic Liquids in the pharmaceutical sector - How can the liquid state help us master the solid state?" Presented by R. D. Rogers to McGill University, Montreal, Quebec, Canada on 08/21/13.
219. "Fine Tuning Double Salt Ionic Liquids and Their Applications in the Pharmaceutical Industry," Presented by R. D. Rogers at Novartis, Basel, Switzerland on 09/11/13.
220. "A study of Ionic Liquids in the pharmaceutical sector" Presented by R. D. Rogers to Nova University, Ft. Lauderdale, FL on 10/11/13.
221. R. D. Rogers, "Liquid Engineering to Crystal Engineering: How Ionic Liquids Can Help Us Master the Pharmaceutical Solid State," Presented by R. D. Rogers to the University of Cologne, Cologne, Germany, 11/28/13.
222. R. D. Rogers, "Liquid Engineering to Crystal Engineering: How Ionic Liquids Can Help Us Master the Pharmaceutical Solid State," Presented by R. D. Rogers to the University of Bochum, Bochum, Germany, 11/29/13.
223. "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin" Presented by R. D. Rogers to Mississippi State University, Starkville, MS on 02/14/14.
224. R. D. Rogers, "Liquid Engineering to Crystal Engineering: How Ionic Liquids Can Help Us Master the Pharmaceutical Solid State," Presented by R. D. Rogers to the University of Rostock, Rostock, Germany, 04/07/14.
225. R. D. Rogers, "Liquid Engineering: Ionic Liquids for the Pharmaceutical Sector in Drug Development, Drug Delivery, and as Drugs," Presented by R. D. Rogers to Takeda Millennium, Cambridge, MA, 05/09/14.
226. R. D. Rogers, "Ideality vs. Reality of Green Chemistry in the Development of Advanced Materials from Renewable Polymers," Presented by R. D. Rogers before the North Alabama Section of the American Chemical Society, Huntsville, AL, 09/08/14.
227. R. D. Rogers, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers to Iowa State University, Ames, IA on 11/03/14.
228. R. D. Rogers, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers to McGill University Macdonald Campus, Montreal, QC Canada on 04/16/15.
229. R. D. Rogers, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers to Institut für Technische und Makromolekulare Chemie, RWTH Aachen, Aachen, Germany on 04/30/15.
230. R. D. Rogers, "Sustainability, from Ideas to Implementation: Can Ionic Liquids Help?" Presented by R. D. Rogers to L'Oréal, Aulnay sous Bois, France on 05/11/15.
231. R. D. Rogers, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers to the University of Calgary (Department of Chemistry), Calgary, AB, Canada on 07/07/15.
232. R. D. Rogers, "Is 'Sustainability' a new paradigm for the future chemical industry? Cross border perspectives and what we need to train the next generation to face," Presented by R. D. Rogers to Alberta Innovates Technology Futures, Calgary, AB, Canada on 07/09/15.
233. "Utilization of Ionic Liquids in Support of Continuous Pharmaceutical Manufacturing: Fine Tunability of Double Salt Ionic Liquids," Presented by R. D. Rogers at Novartis, Basel, Switzerland on 09/14/15.
234. R. D. Rogers, "Liquid Engineering: Ionic Liquids for the Pharmaceutical Sector in Drug Development, Drug Delivery, and as Drugs," Presented by R. D. Rogers to the Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada on 11/09/15.
235. R. D. Rogers, "Innovation is the Gateway to the Biomass Biorefinery and Ultimately A sustainable Bio-based Economy," Presented by R. D. Rogers to Concordia University, Montreal, QC, Canada on 11/13/15.
236. R. D. Rogers, "Innovation is the Gateway to the Biomass Biorefinery and Ultimately A sustainable Bio-based Economy," Presented by R. D. Rogers as a Waterloo Institute for Nanotechnology (WIN) Distinguished Lecture to the University of Waterloo, Waterloo, ON, Canada on 11/19/15.

237. R. D. Rogers, “Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists,” Presented by R. D. Rogers to West Virginia University (Department of Chemical Engineering), Morgantown, WV on 12/04/15.
238. “Before Applications You Need Understanding: Does the Nature of the Bonding in Double Salt Ionic Liquids ‘Prove’ a Difference Between Ionic Liquids and Molecular Liquids?,” Presented by R. D. Rogers to Reliance Industries Limited, Mumbai, India on 01/19/16.
239. “Millions of New Ionic Liquids are Hiding in Plain Sight: Understanding the Nature of the Bonding in Double Salt Ionic Liquids (aka Ionic Liquid Mixtures),” Presented by R. D. Rogers to the PATH Workshop, University of Aveiro, Aveiro, Portugal on 05/09/16.

F. Theses and Dissertations Directed:

1. M. M. Benning, "Actinide/Crown Ether Chemistry," Ph.D., Northern Illinois University, 1988.
2. L. Nuñez, "Structural, Magnetic, and Superconducting Properties of $YBa_2Cu_{3-x}Fe_xO_{7-\delta}$ Single Crystals," Ph.D., Northern Illinois University, 1990.
3. R. F. Henry, "Synthesis and Characterization of Novel Macrocycles and Their Complexes," M. S., Northern Illinois University, 1990.
4. A. N. Rollins, "Controlling the Primary Coordination Sphere: Complexation of the 4-f Elements by Crown Ethers as Models for Potential Extraction Systems," Ph.D., Northern Illinois University, 1993.
5. A. H. Bond, "Heavy Main Group Metal Ions: Structural Chemistry of Polyether Complexes and Aqueous Biphasic Separations," Ph.D., Northern Illinois University, 1995.
6. C. B. Bauer, "Polyether Complexation Chemistry of Hard Metal Ions: Structural Investigation and Partitioning Behavior in Aqueous Biphasic Systems," Ph.D., Northern Illinois University, 1995.
7. J. Zhang, "Polyethylene Glycol (PEG) Chemistry: Partitioning of Chaotropic Ions in PEG-Based Aqueous Biphasic Systems and Structural Investigation of Lanthanide Isothiocyanate/PEG Complexes," Ph.D., Northern Illinois University, 1997.
8. K. S. Granger, non-thesis option, M.S., The University of Alabama, 2000.
9. H. D. Willauer, "Fundamentals of Phase Behavior and Solute Partitioning in ABS and Applications to the Paper Industry," Ph.D., The University of Alabama, 2002.
10. A. E. Visser, "Metal Ion Separations in Aqueous Biphasic Systems and Room Temperature Ionic Liquids," Ph.D., The University of Alabama, 2002. (Recipient of The University of Alabama Award for Excellence in Research by a Doctoral Student)
11. G. A. Broker, non-thesis option, M.S., The University of Alabama, 2003.
12. S. T. Griffin, "The Development and Applications of ABEC Resins," Ph.D., The University of Alabama, 2004.
13. M. Dilip, non-thesis option, M.S., The University of Alabama, 2004.
14. M. A. Klingshirn, "Relating Ionic Liquids and Polyethylene Glycols to Green Chemistry, Organometallic Catalysis, and Materials Science," Ph.D., The University of Alabama, 2005.
15. M. B. Turner, "Ionic Liquids in the Life Sciences: Are Ionic Liquids Useful in the Manipulation of Biomolecules?," Ph.D., The University of Alabama, 2005.
16. W. M. Reichert, "The Effects of Cation-Anion Interactions on the Properties of Ionic Liquids," Ph.D., The University of Alabama, 2005.
17. R. P. Swatloski, "Ionic Liquids as Green Solvents: Enabling New Materials and Technologies," Ph.D., The University of Alabama, 2005.
18. G. A. Broker, "Crystal Engineering Studies of some Nitrogen Containing Multifunctional Ligands," Ph.D., The University of Alabama, 2006.
19. V. A. Cocalia, "Separations, Solvation, and Coordination of Actinides in Ionic Liquids," Ph.D., The University of Alabama, 2006.
20. K. E. Gutowski, "Computational Thermodynamic Studies of the Formation and Stability of Ionic Liquids and Actinide-Ligand Complexes," Ph.D., The University of Alabama, 2006. (Recipient of The University of Alabama Award for Excellence in Research by a Doctoral Student)
21. N. J. Bridges, Ph.D., "Ionic Liquids and Water: An Investigation of Solvation," The University of Alabama, 2007.
22. C. C. Hines, "Ionic Liquids for Crystallization: Echoes of Solvation in the Solid State," M.S., The University of Alabama, 2007 (Recipient of The University of Alabama's Award for Excellence in Research by a Masters Student)
23. M. L. Moody, "A Study of the Influence of Water on Polyethylene Glycol Solutions," Ph.D., The University of Alabama, 2007
24. M. Smiglak, "A Modular "Ionic Liquid" Platform for the Custom Design of Energetic Materials," Ph.D., The University of Alabama, 2007. (Recipient of The University of Alabama Award for Excellence in Research by a Doctoral Student)
25. M. Dilip, "Towards Greener Separations: Role of water in Aqueous Biphasic Systems," Ph.D. The University of Alabama, 2008.
26. W. L. Hough, "Functional Ionic Liquids for Use in Pharmaceutical Applications," Ph.D. The University of Alabama, 2010.
27. N. Sun, "Dissolution and Processing of Cellulosic Materials with Ionic Liquids: Fundamentals and Applications," Ph.D. The University of Alabama, 2010.
28. D. M. Drab, "A Versatile Design Platform for Multi-Heterocyclic Ionic Liquid Synthesis," Ph.D. The University of Alabama, 2011.
29. M. L. Maxim, "Ionic Liquids Platform for Biomass Dissolution Leading to Advanced Biocomposite Materials," Ph.D. The University of Alabama, 2012.
30. P. A. Beasley, "Understanding the Effects of Molecular Additions in Energetic Ionic Liquids," M.S. The University of Alabama, 2013.
31. P. M. McCrary, "Controlling the Properties of Energetic Ionic Liquids by Stabilizing Reactive Nanomaterials," Ph.D. The University of Alabama, 2014.
32. Kelley, S. P., "Isolation of Soft Donor Complexes of d- and f-Block Metals Using Ionic Liquids," Ph.D. The University of Alabama, 2015.

Solid-State Chemistry of Drugs

SECOND EDITION

Stephen R. Byrn
Ralph R. Pfeiffer
Joseph G. Stowell

SSCI, Inc. • West Lafayette, Indiana
www.ssci-inc.com

10

Polymorphs

As discussed in Chapter 1, polymorphs exist when two crystals have the same chemical composition but different internal structure, including different unit cell dimensions and different crystal packing. Compounds that crystallize as polymorphs can show a wide range of different physical and chemical properties, including different melting points and spectral properties. Polymorphs can also differ in their solubility, density, hardness, and crystal shape. While some compounds may exist in only two polymorphs, others may exist in many polymorphs (*e.g.*, progesterone has five polymorphs and water has nine polymorphs). Control of polymorphism is particularly important for pharmaceuticals where changing the polymorph can alter the bulk properties, dissolution rate, bioavailability, chemical stability, or physical stability of a drug. The clearest indication of the existence of polymorphs comes from the X-ray crystallographic examination of single crystals of the various samples that are known to have the same composition. Often, however, X-ray powder diffraction is sufficient to establish the existence of polymorphs.

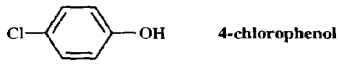
There is, unfortunately, no standard numbering system for polymorphs. In the literature, the various polymorphs have been designated by Roman numerals (preceded by the word "Form," *e.g.*, Form I), Greek letters (with the suffix "-form," *e.g.*, α-form), or in some cases, capital letters (similar to the Roman numeral system). To add to the confusion, some of numbering schemes of polymorphs also include solvates (*e.g.*, the α- and γ-forms of indomethacin are anhydrates, yet the β-form is the benzene solvate). Furthermore, some polymorphs have been identified only by their crystallographic classification (*e.g.*, the two polymorphs of ($\pm$)-β-promedol are designated the monoclinic form and the rhombohedral form). It has been suggested that polymorphs be numbered consecutively in the order of their stability at room temperature or by their melting point. This of course would lead to confusion upon the discovery of a new polymorph having intermediate stability or melting point and thus requiring renumbering of the existing polymorph system. It has also been suggested that polymorphs be numbered consecutively in the order of discovery, but this requires knowledge of their history and a timely access to that information. Whatever the numbering system, it is imperative that it be consistent. Thus, when a new polymorph is discovered and characterized, the designation of the new polymorph should be the next increment in the

previous system. However, this is not always practical when more than one laboratory is involved in the development process at the same time.

10.1 Classic Examples of Polymorphism

This section summarizes several classic examples of polymorphism which have appeared in the chemical literature.

A. 4-Chlorophenol



4-chlorophenol

The crystal structure of both the thermodynamically stable (α) and unstable (β) forms of 4-chlorophenol have been determined (Perrin and Michel, 1973a–b). Both forms belong to the same space group ($P2_1/c$); they both have the same number of molecules per unit cell ($Z = 8$) and nearly identical densities, yet they have different cell parameters (see Table 10.1). The crystal structure of the β-form projected on the (100) plane is shown in Figure 10.1. The packing consists of tetramers of molecules connected by hydrogen bonding. The crystal packing of the α-form (shown in Figure 10.2) also consists of tetramers connected by hydrogen bonds, but the arrangement of the rings is slightly different than that of the β-form. Although the β-form converts to the α-form, no detailed studies of this transformation have been reported.

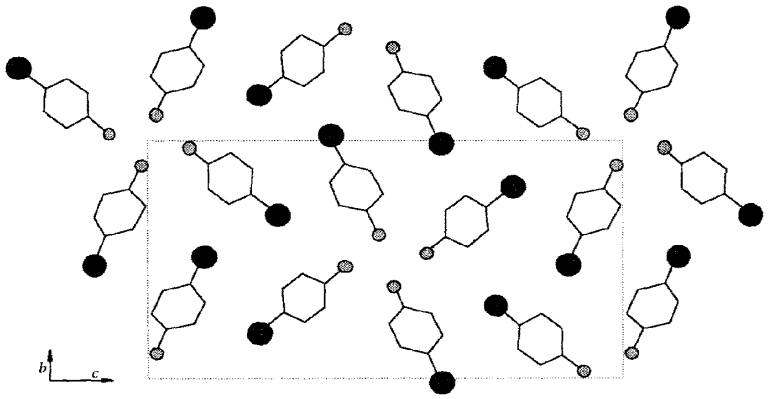


Figure 10.1 Projection of the crystal structure of the β-form of 4-chlorophenol (● chlorine atom, ◍ hydroxyl group) (Perrin and Michel, 1973b).

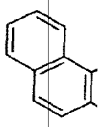
Table 10.1 Crystallograp
4-Chlorophen

Parameter	α-
Space Group	
a (Å)	
b (Å)	
c (Å)	
β	9
Z	
ρ_{calc} (g cm^{-3})	
V (Å^3)	122

a Perrin and Michel, 1973a.

Figure 10.2 Projection of t
◍ hydroxyl gr

B. Dibenz[*a*,*h*]anthra



In an early study of polyr
[*a*,*h*]anthracene (1,2:5,6-
1947; 1956). Although th
groups (Table 10.2) and

Table 10.1 Crystallographic Parameters for Two 4-Chlorophenol Polymorphs

Parameter	α-Form[a]	β-Form[b]
Space Group	$P2_1/c$	$P2_1/c$
a (Å)	8.84	4.14
b (Å)	15.726	12.85
c (Å)	8.790	23.20
β	92.61°	93.00°
Z	8	8
ρ_{calc} (g cm^{-3})	1.40	1.38
V (Å^3)	1220.7	1232.5

a Perrin and Michel, 1973a. *b* Perrin and Michel, 1973b.

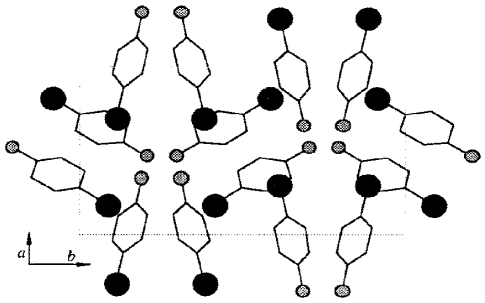
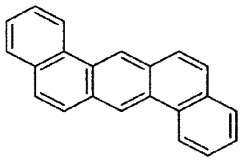


Figure 10.2 Projection of the crystal structure of the α-form of 4-chlorophenol (● chlorine atom, ◍ hydroxyl group) (Perrin and Michel, 1973a).

B. Dibenz[*a*,*h*]anthracene



dibenz[*a*,*h*]anthracene
(1,2:5,6-dibenzanthracene)

In an early study of polymorphism, the crystal structures of Forms I and II of dibenz-[*a*,*h*]anthracene (1,2:5,6-dibenzanthracene) were determined (Robertson and White, 1947; 1956). Although the forms have the same density, they belong to different space groups (Table 10.2) and have quite different packing. The crystal packing of Form I

(orthorhombic form) is shown in Figure 10.3 and the crystal packing of Form II (monoclinic form) is shown in Figure 10.4.

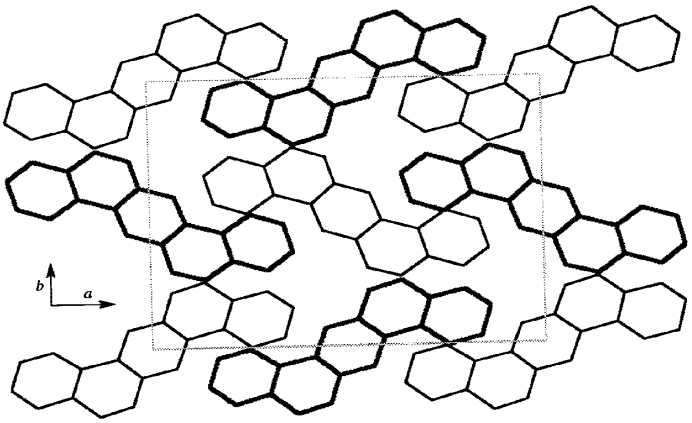


Figure 10.3 Crystal packing of Form I (orthorhombic form) of dibenz[*a*,*h*]anthracene (Robertson and White, 1947).

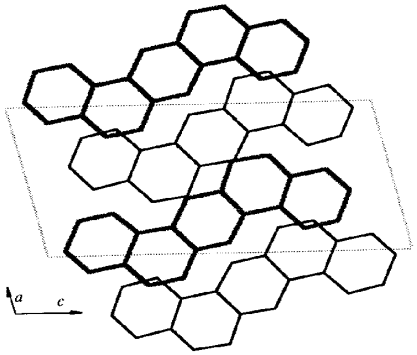


Figure 10.4 Crystal packing drawing of Form II (monoclinic form) of dibenz[*a*,*h*]anthracene (Robertson and White, 1956).

Table 10.2 Crystallographic I
Dibenz[*a*,*h*]anthra

Parameter	Fc
Space group	F
a (Å)	
b (Å)	1
c (Å)	1
β	9
Z	
ρ_{calc} (g cm^{-3})	
V (Å^3)	141
V/molecule	35

Robertson and White, 1947; R

C. Acridine

Acridine crystallizes in fi
Schmidt, 1955). The cry
and are shown in Figures
forms appear to be quite si

Table 10.3 Crystal Parameter

Parameter	α-For
Space group	$P2_1/c$
a (Å)	16.18
b (Å)	18.88
c (Å)	6.08
β	95.67°
Z	8
ρ_{calc} (g cm^{-3})	1.27
V (Å^3)	1848.2
V/*Z* (Å^3)	231.0
Habit	Needle

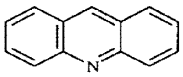
Herbstein and Schmidt, 1955

Table 10.2 Crystallographic Parameters for Two Dibenz[*a*,*h*]anthracene Polymorphs

Parameter	Form I	Form II
Space group	*Pcab*	$P2_1$
a (Å)	8.22	6.59
b (Å)	11.39	7.84
c (Å)	15.14	14.17
β	90.0°	103.5°
Z	4	2
ρ_{calc} (g cm^{-3})	1.29	1.29
V (Å^3)	1417.5	711.9
V/molecule	354.4	355.9

Robertson and White, 1947; Robertson and White, 1956.

C. Acridine



acridine

Acridine crystallizes in five polymorphs as shown in Table 10.3 (Herbstein and Schmidt, 1955). The crystal structures of the α- and γ-forms have been determined and are shown in Figures 10.5 and 10.6, respectively. The crystal packing of these forms appear to be quite similar although the cell parameters are obviously different.

Table 10.3 Crystal Parameters of the Various Polymorphs of Acridine

Parameter	α-Form	β-Form	γ-Form	δ-Form	ε-Form
Space group	$P2_1/a$	*Aa*	*Pnab*	$P2_12_12_1$	$P2_1/n$
a (Å)	16.18	16.37	17.45	15.61	11.37
b (Å)	18.88	5.95	8.89	6.22	5.98
c (Å)	6.08	30.01	26.37	29.34	13.64
β	95.67°	141.33°	90.00°	90.00°	98.67°
Z	8	8	16	12	4
ρ_{calc} (g cm^{-3})	1.27	1.29	1.15	1.24	1.29
V (Å^3)	1848.2	1826.3	4090.8	2848.7	918.2
V/*Z* (Å^3)	231.0	228.3	255.7	237.4	229.5
Habit	Needles	Plates	Laths	Laths	Prisms

Herbstein and Schmidt, 1955

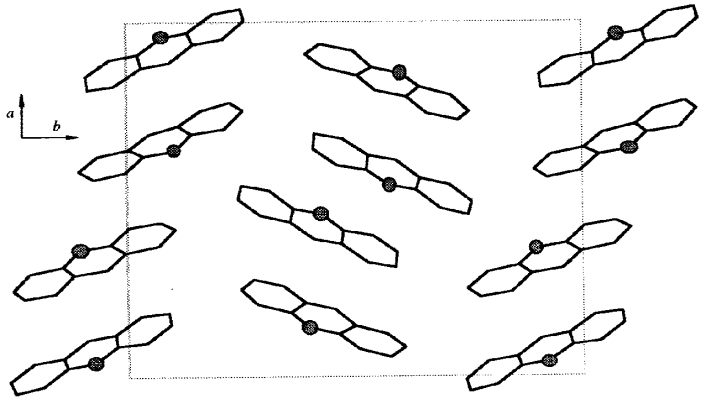


Figure 10.5 Crystal packing of acridine α-form with ● representing the nitrogen atom of the acridine ring (Phillips, 1956).

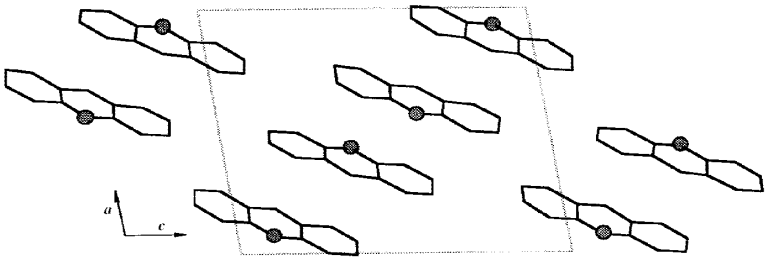


Figure 10.6 Crystal packing of acridine γ-form with ● representing the nitrogen atom of the acridine ring (Phillips *et al.*, 1960).

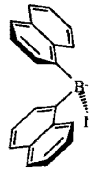
10.2 Conformational and Configurational Polymorphism

In this section, two special types of polymorphism will be discussed. *Conformational polymorphism* occurs when a molecule adopts a significantly different conformation in different crystal polymorphs (Bernstein, 1987). (The term "significantly different" is open to interpretation.) This term does not adequately describe cases where different types of isomers crystallize in different forms. Thus an additional term—*configurational polymorphism*—is defined. Configurational polymorphism exists when different

configurations (*i.e.*, *cis*,
forms.

Crystallization of *ci*
occurs whenever the pu
forms in separate crystal
The crystallization of equ
cantly more interest. W
phism can be used to is
crystalline form.

A. Tri-α-Naphthylb



tri-α-naphth
For

Brown and Sujishi (1948
with the following obser

1. Two crystalli
2. The metastab
room temper
3. The dissociat
stable form.
4. Removal of N
naphthylboro

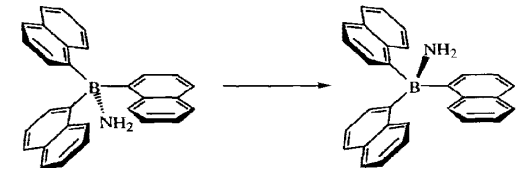
Based on these results,
above. In these forms, th
that the NH_3 is connected
and the less hindered side
ence in dissociation press
the same conformer of tri-
being the most sterically h

Unfortunately, while
formational polymorphism
The example, nevertheles
polymorph formation.

configurations (*i.e.*, *cis,trans* isomers or tautomers) crystallize in separate crystalline forms.

Crystallization of *cis,trans* isomers in different crystalline forms is well known and occurs whenever the pure isomer is crystallized. Crystallization of pure tautomeric forms in separate crystals leads to what may be called *tautomerizational polymorphism*. The crystallization of equilibrating isomers in configurational polymorphs is of significantly more interest. When this occurs, the phenomenon of configurational polymorphism can be used to isolate and study the individual isomers provided they exist in crystalline form.

A. Tri-α-Naphthylboronamine



tri-α-naphthylboronamine
Form A

tri-α-naphthylboronamine
Form B

Brown and Sujishi (1948) reported an early example of conformational polymorphism with the following observations:

1. Two crystalline forms of tri-α-naphthylboronamine are found.
2. The metastable Form A is converted to the stable Form B slowly at room temperature and rapidly above 100 °C.
3. The dissociation pressure of the metastable form is higher than the stable form.
4. Removal of NH_3 from either form gives identical samples of tri-α-naphthylboron.

Based on these results, the two forms were suggested to have structures depicted above. In these forms, the conformation of the tri-α-naphthylboron is the same except that the NH_3 is connected to the boron on the more hindered side for the unstable form and the less hindered side for the stable form. Thus these structures explain the difference in dissociation pressures of the two forms and the fact that removal of NH_3 gives the same conformer of tri-α-naphthylboron. They also explain why the unstable form, being the most sterically hindered, can be converted to the stable form.

Unfortunately, while tri-α-naphthylboron was one of the first suggestions of conformational polymorphism, it was never confirmed by X-ray crystallographic analysis. The example, nevertheless, points out some of the molecular factors that influence polymorph formation.

B. ETHYL 2-[(PHENYLMETHYL)AMINO]-2-BUTENOATE

ethyl Z-2-[(phenylmethyl)-amino]-2-butenoate

ethyl E-2-[(phenylmethyl)-amino]-2-butenoate

Infrared studies (Dabrowski, 1963) and NMR studies (Dudek and Volpp, 1963) indicate that the Schiff base ethyl 2-[(phenylmethyl)amino]-2-butenoate (ethyl β-benzylaminocrotonate) exists in configurational polymorphs; the low-melting form (mp 23 °C) has the *cis*- or *Z*-conformation and the high-melting form (mp 75–80 °C) has the *trans*- or *E*-conformation. These conformers equilibrate in solution, but upon crystallization, the configurations shown are "frozen" out in their respective polymorphic structures.

The crystal structure of the *E*-isomer has been determined in our laboratory (Shieh *et al.*, 1983). Crystals of the *E*-isomer belong to space group $P2_12_12_1$ with a = 19.655 Å, b = 5.778 Å, and c = 10.632 Å. Figure 10.7 shows the structure of this isomer, and indeed it has the structure of the *E*-isomer suggested by spectroscopic evidence (Dudek and Volpp, 1963).

The NMR and IR spectra of ethyl 2-[(phenylmethyl)amino]-2-butenoate are completely consistent with this assignment. A solution-NMR spectrum of the low-melting form (prepared by dissolving crystals at low temperature) indicates that it is indeed the *Z*-isomer (Dudek and Volpp, 1963). In this experiment the isomer present in the solid state predominates in solution because of the low temperature. In our laboratory we have studied the isomerization rate of the *Z*-isomer to the *E*-isomer at ambient temperature in DMSO where it is relatively rapid. Measurement of the rate of this reaction at various temperatures gives an activation energy of 56.9 kJ/mol.

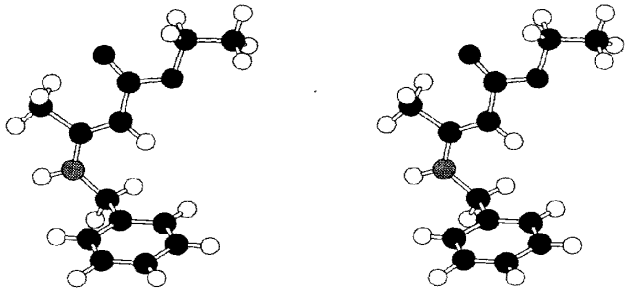
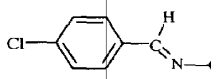


Figure 10.7 Stereoview of ethyl 2-[(phenylmethyl)amino]-2-butenoate in the high-melting *E*-isomer: H ○, C ●, N ◎, O ● (Shieh *et al.*, 1983).

10.

The energies in kJ/mol been calculated using the C employs semiempirical pote each rotamer. These calcu determined by X-ray cryst although the *E*- and Z-isome

C. 4-(*N*-CHLOROBENZYLI



The Schiff base 4-(*N*-chlc morphs (Bernstein and Hagl disordered, it can be seen tha the two polymorphs. Hen Conformational polymorphi 10.11. In the stable (triclini (orthorhombic) form the phe with respect to the H—C=I these two forms is shown ir

Molecular orbital and l for conformational polymo stein and Hagler, 1978).

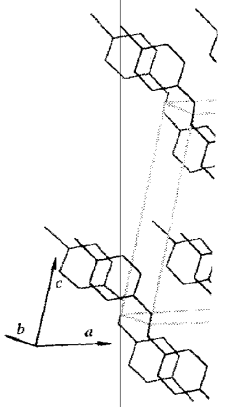
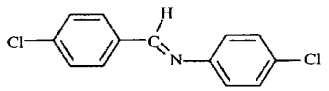


Figure 10.8 Stereoview of 4 and Hagler, 1978)

The energies in kJ/mol for a number of rotamers of the *E*- and *Z*-isomers have been calculated using the *CAMSEQ* program (Weintraub and Hopfinger, 1975) which employs semiempirical potential and electrostatic functions to calculate the energies of each rotamer. These calculations indicate that the conformation of the *E*-isomer as determined by X-ray crystallography is one of the lowest energy conformations, although the *E*- and *Z*-isomers have nearly the same energy in a vacuum.

C. 4-(*N*-Chlorobenzylidene)-4-chloroaniline



4-(*N*-chlorobenzylidene)-4-chloroaniline

The Schiff base 4-(*N*-chlorobenzylidene)-4-chloroaniline crystallizes in two polymorphs (Bernstein and Hagler, 1978). Although the structures of both polymorphs are disordered, it can be seen that the conformation of the molecule is strikingly different in the two polymorphs. Hence, these forms are termed conformational polymorphs. Conformational polymorphism of drugs is discussed in more detail later in Section 10.11. In the stable (triclinic) form, the molecules are planar, whereas in the unstable (orthorhombic) form the phenyl rings are rotated by equal but opposite amounts (24.8°) with respect to the H—C=N least-squares plane of the imine. The crystal packings of these two forms is shown in Figures 10.8 and 10.9.

Molecular orbital and lattice energy calculations were used to analyze the reasons for conformational polymorphism of 4-(*N*-chlorobenzylidene)-4-chloroaniline (Bernstein and Hagler, 1978). Quantum-mechanical calculations for a single molecule

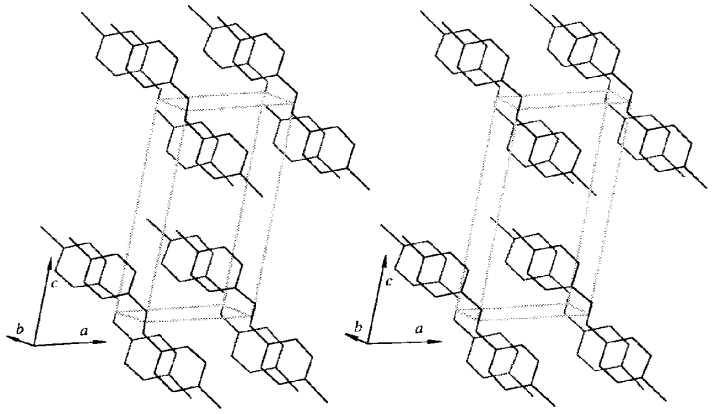


Figure 10.8 Stereoview of 4-(*N*-chlorobenzylidene)-4-chloroaniline triclinic polymorph (Bernstein and Hagler, 1978).

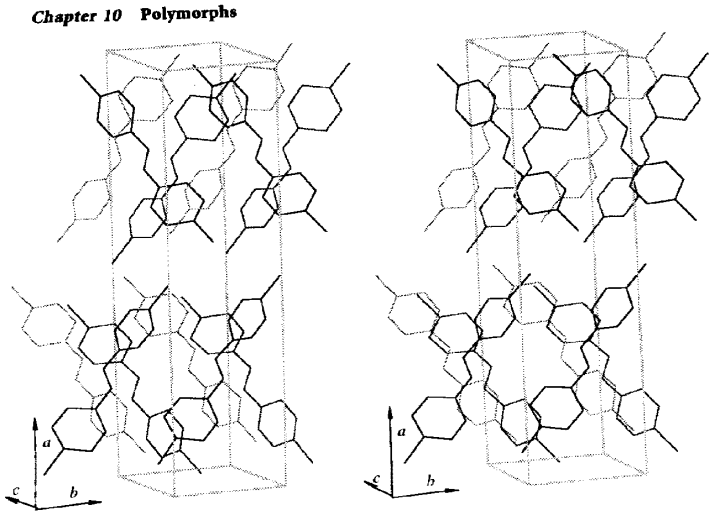
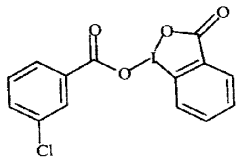


Figure 10.9 Crystal packing stereoview of 4-(*N*-chlorobenzylidene)-4-chloroaniline orthorhombic form. (Bernstein and Hagler, 1978).

showed that the nonplanar conformation was energetically favored by perhaps 2.09–6.28 kJ/mol but the lattice-energy calculations, using semiempirical potential functions, showed that the planar structure (triclinic form) gave a lower lattice energy by about 4.19 kJ/mol. These calculations explain why the triclinic polymorph is the stable crystalline polymorph even though it contains the less stable (planar) conformer.

Programs that calculate the packing energy are now available, for example, *Cerius*[2] (Molecular Simulations, Inc., 1997). These programs alone or in combination with structure elucidations based on powder diffraction data will provide new approaches to the structure analysis of materials when suitable single crystals are not available.

D. 3-Oxo-3*H*-2,1-benzoxiodol-1-yl 3-Chlorobenzoate



3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate

As part of their extensive study of the crystal chemistry of iodoperoxides, Gougoutas and Lessinger (1974) determined the crystal structure of two polymorphs of 3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate. This compound crystallizes in α- and β-forms that both belong to the monoclinic crystal system (Table 10.4).

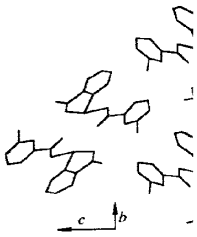


Figure 10.10 The crystal pa
(Gougoutas and

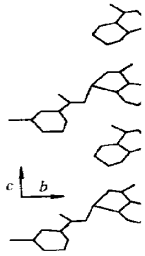


Figure 10.11 The crystal
(Gougoutas and

Table 10.4 Crystallographic
2,1-benzoxiodol-

Parameter
Space Group
a (Å)
b (Å)
c (Å)
β
Z
ρ_{calc} (g cm^{-3})
V (Å^3)

Gougoutas and Lessinger, 19

The α-form is essent
rings make an angle of a
two forms is also quite d

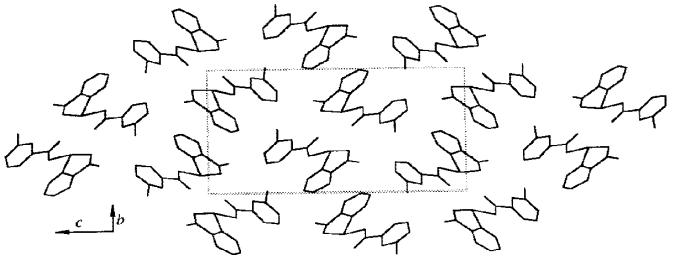


Figure 10.10 The crystal packing of 3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate α-form (Gougoutas and Lessinger, 1974).

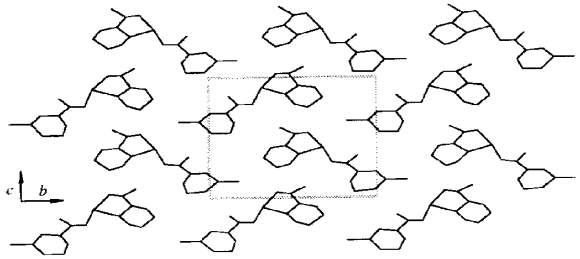


Figure 10.11 The crystal packing of 3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate β-form (Gougoutas and Lessinger, 1974).

Table 10.4 Crystallographic Unit Cell Parameters for 3-Oxo-3*H*-2,1-benzoxiodol-1-yl 3-Chlorobenzoate

Parameter	α-Form	β-Form
Space Group	$P2_1/n$	Pc
a (Å)	6.376	5.057
b (Å)	10.547	13.035
c (Å)	20.066	10.339
β	92.0°	99.5°
Z	4	2
ρ_{calc} (g cm^{-3})	1.984	2.009
V (Å^3)	1348.6	672.2

Gougoutas and Lessinger, 1974.

The α-form is essentially planar in the crystal while in the β-form the two phenyl rings make an angle of approximately 55° with each other. The crystal packing of the two forms is also quite different as shown in Figures 10.10 and 10.11. These two

forms have different solid-state infrared spectra (see Figure 10.12), as expected since the molecule is in different conformation in the two crystal forms.

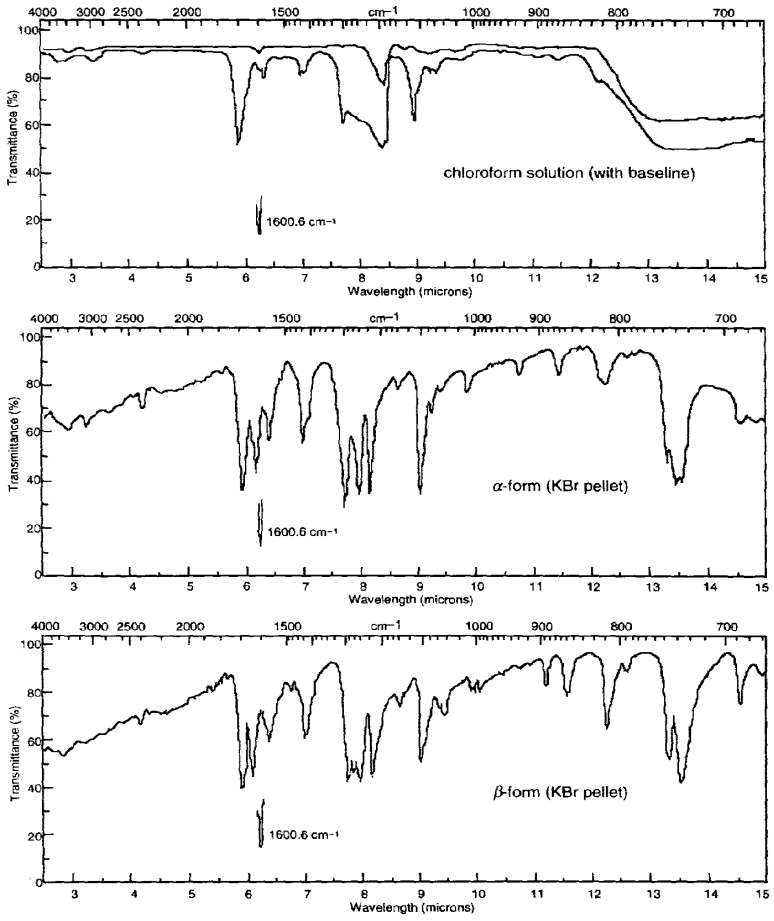
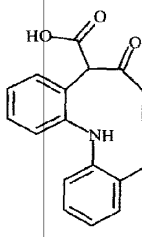


Figure 10.12 Infrared spectra of 3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate (Gougoutas and Lessinger, 1974).

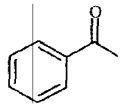
E. TAUTOMERIZATION



keto for
3-(4-chlorop
2-[2-(2-(methoxyca
amino)phenyl]-3-oxo

Schulenberg (1968) ha
phenyl)amino)phenyl]-3
form has a melting point
consistent with the
phenyl)amino)phenyl]-3
110–122 °C and upon di
(4-chlorophenyl)-3-hydr
acid. Addition of triethy
ing 70% of the keto forn

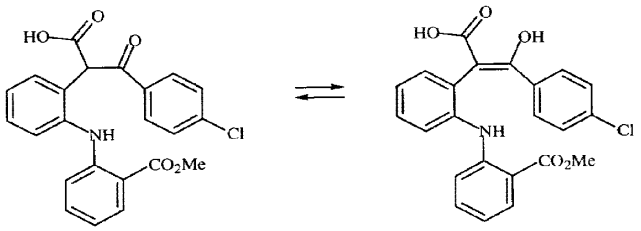
Although the crysta
mined, this study illustr
containing an individual
phism (*cf.* p. 143).



E-conformer of t
1,3-diphenylprop

Several other case
enol of 1,3-diphenylpro
the *E*-isomer and the ot
there are numerous exa
isomer or tautomer out
(1972).

E. Tautomerizational Polymorphism

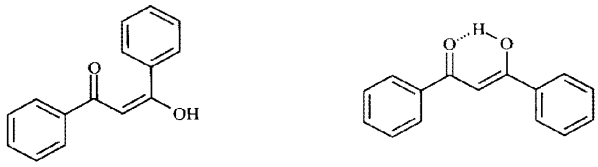


keto form
3-(4-chlorophenyl)-2-[2-(2-(methoxycarboxyphenyl)-amino)phenyl]-3-oxopropanoic acid

enol form
3-(4-chlorophenyl)-3-hydroxy-2-[2-(2-(methoxycarboxyphenyl)-amino)phenyl]propenoic acid

Schulenberg (1968) has reported that 3-(4-chlorophenyl)-2-[2-(2-(methoxycarboxyphenyl)amino)phenyl]-3-oxopropanoic acid crystallizes in two tautomeric forms. One form has a melting point of 93–99 °C that upon dissolution in $CDCl_3$ gave NMR spectra consistent with the keto form, 3-(4-chlorophenyl-2-[2-(2-(methoxycarboxyphenyl)amino)phenyl]-3-oxopropanoic acid. The other form had a melting point of 110–122 °C and upon dissolution gave NMR spectra consistent with the enol form, 3-(4-chlorophenyl)-3-hydroxy-2-[2-(2-(methoxycarboxyphenyl)amino)phenyl]propenoic acid. Addition of triethylamine to either solution gave an equilibrium mixture containing 70% of the keto form and 30% of the enol form.

Although the crystal structures of the keto and enol forms have not been determined, this study illustrates a case in which two different crystalline forms exist, each containing an individual tautomer. This situation is termed tautomerizational polymorphism (*cf.* p. 143).



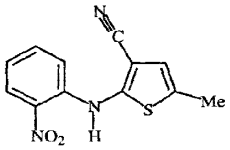
E-conformer of the enolate of
1,3-diphenylpropane-1,3-dione

Z-conformer of the enolate of
1,3-diphenylpropane-1,3-dione

Several other cases of tautomerizational polymorphism exist. For example, the enol of 1,3-diphenylpropane-1,3-dione crystallizes in two forms. One form contains the *E*-isomer and the other contains the *Z*-isomer (Eistert *et al.*, 1952). In addition, there are numerous examples of the crystallization process freezing one configurational isomer or tautomer out of solution. These cases are reviewed by Curtin and Engelmann (1972).

F. Polychromism

One of the most striking differences in physical properties among polymorphs is **polychromism** (*i.e.*, different colors). Polychromism has been reported for only a limited number of cases. Dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate, for example, crystallizes in yellow, light-yellow, and white polymorphs (Byrn *et al.*, 1972; Fletton *et al.*, 1986; Yang *et al.*, 1989; Richardson *et al.*, 1990). The colors of these three polymorphs are attributed to differences in orientation of the carboxylate group with respect to the aromatic ring (see also Sections 10.7E and 20.1A).



5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile
(ROY)

5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile is a dramatic example of polychromism. Crystallization of this compound from ethanol yields a mixture of yellow and red prisms, whereas crystallization from methanol yields orange needles; hence the alias ROY for the red, orange, and yellow forms (Borchardt, 1997). Crystals of the red form also appear to be **pleochroic**, displaying both red and orange colors under polarized illumination.

The three polymorphs are free of solvent and stable at room temperature. The red, orange, and yellow forms are similar in energy with melting points of 106.2, 114.8, and 109.8 °C, respectively (Yu, 1998). The red and orange forms undergo solution-mediated transformation to the yellow form at room temperature, indicating the latter is the most stable at room temperature. The yellow and orange forms are related enantiotropically, with yellow being more stable at low temperature. Between room temperature and the melting point, the red form is always less stable than the yellow form. The heats of melting, as measured by DSC, confirmed these stability relationships. Solid-state phase transitions from red to yellow and from red to orange have been observed between 70—90 °C in a solvent free environment. The transition from red to yellow (at temperatures greater than 90 °C) results in a dramatic change in color but no apparent change in crystal morphology, whereas the transition from red to orange leads to the growth of orange needles from the initial red crystals.

The crystal structures of red, orange, and yellow forms have been determined by single-crystal X-ray diffraction and show that the molecule adopts a dramatically different conformation in each of the forms. Subsequent studies show that these different conformations are the reasons for the different colors. Hydrogen bonding in the polymorphs is exclusively intramolecular—between the adjacent amine and nitro substituents. The heteroatom-to-heteroatom distances of the hydrogen bond in red, orange, and yellow are 2.636(2), 2.607(3), and 2.625(3) Å, respectively. The conformations of the molecule in the three polymorphs are significantly different (Figure 10.13). In the yellow and orange forms, the nitro group is essentially co-planar with the phenyl ring, whereas in the red form it is twisted out-of-plane by 18°. The color of the polymorphs may be related to the degree of electron delocalization, which is related to the angle between the planes of the phenyl and the thiophene moieties (red 46°,

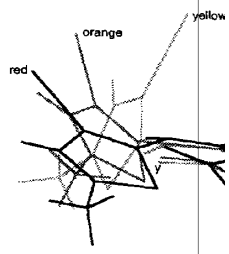


Figure 10.13 Conformations
crystalline form

orange 54°, and yellow 1(
order of the expected w
Section 8.1). Studies ha
direct result of the differer
1998; Yu, 1998). The ol
those calculated from the
^{13}C CP/MAS solid-st
tinguish the polymorphs.
reported for polymorphic
shifts of C3 (the carbon in
97.9, 105.2, and 109.3
covering a range of 11
104.41 ppm in solution.)
red form with respect to t
conjugation effect. Smitl
(total suppression of spin
shift anisotropy (CSA) o
increases in magnitude by
ric as the coplanar angle
electrons between the tw
site.

This parallels the re
quency are 2211, 2223,
tively (see Section 8.1).
the red form from a highe
vations confirm the signi
pronounced color change

A number of deriva
nitrile were synthesized
nitrophenylaminothiophe
Me) crystallized in three
the gold form were un
polymorph" class. How

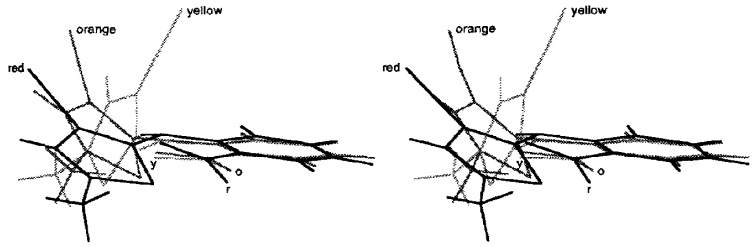


Figure 10.13 Conformations of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile in three crystalline forms.

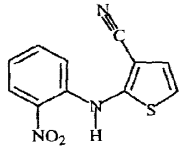
orange 54°, and yellow 106°). The order of these angles appears to correlate with the order of the expected wavelengths of absorption by the colored polymorphs (see Section 8.1). Studies have shown that the different colors of the polymorphs are a direct result of the difference in molecular conformation (Borchardt, 1997; Smith *et al.*, 1998; Yu, 1998). The observed XRPD patterns of the three polymorphs agree with those calculated from the single-crystal structures.

^{13}C CP/MAS solid-state NMR, solid-state FT-IR, and XRPD can be used to distinguish the polymorphs. The observed spectral differences are among the largest reported for polymorphic organic compounds. For example, the ^{13}C NMR chemical shifts of C3 (the carbon in the thiophene ring to which the nitrile group is attached) are 97.9, 105.2, and 109.3 ppm for the red, orange, and yellow forms, respectively, covering a range of 11.4 ppm. (For comparison, the chemical shift of C3 is 104.41 ppm in solution.) This indicates an increase in the electron density of C3 in the red form with respect to the yellow and orange forms, possibly a result of an increased conjugation effect. Smith and coworkers (1998) have used a two-dimensional TOSS (total suppression of spinning sidebands) pulse sequence to investigate the chemical-shift anisotropy (CSA) of C3. These studies show that the extent of the CSA for C3 increases in magnitude by 30 ppm and the line shape appears to become more asymmetric as the coplanar angle increases. This was taken to reflect a greater transfer of π electrons between the two ring systems and hence a greater electron density at the C3 site.

This parallels the results from IR spectroscopy in which the nitrile stretching frequency are 2211, 2223, and 2231 cm^{-1}, for the red, orange, and yellow forms, respectively (see Section 8.1). This shift is indicative of the decreased nitrile bond strength in the red form from a higher degree of conjugation with the aromatic ring. These observations confirm the significant changes in the electronic structure, as demonstrated by pronounced color changes among different polymorphs.

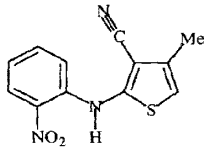
A number of derivatives of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile were synthesized in order to determine the extent of the color polymorphism of nitrophenylaminothiophenes. 2-[(2-Nitrophenyl)amino]-3-thiophenecarbonitrile (NorMe) crystallized in three forms: red, orange, and gold. Numerous attempts to obtain the gold form were unsuccessful thus placing the gold from in the "disappearing polymorph" class. However, crystallization of a newly synthesized lot of NorMe gave

the gold form once again only to disappear when the material was subjected to further crystallization and handling. As with other disappearing polymorphs, this behavior is due to the presence of impurities and the fact that the gold polymorph is unstable in the presence of seeds of the other forms (Dunitz and Bernstein, 1995).

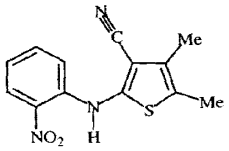


2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (NorMe)

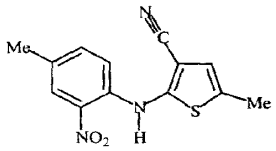
The XRPD patterns of the three forms of NorMe are different from the parent compound. The crystal structure of the red form NorMe was determined (Borchardt, 1997). The red form is nearly coplanar further substantiating the concept that the red color is associated with planarity. The IR spectra of the NorMe polymorphs are quite similar to ROY. The red form has a nitrile stretching absorption at 2210 cm^{-1}, the orange is a 2222 cm^{-1}, and the yellow at 2230 cm^{-1}.



4-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (4-Me)



4,5-dimethyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (4,5-DiMe)



5-methyl-2-[(4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile (4'-Me)

The conformation of the red form of 4-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (4-Me) is the most coplanar of the structures determined (see Figure 10.14). 4,5-Dimethyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (4,5-DiMe) crystallized in two polymorphs: red and orange. As with the previous derivatives, the conformation of the red form as determined by single-crystal X-ray methods is rather coplanar (see Figure 10.14). 5-Methyl-2-[4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile (4'-Me) was crystallized in red, dark red, light red, and orange forms. Only the red form gave crystals suitable for structure determination. As with the previous derivatives, this red form has a nearly coplanar conformation. Figure 10.14 compares the conformation of the various red forms in this nitrophenylaminothiophene series. In all cases, the red form has the most coplanar conformation of the polymorphs. This further supports the conclusion that the conformation of the nitrophenylaminothiophene determines the color of the polymorph.

Griesser and He (1998) have carried out a preliminary study of the solubilities and interconversions of the four forms of 4'-Me and found that all four forms are within 4 kJ/mol or less of each other in energy. These studies allowed the development of the energy–temperature diagram (see Section 5.2) shown in Figure 10.15. Such diagrams

are extremely useft
polymorphs.

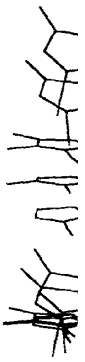


Figure 10.14 Stereovie
the thiop
Hydroger

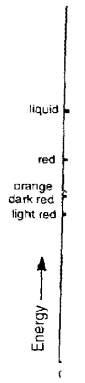


Figure 10.15 Energy–t
phenyl)a

are extremely useful in visualizing the energy–temperature relationships between polymorphs.

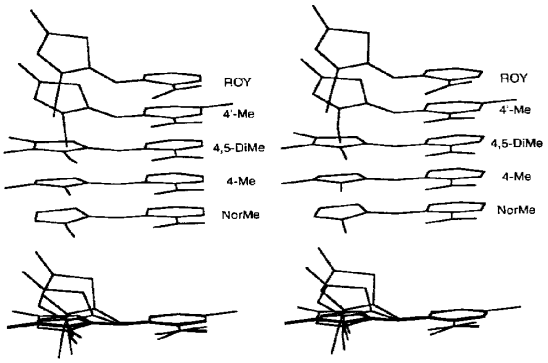


Figure 10.14 Stereoview showing a comparison (both stacked and overlayed) of the conformations of the thiophene and phenyl rings in the nitrophenylaminothiophene series red forms. Hydrogens were omitted for clarity.

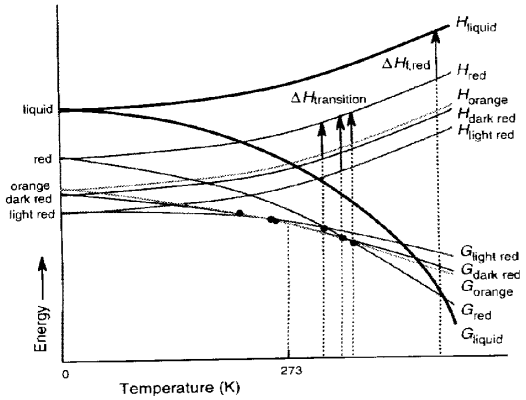


Figure 10.15 Energy–temperature diagram for the four forms of 5-methyl-2-[4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile (Griesser and He, 1998).

10.3 SULFONAMIDES

The polymorphism of sulfonamides has been investigated and reviewed by Kuhnert-Brandstätter (1971). These studies were carried out using microscopy on a Kohfler hot stage (see Section 4.4). Sulfonamides exhibited behavior expected of polymorphs, including successive melting points as the temperature is raised and changes in color under crossed Nicol gratings (crossed polarizers). Table 10.5 summarizes the results of Kuhnert-Brandstätter's (1971) studies on these compounds.

Although all of these studies have not been confirmed by crystallographic data, the crystal structures of several polymorphs of sulfonamides have been determined and will

Table 10.5 Polymorphism of Sulfonamides and Related Compounds[a]

Compound	Melting Point of Form (°C)						
	I	II	III	IV	V	VI	VII
Acetazolamide	258-260	248-250					
Acetyl Sulfisoxazole	190-195	176-177	173-174				
Chlorthalidone	212-224	188-189					
Clofenamide	210-215	203-207	183-185	168-170			
Diphenylmethane-4,4'-disulfonamide	185-187	172-174					
Mafenide HCl	250-260	235-240	220-225	210-212			
4'-(Methylsulfamoyl)-sulfanilanilide	148-151	144-146					
Phthalylsulfathiazole	260-274	230					
Sulfachlorpyridazine	196-197	178-181					
Sulfadicramide	176-180	174-176					
Sulfadimethoxine	194-198	176-177	156-158				
Sulfaethidole	188	181	149				
Sulfaguanidine	187-191	174-176	143-145				
Sulfameline	210-212	197-199	181-183	179-181	176-177	155	
Sulfamerazine	235-238	228					
Sulfamethazine	206-208	199	178	~175			
Sulfamethizole	209	193					
Sulfamethoxazole	169	168	166				
Sulfamethoxypyridazine	180-182	158-159	153-154				
Sulfamidochrysoidine	224-228	217-219	212				
Sulfamoxole	200-204	188-195	177-180				
Sulfanilamide	165	156	153				
N-Sulfanilyl-3,4-xylamide	215-218	208	203	196			
Sulfapyridine	192	185	179	176	174	167	149
Sulfathiazole	202	175	162	158			
Sulfathiourea	178-180	168-171					
Sulfatriazine	158-166	132-135					
Sulfazamet	182-185	176-178					
Sulfisoxazole	190-195	131-133					
Tolbutamide	127	117	106				

[a] Kuhnert-Brandstätter (1971).

be discussed next. In gen
polymorphs. Thus, in th
ble for polymorphism.

A. SULFANILAMIDE

NH

Sulfanilamide exists in th
ters shown in Table 10.6
(O'Conner and Maslen,
phenyl rings. In each sta
···amino···sulfonamide··
substituent in each stack.

The crystal packing
the α-form (Allcaume an
but the order of the s
···amino···sulfonamide··
stack.

The crystal packing
10.18 appears, in genera
sulfonamide amino grou
successive rings in a st
which resembles that of t

The density of the
(see Table 10.6). The pc
sulfanilamide have been
diagram constructed. It i
group is similar in all for
plane of the phenyl ring
relationships between th
depicted in Figures 10.1
10.19.

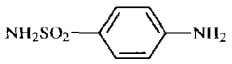
Table 10.6 Crystallographi

Parameter	
Space group	
a (Å)	
b (Å)	
c (Å)	
β	
Z	
ρ_{calc} (g cm^{-3})	
V (Å^3)	

O'Conner and Maslen, 1965

be discussed next. In general, the conformations of the drug are similar in the different polymorphs. Thus, in these cases, differences in crystal packing are mainly responsible for polymorphism.

A. Sulfanilamide



sulfanilamide

Sulfanilamide exists in three crystalline forms which have the crystallographic parameters shown in Table 10.6. The α-form has the crystal packing shown in Figure 10.16 (O'Conner and Maslen, 1965). The crystal packing of this form contains layers of phenyl rings. In each stack, the order of the substituent groups on successive rings is ···amino···sulfonamide···sulfonamide···amino···, etc., resulting in alternating pairs of substituent in each stack.

The crystal packing of the β-form shown in Figure 10.17 is quite different from the α-form (Alleaume and Decap, 1965). There are, again, columns of phenyl rings but the order of the substituent groups on successive rings is ···sulfonamide··· ···amino···sulfonamide···amino···, etc., resulting in alternating substituents in the stack.

The crystal packing of the γ-form (Alleaume and Decap, 1966) shown in Figure 10.18 appears, in general, to be similar to the α-form with layers of phenyl rings and sulfonamide amino groups. In these columns, the order of substituent groups on successive rings in a stack is ···amino···sulfonamide···amino···sulfonamide···, etc., which resembles that of the β-form.

The density of the β-form (the most thermodynamically stable form) is greatest (see Table 10.6). The polymorphic interconversions and thermodynamic properties of sulfanilamide have been investigated by Burger (1973a–b) and an energy-temperature diagram constructed. It is interesting to note that the conformation of the sulfanilamide group is similar in all forms, with the nitrogen atom being the atom furthest out of the plane of the phenyl ring. A comparison of the α-, β-, and γ-forms showing the relationships between the arrangement of the substituents in successive molecules depicted in Figures 10.16, 10.17, and 10.18 is illustrated in a stereoview in Figure 10.19.

Table 10.6 Crystallographic Data for the Polymorphs of Sulfanilamide

Parameter	Form α	Form β	Form γ
Space group	*Pbca*	$P2_1/c$	$P2_1/c$
a (Å)	5.65	8.98	7.95
b (Å)	18.51	9.01	12.95
c (Å)	14.79	10.04	7.79
β	90.00°	111.43°	106.50°
Z	8	4	4
ρ_{calc} (g cm^{-3})	1.47	1.51	1.49
V (Å^3)	1547.1	755.2	768.7

O'Conner and Maslen, 1965

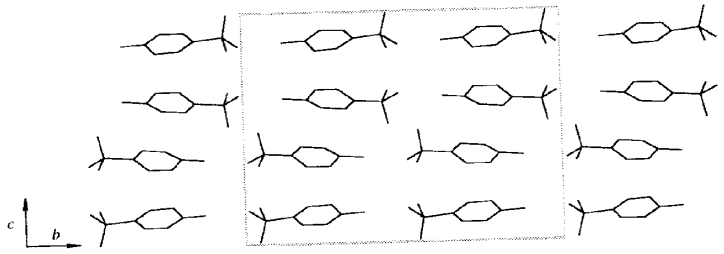


Figure 10.16 Molecular packing of the α-form of sulfanilamide (O'Conner and Maslen, 1965).

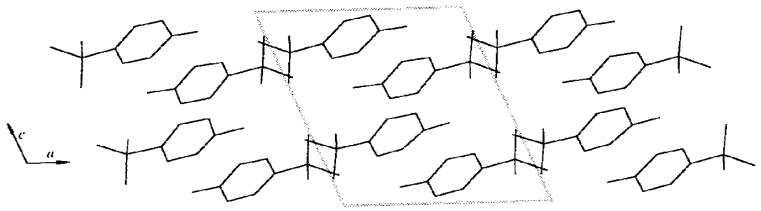


Figure 10.17 The crystal packing of the β-form of sulfanilamide (Alleaume and Decap, 1965).

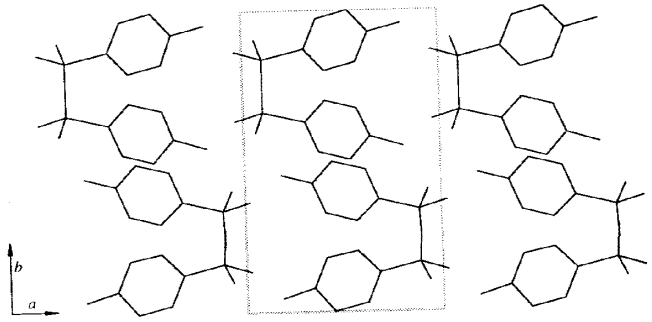


Figure 10.18 Crystal packing of the γ-form of sulfanilamide (Allcaume and Decap, 1966).

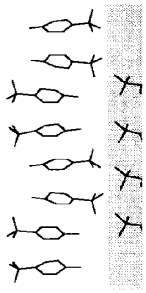


Figure 10.19 Stereovie
α-, β-, ar

B. SULFATHIAZOLE

NH_2

Table 10.7 indicates
(1983) have studied
the four polymorphs.
dynamically stable at
of all three polymorp
mide group is the at
This is in marked si
molecule in all three
between these forms

Table 10.7 Crystallogr

Parameter
Space Group
a (Å)
b (Å)
c (Å)
β
Z
ρ_{meas} (g cm^{-3})
V (Å^3)
Habit
Melting point
Transition point

a Kruger and Gafner, 19

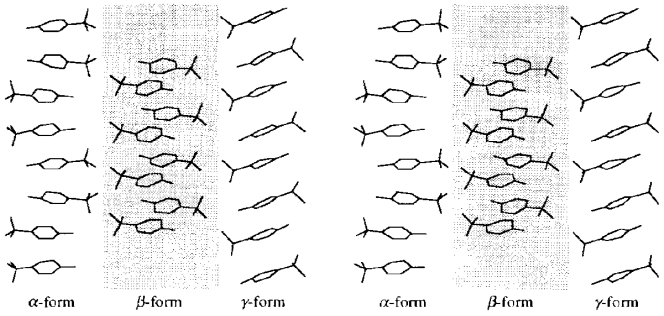
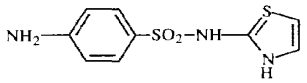


Figure 10.19 Stereoview showing the molecular arrangement of sulfanilamide columns in the α-, β-, and γ-forms.

B. Sulfathiazole



sulfathiazole

Table 10.7 indicates that sulfathiazole exists in four polymorphs. Burger and Dialer (1983) have studied this system and have produced an energy-temperature diagram of the four polymorphs. Form I is the least stable of the four forms; Form III is thermodynamically stable at room temperature. Figures 10.20–10.22 show packing drawings of all three polymorphs of sulfathiazole. It is obvious that the nitrogen of the sulfonamide group is the atom that is the greatest distance from the plane of the phenyl ring. This is in marked similarity to sulfanilamide. In addition, the conformation of the molecule in all three forms is very similar. The major crystallographic difference between these forms is the nature and type of hydrogen bonds.

Table 10.7 Crystallographic Parameters for the Polymorphs of Sulfathiazole

Parameter	Form I[a]	Form II[b]	Form III[a]
Space Group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	10.554	8.235	17.570
b (Å)	13.220	8.550	8.574
c (Å)	17.050	15.558	15.583
β	108.06°	93.67°	112.93°
Z	8	4	8
ρ_{meas} (g cm^{-3})	1.50	1.55	1.57
V (Å^3)	2261.7	1093.2	2162.0
Habit	Rods	Hexagonal prisms	Hexagonal plates
Melting point	200-202	200-202	173-175 (or 200-202)
Transition point	...	173-175	173-175

a Kruger and Gafner, 1971a. *b* Kruger and Gafner, 1971b.

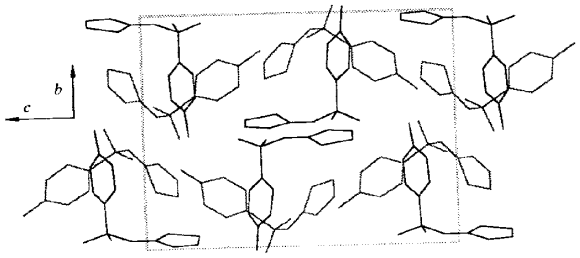


Figure 10.20 Crystal packing of sulfathiazole Form I (Kruger and Gafner, 1971a).

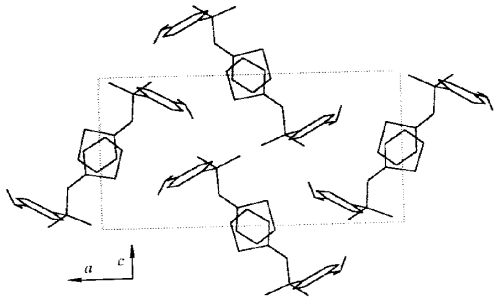


Figure 10.21 Crystal packing of sulfathiazole Form II (Kruger and Gafner, 1971b).

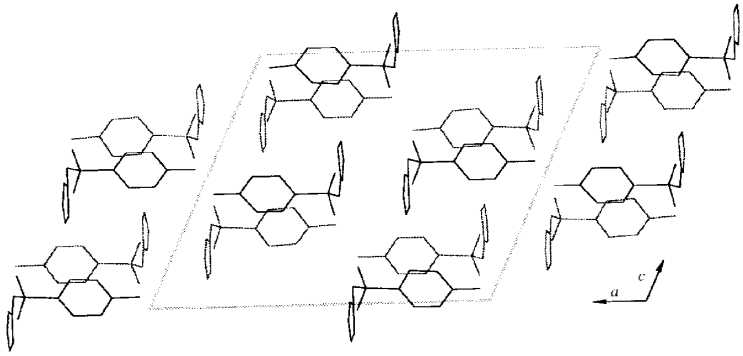


Figure 10.22 Crystal packing of sulfathiazole Form III (Kruger and Gafner, 1971a).

Table 10.8 Dissolution Rate

Temperature (°C)	Form (mg cm^{-2}
59.1	0.18
48.8	0.10
39.4	0.05
29.6	0.03
24.1	0.02
20.4	0.02

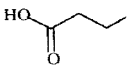
Milosovich, 1964.

The crystallographic
morphs of sulfathiazole; I
polymorphism of this dru
Kuhnert-Brandstätter rep
stage microscopy. In the
lory (1967), and Higuchi
Shenouda (1970) also ir
Mesley (1971) using IR,
of three polymorphs. He
with mixtures of the three
these findings and charac
microscopy, solubility, a

To avoid prolonged
involve separation of hal
each habit. X-ray powe
crystal X-ray data and
approach would make su

The physical propert
and Eisen, 1971; Miloso
the dissolution rate under
results in Table 10.8 sho
solubility than Form I. T
II should have a slower d

C. Succinylsulfathi



In early studies of succi
and Higuchi, 1963) a lar

Table 10.8 Dissolution Rate and Solubility of Forms I and II of Sulfathiazole

Temperature (°C)	Dissolution Rate		Solubility	
	Form I ($mg\ cm^{-2}\ sec^{-1}$)	Form II ($mg\ cm^{-2}\ sec^{-1}$)	Form I (g/1000 gm)	Form II (g/1000 gm)
59.1	0.185	0.239	31.5	40.7
48.8	0.102	0.145	19.8	28.1
39.4	0.0598	0.0913	14.0	21.4
29.6	0.0355	0.0597	9.93	16.7
24.1	0.0237	0.0413	8.15	14.2
20.4	0.0201	0.0371	7.10	13.1

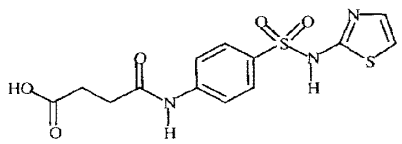
Milosovich, 1964.

The crystallographic data clearly established the existence of at least four polymorphs of sulfathiazole; however, at this point, it is worthwhile to review studies of the polymorphism of this drug using other techniques. As reported earlier in this section, Kuhnert-Brandstätter reported that sulfathiazole has four polymorphs based on hot stage microscopy. In the 1960's, three groups of workers [Milosovich (1964), Guillory (1967), and Higuchi *et al.* (1967)] reported only two polymorphs. DSC work by Shenouda (1970) also indicated the existence of only two polymorphs. Studies by Mesley (1971) using IR, DSC, and X-ray powder diffractometry showed the existance of three polymorphs. He suggested that most of the earlier workers had been dealing with mixtures of the three polymorphic forms. Burger and Dialer (1983) reinvestigated these findings and characterized four polymorphs by IR-spectroscopy, DSC, thermomicroscopy, solubility, and density.

To avoid prolonged confusion of this sort, studies of unfamiliar systems should involve separation of habits under a microscope and then crystallographic studies of each habit. X-ray powder diffraction patterns should be calculated from the single crystal X-ray data and compared with the experimentally observed XRPDs. This approach would make sure that mixtures of polymorphs are not involved.

The physical properties of sulfathiazole Forms I and II have been studied (Sunwoo and Eisen, 1971; Milosovich, 1964). These studies, which used a flow cell, measured the dissolution rate under conditions where Form II did not transform to Form I. The results in Table 10.8 show that Form II has a significantly higher dissolution rate and solubility than Form I. This is not consistent with the densities which predict that Form II should have a slower dissolution rate and be less soluble than Form I.

C. Succinylsulfathiazole



succinylsulfathiazole

In early studies of succinylsulfathiazole (Armour Research Foundation, 1949; Shefter and Higuchi, 1963) a large number of different crystal forms were found. The studies

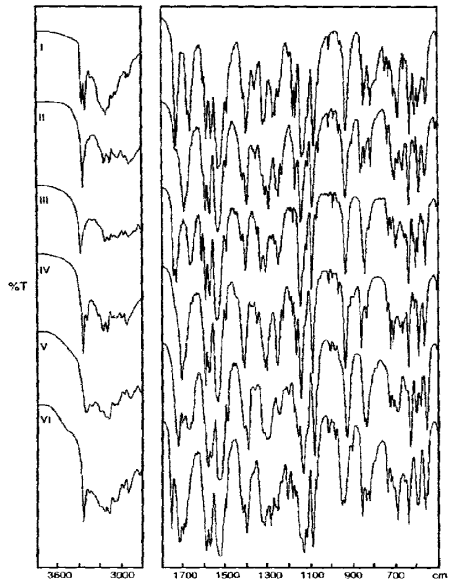


Figure 10.23 IR spectra (KBr pellets) of the unsolvated crystal forms of succinylsulfathiazole (Burger and Griesser, 1989).

by Burger and Griesser (1989; 1991) provide the most complete summary of the solid-state behavior of this compound. As summarized in Table 10.9, they found that succinylsulfathiazole crystallized in six anhydrous crystal forms, three polymorphic monohydrates, as well as an acetone solvate and an *n*-butanol solvate. These different crystal forms were prepared by a variety of methods involving crystallization from different solvents and by drying the different solvates. For example, Form IV was prepared by drying the acetone solvate at 150 °C. Form VI was prepared by dehydration of one of the monohydrates in vacuum at 100 °C. The three monohydrates are termed "polymorphic" because they contain the same chemical composition (compound and solvent) but exist in different crystal structures. The IR spectra of all eleven crystal forms were measured in KBr pellets. The polymorphs and solvates were also characterized by thermal microscopy and DSC. Figure 10.23 shows the IR spectra of the six unsolvated crystal forms and Figure 10.24 shows the DSC thermograms of these polymorphs. The IR spectra of the different crystal forms are different and indicate that these are different polymorphs. The DSC thermograms of Forms I through V show destinctive differences in melting points. The DSC thermogram of Form VI shows an incongruent melting process. However, IR appears to be better than DSC for distinguishing these forms. Figure 10.25 shows the X-ray powder diffraction patterns of the six crystal forms which are all different and confirm the IR results.

Table 10.9 Comparisor of Succinyl

Form	Stability (20 °C)	
I	Stable[a]	Suspens solv
II	< I	Evapor EtO
III	< II	Dehydr °C
IV	< III	Suspens EtO
V	< IV	Anneali 160
VI	< V	Dehydra
H_I	Stable	Suspens water
H_{II}	< H_I	Crystalli
H_{III}	< H_{II}	Suspens for 1

a in the absence of water. water at 20 °C. (Burger a

Figure 10.24 DSC therr Griesser, 1

Table 10.9 Comparison of the Physical Properties of the Polymorphic Anhydrates and Monohydrates of Succinylsulfathiazole

Form	Stability (20 °C)	Preparation	MP[b] (°C)	MP[c] (°C)	1st Peak in IR (cm^{-1})	Density (g cm^{-3})	Solubility[d] Ratio to H_I
I	Stable[a]	Suspension of acetone solvate in EtOAC	204	205	3361	1.592	3.24
II	< I	Evaporation of absolute EtOH solution	195-199	195	3360	1.535	5.69
III	< II	Dehydration of H_I at 100 °C	189-194	188-191	3372	1.571	6.15
IV	< III	Suspension of V or VI in EtOAC	187-191	189	3338	1.518	9.26
V	< IV	Annealing of I at 160 °C	182-185	182-187	3330	1.488	~12.7
VI	< V	Dehydration of H_{II}	139-143	135-138	3350	1.463	—
H_I	Stable	Suspension of any form in water	123-125		3480 (OH) 3320 (NH)	1.527	1.00
H_{II}	< H_I	Crystallization from water	~110		3500 (OH) 3350 (NH)	1.520	1.81
H_{III}	< H_{II}	Suspension of III in water for 15 min	105		3450 (OH) 3335 (NH)		

a in the absence of water. *b* by thermomicroscopy. *c* by differential scanning calorimetry (DSC). *d* in water at 20 °C. (Burger and Griesser, 1991)

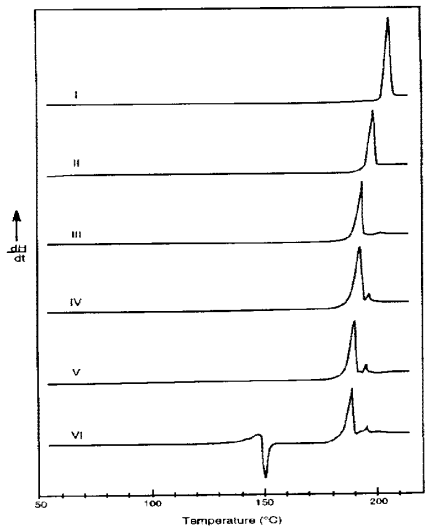


Figure 10.24 DSC thermograms of the unsolvated crystal forms of succinylsulfathiazole (Burger and Griesser, 1989).

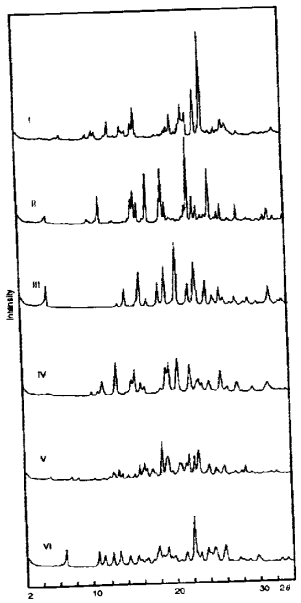


Figure 10.25 X-ray powder diffraction patterns of the six unsolvated crystal forms of succinylsulfathiazole (Burger and Griesser, 1989).

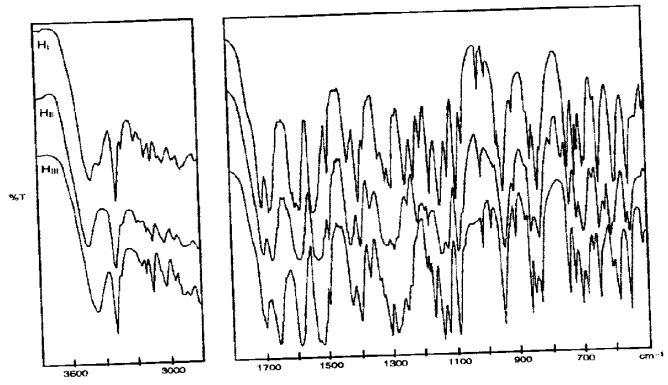


Figure 10.26 IR spectra of the polymorphic monohydrates of succinylsulfathiazole (Burger and Griesser, 1989).

Figure 10.26 shows
sulfathiazole. The IR sp
are different polymorph
tion patterns shown in F

The physical stabili
of succinylsulfathiazole
Figure 10.28. The mo
variety of methods used
crystal forms have diff
high humidity. The solu

Figure 10.27 X-ray powde
(Burger and

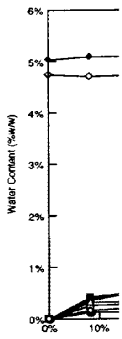


Figure 10.28 Water vapor
(Burger and

Figure 10.26 shows the IR spectra of the polymorphic monohydrates of succinylsulfathiazole. The IR spectra of these materials are also different establishing that these are different polymorphs. This conclusion is confirmed by the X-ray powder diffraction patterns shown in Figure 10.27.

The physical stability, water sorption, and solubility of the different crystal forms of succinylsulfathiazole have also been studied and are summarized in Table 10.9 and Figure 10.28. The most stable forms are Form I and hydrate H_I. In addition, the variety of methods used to prepare the different crystal forms are noted. The different crystal forms have differences in hygroscopicity and interconvert in the presence of high humidity. The solubilities of the different forms are also different. Most notable

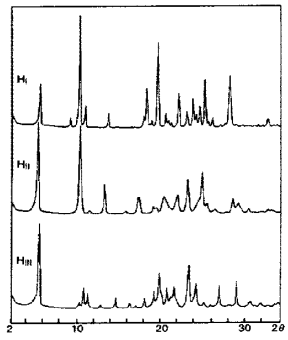


Figure 10.27 X-ray powder diffraction patterns of the three monohydrates of succinylsulfathiazole (Burger and Griesser, 1989).

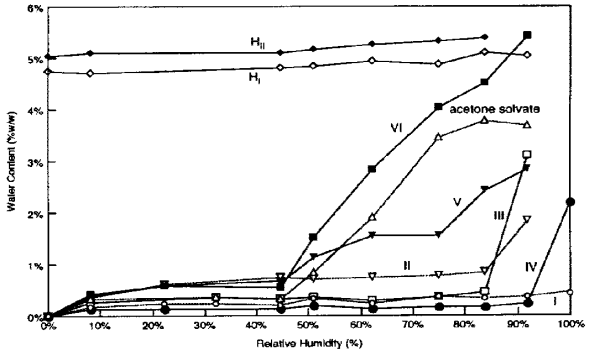


Figure 10.28 Water vapor sorption isotherms of the different crystal forms of succinylsulfathiazole (Burger and Griesser, 1991).

is that the differences in solubility among the anhydrate crystal forms is as large as a factor of 4 and that differences in solubility between anhydrate and hydrate crystal forms are as large as a factor of 12. This is one of many cases where anhydrate crystal forms have significantly higher solubilities than the hydrate.

Figure 10.28 shows the water vapor sorption isotherms for the different succinylsulfathiazole crystal forms. It is clear that some of the anhydrate forms absorb water relatively easily; furthermore, this data shows that the metastable forms are more hygroscopic.

Figure 10.29 shows the dissolution behavior of the different crystal forms of succinylsulfathiazole in buffer solution at pH 1.20 at 20 °C. It is clear that at equilibrium many of the anhydrates recrystallize and approach the solubility of the hydrates as might be expected. Figure 10.30 shows a van't Hoff plot for four of the crystal forms of succinylsulfathiazole. These curves do not cross in the temperature ranges studied and this indicates, in connection with the thermodynamic data, that all of the forms are monotropically related. Recall that monotropic forms retain the order of stability at all temperatures (see Section 5.2).

Figure 10.31 shows a scheme which illustrates the interconversion of the different crystal forms and methods to prepare each form. This figure illustrates how complicated interconversion of the different crystal forms can be. The van't Hoff plot clearly shows that the transformation of the more soluble form into the less soluble hydrate will occur at room temperature. This indicates the complications that can arise by relying on just one study and shows that several different approaches should be used to try to understand the interconversion of different crystal forms.

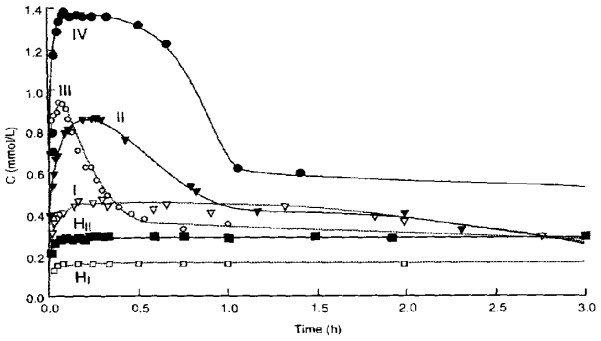


Figure 10.29 Dissolution behavior of the different crystal forms of succinylsulfathiazole in buffer solution, pH 1.3 at 20 °C (Burger and Griesser, 1991).

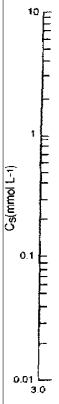


Figure 10.30 Van't Hoff pl
pH 1.3 (Burge

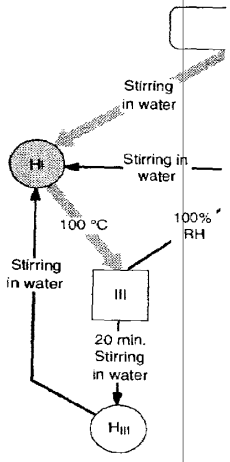


Figure 10.31 Diagram illu
produce the
mark paths w
most stable f

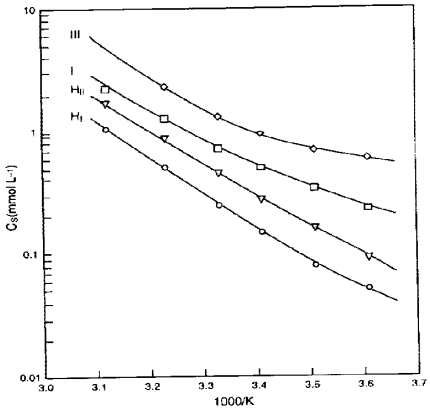


Figure 10.30 Van't Hoff plot of the solubility of four of the crystal forms of succinylsulfathiazole at pH 1.3 (Burger and Griesser, 1991).

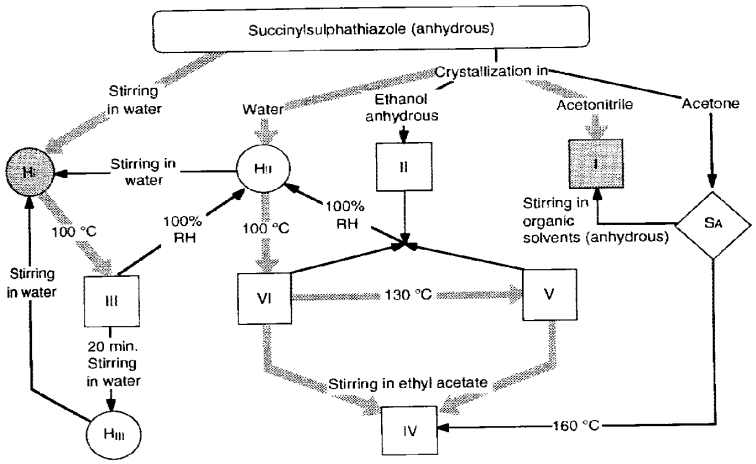
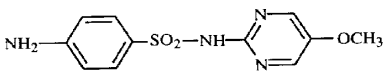


Figure 10.31 Diagram illustrating the most important transformation paths and production ways to produce the different crystal forms of succinylsulfathiazole. The thick, gray arrows mark paths whereby the different crystal forms can be produced in gram quantities. The most stable forms, Forms I and H_I, are shaded (Burger and Griesser, 1991).

D. SULFAMETER



sulfameter

Sulfameter (sulfamethoxydiazine) exists in at least six different forms (Moustafa *et al.*, 1971). Form I (see Figure 10.32 and Table 10.10) is obtained by crystallization from boiling water or by heating any other form to 150 °C. Form II is prepared by rapid cooling of a saturated ethanol solution. Form III (see Figure 10.33 and Table 10.10) is obtained from a number of solvents including methanol, isopropanol, and ethanol. Forms IV and V are probably solvates and are obtained from dioxane and chloroform, respectively. An amorphous form is also known.

These forms were characterized by their infrared spectra, which are all slightly different, particularly in the 800-875, 900-970, 1550-1600, and 3000-3500 cm^{-1} regions of the spectrum. The powder diffraction patterns of these forms are also significantly different.

The forms can be interconverted by heating or grinding. Heating converts all forms to Form I, while grinding or suspension in water converts all forms to Form III. This behavior is discussed in more detail in the interconversion section (see Section 13.2B).

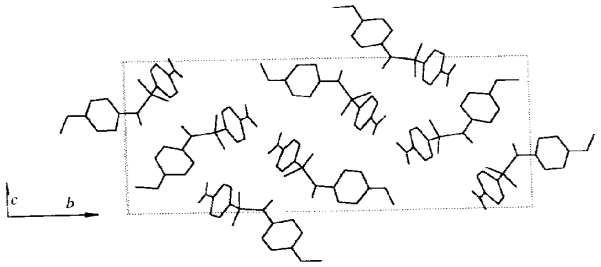


Figure 10.32 Crystal packing of sulfameter Form I (Giuseppetti *et al.*, 1977).

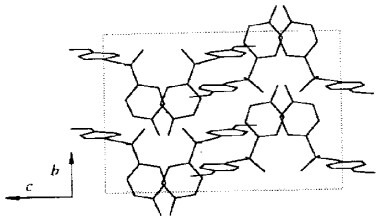


Figure 10.33 Crystal packing of sulfameter Form III (Giuseppetti *et al.*, 1977).

Table 10.10 Crystallographi

Parameter	
Space Group	
a (Å)	
b (Å)	
c (Å)	
β	
Z	
ρ_{calc} (gm cm^{-3})	
V (Å^3)	

Giuseppetti *et al.*, 1977.

The dissolution rates
their relative bioavailabilit
ments are shown in Figu
dissolve most rapidly. F
Form II. It is also interest
amorphous form, sugges
surface area of Form II ma

Commercial preparati
mixtures of Forms I and I
ing. The significance of a
to be determined in separa

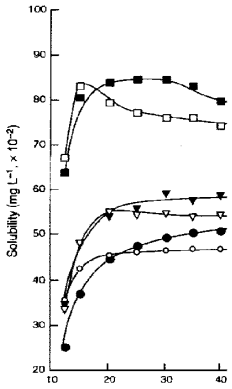


Figure 10.34 Dissolution rate

Table 10.10 Crystallographic Parameters for Sulfameter Forms I and III

Parameter	Form I	Form III
Space Group	$P2_1/c$	$C2/c$
a (Å)	8.358	13.370
b (Å)	26.833	11.735
c (Å)	11.964	15.928
β	111.36°	97.90°
Z	8	8
ρ_{calc} (gm cm^{-3})	1.490	1.504
V (Å^3)	2499	2475

Giuseppetti *et al.*, 1977.

The dissolution rates of these forms have been measured as a means of estimating their relative bioavailabilities (Moustafa *et al.*, 1971). The results of these measurements are shown in Figure 10.34. Obviously, Form II and the amorphous form dissolve most rapidly. Form III has the slowest dissolution rate, about half that of Form II. It is also interesting to note that Form II has a faster dissolution rate than the amorphous form, suggesting that the amorphous form may crystallize or that the surface area of Form II maybe much larger than that of the amorphous form.

Commercial preparations were also studied and, in general, contained Form I or mixtures of Forms I and III. These forms are the most stable and the slowest dissolving. The significance of any such differences with respect to bioavailability would have to be determined in separate experiments.

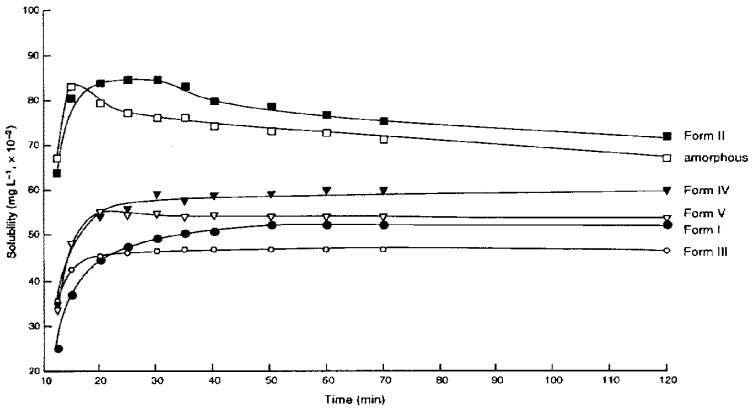
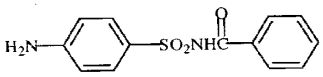


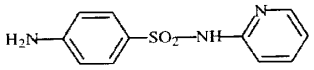
Figure 10.34 Dissolution rates of the different forms of sulfameter (Moustafa *et al.*, 1971).

E. Other Sulfonamides



sulfabenzamide

Sulfabenzamide. Sulfabenzamide exists in four polymorphs and three solvates (Yang and Guillory, 1972). Form III can be transformed to Form I by **trituration**, and Form IV can be transformed to Form III and then Form I by heating. Desolvation of two of the solvates yielded Form II (see Figure 10.35).



sulfapyridine

Sulfapyridine. Sulfapyridine (see Figures 10.35–10.39) exists in at least four polymorphs and one amorphous form (Yang and Guillory, 1972). The infrared spectra of two of these forms are identical, but their X-ray diffraction patterns are completely different. In addition, hot-stage experiments indicated that sulfapyridine crystallized in at least seven forms (Kuhnert-Brandstätter, 1971).

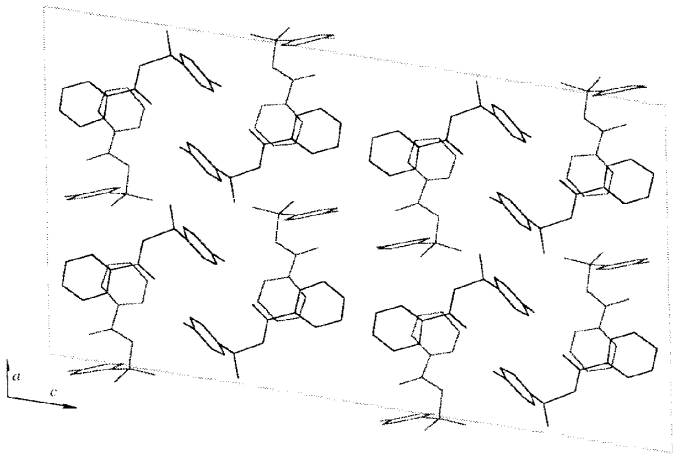


Figure 10.35 Crystal packing of sulfabenzamide Form II (Rambaud *et al.*, 1980).

Figure 10.36 Cryst

Figure 10.37 Cryst

Figure 10.38 Cryst

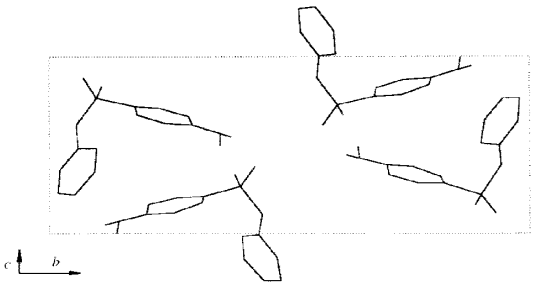


Figure 10.36 Crystal packing of sulfapyridine Form II (Bar and Bernstein, 1985).

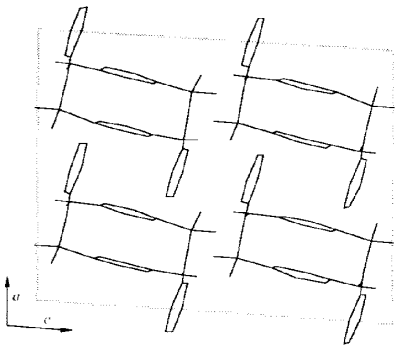


Figure 10.37 Crystal packing of sulfapyridine Form III (Basak *et al.*, 1984).

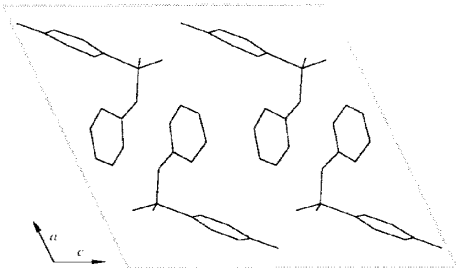


Figure 10.38 Crystal packing of sulfapyridine Form IV (Bernstein, 1988).

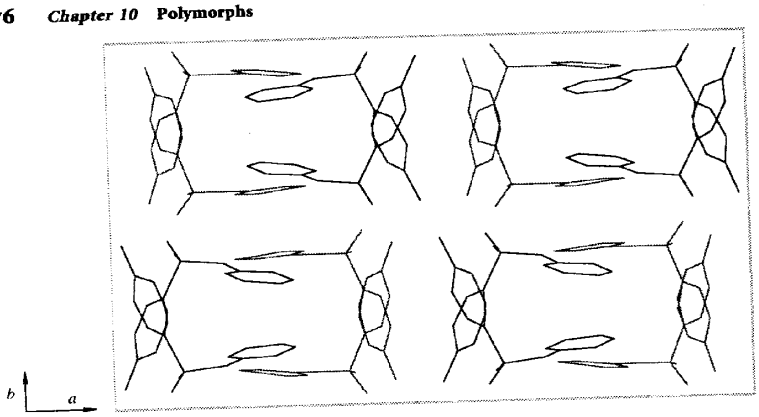


Figure 10.39 Crystal packing of sulfapyridine Form V (Bar and Bernstein, 1985).

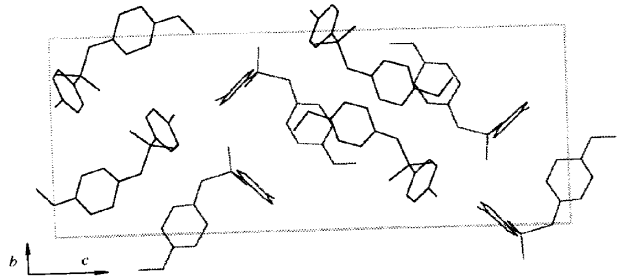
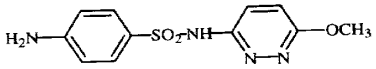
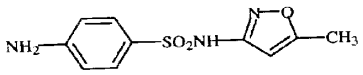


Figure 10.40 Crystal packing of sulfamethoxypyridiazine Form I (Basak *et al.*, 1987).



sulfamethoxypyridazine

Sulfamethoxypyridiazine. Sulfamethoxypyridiazine (see Figure 10.40) exists in at least three crystalline forms (Yang and Guillory, 1972). Form II can be transformed to Form I at 154 °C.



sulfamethoxazole

Sulfamethoxazole. Sulfamethoxazole (see Figures 10.41–10.42) exists in three polymorphs, and Form II can be converted to Form I at 164 °C (Yang and Guillory, 1972). These studies are in agreement with Kuhnert-Brandstätter (1971) who also

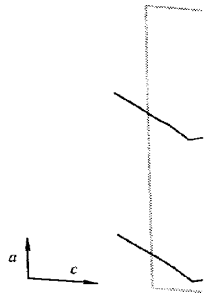


Figure 10.41 Crystal packing

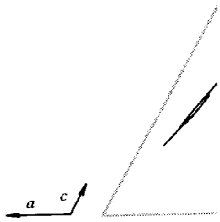
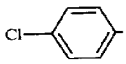


Figure 10.42 Crystal packing

showed there were three p
two forms of sulfamethox
10.41 and 10.42 show the
the conformations of the n



Chlorpropamide. Cl
morphs that have differe
obtained from aqueous et
or II at 110 °C. The infi

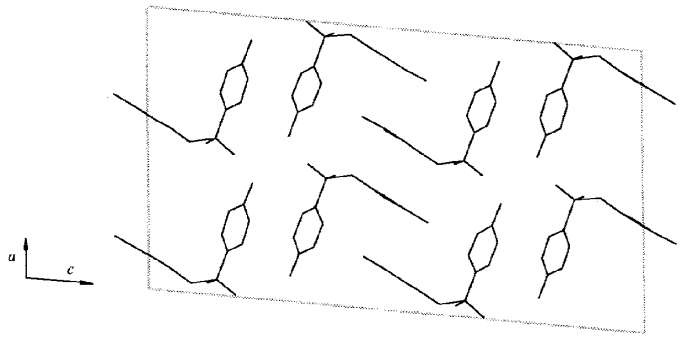


Figure 10.41 Crystal packing of sulfamethoxazole Form I (Bettinetti *et al.*, 1982).

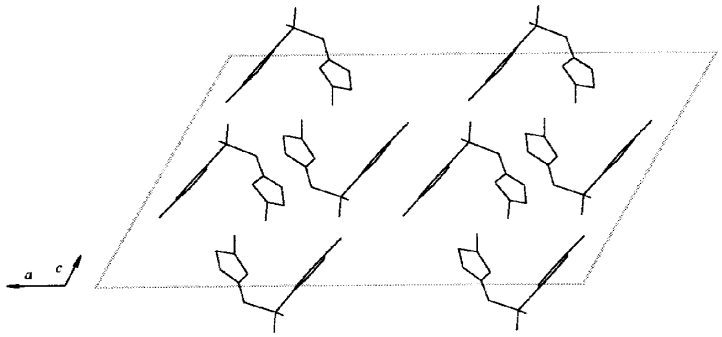
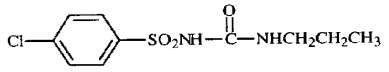


Figure 10.42 Crystal packing of sulfamethoxazole Form II (Bettinetti *et al.*, 1982).

showed there were three polymorphs of sulfamethoxazole. The crystal structures of the two forms of sulfamethoxazole were determined by Bettinetti *et al.* (1982). Figures 10.41 and 10.42 show the crystal packing in these two different forms. It appears that the conformations of the molecule in the two crystal forms are similar.



chlorpropamide

Chlorpropamide. Chlorpropamide (see Figure 10.43) exists in at least three polymorphs that have different diffraction patterns (Simmons *et al.*, 1973). Form I is obtained from aqueous ethanol, Form II from benzene, and Form III by heating Form I or II at 110 °C. The infrared spectra of all three forms are slightly different and the

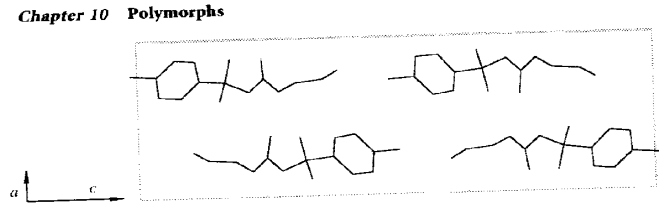
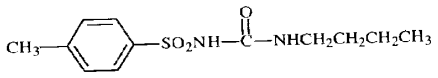


Figure 10.43 Crystal packing of chlorpropamide Form I (Koo *et al.*, 1980).

X-ray powder patterns of all three forms are significantly different, whereas the DSC thermograms obtained for the three forms are very similar.

The three forms of chlorpropamide have different dissolution rates. The dissolution rates of Forms I and III in water are identical, while Form II dissolves about half as fast. However, in beagle dogs, the serum levels following oral administration are identical for all three forms (Simmons *et al.*, 1973). Further single-crystal studies are necessary to completely characterize these forms and explain these results.



tolbutamide

Tolbutamide. Early studies (Simmons *et al.*, 1972) showed that tolbutamide crystallizes in two forms. Form I (see Figure 10.44) is obtained from benzene-hexane, and the crystals are prismatic with mp 127–128 °C. Form II is obtained from aqueous ethanol and the crystals are plates with mp 126–128 °C. Both the infrared spectra and the DTA thermograms of Forms I and II are slightly different. The DTA of Form II shows an endotherm at 113 °C that is not present in Form I. This endotherm apparently corresponds to the conversion of Form II to Form I. The dissolution rates of Forms I and II are the same in water at pH 5.5 and 7.3. The serum levels of these two forms are also identical. One explanation of this data is that, upon exposure to liquid, Form II is converted to Form I by a solution-mediated phase transformation.

More recent studies showed that tolbutamide exists in four crystal forms (Burger, 1975). In addition, aqueous suspensions of tolbutamide were found to thicken to an unpourable state upon occasional agitation. Analysis of the IR spectra and X-ray diffraction patterns confirmed that Form III had crystallized (Rowe and Anderson,

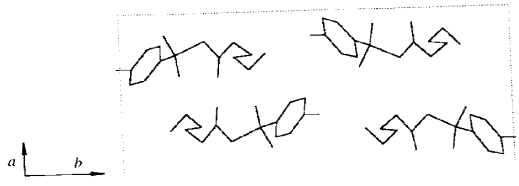


Figure 10.44 Crystal packing of tolbutamide Form I (Donaldson *et al.*, 1981; Nirmala and Gowda, 1981).

Figure 10.45 Van
trans

1984). This is su
thought to be the
shown in Figure
close. Because
suspensions; how
lower energy for
other solvents.

These data s
and that Form I is
was verified by
were placed in m
for several hours
the temperature v
grow throughout
room temperatur
dissolved. These
shown in Figure
thermal microsco

F. Conclusion

This section sho
polymorphism of
availability of a
number of ring-

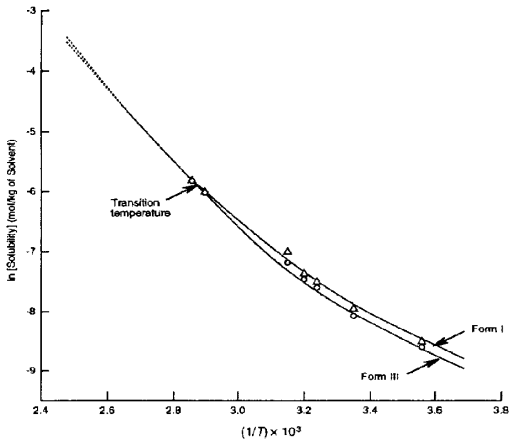


Figure 10.45 Van't Hoff plot of the solubilities of Forms I and III of tolbutamide showing the transition temperature (Rowe and Anderson, 1984).

1984). This is surprising since the suspensions were prepared with Form I which was thought to be the most stable polymorph. Solubility studies gave the van't Hoff plot shown in Figure 10.45. The aqueous solubilities of Form I and Form III are very close. Because of this, Form I may appear to be quite stable at low temperatures in suspensions; however, given sufficient time, Form I will transform to the Form III, the lower energy form. This interconversion was observed at room temperature in ten other solvents.

These data suggests that Form III is more stable than Form I at room temperature and that Form I is more stable than Form III at higher temperatures. This observation was verified by microscopy (Rowe and Anderson, 1984) in which Form III crystals were placed in mineral oil on a microscope hot stage. The sample was heated at 100 °C for several hours with periodic agitation by pressing and rotating the cover slip. When the temperature was reduced to 95 °C, prismatic crystals, typical of Form I, began to grow throughout the oil mixture and the Form III crystals dissolved. Upon cooling to room temperature, fine needles, typical of Form III, grew and the Form I crystals dissolved. These observations experimentally verify the result of the van't Hoff plot shown in Figure 10.45. These studies show the power of van't Hoff plots and also thermal microscopy in studying the interconversion of polymorphs.

F. Conclusion

This section shows the extent of polymorphism in the sulfonamides. The fact that polymorphism of these drugs is widespread yet unpredictable is probably due to (a) the availability of a variety of hydrogen-bonding schemes and (b) the occurrence of a number of ring-ring stacking modes. Further study of the polymorphism of these

compounds using single-crystal X-ray techniques should, no doubt, lead to a better general understanding of polymorphism.

10.5 STEROIDS

Steroids exhibit widespread polymorphism that may affect their bioavailability. A few examples of the polymorphism of steroids have been discussed in preceding sections.

Kuhnert-Brandstätter (1971) has studied the polymorphism of steroids using a Kofler hot stage, and the results of her studies are summarized in Table 10.11. This table clearly shows the extent of polymorphism in this important class of compounds. It should be noted that these studies are based mainly on hot-stage results. Other methods would be useful to verify the existence of these polymorphs and clarify the possible involvement of solvates.

Table 10.11 Melting Points of Polymorphic Steroids[a]

Compound	Forms I	II	III	IV	V
Allopregnane-3β,20α-diol	215–219	162–168			
Allopregnane-3,20-dione	202–206	198–203			
Androstane-3β,17β-diol	168–169	163–164	158–161	146–147	
Androstane-3,17-dione	132–134	128–130			
Androstanolone	182	168			
Δ^5-Androstene-3β,17α-diol	202–205	180–195			
Δ^5-Androstene-3β,17β-diol	181–185	177–180	155–158		
Δ^4-Androstene-3,17-dione	170–174	142–145			
Corticosterone	180–186	175–179	162–168	155–160	
Cortisone enanthate	138–140	135–137	129–132		
Dehydroepiandrosterone	149–153	139–141	137–140	130–136	
Dehydroepiandrosterone acetate	170–172	132–135	94–96	65–69	
Epiandrosterone	174–176	167–169			
α–Estradiol	225	223			
β–Estradiol	178	169			
Estradiol benzoate	188–195	177.5	176		
Estradiol dipropionate	107	97	82		
Estradiol 17-propionate	198–200	154–156			
Estrone	260–263	256	254		
Estrone methyl ether	172–174	123–126	88–92		
Etiocholane-3α-ol-17-one	150–152	141–143	133		
Etiocholane-17β-ol-3-one	141–143	103			
Fluorocortisone trimethylacetate	192–198	184–190			
9α-Fluorohydrocortisone acetate	225–233	208–212	205–208		
Hydrocortisone hemisuccinate	198–205	182–188	168–172		
Methandriol	205–208	202–205	196–198		
Methandriol dipropionate	83–86	74–75			
17α-Methandrostane-3β,17β-diol	213	205			

a Data from Kuhnert-Brandstätter (1971)

Table 10.11 (continued) Me

Compound
1-Methylandrostenolone acet
17α-Methylestradiol
6α-Methylprednisolone aceta
17-Norethisterone
Prednisolone
Prednisolone acetate
Progesterone
Testosterone
Testosterone isobutyrate
Testosterone nicotinate
Testosterone propionate

a Data from Kuhnert-Brandstät

A. ESTRONE

HO

As indicated in Table 10.1 of all three polymorphs ha of the estrone molecule is three forms is shown in molecules, but not obviou and stacks of estrone mol molecules. The crystal pa of 2.26 and 2.47 Å; the c

Table 10.12 Crystallographic

	Form I
Space group	$P2_12_12_1$
a (Å)	12.188
b (Å)	16.301
c (Å)	7.463
β	90.00°
Z	4
V (Å^3)	1481
Source	Sublimati

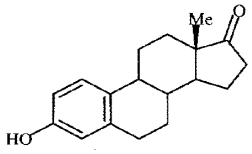
Busetta *et al.*, 1973

Table 10.11 (continued) Melting Points of Polymorphic Steroids[a]

Compound	Forms I	II	III	IV	V
1-Methylandrostenolone acetate	143	106			
17α-Methylestradiol	190–194	188			
6α-Methylprednisolone acetate	225–229	208–212	205–210		
17-Norethisterone	200–207	199			
Prednisolone	218–234	215			
Prednisolone acetate	232–241	225–228	217–220		
Progesterone	131	123	111	106	100
Testosterone	155	148	144	143	
Testosterone isobutyrate	131–133	88–90			
Testosterone nicotinate	194–196	185–188			
Testosterone propionate	122	74			

a Data from Kuhnert-Brandstätter (1971)

A. Estrone



estrone

As indicated in Table 10.12 estrone exists in three polymorphs. The crystal structures of all three polymorphs have been determined (Busetta *et al.*, 1973). The conformation of the estrone molecule is similar in all three polymorphs. The crystal packing of these three forms is shown in Figures 10.46–10.48. Form I contains layers of estrone molecules, but not obvious stacks of estrone molecules. Form III contains both layers and stacks of estrone molecules. Form II has a herringbone arrangement of estrone molecules. The crystal packing of Form I appears to be controlled by H···H contacts of 2.26 and 2.47 Å; the crystal packing of Form II appears to be controlled by C···C

Table 10.12 Crystallographic Parameters of Three Estrone Polymorphs

	Form I	Form II	Form III
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
a (Å)	12.188	10.043	9.271
b (Å)	16.301	18.424	22.285
c (Å)	7.463	7.787	7.610
β	90.00°	90.00°	111.45°
Z	4	4	4
V (Å^3)	1481	1440	1461
Source	Sublimation	Acetone	Sublimation

Busetta *et al.*, 1973

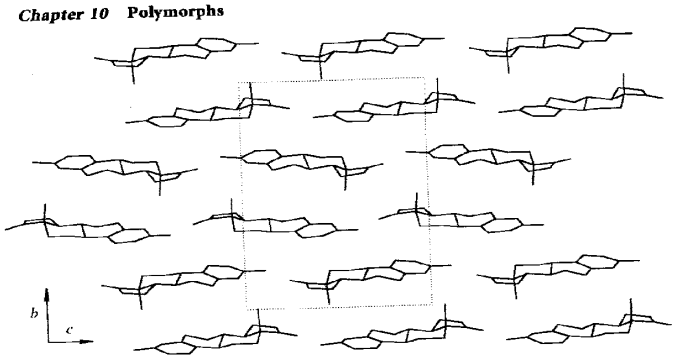


Figure 10.46 Crystal packing of estrone Form I (Busetta *et al.*, 1973).

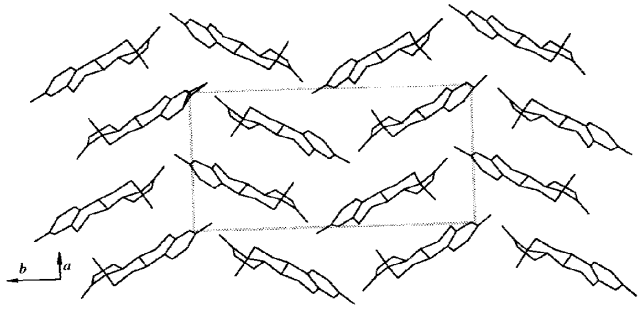


Figure 10.47 Crystal packing of estrone Form II (Busetta *et al.*, 1973).

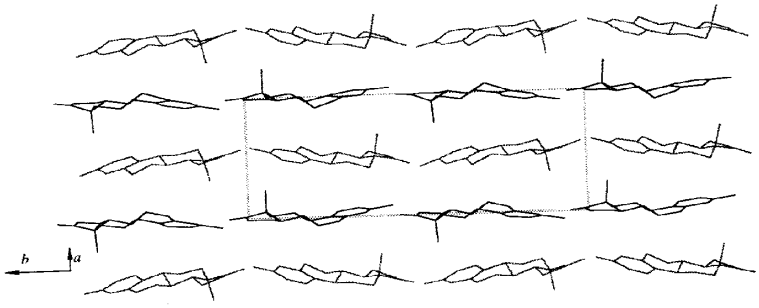


Figure 10.48 Crystal packing of estrone Form III (Busetta *et al.*, 1973).

contacts of 3.35
reported; howeve

B. PREDNISOLO

In our laboratory
Three crystal forn
parameters and c
10.13. The cryst
ture of Form III
prednisolone in t

Table 10.13 Cryst

Space Group
a (Å)
b (Å)
c (Å)
β
Z
ρ_{calc} (g cm^{-3})
V (Å^3)
R

Sutton, 1984

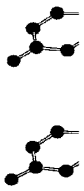
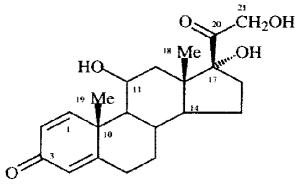


Figure 10.49 Stereo
(Sutto

contacts of 3.35 Å. No transformations or interconversions of these forms have been reported; however, it is likely that the densest form, Form II, is the most stable.

B. Prednisolone



prednisolone

In our laboratory we have investigated the polymorphs of prednisolone (Sutton, 1984). Three crystal forms were obtained by crystallization from various solvents. The cell parameters and other crystallographic data for these three forms are shown in Table 10.13. The crystal structures of Forms I and II were determined but the crystal structure of Form III could not be refined to an acceptable R value. The conformation of prednisolone in the two crystal forms (Forms I and II) is shown in Figure 10.49 and

Table 10.13 Crystallographic Data for the Polymorphs of Prednisolone

	Form I	Form II	Form III
Space Group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	6.350 (3)	11.808 (7)	24.56 (2)
b(Å)	12.985 (8)	6.009 (2)	24.77 (4)
c (Å)	10.971 (9)	25.643 (12)	6.415 (3)
β	91.24°	90.00°	90.00°
Z	2	4	8
ρ_{calc} (g cm^{-3})	1.32	1.32	1.29
V (Å^3)	904.4	1819.5	3903.5
R	0.672	0.672	> 0.10

Sutton, 1984

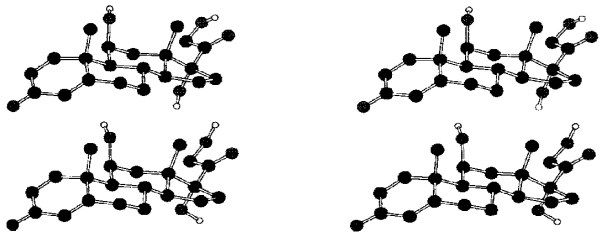


Figure 10.49 Stereoview of prednisolone Forms I (upper) and II (lower) conformations in the crystal (Sutton, 1984).

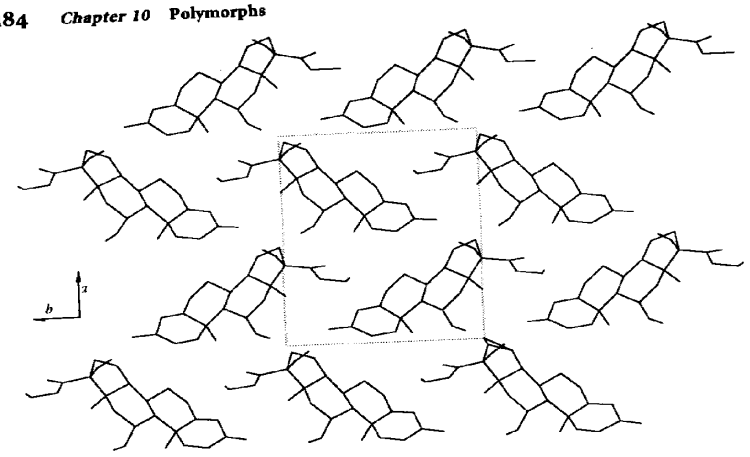


Figure 10.50 Crystal packing stereoview of prednisolone Form I (Sutton, 1984).

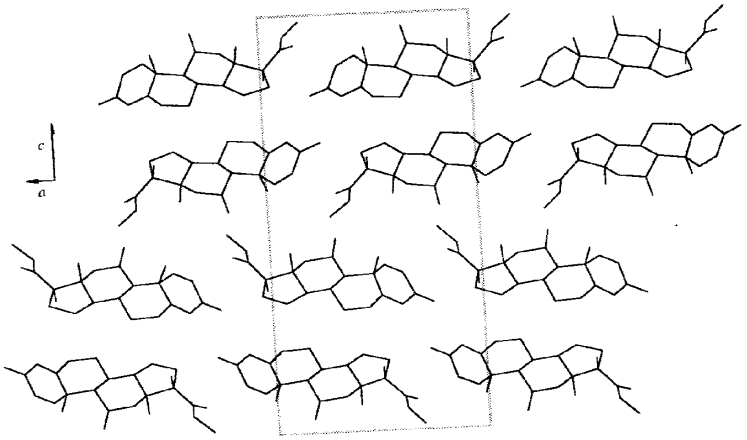


Figure 10.51 Crystal packing stereoview of prednisolone Form II (Sutton, 1984).

the crystal packing is shown in Figures 10.50–10.51.

The crystal packing shows that the arrangements of the prednisolone molecules in the unit cells of Forms I and II are similar but not identical. However, the solid-state NMR spectra of Forms I and II of prednisolone are different as illustrated by the spectra and the chemical shifts in Figure 10.52 and Table 10.14 (Saindon *et al.*, 1993).

Especially important for pu
the resonances assigned to
respectively.

The solid-state CP/M
(labeled amount of 5 mg)
10.53 and required long
comprises only about 5%
spectra shows that product
Further analysis showed th

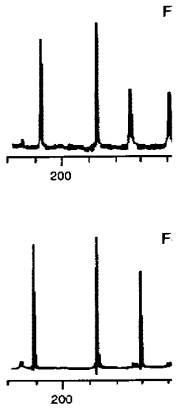


Figure 10.52 Solid-state CP/
(Saindon *et al.*,

Table 10.14 ^{13}C NMR Chem

Atom	Form I	Form II
C20	209.5	211.8
C3	188.1	187.g
C5	175.1	171.0
C13	159.8	157.3
C2	125.9	130.2
C4	121.8	123.8
C17	91.4	90.2
C11	69.9	70.4
C21	67.1	67.7
C9	55.4	54.8
C14	52.2	52.8

4 The assignment of this peak

Especially important for purposes of identification is the difference in chemical shifts of the resonances assigned to carbons C2 and C4 which occur between 120 and 140 ppm, respectively.

The solid-state CP/MAS ^{13}C NMR spectra of three generic prednisolone products (labeled amount of 5 mg) were also determined. These spectra are shown in Figure 10.53 and required long acquisition times since the active ingredient (prednisolone) comprises only about 5% of the approximately 100 mg tablets. Inspection of these spectra shows that products A and B contain Form I while product C contains Form II. Further analysis showed that all three products passed the USP dissolution test. Thus,

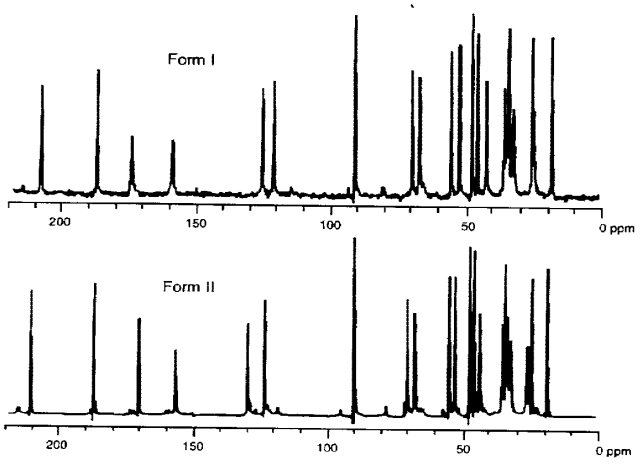


Figure 10.52 Solid-state CP/MAS ^{13}C NMR spectra of prednisolone Forms I (top) and II (bottom) (Saindon *et al.*, 1993).

Table 10.14 ^{13}C NMR Chemical Shifts of Prednisolone in the Solid-State and Solution

Atom	Form I	Form II	Solution	Atom	Form I	Form II	Solution
C20	209.5	211.8	211.5	C13	47.5	47.1	46.7
C3	188.1	187.g	185.1	C10	45.3	45.1	43.9
C5	175.1	171.0	170.5	C12	42.1	43.1	39.0
C13	159.8	157.3	156.8	C8[a]	35.3	34.7	34.1
C2	125.9	130.2	127.2	C16[a]	34.3	33.5	33.0
C4	121.8	123.8	121.7	C15[a]	33.5	32.7	32.7
C17	91.4	90.2	88.5	C6[a]	31.8	31.5	31.6
C11	69.9	70.4	68.6	C7[a]	24.6	25.4	31.2
C21	67.1	67.7	66.1	C18[a]	23.9	23.7	21.0
C9	55.4	54.8	55.5	C19[a]	17.3	18.1	17.0
C14	52.2	52.8	51.2				

[a] The assignment of this peak should be considered tentative (Saindon *et al.*, 1993)

molecules in
he solid-state
trated by the
et al., 1993).

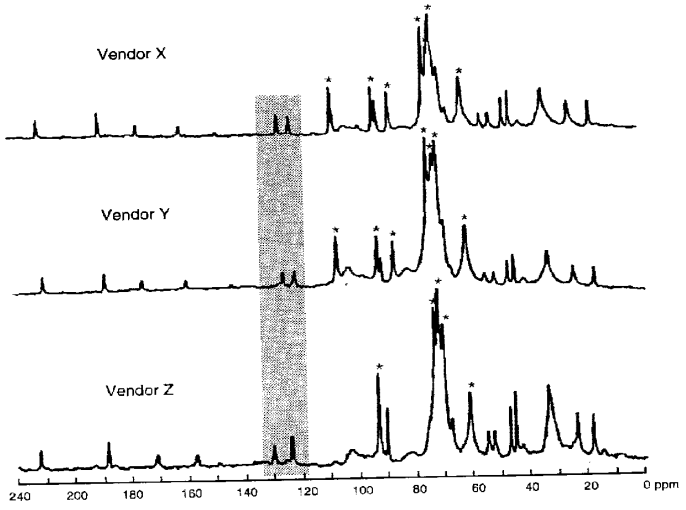
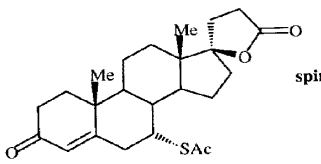


Figure 10.53 Solid-state CP/MAS ^{13}C NMR spectra of prednisolone tablets from three different vendors. The most evident differences are noted within the shaded region and the excipient signals are labeled with a star. (Byrn *et al.*, 1988).

these tablets represent a control problem because they contain different crystal forms but hopefully do not represent a serious clinical problem since they all meet the USP dissolution test.

C. Spironolactone



spironolactone

The polymorphism of spironolactone has been carefully studied using X-ray crystallography (Agafonov *et al.*, 1991). The data for the different forms are described in Table 10.15.

Spironolactone is of interest because it shows variable solubility and dissolution rate as well as pharmaceutical performance as an oral drug. Recently, a number of crystal forms of this compound have been discovered (see Table 10.15). As is the case for many steroids, both solvated and unsolvated crystal forms have been obtained. Figure 10.54 shows the TGA curves of the different crystal forms, clearly Forms III

Table 10.15 Spironolacto

Solvent	Method[a]
Acetone	1
Acetone	2
Dioxane	1
Dioxane	2
Chloroform	1
Chloroform	2
Acetonitrile	—[b]
Ethanol	—[b]
Ethyl acetate	—[b]
Methanol	—[b]

a Method 1—the sample is
0° C within a few hours; m
ture and the solvent allowe
the two methods of prepar
fraction pattern. (Agafono

through VI are solvate
crystal forms confirmin

Table 10.16 lists t
spironolactone, clearly
10.17 tabulates the pow
that Forms I through I
(Agafonov *et al.*, 1991
crystal forms of spiron
(Form I) is shown in Fi
Figure 10.57. The conf
it is clear that the crystal

Mass (mg)

Figure 10.54 TGA curves

Table 10.15 Spironolactone Single-Crystal Preparation Methods and Thermodynamic Data

Solvent	Method[a]	Form Obtained	T_{dec} (°C)	ΔH_{dec} (J/g)	T_f (°C)	ΔH_f (J/g)
Acetone	1	I	...	...	205 ± 1	48 ± 3
Acetone	2	II	...	...	210 ± 1	53 ± 4
Dioxane	1	Glass[c]	...	...	...	...
Dioxane	2	II	...	...	210 ± 1	53 ± 4
Chloroform	1	Glass[c]	...	...	...	...
Chloroform	2	II	...	...	210 ± 1	53 ± 4
Acetonitrile	—[b]	Solvate (2:1) (III)	137 ± 2	38 ± 2	210 ± 1	52 ± 4
Ethanol	—[b]	Solvate (2:1) (IV)	100 ± 2	28 ± 2	210 ± 1	54 ± 4
Ethyl acetate	—[b]	Solvate (4:1) (V)	102 ± 6	28 ± 1	210 ± 1	54 ± 4
Methanol	—[b]	Solvate (1:2) (VI)	25-126	50 ± 2	210 ± 1	52 ± 3

a Method 1—the sample is dissolved in the solvent at close to its boiling point and cooled to 0° C within a few hours; method 2—the sample is dissolved in the solvent at room temperature and the solvent allowed to evaporate slowly during several weeks. *b* For these solvents, the two methods of preparation give the same results. *c* Glass-like solid without X-ray diffraction pattern. (Agafonov *et al.*, 1991)

through VI are solvates. Figure 10.55 shows the DSC thermograms of the different crystal forms confirming that Forms III through VI contain solvent of crystallization.

Table 10.16 lists the crystallographic parameters of the different crystal forms of spironolactone, clearly showing that the different forms have distinct structures. Table 10.17 tabulates the powder patterns for Forms I through III. It is clear from this table that Forms I through III have different powder diffraction patterns. These workers (Agafonov *et al.*, 1991) were able to determine the crystal structures of three of the crystal forms of spironolactone and the contents of the unit cell for the needle form (Form I) is shown in Figure 10.56, the contents of the unit cell for Form II is shown in Figure 10.57. The conformation of the steroid is the same in all three crystal forms but it is clear that the crystal packing is different.

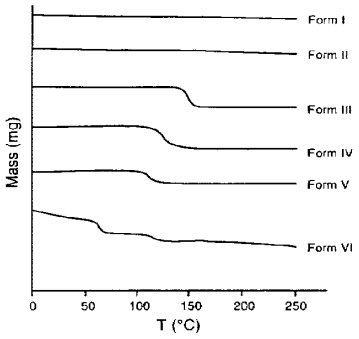


Figure 10.54 TGA curves of spironolactone crystal forms (Agafonov *et al.*, 1991).

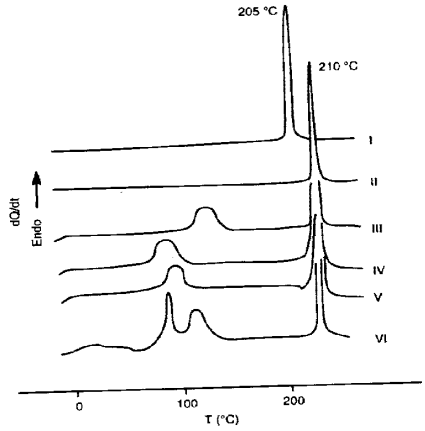


Figure 10.55 DSC thermograms of spironolactone crystal forms (Agafonov *et al.*, 1991).

Table 10.16 Crystallographic Data for the Crystal Forms of Spironolactone

Parameter	Form I	Form II	Form III	Form IV	Form V
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	9.979	10.584	11.857	10.14	10.15
b (Å)	35.573	18.996	19.655	36.21	36.22
c (Å)	6.225	11.005	11.346	6.28	6.29
β	90.00	90.00	118.13	90.00	90.00
Z	4	4	2	4	4
V (Å^3)	2209.8	2212.6	2318.7	2306	2315
Crystal System	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic
Morphology	Needle-like	Prisms	Trigonal prisms	Needle-like	Needle-like
Solvate	...	...	½ acetonitrile	½ ethanol	¼ ethyl acetate

Agafonov *et al.*, 1991.

Table 10.17 X-ray Powder Diffraction Data for the Different Crystal Forms of Spironolactone

Form I			Form II			Form III		
d_{hkl} (Å)	I^a	$h\ k\ l$	d_{hkl} (Å)	I^a	$h\ k\ l$	d_{hkl} (Å)	I^a	$h\ k\ l$
17.8	w	0 2 0	9.5	s	0 2 0	9.8	s	0 2 0
8.9	m	0 4 0	7.63	w	1 0 1	8.9	w	0 1 1
8.7	vs	1 2 0	7.00	m	1 2 0	8.8	w	1 1 1
7.63	s	1 3 0	5.43	s	1 3 0	6.99	w	1 2 1
6.64	m	1 4 0	5.29	s	0 1 2	5.55	s	1 3 0

a vs–very strong intensity, s–strong intensity, m–medium intensity, w–weak intensity, vw–very weak intensity (Agafonov *et al.*, 1991).

Table 10.17 (continued)

Form I		
d_{hkl} (Å)	I^a	$h\ k\ l$
6.13	w	0 1 1
5.93	vw	0 6 0
5.10	w	1 6 0
4.94	m	2 1 0
4.68	vs	0 5 1
4.599	s	2 3 0
4.528	s	1 7 0
4.351	m	2 4 0
3.870	m	2 0 1
3.699	m	1 9 0

a vs–very strong intensit
intensity (Agafonov *et a*

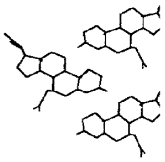


Figure 10.56 Contents o

Figure 10.57 Contents of

Table 10.17 (continued) X-ray Powder Diffraction Data for the Different Crystal Forms of Spironolactone

Form I			Form II			Form III		
d_{hkl} (Å)	I^a	*h k l*	d_{hkl} (Å)	I^a	*h k l*	d_{hkl} (Å)	I^a	*h k l*
6.13	w	0 1 1	5.10	m	2 1 0	5.48	s	0 3 1
5.93	vw	0 6 0	4.87	w	1 0 2	5.46	s	1 3 1
5.10	w	1 6 0	4.73	w	1 1 2	5.09	s	1 2 1
4.94	m	2 1 0	4.333	m	1 4 0	5.05	w	2 1 0
4.68	vs	0 5 1	4.263	w	2 1 2	4.97	m	2 0 –2
4.599	s	2 3 0	4.032	m	1 4 1	4.91	s	0 4 0, 1 2 2
4.528	s	1 7 0	3.815	w	2 0 2	4.456	m	0 2 2, 1 4 0
4.351	m	2 4 0	3.741	w	2 1 2	4.287	m	1 3 2
3.870	m	2 0 1	3.576	w	1 5 0	3.931	w	2 0 1
3.699	m	1 9 0	3.540	w	2 2 2	3.837	w	3 1 1, 3 0 2

a vs–very strong intensity, s–strong intensity, m–medium intensity, w–weak intensity, vw–very weak intensity (Agafonov *et al.*, 1991).

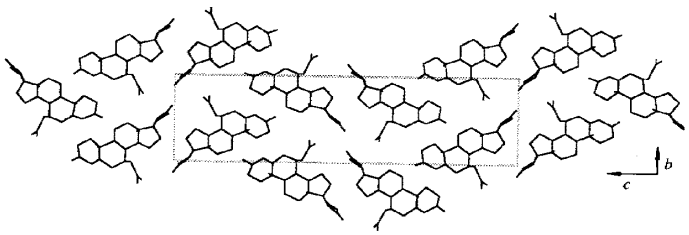


Figure 10.56 Contents of the unit cell of Form I of spironolactone (Dideberg *et al.*, 1972).

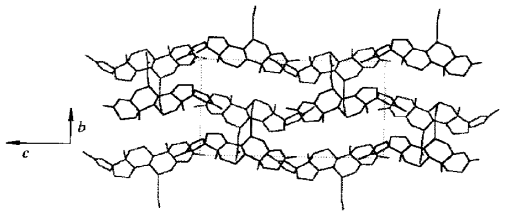
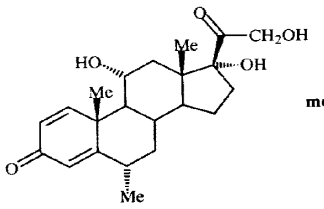


Figure 10.57 Contents of the unit cell of Form II of spironolactone (Agafonov *et al.*, 1989).

D. Methylprednisolone



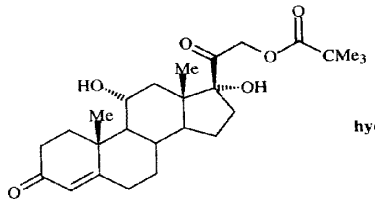
methylprednisolone

Methylprednisolone exists in two polymorphs. Form I can be prepared by recrystallization from acetone, and Form II by sublimation at 190 °C (Hamlin *et al.*, 1962). Dissolution rates of pellets of these two forms were studied under varying conditions of agitation. Under all conditions, except the most rapid agitation, Form II has a faster dissolution rate than Form I. *In vivo* tests of the rate of dissolution of Forms I and II using pellet implants in rats showed that Form II has a faster dissolution rate than Form I.

Studies of the intrinsic dissolution rates (see Chapter 6) of Forms I and II also showed that Form II has a faster dissolution rate than Form I. At increased stirring rates, Forms I and II had more similar dissolution rates. These studies also indicated that low agitation rates give data that correlate with the pellet-implant *in vivo* data, while higher agitation rates are required to give results that correlate with data from trials involving tablets dissolving in the stomach (Levy and Procknal, 1964).

Infrared spectroscopy showed that the surfaces of pellets of Form II revert to Form I in water, even after only a 2-minute exposure. This appears to be a water-mediated phase transformation of the type discussed by Haleblian and McCrone (1969). This observation explains some of the conflicting data obtained in measuring the dissolution rates of Form II in water (Higuchi *et al.*, 1969).

E. Hydrocortisone 21-*tert*-Butylacetate



hydrocortisone 21-*tert*-butylacetate

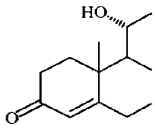
Biles (1963) reported that hydrocortisone 21-*tert*-butylacetate crystallizes in three forms. X-ray diffraction studies in our laboratory indicate that there are actually at least four different forms, and elemental analysis shows that two of these forms contain different amounts of ethanol. The results of these studies are shown in Table 10.18. Several other forms (from other solvents or from desolvation of a solvate by heating) are also known and have a melting point of 234–238 °C (Lin *et al.*, 1982).

Table 10.18 Crysta

Crystal Form
I
II
III
IV

a The exact melting
at this temperature r
melt resolidified as

During recry
III, often formed
new form, design
120 °C. Forms I
while Form III ch



hydrocortiso

All crystal fo
light. Form I
ultraviolet light ir
°C. The formatio
NMR chemical sh
by gas chromato
21-*tert*-butylaceta

Table 10.19 Desol
Butyl

Days
1
2
3
6
10
14
21

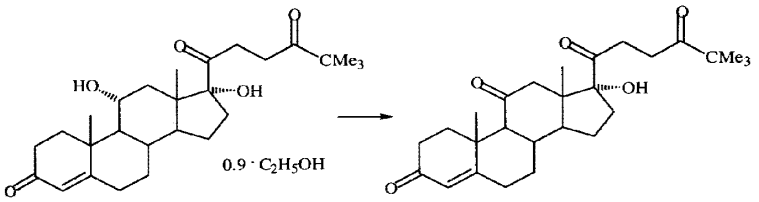
Lin *et al.*, 1982.

Table 10.18 Crystal Forms of Hydrocortisone 21-*tert*-Butylacetate

Crystal Form	Ethanol Content (mole ratio)	Oxidation in UV Light	Mp[a] (°C)
I	0.9 (variable)	Reaction	170-180
II	1.0	No Reaction	110-120[b]
III	0	No Reaction	123-126[c]
IV	0	No Reaction	234-238

a The exact melting temperature may vary from one crystal to another. *b* Opaque at this temperature range with final melting at 234–238 °C. *c* After melting, the melt resolidified as the temperature was increasing. (Lin *et al.*, 1982)

During recrystallization from ethanol, a mixture of crystal forms, Forms I, II, and III, often formed but a pure single form could be obtained under certain conditions. A new form, designated Form IV, was produced when Forms I, II, and III were heated at 120 °C. Forms I and II underwent desolvation and phase transformation to Form IV, while Form III changed from one phase to another.



hydrocortisone 21-*tert*-butylacetate **cortisone 21-*tert*-butylacetate**

All crystal forms, except for Form I, were stable upon irradiation with ultraviolet light. Form I was oxidized to cortisone 21-*tert*-butylacetate upon irradiation with ultraviolet light in air. A known weight of crystals was put in vials and irradiated at 30 °C. The formation of cortisone 21-*tert*-butylacetate was determined by the change in the NMR chemical shift of the C18 methyl signal, and the content of ethanol was measured by gas chromatography. The percent of desolvation and oxidation of hydrocortisone 21-*tert*-butylacetate to cortisone 21-*tert*-butylacetate is shown in Table 10.19. The loss

Table 10.19 Desolvation and Oxidation of Crystalline Hydrocortisone 21-*tert*-Butylacetate Form I (0.9 Ethanolate) upon Exposure to UV Light

Days	% Oxidation	Ethanol Lost
1	20.0	43.3%
2	38.9	75.6%
3	50.0	83.3%
6	52.9	88.9%
10	56.3	93.3%
14	66.7	95.6%
21	71.4	96.7%

Lin *et al.*, 1982.

of ethanol is faster than oxidation but does not completely precede oxidation. In addition, ethanol loss does not occur from crystals stored in the dark, indicating that oxidation is required for ethanol loss to begin. Further studies of this interesting reaction are in order. This behavior is different from that of dihydrophenylalanine hydrate, in which water loss almost completely preceded oxidation (Byrn and Lin, 1976).

F. Conclusion

The steroids exhibit a wide range of polymorphic and solvate behavior which appears to affect both the bioavailability and stability of these compounds. Of particular interest are the cases where one form is chemically reactive in the solid state while the others are stable.

10.6 Barbiturates

Barbiturates are another class of drugs which generally exhibit polymorphism. As in the discussions of the polymorphism of sulfonamides and steroids just presented, this section begins with Table 10.20 describing the results of hot-stage experiments on barbiturates (Kuhnert-Brandstätter, 1971).

Table 10.20 Melting Points of Polymorphs of Barbiturates[a]

Compound	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
Allobarbital	173	~122									
5-Allyl-5-(2-Cyclopentenyl-1-yl)barbituric acid	148	126	124	115	—						
5-Allyl-5-phenyl-barbituric acid	159	133	130	129	128	126					
Amobarbital	157	151									
Aprobarbital	141	139	133	130	~116	~95					
Barbital	190	184	183	181	176	159					
Butallylonal	131	128	104								
Buthalitone	149	117	~95								
5-Crotyl-5-ethyl-barbituric acid	117	90									
Cyclobarbital	173	161									
Dipropylbarbital	148	146	126	120	~110	105	85				
Dormovit	171	146									
Ethallobarbital	160	149	137	129	117	108					
5-Ethyl-5-(1-piperidyl)-barbituric acid	217	210	204								
Heptabarbital	174	150	145	143	141	137	127	100			
Hexobarbital	146										

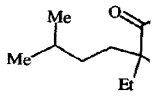
a Kuhnert-Brandstätter (1971).

Table 10.20 (continued) Melting Points

Compound	I
5-Methyl-5-phenyl-barbituric acid	226
Pentobarbital	129
Phenobarbital	176
Propallylonal	184
Secobutabarbital	166
Thialbarbital	146
Thiothyr	176
Vinbarbital	166

a Kuhnert-Brandstätter (1971).

A. Amobarbital



ven and Vizzini (1969) have det
phs of amobarbital (5-ethyl-5-iso
parameters shown in Table 10.21
The conformation of amobarbita
rystal packing is different (see F
double-ribbon arrangement; ho
ets, while in Form II an interl
density.

.21 Crystallographic Parameters f

eter	Form I
oup	*C2/c*
	21.480
	11.590
	10.370
	97.07°
	8
	2562.0
$^{-3}$)	1.171
it	Plates developed on
	154–156

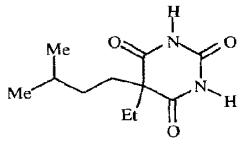
zini, 1969.

Table 10.20 (continued) Melting Points of Polymorphs of Barbiturates[a]

Compound	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
5-Methyl-5-phenyl-barbituric acid	226	226	200								
Pentobarbital	129	114	108								
Phenobarbital	176	174	167	163	160	157	153	141	133	126	112
Propallylonal	184	180	~179	~127	~123						
Secobutabarbital	166	—									
Thialbarbital	146	125									
Thiothyr	176	172									
Vinbarbital	166	129	106								

a Kuhnert-Brandstätter (1971).

A. Amobarbital



amobarbital

Craven and Vizzini (1969) have determined the crystal structures of the two polymorphs of amobarbital (5-ethyl-5-isopentylbarbituric acid). The two forms have the cell parameters shown in Table 10.21.

The conformation of amobarbital is virtually identical in the two polymorphs but the crystal packing is different (see Figures 10.58–10.59). Both forms show the so-called double-ribbon arrangement; however, in Form I there is no interaction between the sheets, while in Form II an interlocking structure is present resulting in a slightly higher density.

Table 10.21 Crystallographic Parameters for the Two Forms of Amobarbital

Parameter	Form I	Form II
Space group	$C2/c$	$P2_1/c$
a (Å)	21.480	10.281
b (Å)	11.590	22.061
c (Å)	10.370	11.679
β	97.07°	109.10°
Z	8	8
V (Å^3)	2562.0	2503.1
ρ_{calc} (g cm^{-3})	1.171	1.178
Crystal habit	Plates developed on 1 0 0	Needles elongated along b-axis
Mp (°C)	154–156	160–162

Craven and Vizzini, 1969.

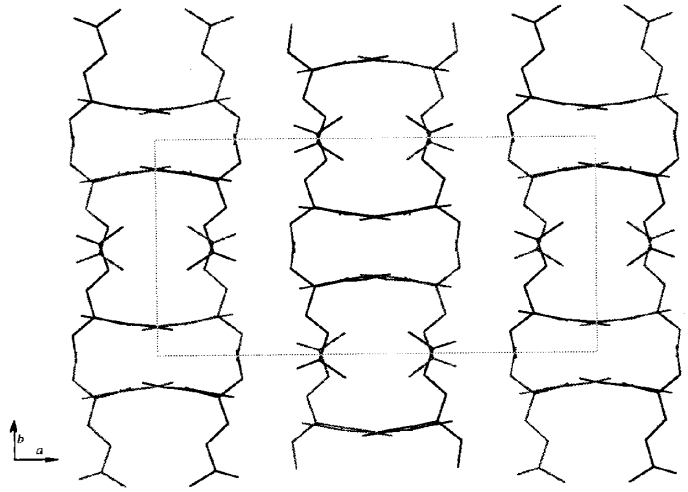


Figure 10.58 The crystal structure of Form I of amobarbital viewed down the *c* axis (Craven and Vizzini, 1969).

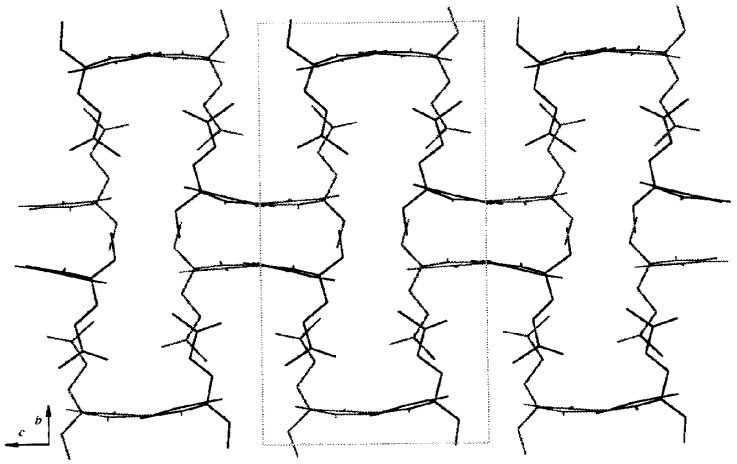


Figure 10.59 The crystal structure of Form II of amobarbital viewed down the *a* axis (Craven and Vizzini, 1969).

B PHENOBARBITAL

Phenobarbital (5-ethyl-5-ph
many as thirteen modificati
least four distinct anhydrou

The crystal structures
have been determined (W
phenobarbital, including the
two forms. The crystal pac
somewhat different; howev
hydrogen-bonded pyrimidi

Kopp *et al.* (1988) repo
of polymorphic phenobarbi
can easily lead to misunder
to identify the different cry
obtained if different heating
also influenced the DSC re
DSC methodology outlined

A study by Szabó-Révé
ers Avicel® PH 101 or Hew
(obtained by heating a comr
two commercial sources lab
phenobarbital. The dissolut
were different as shown in
and other similar observat
dissolution rates.

Table 10.22 Crystallographic I

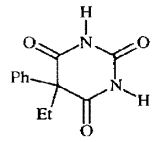
Parameter	Form I[a]
Space group	$P2_1/n$
a (Å)	6.800
b (Å)	47.174
c (Å)	10.695
α	90.00°
β	94.18°
γ	90.00°
Z	12
V (Å^3)	3421.7
ρ_{calc} (gm cm^{-3})	1.352

a Williams, 1973. *b* Williams,

c axis (Craven and

e *a* axis (Craven and

B PHENOBARBITAL



phenobarbital

Phenobarbital (5-ethyl-5-phenylbarbituric acid) has been reported to crystallize in as many as thirteen modifications. Single-crystal studies of these polymorphs revealed at least four distinct anhydrous forms and one hydrate (see Table 10.22).

The crystal structures of the hydrate (Form XIII) and of Forms I, II, III, and V have been determined (Williams, 1973; Williams, 1974). The conformations of phenobarbital, including the angle between the two rings, are slightly different in these two forms. The crystal packing of these two forms, shown in Figures 10.60–10.61, is somewhat different; however, both forms contain layers of phenyl rings and layers of hydrogen-bonded pyrimidine rings.

Kopp *et al.* (1988) reported a study of DSC and X-ray powder diffraction patterns of polymorphic phenobarbital. Their work demonstrates that using one technique alone can easily lead to misunderstandings. It was not possible to use the DSC thermograms to identify the different crystal forms of phenobarbital because different results were obtained if different heating rates were used. In addition, they found that particle size also influenced the DSC results. These results are consistent with the discussion of DSC methodology outlined in Chapter 5.

A study by Szabó-Révész *et al.* (1987) used direct compression with the dry binders Avicel® PH 101 or Heweten® 40 to evaluate manufactured tablets containing Form I (obtained by heating a commercial product near 160 °C for 3 h), Form II (obtained from two commercial sources labeled II_1 and II_2), or Form III (obtained by spray drying) of phenobarbital. The dissolution rates of the tablets containing the various crystal forms were different as shown in Figure 10.62 but by only a few percent. This observation and other similar observations suggest that different polymorphs may give similar dissolution rates.

Table 10.22 Crystallographic Parameters for the Crystal Forms of Phenobarbital.

Parameter	Form I[a]	Form II[a]	Form III[b]	Form V[a]	Form XIII (hydrate)[a]
Space group	$P2_1/n$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$Pbca$
a (Å)	6.800	6.784	9.534	12.66	7.157
b (Å)	47.174	23.537	11.855	6.75	30.879
c (Å)	10.695	10.741	10.794	27.69	10.87
α	90.00°	91.89°	90.00°	90.00°	90.00°
β	94.18°	94.43°	111.56°	106.9°	90.00°
γ	90.00°	89.03°	90.00°	90.00°	90.00°
Z	12	6	4	8	8
V (Å^3)	3421.7	1708.8	1134.6	2264.1	2402.3
ρ_{calc} (gm cm^{-3})	1.352	1.354	1.360	1.362	1.384

a Williams, 1973. *b* Williams, 1974.

The effect of additives on the crystallization of phenobarbital has also been investigated (Kato *et al.*, 1984). Kato and co-workers prepared two forms of phenobarbital by adding barbital or cyclobarbital to the crystallization. In these studies rather large quantities of additive (7.5% for barbital and 7% cyclobarbital) were required to achieve the effect.

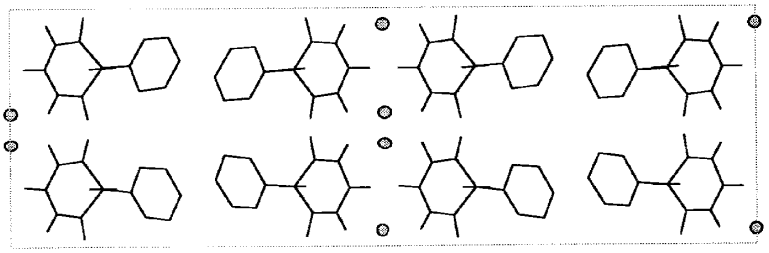


Figure 10.60 Crystal packing of phenobarbital Form XIII hydrate (◎ water molecule) viewed down the *z* axis. (Williams, 1973).

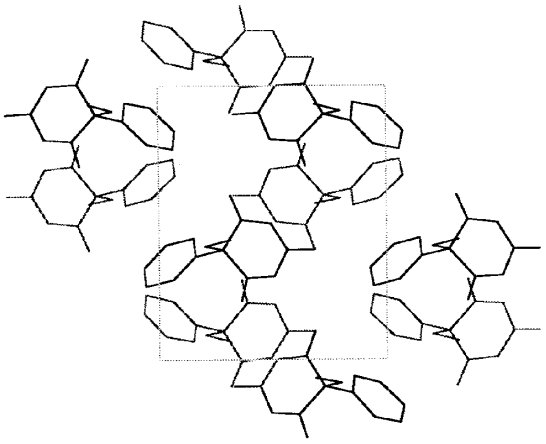


Figure 10.61 Crystal packing of phenobarbital Form III viewed down the *b* axis (Williams, 1974).

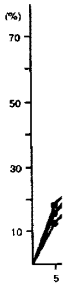
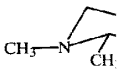


Figure 10.62 Dissolution rate of
pressure of 20 kN,
cial sources), and H

10.7 OTHER DRUGS

In this section the polymorph
this review is not exhaustive,
pharmaceuticals.

A. PROMEDOL ALCOHOL



DeCamp and Ahmed (1972
monoclinic and rhombohedr
methyl-4*e*-phenylpiperidin-4*e*
alcohol is the same in bot

Table 10.23 Crystallographic Pa

Parameter	Monoc
Space Group	
a (Å)	
b (Å)	
c (Å)	
β	
Z	
V (Å^3)	1
ρ_{calc} (gm-cm^{-3})	

a DeCamp and Ahmed, 1972a. *b* I

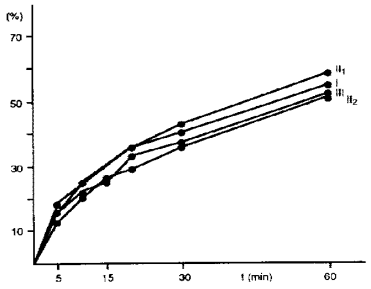
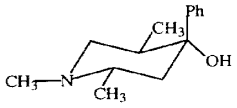


Figure 10.62 Dissolution rate of phenobarbital tablets prepared using the binder Heweten® 40, a pressure of 20 kN, and the four different crystal forms. Forms I, II (from two commercial sources), and III (Szabó-Réveśz *et al.*, 1987).

10.7 OTHER DRUGS

In this section the polymorphic properties of several other drugs are reviewed. While this review is not exhaustive, it illustrates several important studies of polymorphism in pharmaceuticals.

A. PROMEDOL ALCOHOL



(±)-β-promedol alcohol

DeCamp and Ahmed (1972a–b) have determined the crystal structure of both the monoclinic and rhombohedral forms of (±)-β-promedol alcohol, (±)-α-1,2*a*,5*e*-trimethyl-4*e*-phenylpiperidin-4*a*-ol, (see Table 10.23). The conformation of β-promedol alcohol is the same in both forms, but the crystal packing differs (see Figures

Table 10.23 Crystallographic Parameters for the Two Forms of (±)-β-Promedol Alcohol

Parameter	Monoclinic Form[a]	Rhombohedral Form[b]
Space Group	$P2_1/n$	$R\bar{3}$
a (Å)	13.298	29.754
b (Å)	7.721	29.754
c (Å)	12.776	7.713
β	90.09°	60.0°
Z	4	18
V (Å^3)	1311.8	5913.5
ρ_{calc} (gm·cm^{-3})	1.109	1.110

a DeCamp and Ahmed, 1972a. *b* DeCamp and Ahmed, 1972b

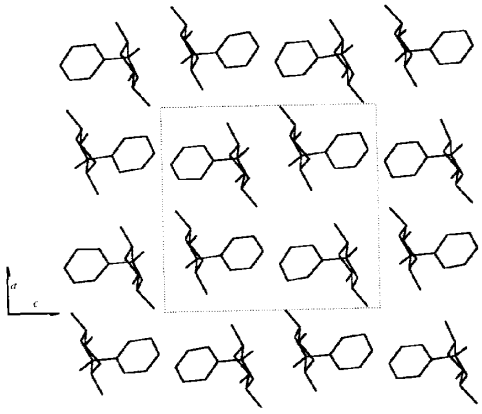


Figure 10.63 Crystal packing of (±)-β-promedol alcohol monoclinic form (DeCamp and Ahmed, 1972a).

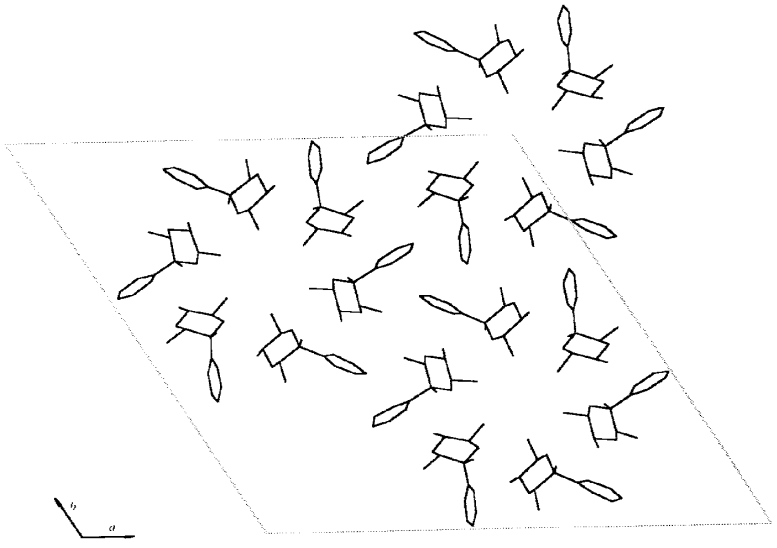


Figure 10.64 Crystal packing of (±)-β-promedol alcohol rhombohedral form (DeCamp and Ahmed, 1972b).

10.63–10.64). In the
same chirality to forı
gen bonds; however,
Despite the differenc
have almost the sar
104.5–105 °C, where
difference in melting
since the OH···N dis
the densities indicate
DeCamp and Ahmed
rings of molecules of
molecules of the san
ordering results in a
monoclinic form. S
(1971).

B. ENALAPRIL MA

This example illustra
morphs. Enalapril
different solid-state
ethyl ester methyl a
respectively. The
forms as shown in F
of the two crystal fc
the DSC analysis, tl
solution data, as sho
dissolution for the

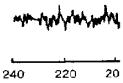
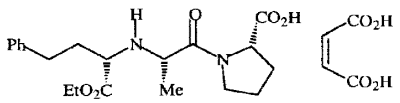


Figure 10.65 Solid-st

10.63–10.64). In the monoclinic form, OH···N hydrogen bonds link molecules of the same chirality to form chains. In the rhombohedral form, there are also OH···N hydrogen bonds; however, these link molecules of alternating chirality into hexameric rings. Despite the differences in crystal packing, the monoclinic and rhombohedral crystals have almost the same density. The melting point of the rhombohedral form is 104.5–105 °C, whereas the melting point of the monoclinic form is 90.5–91 °C. This difference in melting point is probably not related to differences in hydrogen bonding since the OH···N distances are approximately the same in the two forms. In addition, the densities indicate that the two forms have nearly equal packing energies. Thus, DeCamp and Ahmed (1972a) suggested that, since the rhombohedral form contains rings of molecules of alternating chirality while the monoclinic form contains stacks of molecules of the same chirality, the monoclinic form is more ordered. This increased ordering results in an entropy difference that results in a lower melting point for the monoclinic form. Similar arguments were also advanced by Krigbaum and Wildman (1971).

B. Enalapril Maleate



enalapril maleate

This example illustrates the need for using more than one method in looking for polymorphs. Enalapril maleate (Ip *et al.*, 1986) exists in two crystal forms which give different solid-state ^{13}C NMR spectra. (Figures 10.65 and 10.66). The signals of the ethyl ester methyl and maleate carbon signals are at 11–13 ppm and 137–138 ppm, respectively. The XRPD patterns also display a difference between the two crystal forms as shown in Figures 10.67 and 10.68. However, the FT-IR and Raman spectra of the two crystal forms are very similar. Under the experimental conditions used in the DSC analysis, the thermograms of both forms cannot be distinguished. Heat of solution data, as shown in Table 10.24, indicate that there are differences in the heats of dissolution for the two forms, although both crystal forms have virtually identical

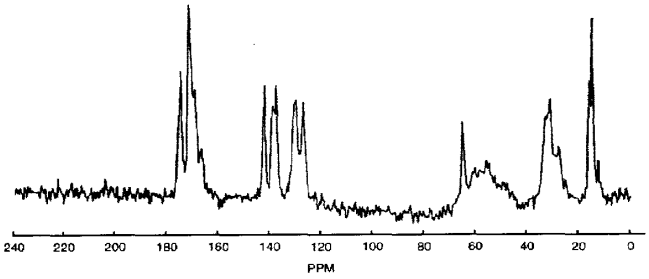


Figure 10.65 Solid-state ^{13}C NMR of enalapril maleate Form I (Ip *et al.*, 1986).

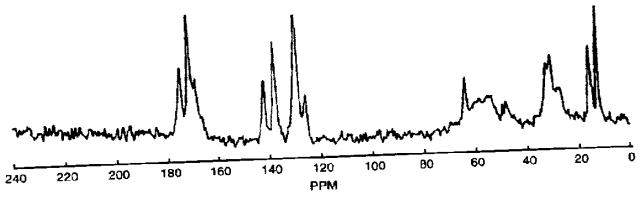


Figure 10.66 Solid-state ^{13}C NMR of enalapril maleate Form II (Ip *et al.*, 1986).

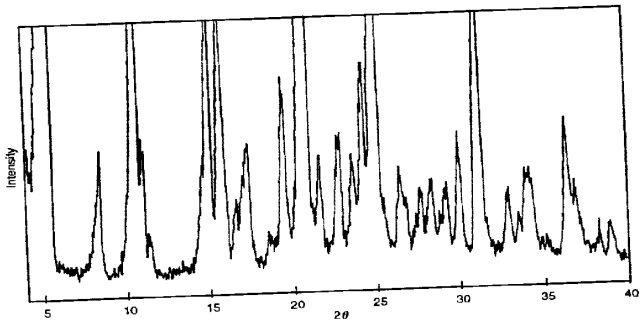


Figure 10.67 Powder X-ray diffraction pattern of enalapril maleate Form I (Ip *et al.*, 1986).

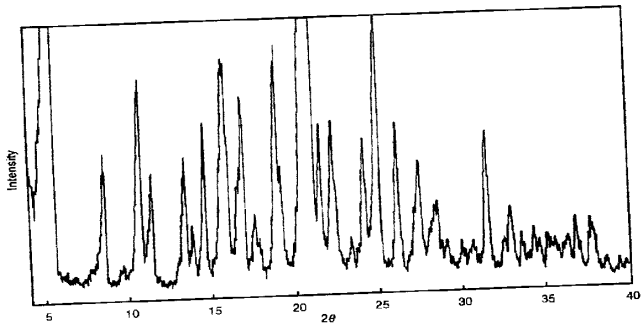


Figure 10.68 Powder X-ray diffraction pattern of enalapril maleate Form II (Ip *et al.*, 1986).

in vitro dissolution rates (s
number of methods on two
two crystal forms are very
properties.

Table 10.24 Heats of Solution

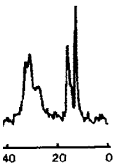
Solvent	Form I Δ (kJ/mo
Methanol	36.5(
	35.6
	35.9
	36.2(
	36.4
Mean ± S.D.	36.33 ±
Acetone	59.4
	59.7
	59.1
	59.7
Mean ± S.D.	59.52 ±

Ip *et al.*, 1986.

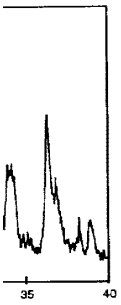
Table 10.25 Dissolution Dat

Enalapril Maleate Formulation	Crys
Capsules	
	I
	I
Tablets	

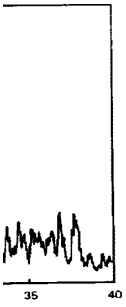
Ip *et al.*, 1986.



86).



p *et al.*, 1986).



(Ip *et al.*, 1986).

in vitro dissolution rates (see Table 10.25). In summary, this represents a study by a number of methods on two crystal forms of an important compound. It is clear that the two crystal forms are very similar in structure and have very similar pharmaceutical properties.

Table 10.24 Heats of Solution and Transition of Enalapril Maleate Polymorphs

Solvent	Form I ΔH_{soln} (kJ/mol)	Form II ΔH_{soln} (kJ/mol)	$\Delta H_{Trans.}$ (kJ/mol)
Methanol	36.50	38.47	
	35.64	38.21	
	35.95	38.54	
	36.20	38.62	
	36.46		
Mean ± S.D.	36.33 ± 0.25	38.46 ± 0.11	2.05
Acetone	59.44	62.71	
	59.73	61.99	
	59.19	62.66	
	59.73	62.54	
Mean ± S.D.	59.52 ± 0.25	62.41 ± 0.29	2.89

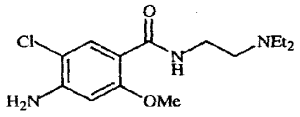
Ip *et al.*, 1986.

Table 10.25 Dissolution Data for Enalapril Maleate Capsules and Tablets

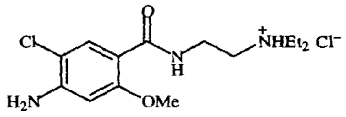
Enalapril Maleate Formulation	Crystal Form	Potency (mg)	Average Percent Dissolved at 30 min
Capsules	II	2.5	89
	I	2.5	100
	I and II	2.5	101
	I	2.5	96
	I and II	20	82
	I	20	99
	II	20	95
	I	20	92
Tablets	I	10	100
	II	10	99
	I	10	99
	I and II	10	98
	I	40	103
	I and II	40	102
	II	40	96

Ip *et al.*, 1986.

C. Metoclopramide and Metoclopramide Monohydrochloride



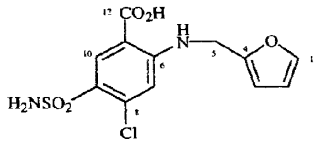
metoclopramide



metoclopramide monohydrochloride

Mitchell (1985) has studied the polymorphism of both metoclopramide and metoclopramide monohydrochloride. Each exists in two crystal forms and metoclopramide monohydrochloride also forms a monohydrate. Metoclopramide exists in two enantiotropic polymorphs with a transition temperature of 125 °C from Form I (stable at low temperature) to Form II (stable at high temperature) having a melting point of 147 °C. This process can also be reversed. Dehydration of metoclopramide monohydrochloride monohydrate, depending on the conditions, give rise to one of two anhydrous polymorphs; Form I (mp 187 °C) is formed from the melt under slow crystallization conditions, whereas, Form II (mp 155 °C) is formed from the melt under fast crystallization conditions. All of these crystal forms were detected by DSC, thermal microscopy, X-ray diffraction, and infrared spectroscopy.

D. Furosemide



furosemide

Doherty and York (1988) described the two crystal forms of furosemide readily detected by X-ray powder diffraction. In a more recent study, Matsuda and Tatsumi (1990) discovered three additional polymorphs as well as two solvates and an amorphous form. Interestingly, it was found that the forms produced could be related to the boiling point of the solvent. Thus, Form I was obtained from the lower boiling solvents used [acetone (bp 57 °C), methanol (bp 65 °C), ethanol (bp 79 °C), and methyl ethyl ketone (bp 80 °C)], Form II was obtained from the higher boiling solvents used [isobutyl alcohol (bp 108 °C), butanol (bp 118 °C), and pentanol (bp 138 °C)], and mixtures of both forms were obtained from solvents with intermediate boiling points used [isopropyl alcohol (bp 83 °C) and propanol (bp 97 °C)] by slow crystallization from a hot solution. To our knowledge this is the first such relationship which has been reported. In addition, they reported that the rate of solvent evaporation affected the crystal form obtained. Figure 10.69 shows the XRPDs of furosemide and Figure 10.70 shows the IR spectra of the different crystal forms.

Doherty and York (1988) also showed that Forms I and II had different solid-state NMR spectra as shown in Figure 10.71. Figure 10.72 shows the DSC and TG

thermograms of the six dif
all forms are unique and w

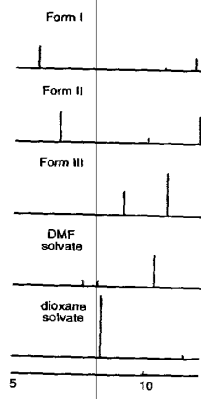


Figure 10.69 X-ray powder di
and Tatsumi, 19

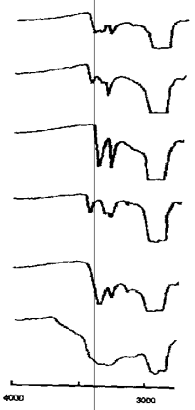


Figure 10.70 Infrared spectr
1990).

thermograms of the six different forms of furosemide. It is clear from these studies that all forms are unique and well characterized.

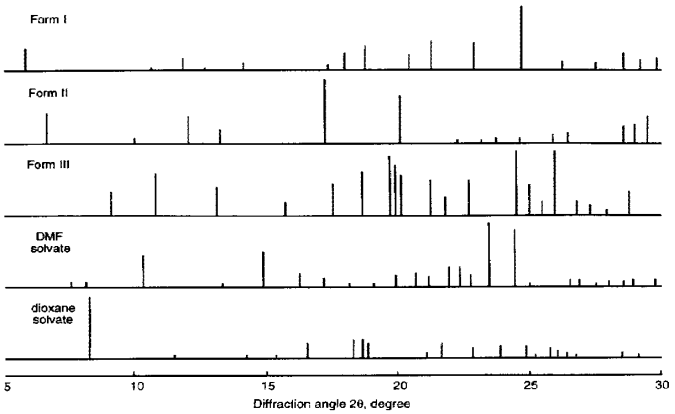


Figure 10.69 X-ray powder diffraction patterns of the different crystal forms of furosemide (Matsuda and Tatsumi, 1990).

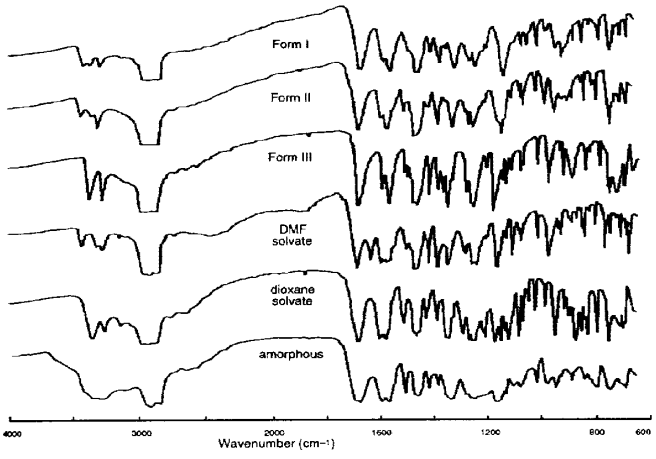


Figure 10.70 Infrared spectra of the different crystal forms of furosemide (Matsuda and Tatsumi, 1990).

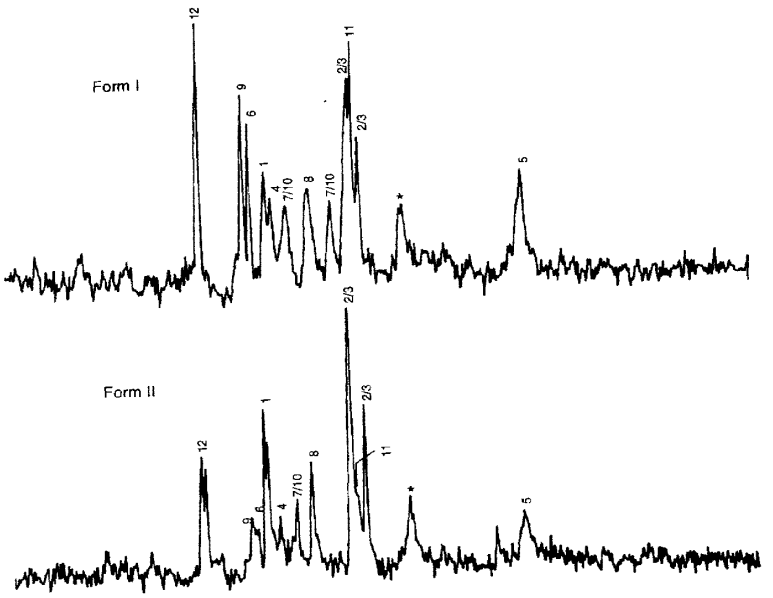


Figure 10.71 Solid-state ^{13}C CP/MAS NMR spectra for two furosemide forms at ambient temperature with peak assignments. The peaks marked with a star are due to the Delrin® rotor (Doherty and York, 1988).

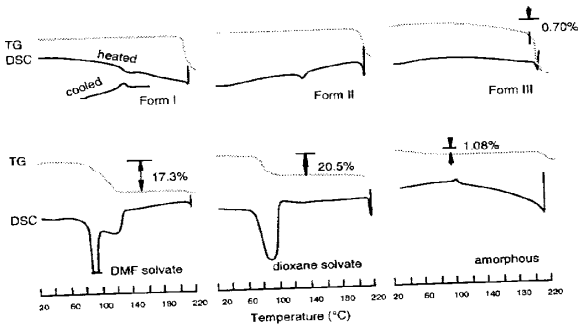


Figure 10.72 DSC and TG thermograms of the different crystal forms of furosemide (Matsuda and Tatsumi, 1990).

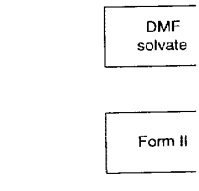


Figure 10.73 Interconvers
and Tatsum

Matsuda and Tats
which could be obtaine
studied the interconvers
rized in Figure 10.73.
most stable form, Form
Form I upon heating (s
Matsuda and Tats

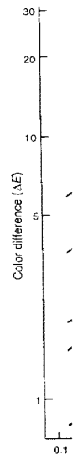


Figure 10.74 Double-log
forms unde

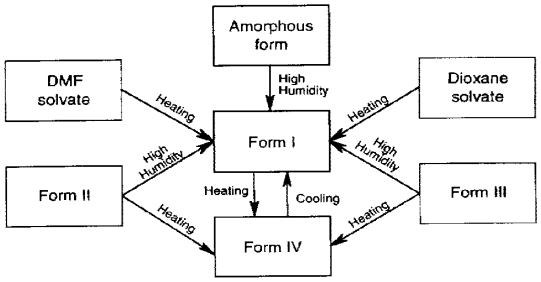


Figure 10.73 Interconversion scheme of furosemide crystal forms under various conditions. (Matsuda and Tatsumi, 1990).

Matsuda and Tatsumi (1990) found a high temperature crystal form (Form IV) which could be obtained by heating Forms I, II, or III to 180 °C. In addition, they studied the interconversion of the crystal forms and these interconversions are summarized in Figure 10.73. It is clear that all of the crystal forms can be converted into the most stable form, Form I, at room temperature. The solvated forms also converted to Form I upon heating (see Figure 10.73).

Matsuda and Tatsumi also studied the physical and chemical properties of the

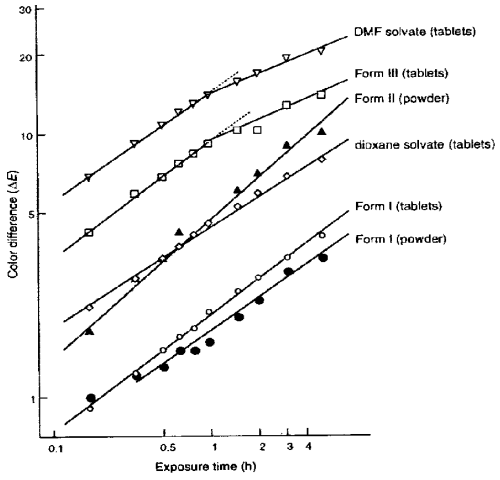


Figure 10.74 Double-logarithmic plots for the coloration process of different furosemide crystal forms under irradiation by a mercury vapor lamp (Matsuda and Tatsumi, 1990).

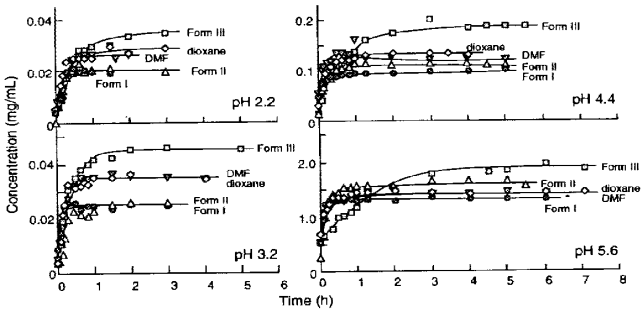
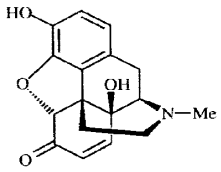


Figure 10.75 Dissolution profiles of the different crystal forms of furosemide in buffer solution at various pH values at 37° C (Matsuda and Tatsumi, 1990).

different crystal forms of furosemide. Figure 10.74 shows the studies on the photostability of the different crystal forms. It is apparent that the different crystal forms have a different amount of coloration initially but that the rate of change in coloration is about the same for all crystal forms. However, the relationship between coloration and degradation remains unknown.

Figure 10.75 shows the dissolution profiles of furosemide at different pH (2.2, 3.2, 4.4, and 5.6). It is apparent that Form II reaches the highest solubility at all pH's and that Form II and the DMF solvate are the least soluble. Judging by these profiles, some of the forms appear to interconvert in these experiments.

E. 14-Hydroxymorphinone—Color Dimorphism



14-hydroxymorphinone

The phenolic α,β-unsaturated ketone 14-hydroxymorphinone exists in two crystalline modifications (see Table 10.26), which are interconvertible by dissolution and recrystallization (Chiang *et al.*, 1978). Recrystallization from polar solvents (ethanol) yields yellow crystals, while crystallization from benzene gives colorless (white) crystals. Both forms are stable indefinitely in the solid state.

Infrared spectra show that the yellow form has a carbonyl absorption at 1685 cm^{-1}, while the colorless form has a carbonyl absorption at 1660 cm^{-1}. Since both forms have a carbonyl absorption, neither form contains an enol tautomer.

Crystallographic studies show that the conformation of 14-hydroxymorphinone in the two forms is similar; however, the yellow form contains an intermolecular OH···O

Table 10.26 Crystallogr

Parameter
Space group
a (Å)
b (Å)
c (Å)
Z
ρ_{calc} (g cm^{-3})
V (Å^3)

Chiang *et al.*, 1978.

hydrogen bond, while bond.

The color of the y hydrogen bond, since dihydroxyterephthalate is that there is a weak adjacent phenyl ring in tion between these two

Numerous other re that are not drugs. The *et al.*, 1978; Byrn *et a* important compound f thebaine gave metathe sodium bicarbonate and NaOH or NH_3 and recr melting point, and both solution in benzene. U color and no investigati been reported.

M

F

F. Miscellaneous St

Kuhnert-Brandstätter an polymorphs of pharmace spectroscopy, and in sor shown in Table 10.27. I of the different polymor

Table 10.26 Crystallographic Parameters for the Two Forms of 14-Hydroxymorphinone

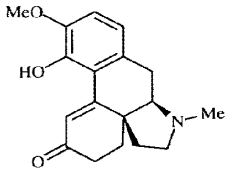
Parameter	Colorless Form	Yellow Form
Space group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	12.918	13.150
b (Å)	14.074	13.508
c (Å)	8.035	7.837
Z	4	4
ρ_{calc} (g cm^{-3})	1.36	1.428
V (Å^3)	1460.8	1392.1

Chiang *et al.*, 1978.

hydrogen bond, while the white form contains an intramolecular OH···O hydrogen bond.

The color of the yellow form may, in part, result from the intermolecular OH···O hydrogen bond, since a similar effect was found for dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate (Byrn *et al.*, 1972; see Section 8.1). An alternative explanation is that there is a weak charge-transfer interaction between the C=O group and an adjacent phenyl ring in the yellow form, but not in the colorless form. A clear distinction between these two explanations is not possible.

Numerous other reports of color dimorphism have been published for compounds that are not drugs. These reports are briefly reviewed by (Desiraju *et al.*, 1977; Chiang *et al.*, 1978; Byrn *et al.*, 1972). Color dimorphism of at least one other biologically important compound has been reported (Small and Meitzner, 1933); reduction of thebaine gave metathebainone. Neutralization of a metathebainone solution with sodium bicarbonate and recrystallization gave yellow crystals, while neutralization with NaOH or NH_3 and recrystallization gave colorless crystals. Both crystals had the same melting point, and both gave a yellow solution in ethanol or water and a colorless solution in benzene. Unfortunately, no structural explanations of these differences in color and no investigation of differences in polymorphism of these compounds have been reported.



metathebainone

F. Miscellaneous Studies by Kuhnert-Brandstätter and Co-workers

Kuhnert-Brandstätter and co-workers have carried out an extensive study on the polymorphs of pharmaceuticals. Their studies generally use thermal microscopy, IR spectroscopy, and in some cases powder diffraction. The results of these studies are shown in Table 10.27. In many cases they were able to determine the relative stability of the different polymorphs and whether they were monotropic (one forms is most

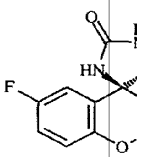
Table 10.27 Studies of Polymorphic Pharmaceuticals by Kuhnert-Brandstätter's Group

Pharmaceutical	No. of Forms	Thermodynamics*	Reference
Amiperone	2	II → I	Kuhnert-Brandstätter and Porsche, 1989b
Anilamate	3	III → II, II → I	Kuhnert-Brandstätter *et al.*, 1982c
Benactyzine HCl	2	II → I	Kuhnert-Brandstätter. and Wurian, 1982a
Bentiromide	3 + hydrates	II → I, ···	Kuhnert-Brandstätter and Porsche, 1989b
Bromopride	2	II → I	Kuhnert-Brandstätter *et al.*, 1982b
Brotizolam	4	IV → III, III → I, ···	Kuhnert-Brandstätter and Porsche, 1989b
Bumetanide	2	II → I	Kuhnert-Brandstätter *et al.*, 1982b
Bupicomide	3	Monotropic	Kuhnert-Brandstätter and Porsche, 1989a
Buspirone HCl	2	Monotropic	Kuhnert-Brandstätter and Porsche, 1989a
Clenbuterol HCl	2	II → I	Kuhnert-Brandstätter. and Wurian, 1982a
Dimethoxanate HCl	2	II → I	Kuhnert-Brandstätter *et al.*, 1982c
Diphenadione	2	II → I	Kuhnert-Brandstätter *et al.*, 1982c
Diphenidol HCl	3	III → II, III → I	Kuhnert-Brandstätter. and Wurian, 1982a
Dipyridamole	2	II → I	Kuhnert-Brandstätter. and Wurian, 1982a
Dobutamine HCl	4	···	Kuhnert-Brandstätter and Porsche, 1989b
Famotidine	2	II → I	Kuhnert-Brandstätter and Porsche, 1990
Fenbufen	3	III → II, III → I	Kuhnert-Brandstätter and Porsche, 1989b
Flucabril	2	II → I	Kuhnert-Brandstätter *et al.*, 1982b
Flupirtine Maleate	2	II → I	Kuhnert-Brandstätter and Porsche, 1990
Gallic Acid Ethyl Ester	3	III → II, III → I	Kuhnert-Brandstätter. and Wurian, 1982a
Halofenate	3	Monotropic	Kuhnert-Brandstätter and Völlenklee, 1986
Heptolamide	3	···	Kuhnert-Brandstätter and Porsche, 1989a
Iprindol HCl	3	III → II, ···	Kuhnert-Brandstätter *et al.*, 1982b
Levobunolol HCl	5		Kuhnert-Brandstätter and Porsche, 1989a
Lorcainide HCl	2	II → I	Kuhnert-Brandstätter and Völlenklee, 1986
Maprotiline HCl	3	III → II, II → I	Kuhnert-Brandstätter *et al.*, 1982c
Mexiletine HCl	3	III → I, II → I	Kuhnert-Brandstätter and Völlenklee, 1987
Minoxidil	3	III → II, II → I	Kuhnert-Brandstätter and Völlenklee, 1986
Mopidamol	4	IV → I, II → I, ···	Kuhnert-Brandstätter and Völlenklee, 1986
Nafoxidine HCl	3	III → I, II → I	Kuhnert-Brandstätter *et al.*, 1982c
Naftifine HCl	3	Monotropic	Kuhnert-Brandstätter and Porsche, 1989a
Oxypendyl 2HCl	4	III → I, II → I, ···	Kuhnert-Brandstätter and Völlenklee, 1987
Paxamate	2	II → I	Kuhnert-Brandstätter and Porsche, 1990
Penbutolol Sulfate	4	IV → III, III → II, ···	Kuhnert-Brandstätter and Völlenklee, 1987
Piretanide	4	II → I, ···	Kuhnert-Brandstätter and Porsche, 1989a
Pirprofene	2	Monotropic	Kuhnert-Brandstätter and Völlenklee, 1987
Propentofylline	4	Monotropic	Kuhnert-Brandstätter and Porsche, 1990
Renytoline HCl	3	III → II, II → I	Kuhnert-Brandstätter *et al.*, 1982b
Terconazole	2	Monotropic	Kuhnert-Brandstätter and Porsche, 1989b
Triclabendazole	2	Monotropic	Kuhnert-Brandstätter and Porsche, 1990

* Some forms undergo inhomogeneous melting rather than transformation.

stable at all temperatures) o
peratures). Specifically, Ku
this table as cases where the
the highest melting point.

G. (2*R*,4*S*)-6-FLUORO-2-M



This aldose reductase inhil
studied by DSC, X-ray pow
1988). Figure 10.76 shov
indicates that the β-form is
tent with the X-ray powder
sion of the β-form to the α
the α- and β-forms as wel
heating the β-form, indicati
α-form to the β-form appe

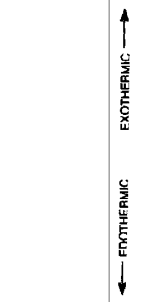
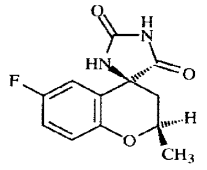


Figure 10.76 The DSC curv
dione (Ashizawa

stable at all temperatures) or enantiotropic (different forms are stable at different temperatures). Specifically, Kuhnert-Brandstätter defined enantiotropy for the purposes of this table as cases where the most stable form at room temperature is not the form with the highest melting point.

G. (2*R*,4*S*)-6-Fluoro-2-methylspiro[chroman-4,4′-imidazoline]-2′,5-dione



(2*R*,4*S*)-6-fluoro-2-methylspiro-[chroman-4,4′-imidazoline]-2′,5-dione

This aldose reductase inhibitor exists in two crystal forms, α and β, which were studied by DSC, X-ray powder diffraction, and infrared spectroscopy (Ashizawa *et al.*, 1988). Figure 10.76 shows the DSC behavior of the β–form. This thermogram indicates that the β–form is converted to the α–form at high temperature and is consistent with the X-ray powder diffraction and infrared spectra which showed interconversion of the β–form to the α-form. Figure 10.77 shows the X-ray powder patterns of the α– and β–forms as well as that of a 1:1 mixture and the product obtained upon heating the β–form, indicating it is being transformed into the α–form. Addition of the α–form to the β–form appears to provide nuclei which allow the conversion to occur

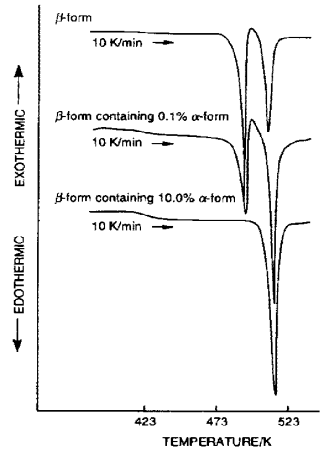


Figure 10.76 The DSC curve for (2*R*,4*S*)-6-fluoro-2-methylspiro[chroman-4,4′-imidazoline]-2′,5-dione (Ashizawa *et al.*, 1988).

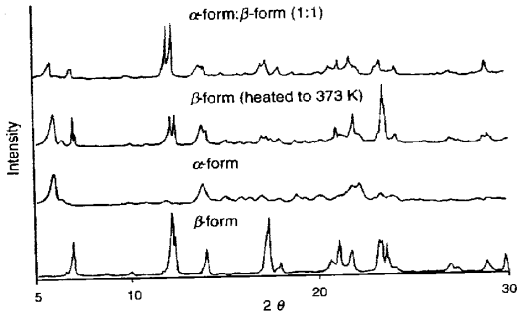
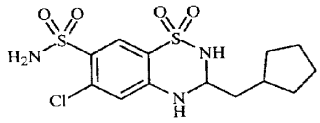


Figure 10.77 X-ray diffraction patterns of (2*R*,4*S*)-6-fluoro-2-methylspiro[chroman-4,4′-imidazoline]-2′,5-dione (Ashizawa *et al.*, 1988).

before melting of the β–form. This indicates the importance of nucleation in polymorphic interconversions.

The crystal structure of the β–form has been determined by single crystal X-ray methods (Ashizawa, 1989). They suggested that the crystal structure of the α–form is disordered and thus the structure could not be determined.

H. Cyclopenthiazide



cyclopenthiazide

The diuretic cyclopenthiazide exists in three polymorphic forms which are obtained by crystallization from ethanol:heptane:methanol (Form I), ethanol (Form II), and ethanol:water (Form III) (Gerber *et al.*, 1991).

These forms were characterized by DSC, thermomicroscopy, X-ray powder diffraction, scanning electron micrographs, IR, solid-state NMR, solution calorimetry, dissolution rates, and solubility determinations.

Figure 10.78 shows the DSC thermograms, Figure 10.79 shows the X-ray powder diffraction patterns, and Figure 10.80 shows the solid-state CP/MAS spectra. The DSC thermograms gave the following heats of fusion for the different polymorphs: Form I, 105.5 kJ/mol; Form II, 98.4 kJ/mol and Form III, 62.5 kJ/mol. The value for Form III is too low to be the ΔH_f and most likely represents a transformation process This was confirmed by thermomicroscopy in which Form III melted at 181 °C and recrystallized to Form I.

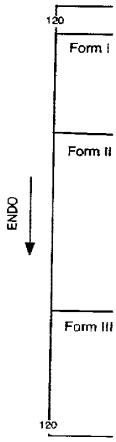


Figure 10.78 DSC the
238 °C;

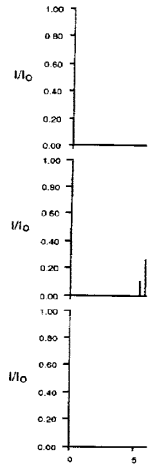


Figure 10.79 X-ray pov
1991).

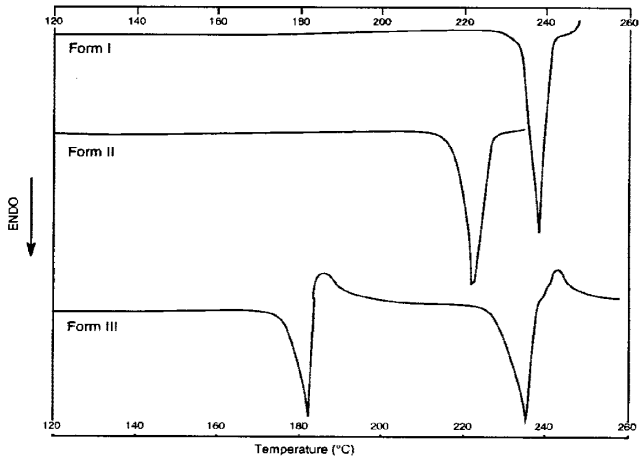


Figure 10.78 DSC thermograms of cyclopentathiazide polymorphs with melting points: Form I, 238 °C; Form II, 225 °C; and Form III, 181° and 235 °C (Gerber *et al.*, 1991).

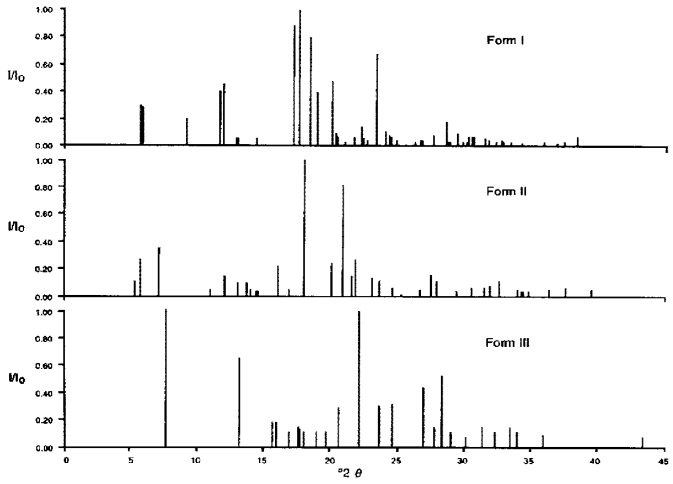


Figure 10.79 X-ray powder diffraction patterns of cyclopentathiazide polymorphs (Gerber *et al.*, 1991).

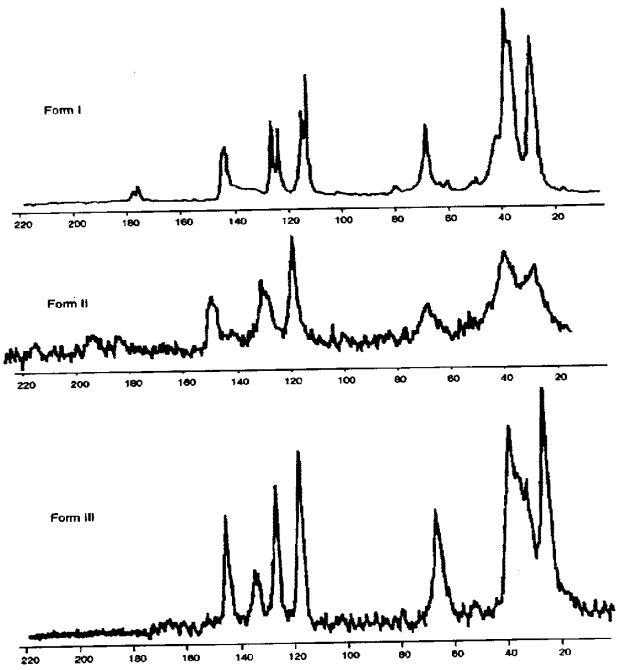


Figure 10.80 Solid-state ^{13}C NMR spectra of cyclopentathiazide polymorphs (Gerber *et al.*, 1991).

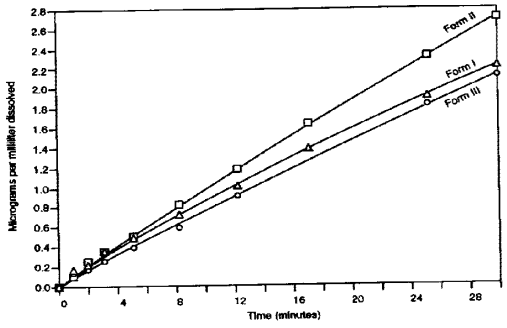
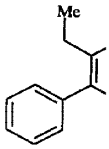


Figure 10.81 Intrinsic dissolution rates of cyclopentathiazide polymorphs (Gerber *et al.*, 1991).

It is evident from
of solution of the diff
Form I, 0.34 kJ/mol; F
these measurements ra
solution within experi
were measured and are
tion rates but Form II h
three forms were also
solubility was Form II
most stable polymorph

I. TAMOXIFEN CITR



Tamoxifen citrate is w
(1987) have reported th
Form B. Figure 10.82
morph of tamoxifen citr
of Form A; however, t
organized and less sta

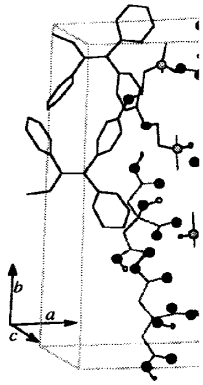
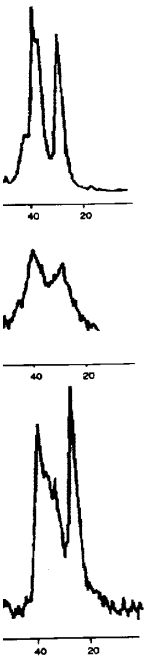
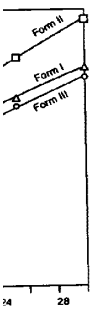


Figure 10.82 Stereoview o
Becker, 1987)



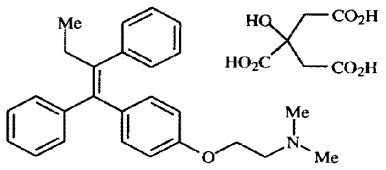
orphs (Gerber *et al.*, 1991).



hs (Gerber *et al.*, 1991).

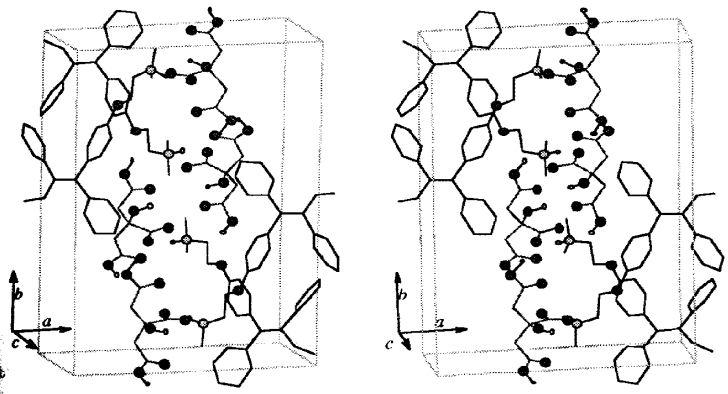
It is evident from all these data that these are truly different polymorphs. The heats of solution of the different polymorphs in 95% ethanol were also determined and are: Form I, 0.34 kJ/mol; Form II, 0.35 kJ/mol; and Form III, 0.86 kJ/mol. The errors in these measurements range 0.03–0.06 kJ/mol; thus Forms I and II have the same heat of solution within experimental error. The intrinsic dissolution rates of the three forms were measured and are shown in Figure 10.81. Forms I and III have similar dissolution rates but Form II has a significantly higher dissolution rate. The solubilities of the three forms were also determined in several solvents and in all cases the order of solubility was Form II > Form I > Form III. These data suggest that Form III is the most stable polymorph.

I. Tamoxifen Citrate



tamoxifen citrate

Tamoxifen citrate is well known as an antiestrogenic agent. Goldberg and Becker (1987) have reported the crystal structure of the more stable of two polymorphic forms, Form B. Figure 10.82 shows a stereoview of the crystal packing of the stable polymorph of tamoxifen citrate. Unfortunately they were not able to determine the structure of Form A; however, they point out that there are several indications that it is a less organized and less stable structure. For instance, they observed that at room



re 10.82 Stereoview of the crystal structure of Form B of tamoxifen citrate (Goldberg and Becker, 1987).

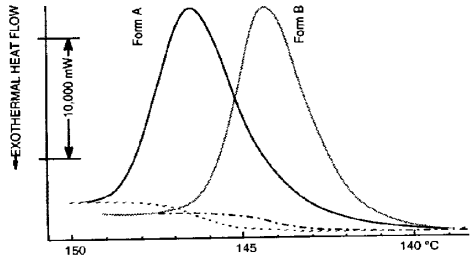


Figure 10.83 DSC thermograms of the two crystal forms of tamoxifen citrate (Goldberg and Becker, 1987).

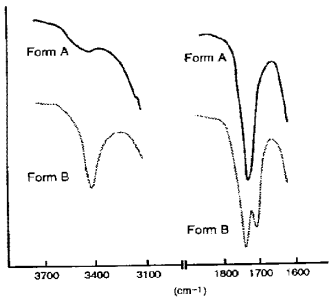


Figure 10.84 Infrared spectra of the two crystal forms of tamoxifen citrate: Form A, solid lines; Form B, dashed lines (Goldberg and Becker, 1987).

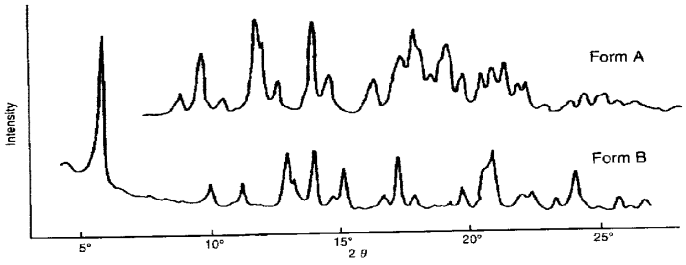


Figure 10.85 X-ray powder diffraction patterns of the two crystal forms of tamoxifen citrate (Goldberg and Becker, 1987).

temperature in an etl
They also reported
10.84), and the XRP

J. ANTIULCER AGE

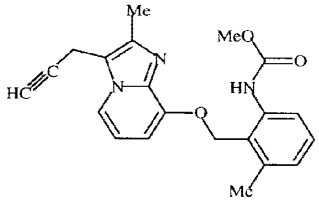
HC

Miyamac and co-worl
phism of an orally-ac
benzyloxy)-2-methyl-
in two crystal Forms
crystal forms which
10.86–10.87). In ad
diffraction patterns an
IR spectra of the two c
complicated absorption
might be caused by dif

Figure 10.86 Stereoview of

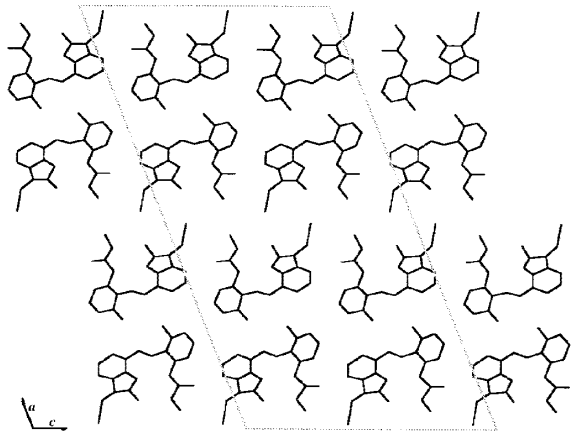
temperature in an ethanol suspension, Form A rearranges spontaneously to Form B. They also reported the DSC thermograms (Figure 10.83), the IR spectra (Figure 10.84), and the XRPDs (Figure 10.85) of the two polymorphs.

J. Antiulcer Agent FR101853



8-(2-methoxycarbonyl-amino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-*a*]pyridine (FR101853)

Miyamae and co-workers (1990) have carried out an extensive study of the polymorphism of an orally-active antiulcer compound 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-*a*]pyridine (FR101853) which exists in two crystal Forms A and B. Table 10.28 shows the crystallographic data for the two crystal forms which exhibit significantly different crystal packing (see Figures 10.86–10.87). In addition, the different crystal forms have different X-ray powder diffraction patterns and different DSC thermograms (Figure 10.88). Interestingly, the IR spectra of the two crystal forms are very similar (Figure 10.89) perhaps because the complicated absorptions of the molecule obscure any differences in infrared spectra that might be caused by different crystal packing.



re 10.86 Stereoview of the crystal packing of FR101853, Form A (Miyamae *et al.*, 1990).

Table 10.28 Crystal Data for the Two Crystal Forms of FR101853

Parameter	Form A	Form B
Space Group	$C2/c$	$P2_1/c$
a (Å)	42.936(14)	4.367(1)
b (Å)	4.356(1)	38.214(3)
c (Å)	21.536(6)	11.253(1)
β	109.92(4)°	95.47(2)°
Z	8	4
ρcalc (g cm^{-3})	1.275	1.292
V (Å^3)	3786.7(20)	1869.4(3)

Miyamae *et al.*, 1990.

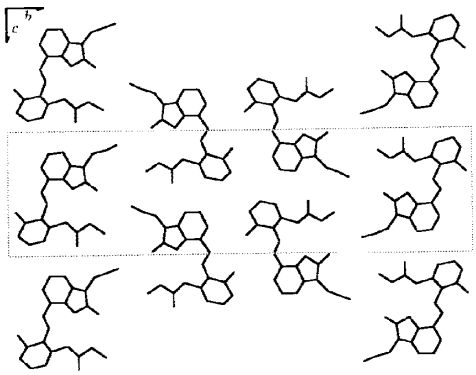


Figure 10.87 Stereoview of the crystal packing of FR101853, Form B (Miyamae *et al.*, 1990).

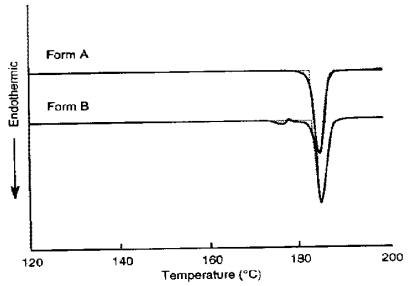


Figure 10.88 DSC thermograms of the different crystal forms of FR101853 (Miyamae *et al.*, 1990).

Form

Form

Figure 10.89 Infrared spect

10.8 CARBOHYDRAT

In this section, polymor substantial interest since ous carbohydrates exhib have been reported.

Mannitol exists in f isolated in the pure stat impurity. In addition, a The different compressib implications for their use tion patterns of the α- shows the X-ray powde apparent that material fr other preparations. The cial products were deter also carried out and it w tablets of different hardr but different amounts o related to the crystal form urements may be subject in the different crystal preparation and demonst excipients used in tablets

Several other carbol drate 4-methoxyphenyl- Each form has a distinct 161 °C (Shafizadeh an pyranoside also exists in can be converted to For acetamidotri-*O*-acetyl-β-

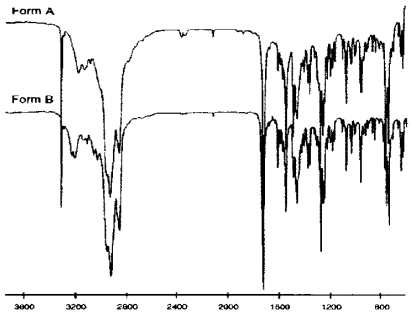


Figure 10.89 Infrared spectra of the different crystal forms of FR101853 (Miyamae *et al.*, 1990).

10.8 CARBOHYDRATES

In this section, polymorphism of carbohydrates is briefly discussed. This area is of substantial interest since carbohydrates are often used as excipients. Although numerous carbohydrates exhibit polymorphism, relatively few studies of these compounds have been reported.

Mannitol exists in four forms (Debord *et al.*, 1987). The α- and β-form have been isolated in the pure state, the δ-form has been isolated containing the α-form as an impurity. In addition, a fourth form was found but could not be characterized further. The different compressibilities and particle shapes of these forms could have important implications for their use as excipients. Figure 10.90 shows the X-ray powder diffraction patterns of the α- and β-forms as well as the "unknown" form. Figure 10.91 shows the X-ray powder patterns of different commercial products of mannitol. It is apparent that material from supplier 4 (S_4) contains a crystal form different from the other preparations. The water contents of the crystal forms and the different commercial products were determined after two months storage. Compression studies were also carried out and it was found that compression of the different samples produced tablets of different hardness. The different products and crystal forms took up small but different amounts of water, but the amount of water uptake did not seem to be related to the crystal form. The amounts of water uptake are so small that these measurements may be subject to variations from the amount of amorphous material present in the different crystal forms. Such studies have important implications for tablet preparation and demonstrate that it may be important to control the polymorphic form of excipients used in tablets.

Several other carbohydrates also exist in polymorphs. For example, the carbohydrate 4-methoxyphenyl-β-D-glucopyranoside exists in two forms (Forms I and II). Each form has a distinct powder pattern, and Form II can be converted to Form I at 161 °C (Shafizadeh and Susott, 1973). Phenyl-2-acetamidotri-*O*-acetyl-β-D-glucopyranoside also exists in two polymorphs that have different powder patterns. Form II can be converted to Form I at 185 °C (Shafizadeh and Susott, 1973). 4-Methoxy-2-acetamidotri-*O*-acetyl-β-D-glucopyranoside exists in four forms which have different

powder patterns (Shafizadeh and Susott, 1973). Form IV is converted to Form III at 158 °C, Form III can be converted to Form II at 177 °C, and Form II can be converted to the least stable form, Form I, at 183 °C. Form I melts at 192 °C.

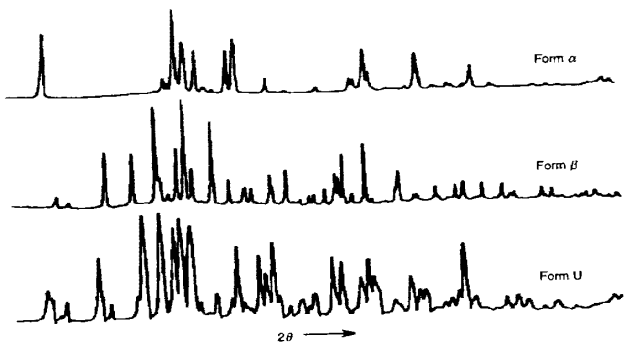


Figure 10.90 X-ray powder diffraction patterns of the α-, β-, and unknown forms of mannitol (Debord *et al.*, 1987).

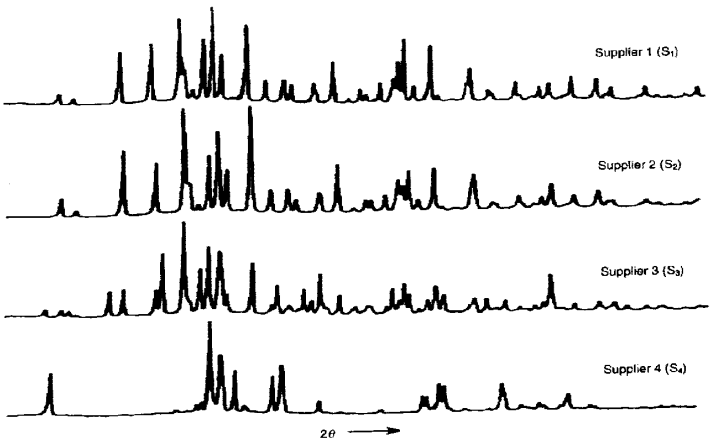


Figure 10.91 X-ray powder diffraction patterns of the commercial mannitol products S_1 through S_4 (Debord *et al.*, 1987).

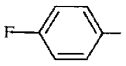
10.9 POLYMORPHS OF A

Antibiotics exhibit polym
In addition, cephalosporir
solvates as discussed in C

For the polyene antib
tallization have resulted in
differences are not due to p
mepartricin in methylene
which crystallized upon st
and between one-sixth an
tained by cooling an aceto

Studies of nystatin s
ter–methyl ethyl ketone so
ganisms, but half the solub
chloroform–methanol–amr
been proven by X-ray pov
that the differences in acti
solution rate. These solubi
ences.

A. CONFORMATIONAL PO



Azibi *et al.* (1983) describ
compound exists in two cr
10.92–10.93 and Table 10.
°C. The infrared spectra of

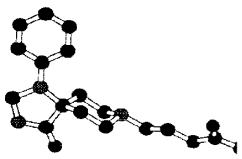


Figure 10.92 Stereoview of the
● N, ● O (Azit

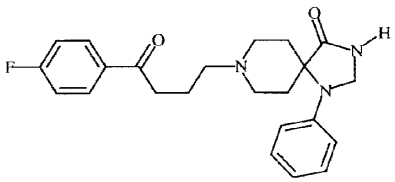
10.9 POLYMORPHS OF ANTIBIOTICS

Antibiotics exhibit polymorphism which could affect their stability and bioavailability. In addition, cephalosporin antibiotics crystallize in an extensive series of hydrates and solvates as discussed in Chapter 11.

For the polyene antibiotics, mepartricin and nystatin, different conditions of crystallization have resulted in products with different activity and acute toxicity. These differences are not due to particle size effects (Ghielmetti *et al.*, 1976). Evaporation of mepartricin in methylene chloride–methanol (9:1) at room temperature gave an oil which crystallized upon standing to form a solid which had one-fourth the oral activity and between one-sixth and one-tenth the LD_{50} (for mice) compared to the solid obtained by cooling an acetone–water–ether solution.

Studies of nystatin showed that crystals obtained by crystallization of a water–methyl ethyl ketone solution had approximately the same activity against microorganisms, but half the solubility and half to one-tenth the LD_{50} of crystals obtained from chloroform–methanol–ammonia. While the existence of nystatin polymorphs has not been proven by X-ray powder diffraction or other experimental techniques, it is likely that the differences in activity of the crystals are due to differences in solubility and solution rate. These solubility differences may, in turn, be due to polymorphic differences.

A. CONFORMATIONAL POLYMORPHISM OF SPIPERONE



spiperone

Azibi *et al.* (1983) described the conformational polymorphism of spiperone. This compound exists in two crystal forms (the structures and data are shown in Figures 10.92–10.93 and Table 10.29). Form I melted at 208.9 °C and Form II melted at 207 °C. The infrared spectra of the two crystal forms are different, and the crystal structure

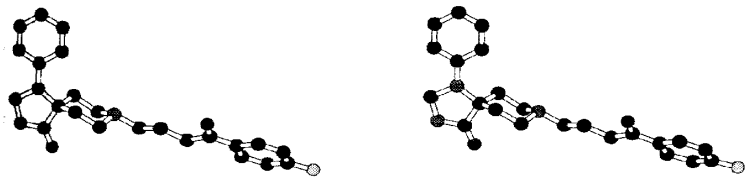


Figure 10.92 Stereoview of the molecular conformation of spiperone in Form I where: ● C, ○ F, ● N, ● O (Azibi *et al.*, 1983).

Figure 10.93 Stereoview of the molecular conformation of spiperone in Form II where: ● C, ◎ F, ● N, ● O (Koch and Germain, 1972).

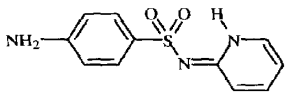
Table 10.29 Crystal Data of Spiperone Forms I and II

Parameter	Form I[a]	Form II[b]
Space Group	$P2_1/a$	$P2_1/c$
a (Å)	12.722	18.571
b (Å)	7.510	6.072
c (Å)	21.910	20.681
β	95.08°	118.69°
Z	4	4
V (Å^3)	2085.1	2045.7

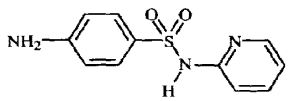
a Azibi *et al.*, 1983. *b* Koch and Germain, 1972.

showed that the conformation of the two forms are significantly different (see Figures 10.92–10.93). The authors analyzed the crystal packing and determined that hydrogen bonding was responsible for the polymorphism.

B. Sulfapyridine



"imide"



"amide"

Bar and Bernstein (1985) described the conformational polymorphism of 4-amino-*N*-2-pyridinylbenzenesulfonamide, sulfapyridine. The crystal structures of four forms of sulfapyridine were determined and are summarized in Table 10.30. The bond lengths and bond angles among the four structures are virtually identical, and are consistent with the imide structure. However, the conformations of the molecules are different in the different crystal structures, producing the phenomenon termed "conformational polymorphism." The conformations of the four different crystal forms are shown in Figure 10.94. It is clear that there is a different conformation about the —SO_2— bond in different molecules with some of the sulfapyridine rings pointing to the left in some forms and to the right in other forms.

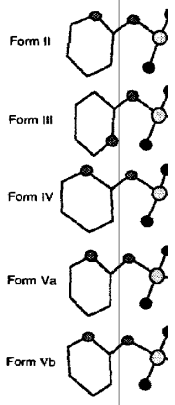


Figure 10.94 Stereoview of the
Bernstein, 1985; I

Table 10.30 Crystal Data for Su

Parameter	Form II[a]
Space group	$P2_1/c$
a (Å)	6.722
b (Å)	20.593
c (Å)	8.505
β	101.14°
Z	4
ρ_{calc} (g cm^{-3})	1.43
V (Å^3)	1155.1

a Bar and Bernstein, 1985. *b* Ba

Bar and Bernstein (19
dine in the different crystal
tions showed that all four fc

Finally, the authors co
single crystal structures obt
the different crystal forms.
well with the published diff
of Form II and III did not
that there are additional cry
that a given powder patter
calculated pattern from a su
either from observed single
nates using a program such

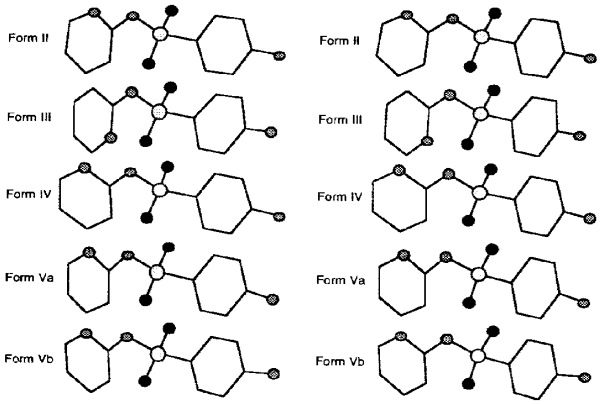


Figure 10.94 Stereoview of the molecular conformations in the four forms of sulfapyridine (Bar and Bernstein, 1985; Basak *et al.*, 1984; Bernstein, 1988).

Table 10.30 Crystal Data for Sulfapyridine

Parameter	Form II[a]	Form III[b]	Form IV[c]	Form V[d]
Space group	$P2_1/c$	$C2/c$	$P2_1/c$	$Pbca$
a (Å)	6.722	12.830	13.560	24.722
b (Å)	20.593	11.714	6.480	15.710
c (Å)	8.505	15.400	14.120	12.147
β	101.14°	94.12°	113.70	...
Z	4	8	4	16
ρ_{calc} (g cm^{-3})	1.43	1.44	1.46	1.41
V (Å^3)	1155.1	2308.5	1136.1	4717.7

a Bar and Bernstein, 1985. *b* Basak *et al.*, 1984. *c* Bernstein, 1988.

Bar and Bernstein (1985) also investigated the molecular energetics of sulfapyridine in the different crystal forms using extended Hückel calculations. These calculations showed that all four forms are within about 2.1 kJ/mol in energy.

Finally, the authors compared their data to research from other laboratories. The single crystal structures obtained allowed calculation of the X-ray powder patterns of the different crystal forms. The calculated X-ray powder pattern of Form I compared well with the published diffractogram. However, the calculated X-ray powder patterns of Form II and III did not agree with any previously reported patterns. This suggests that there are additional crystal forms. This study illustrates that the best way to prove that a given powder pattern is that of a pure polymorph is by comparing it with a calculated pattern from a single crystal structure. The powder pattern may be calculated either from observed single crystal diffraction intensity data or from the atomic coordinates using a program such as *Cerius*[2] (see Section 3.5).

10.10 POLYMORPHISM AND CHEMICAL STABILITY

Because polymorphs have different properties, including different melting points, densities, and crystal structures, it is not surprising that polymorphs have different chemical stabilities.

Perhaps the most striking effect of polymorphism on chemical reactivity is seen in the polymorphs of *trans*-2-ethoxycinnamic acid (see Figure 10.95). Irradiation of this compound in solution produces *trans*- to *cis*-isomerization, but no dimerization (Cohen and Green, 1973). Crystallization of this cinnamic acid yields three polymorphs, α, β, and γ. The α-form is obtained from ethyl acetate, ether, or acetone; the β-form is obtained from benzene or petroleum ether; and the γ-form is obtained from aqueous ethanol. Irradiation of the α-form gives the centrosymmetric dimer, irradiation of the β-form gives the mirror symmetric dimer, and irradiation of the γ-form produces no reaction. These reactions are summarized in Figure 10.95. Numerous examples of similar behavior have been found in other cinnamic acid derivatives and in anthracene dimerizations.

A number of pharmaceutical examples of different stabilities of polymorphs are also known. For example, methylprednisolone crystallizes in two forms. One form is stable while the other is reactive when exposed to heat, ultraviolet light, or high humidity (Munshi, 1973).

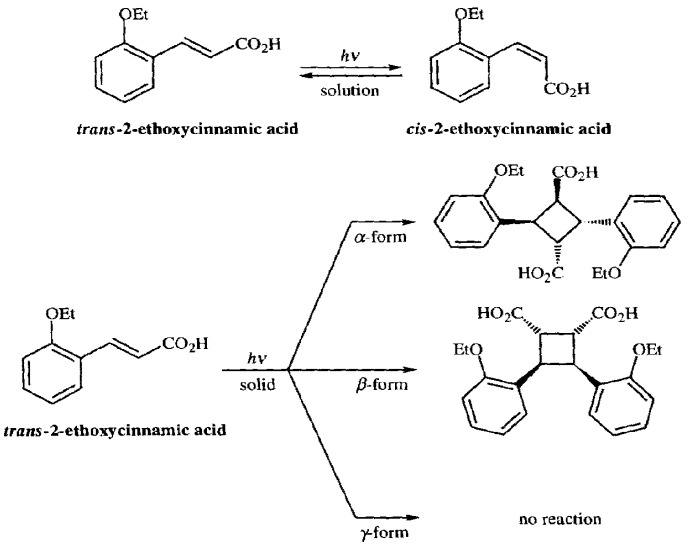


Figure 10.95 Summary of the reactivities of the α-, β-, and γ-crystalline forms of *trans*-2-ethoxycinnamic acid upon exposure to ultraviolet light (Cohen and Green, 1973).

In closely related stu
been reported. In our lab
polymorphs of hydrocort
ethanol in three crystalline
light, one of the solvates is
there are numerous cases
crystalline form. Macek (1
potassium penicillin G are
of the potassium salt can w
of the amorphous form re
have found similar differ
applied to sensitivity discs
detail in Chapter 12 (see S
This discussion clearly
there is a need for careful c

10.11 POLYMORPHISM AN

The rate of absorption of a
dissolution rate is affected
the lowest solubility and, i
polymorphs will usually
ignored, significant dose-t
In a particular striking
taining various ratios of F
(*i.e.*, blood levels) (Aguia

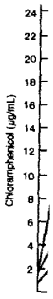


Figure 10.96 Comparison
suspensions
oral dose equi
creases, the pe
the next 25%
McCrone, 19

In closely related studies, different stabilities of polymorphs and solvates have been reported. In our laboratory, we have reinvestigated the behavior of the various polymorphs of hydrocortisone 21-*tert*-butylacetate. This steroid crystallizes from ethanol in three crystalline forms, one anhydrous and two solvates. When exposed to light, one of the solvates is reactive while the other two forms are stable. In addition, there are numerous cases where amorphous forms are much more reactive than the crystalline form. Macek (1965) has reported that the amorphous forms of sodium and potassium penicillin G are significantly less stable than the crystalline forms. Crystals of the potassium salt can withstand heating for several hours, while identical treatment of the amorphous form results in a significant loss of activity. Pfeiffer *et al.* (1976) have found similar differences between amorphous and crystalline cephalosporins applied to sensitivity discs. The reactivity of amorphous drugs is discussed in more detail in Chapter 12 (see Sections 12.1C–D).

This discussion clearly shows that in cases where chemical stability is a problem, there is a need for careful control of the polymorph or solvate.

10.11 Polymorphism and Bioavailability

The rate of absorption of a drug is sometimes dependent upon the dissolution rate. The dissolution rate is affected by the polymorph present, with the most stable form having the lowest solubility and, in most cases, the slowest dissolution rate. Other less stable polymorphs will usually have higher dissolution rates. Thus, if polymorphism is ignored, significant dose-to-dose variations can occur (Haleblian and McCrone, 1969).

In a particular striking example, a suspension of chloramphenicol palmitate containing various ratios of Form A and B showed significant variations in bioavailability (*i.e.*, blood levels) (Aguiar *et al.*, 1967). Figure 10.96 shows a comparison of mean

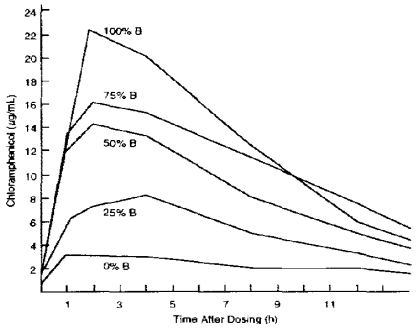


Figure 10.96 Comparison of the mean serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of the A and B polymorphs following a single oral dose equivalent to 1.5 gm of chloramphenicol palmitate. As the blood level increases, the percent of polymorph B increases. The lowest curve corresponds to 0% B, the next 25% B, the next 50% B, then 75% B, and the highest 100% B (Haleblian and McCrone, 1969).

blood serum levels of suspensions containing varying ratios of Form A and B. Clearly, the maximum blood levels are quite different, ranging from 3 to 22 μg/mL or by approximately a factor of seven. (Interestingly, a plot of peak blood levels versus percent Form B gave a straight line, as shown in Figure 10.97.) These data show that bioavailability is influenced by the type and concentration of the polymorph present. Obviously, if products are manufactured containing Form A, they will be largely inactive, while products containing Form B will show activity.

In another study, serum levels of the amorphous form and Form A of chloramphenicol palmitate have been compared in both children and Rhesus monkeys. Table 10.31 lists the results of these studies (Banerjee *et al.*, 1971) which show that the amorphous form has greater bioavailability than Form A.

Fluprednisolone crystallizes in three polymorphs and two solvates. These forms were pressed into pellets and implanted into rats, and their *in vivo* dissolution rates

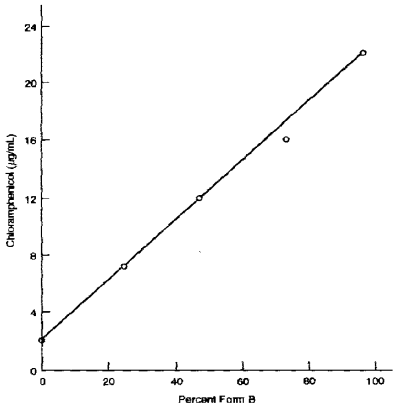


Figure 10.97 Plot of the peak chloramphenicol palmitate blood levels versus the percent of polymorph B (Haleblian and McCrone, 1969).

Table 10.31 Blood Levels (μg/100 mL) for Various Suspensions of Chloramphenicol Palmitate[a]

Suspension used	Hours after Feeding 2	4	6	8
		In Children		
Amorphous	102	60	42	26
Polymorph A	34	35	57	23
		In Rhesus Monkeys		
Amorphous	58	39	18	
Polymorph A	22	17	17	

a Banerjee *et al.*, 1971.

were measured (Hale
following order and
M^{-1}) > Form II (0.18
monohydrate (0.147
mately a factor of 1.6

The examples dis
matically affect the bic

10.12 POLYMORPHISM

Because polymorphs
choose the proper pol
22.10). In general, t
answers to the followi

1. What are
2. Can pure,
3. Will the f

Furthermore, several

1. How man
2. What is t
morphs?
3. Can the m

These basic quest
be determined by mic
DSC, IR, solid-state
(see Section 22.3).
solution phase transfo
in a drop of saturate
crystals of less stable
until only the most sta
of forms in successio
can also be used to pr
or decreased to the te
experiment repeated.

There are numer
tion of polymorphism
Tableting behavior d
(1972) showed that
causes **powder brid**
A, which is not plate

The behavior of
wrong polymorph of
occur producing a ch
is often undesirable a
syringeability of the

were measured (Haleblian and McCrone, 1969). The dissolution rates showed the following order and value: Form I (0.237 mg cm^{-2} M^{-1}) > Form III (0.209 mg cm^{-2} M^{-1}) > Form II (0.186 mg cm^{-2} M^{-1}) > β-monohydrate (0.162 mg cm^{-2} M^{-1}) > α-monohydrate (0.147 mg cm^{-2} M^{-1}). Thus, the variation in dissolution rate is approximately a factor of 1.6 when comparing Form I to the α-monohydrate.

The examples discussed in this section show that the polymorph present can dramatically affect the bioavailability of a drug.

10.12 Polymorphism and Its Pharmaceutical Application

Because polymorphs have different physical properties, it is often advantageous to choose the proper polymorph for the desired pharmaceutical application (see Section 22.10). In general, the pharmaceutical applications of polymorphism depends on the answers to the following questions:

1. What are the solubilities of each form?
2. Can pure, stable crystals of each form be prepared?
3. Will the form survive processing, micronizing, and tableting?

Furthermore, several more basic questions about polymorphs also need to be answered:

1. How many polymorphs exist?
2. What is the chemical and physical stability of each of these polymorphs?
3. Can the metastable states be stabilized?

These basic questions can be answered as follows: The number of polymorphs can be determined by microscopic examination and by subsequent analytical studies using DSC, IR, solid-state NMR, X-ray powder diffraction, and single-crystal X-ray studies (see Section 22.3). The physical stability of each form can be determined using the solution phase transformation method. This method involves placing two polymorphs in a drop of saturated solution under the microscope. Under these conditions, the crystals of less stable form will dissolve and crystals of the more stable form will grow until only the most stable form remains. Comparison of the relative stabilities of pairs of forms in succession gives the order of stability of the various forms. This method can also be used to prepare metastable forms. In this case, the temperature is increased or decreased to the temperature where the metastable form is most stable and then the experiment repeated.

There are numerous activities in the pharmaceutical industry that require consideration of polymorphism; these have been reviewed by Haleblian and McCrone (1969). Tableting behavior depends upon the polymorph present. For example, Simmons *et al.* (1972) showed that tolbutamide exists in Forms A and B. Form B is plate-like and causes **powder bridging** in the hopper and **capping** problems during tableting. Form A, which is not plate-like, showed no problems during tableting.

The behavior of suspensions also depends upon the polymorph present. If the wrong polymorph of a drug is used, a phase transformation to a more stable form may occur producing a change in crystal size and possibly caking. A change in particle size is often undesirable as it may cause serious caking problems, as well as changes in the syringeability of the suspension. In addition, the new polymorph may have altered

dissolution properties and, thus, bioavailability. Caking is a particularly serious problem since a caked suspension cannot be resuspended upon shaking. For example, oxyclozanide, upon standing in quiescent (undisturbed) suspensions, undergoes an increase in particle size (Pearson and Varney, 1969). This is due to a solvent-mediated phase transformation between two polymorphs. As discussed earlier, under these conditions, crystals of the more stable form grow and those of the less stable form dissolve. This produces cakes that cannot be resuspended by shaking.

REFERENCES

Agafonov, V., B. Legendre, and N. Rodier (1989) "A new crystalline modification of spironolactone" *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **45** 1661–1663.

Agafonov, V., B. Legendre, N. Rodier, D. Wouessidjewe, and J.-M. Cense (1991) "Polymorphism of spironolactone" *J. Pharm. Sci.* **80** 181–185.

Aguiar, Arondo J., John Krc, Jr., Arlyn W. Kinkel, and Joseph C. Samyn (1967) "Effect of polymorphism on the absorption of chloramphenicol from chloramphenicol palmitate" *J. Pharm. Sci.* **56** 847–853.

Alleaume, Marc, and Joseph Decap (1965) "Tridimensional refinement of β-sulfanilamide" *Acta Crystallogr.* **18** 731–736.

Alleaume, Marc, and Joseph Decap (1966) "Tridimensional refinement of γ-sulfanilamide" *Acta Crystallogr.* **19** 934–938.

Armour Research Foundation (1949) "Sulfasuxidine (*p*-2-thiazolylsulfamylsuccinanilic acid)" *Anal. Chem.* **21** 1293–1294.

Ashizawa, Kazuhide, Kiyohiko Uchikawa, Teiichi Hattori, Tadashi Sato and Yasuo Miyake (1988) "Polymorphic differences in α- and β-form crystals of 2*R*,4*S*,6-fluoro-2-methyl-spiro[chroman-4,4'-imidazoline]-2',5-dione (M79175) as determined by X-ray diffraction, infrared spectroscopy, and differential scanning calorimetry" *J. Pharm. Sci.* **77** 635–637.

Ashizawa, Kazuhide (1989) "Polymorphism and crystal structure of 2*R*,4*S*,6-fluoro-2-methyl-spiro[chroman-4,4'-imidazoline]-2',5-dione (M79175)" *J. Pharm. Sci.* **78** 256–260.

Azibi, M., M. Draguet-Brughmans, R. Bouche, B. Tinant, G. Germain, J. P. DeClercq, and M. Van Meerssche (1983) "Conformational study of two polymorphs of spiperone: possible consequences on the interpretation of pharmacological activity" *J. Pharm. Sci.* **72** 232–235.

Banerjee, Sachchidananda, Asok Bandyopadhyay, Ramesh Chandra Bhattacharjee, Arun Kumar Mukherjee, and Arup Kumar Halder (1971) "Serum levels of chloramphenicol in children, rhesus monkeys, and cats after administration of chloramphenicol palmitate suspension" *J. Pharm. Sci.* **60** 153–155.

Bar, I. and J. Bernstein (1985) "Conformational polymorphism. VI. The crystal and molecular structures of Form II, Form III, and Form V of 4-amino-*N*-2-pyridinylbenzenesulfonamide (sulfapyridine)" *J. Pharm. Sci.* **74** 255–263.

Basak, A. K., S. Chaudhuri, and S. K. Mazumdar (1984) "Structure of 4-amino-*N*-2-pyridylbenzenesulfonamide (sulfapyridine), $C_{11}H_{11}N_3O_2S$" *Acta Crystallogr., Sect. C, Cryst. Struct. Commun.* **C40** 1848–1851.

Basak, A. K., S. K. Mazumdar, and S. Chaudhuri (1987) "Structure of N'-(6-methoxy-3-pyridazinyl)sulfanilamide (sulfamethoxypyridazine)" *Acta Crystallogr., Sect. C, Cryst. Struct. Commun.* **C43** 735–738.

Bernstein, J. and A. T. Hagler (1978) "Conformational polymorphism. The influence of crystal structure on molecular conformation" *J. Am. Chem. Soc.* **100** 673–681.

Bernstein, Joel (1987) "Conformational polymorphism" in *Organic Solid State Chemistry*; G. R. Desiraju, Ed.; Studies in Organic Chemistry 32; Elsevier: Amsterdam; Chapter 13.

Bernstein, J. (1988) "Polymorph IV of 4-amino-*N*-2-pyridinylbenzenesulfonamide (sulfapyridine)" *Acta Crystallogr., Sect. C, Cryst. Struct. Commun.* **C44** 900–902.

Bettinetti, G. P., F. Giordano, and A. La Manna (1982) "Solid state molecular arrangements of sulfamethoxazole $C_{10}H_{11}N_3O_3S$: the crystal structure of two polymorphs" *Cryst. Strucut. Comm.* **11** 821–828.

Biles, John A. (1963) "So
hydrocortisone" *J. Phc*

Borchardt, Thomas B. (19
pharmaceutical precurs
due University: West L

Brown, Herbert C. and Sei
ease of polymorphism

Burger, A. (1973) "The pol

Burger, A. (1973) "Solubil
pharmaceutical (sulfani

Burger, Artur (1975) "Poly

Burger, Artur and Regine I
zole" *Pharm. Acta Hel*

Burger, A. and U. J. Gries
poeia. IV. Identificat
Pharm. **57** 293–305.

Burger, Artur and Ulrich J
succinylsulfathiazole ci
poeia. VII" *Eur. J. Phc*

Busetta, Bernard, Christian
three polymorphous fo

Byrn, Stephen R., David Y.
white forms of dimeth
the yellow form to the

Byrn, Stephen R. and Chun
of hydrate crystals of
4004–4005.

Byrn, Stephen R., Brian Tc
Kozlowski (1988) "Re
morphs and solvates of

Chiang, Chian C., Wilson
Weiss (1978) "Color d
talline modifications"

Cohen, M. D. and Beman
490–497.

Craven, B. M. and E. A
isoamylbarbituric acid

Curtin, D. Y. and S. R.
hydrogen bonding. St
2,5-dihydroxyterephth

Curtin, David Y. and John
of 6-aroyloxyphenanth

Dabrowski, Janusz (1963)
pounds. I. Enamino I

Debord, B., C. Lefebvre,
"Study of different cry
Dev. Ind. Pharm. **13** 1

DeCamp, Wilson H. and F
and molecular structu
B., Struct. Sci. **B28** 1

DeCamp, Wilson H. and F
and molecular structu
Sect. B., Struct. Sci. 1

Desiraju, Gautam R., Iain
yellow to the red for
anisotropy of the reac

Biles, John A. (1963) "Some crystalline modifications of the *tert*-butylacetates of prednisolone and hydrocortisone" *J. Pharm. Sci.* **52**, 1066–1070.

Borchardt, Thomas B. (1997) "The derivatization, solid-state characterization, and crystallization of a pharmaceutical precursor that expresses color polymorphism in the solid state" Ph.D. Thesis, Purdue University: West Lafayette, IN 47907-1333.

Brown, Herbert C. and Sei Sujishi (1948) "Tri-1-naphthylboron as a highly hindered reference acid: a case of polymorphism ascribed to hindered rotation" *J. Am. Chem. Soc.* **70** 2793–2802.

Burger, A. (1973) "The polymorphs of sulfanilamide" *Sci. Pharm.* **41** 290–303.

Burger, A. (1973) "Solubility studies in the determination of thermodynamic data of a polymorphic pharmaceutical (sulfanilamide)" *Sci. Pharm.* **41** 303–314.

Burger, Artur (1975) "Polymorphism of oral antidiabetics. II. Tolbutamide" *Sci. Pharm.* **43** 161–168.

Burger, Artur and Regine D. Dialer (1983) "New research results on the polymorphism of sulfathiazole" *Pharm. Acta Helv.* **58** 72–78.

Burger, A. and U. J. Griesser (1989) "The polymorphic drug substances of the European Pharmacopoeia. IV. Identification and characterization of 11 crystal forms of succinylsulfathiazole" *Sci. Pharm.* **57** 293–305.

Burger, Artur and Ulrich J. Griesser (1991) "Physical stability, hygroscopicity and solubility of succinylsulfathiazole crystal forms. The polymorphic drug substances of the European Pharmacopoeia. VII" *Eur. J. Pharm. Biopharm.* **37** 118–124.

Busetta, Bernard, Christian Courseille, and Michel Hospital (1973) "Crystal and molecular structure of three polymorphous forms of estrone" *Acta Crystallogr., Sect. B., Struct. Sci.* **B29** 298–313.

Byrn, Stephen R., David Y. Curtin, and Iain C. Paul (1972) "X-ray crystal structures of the yellow and white forms of dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate and a study of the conversion of the yellow form to the white form in the solid state" *J. Am. Chem. Soc.* **94** 890–898.

Byrn, Stephen R. and Chung-Tang Lin (1976) "The effect of crystal packing and defects on desolvation of hydrate crystals of caffeine and L-(–)-1,4-cyclohexadiene-1-alanine" *J. Am. Chem. Soc.* **98** 4004–4005.

Byrn, Stephen R., Brian Tobias, Donald Kessler, James Frye, Paul Sutton, Patricia Saindon, and John Kozlowski (1988) "Relationship between solid state NMR spectra and crystal structures of polymorphs and solvates of drugs" *Trans. Am. Crystallogr. Assoc.* **24** 41–54.

Chiang, Chian C., Wilson H. DeCamp, David Y. Curtin, Iain C. Paul, Sidney Shifrin, and Ulrich Weiss (1978) "Color dimorphism of 14-hydroxymorphinone. X-ray analysis of two different crystalline modifications" *J. Am. Chem. Soc.* **100** 6195–6201.

Cohen, M. D. and Bernard S. Green (1973) "Organic chemistry in the solid state" *Chem. Brit.* **9** 490–497.

Craven, B. M. and E. A. Vizzini (1969) "Crystal structures of two polymorphs of 5-ethyl-5-isoamylbarbituric acid (amobarbital)" *Acta Crystallogr., Sect. B., Struct. Sci.* **B25** 1993–2009.

Curtin, D. Y. and S. R. Byrn (1969) "Stereoisomerism at the oxygen-carbon single bond due to hydrogen bonding. Structures of the yellow and white crystalline forms of dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate" *J. Am. Chem. Soc.* **91** 1865–1866.

Curtin, David Y. and John H. Englemann (1972) "Intramolecular oxygen-nitrogen benzoyl migration of 6-aroyloxyphenanthridines" *J. Org. Chem.* **37** 3439–3443.

Dabrowski, Janusz (1963) "Infrared spectra and structure of substituted unsaturated carbonyl compounds. I. Enamino ketones with primary amino group" *Spectrochim. Acta* **19** 475–496.

Debord, B., C. Lefebvre, A. M. Guyot-Hermann, J. Hubert, R. Bouché, and J. C. Guyot (1987) "Study of different crystalline forms of mannitol: comparative behavior under compression" *Drug Dev. Ind. Pharm.* **13** 1533–1546.

DeCamp, Wilson H. and F. R. Ahmed (1972a) "Structural studies of synthetic analgesics. II. Crystal and molecular structure of the monoclinic form of (±)-β-promedol alcohol" *Acta Crystallogr., Sect. B., Struct. Sci.* **B28** 1796–1800.

DeCamp, Wilson H. and F. R. Ahmed (1972b) "Structural studies of synthetic analgetics. III. Crystal and molecular structure of the rhombohedral form of (±)-β-promedol alcohol" *Acta Crystallogr., Sect. B., Struct. Sci.* **B28** 3484–3489.

Desiraju, Gautam R., Iain C. Paul, and David Y. Curtin (1977) "Conversion in the solid state of the yellow to the red form of 2-(4'-methoxyphenyl)-1,4-benzoquinone. X-ray crystal structures and anisotropy of the rearrangement" *J. Am. Chem. Soc.* **99** 1594–1601.

Dideberg, O., and L. Dupont (1972) "Crystal and molecular structure of spironolactone, 7α-acetylthio-3-oxo-17α-4-pregnene-21,17β-carbolactone" *Acta Crystallogr., Sect. B., Struct. Sci.* **28** 3014–3022.

Doherty, Chris and Peter York (1988) "Frusemide crystal forms; solid state and physiochemical analyses" *Int. J. Pharm.* **47** 141–155.

Donaldson, J. D., J. R. Leary, S. D. Ross, M. J. K. Thomas, and C. H. Smith (1981) "The structure of the orthorhombic form of tolbutamide (1-*n*-butyl-3-*p*-toluenesulphonylurea)" *Acta Crystallogr., Sect. B., Struct. Sci.* **B37** 2245–2248.

Dudek, Gerald O. and Gert P. Volpp (1963) "Nuclear magnetic resonance studies of keto-enol equilibria. V. Isomerization in aliphatic Schiff bases" *J. Am. Chem. Soc.* **85** 2697–1702.

Dunitz, Jack D. and Joel Bernstein (1995) "Disappearing polymorphs" *Acc. Chem. Res.* **28** 193–200.

Eistert, Bernd, Friedrich Weygand, and Ernst Csendes (1952) "Polymorphism of the chalcones" *Chem. Ber.* **85** 164–168.

Fletton, Richard A., Robert W. Lancaster, Robin K. Harris, Alan M. Kenwright, Kenneth J. Packer, David N. Waters, and Alan Yeadon (1986) "A comparative spectroscopic investigation of two polymorphs of 4'-methyl-2'-nitroacetanilide using solid-state infrared and high-resolution solid-state nuclear magnetic resonance spectroscopy" *J. Chem. Soc., Perkin Trans. 2* **1986** 1705–1709.

Gerber, J. J., J. G. vander Watt, and A. P. Lötter (1991) "Physical characterization of solid forms of cyclopenthiazide" *Int. J. Pharm.* **73** 137–145.

Ghielmetti, G., T. Bruzzese, C. Bianchi, and F. Recusani (1976) "Relationship between acute toxicity in mice and polymorphic forms of polyene antibiotics" *J. Pharm. Sci.* **65** 905–907.

Giuseppetti, G., C. Tadini, G. P. Bettinetti, and F. Giordano (1977) "2-Sulfanilamido-5-methoxypyrimidine, $C_{11}H_{12}N_4O_3S$" *Cryst. Struct. Commun.* **6** 263–274.

Goldberg, Israel and Yigal Becker (1987) "Polymorphs of tamoxifen citrate: detailed structural characterization of the stable form" *J. Pharm. Sci.* **76** 259–264.

Gougoutas, J. Zanos and L. Lessinger (1974) "Solid state chemistry of organic polyvalent iodine compounds. III. The crystal structures of 3-oxo-3*H*-2,1-benzoxiodol-1-yl *m*-chlorobenzoate (two polymorphs) and its isostructural derivative, 3-oxo-3*H*-2,1-benzoxiodol-1-yl benzoate" *J. Solid State Chem.* **9** 155–164.

Griesser, Ulrich J. and Xiaorong He (1998) Personal communication; Purdue University: West Lafayette, IN 47907-1336.

Guillory, J. Keith (1967) "Heats of transition of methylprednisolone and sulfathiazole by a differential thermal analysis method" *J. Pharm. Sci.* **56** 72–76.

Haleblian, John and Walter McCrone (1969) "Pharmaceutical applications of polymorphism" *J. Pharm. Sci.* **58** 911-929.

Hamlin, W. E., E. Nelson, B. E. Ballard, and J. G. Wagner (1962) "Loss of sensitivity in distinguishing real differences in dissolution rates due to increasing intensity of agitation" *J. Pharm. Sci.* **51** 432–435.

Herbstein, F. H. and G. M. J. Schmidt (1955) "The crystal and molecular structures of heterocyclic compounds. I. The analysis of the crystal structure of α-phenazine" *Acta Crystallogr.* **8** 399–405.

Higuchi, W. I., P. D. Bernardo, and S. C. Mehta (1967) "Polymorphism and drug availability. II. Dissolution rate behavior of the polymorphic forms of sulfathiazole and methylprednisolone" *J. Pharm. Sci.* **56** 200–207.

Higuchi, W. I., W. E. Hamlin, S. C. Mehta (1969) "Infrared attenuated total reflectance (ATR) method for observing the water-mediated surface phase reversion of methylprednisolone II to I during dissolution" *J. Pharm. Sci.* **58** 1145–1146.

Ip, Dominic P., Gerald S. Brenner, James M. Stevenson, Siegfried Lindenbaum, Alan W. Douglas, S. David Klein, and James A. McCauley (1986) "High resolution spectroscopic evidence and solution calorimetry studies on the polymorphs of enalapril maleate" *Int. J. Pharm.* **28** 183–191.

Kato, Yuriko, Yumi Okamoto, Sayoko Nagasawa, and Ichiko Ishihara (1984) "New polymorphic forms of phenobarbital" *Chem. Pharm. Bull.* **32** 4170–4174.

Koch, Michael H. J. and Gabriel Germain (1972) "Crystal and molecular structure of 4-[1-(4-hydroxy-4-*p*-fluorophenyl)piperidinyl]-4'-fluorobutyrophenone and its hydrochloride" *Acta Crystallogr., Sect. B., Struct. Sci.* **B28** 121–125.

Koo, Chung Hoe, Sung Il Cho, and Young Hee Yeon (1980) "The crystal and molecular structure of chlorpropamide" *Arch. Pharmacal. Res.* **3** 37–49.

..., 7α-acetylthio-
...ruct. Sci. 28

physiochemical

...) "The structure
...cta Crystallogr.,

...ies of keto-enol
...97-1702.

...cs 28 193-200.

...halcones" Chem.

...enneth J. Packer,
...estigation of two
...olution solid-state
1705-1709.

...of solid forms of

...een acute toxicity
...07

...2-Sulfanilamido-5-

...detailed structural

polyvalent iodine
...lorobenzoate (two
...benzoate" J. Solid

University: West

...de by a differential

...polymorphism" J.

...vity in distinguish-
..." J. Pharm. Sci. 51

...ures of heterocyclic
...Acta Crystallogr. 8

...ng availability. II.
...thylprednisolone" J.

...tance (ATR) method
...e II to I during disso-

...Alan W. Douglas, S.
...vidence and solution
...183-191.

..."New polymorphic

...of 4-[1-(4-hydroxy-4-
...ta Crystallogr., Sect.

...molecular structure of

Kopp, Sabine, Christian Beyer, Engelbert Graf, [illegible] (1988) "Potential misinterpretations of DTA/DSC [illegible] phenobarbital" Acta Pharm. Technol. 34 [illegible]

Krigbaum, W. R. and [illegible] [illegible]bromotoluene" Acta Crystallogr., Sect. B: [illegible] B27 [illegible]

Kruger, G. J. and G. Gafner (1971a) [illegible] sulfathiazole" Acta Crystallogr., Sect. B: [illegible] B27 [illegible]

Kruger, G. J. and G. Gafner (1971b) [illegible] [illegible]allogr., Sect. B: Struct. Sci. B27 326-[illegible]

Kuhnert-Brandstatter, M. [illegible] [illegible]icals. Pergamon, New York, NY.

Kuhnert-Brandstätter, M. and [illegible] [illegible]mical investigations on enantiotropic polymorphs [illegible]

Kuhnert-Brandstätter, M., [illegible] [illegible] IR spectroscopical investigations on enantiotropic [illegible] 50 [illegible]

Kuhnert-Brandstätter, M., [illegible] and IR spectroscopical investigations on enantiotropic [illegible] 50 [illegible]-216.

Kuhnert-Brandstätter, M. and R. [illegible] [illegible] of Drugs. II. Halofenate, lorcainide [illegible] Sci. Pharm. 51 71-82.

Kuhnert-Brandstätter, M. [illegible] of Drugs. III. Mexiletine hydrochloride [illegible] pirprofene" Sci. Pharm. 55 13-25.

Kuhnert-Brandstätter, M. and [illegible] of Drugs. VI. Bupicomide, buspirone hydrochloride [illegible] naftifine hydrochloride and piretanide [illegible] 58 [illegible]

Kuhnert-Brandstätter, M. [illegible] of Drugs. [illegible] Amiperone, bentiom[illegible] [illegible]conazole" Sci. Pharm. 57 81-96.

Kuhnert-Brandstätter, M. [illegible] of Drugs. VII. Famotidine, flupirtine [illegible] [illegible]abendazole" Sci. Pharm. 58 55-62.

Levy, Gerhard and Joseph [illegible] [illegible]methylprednisolone polymorphs" J. Pharm. [illegible]

Lin, Chung-Tang, Phillipe [illegible] Byrn (198[illegible]) "Solid-state photooxidation [illegible] [illegible]acetate" J. Org. Chem. 47 2978-298[illegible].

Macek, Thomas J. (1965) [illegible] [illegible]ration of dosage forms for new pharmaceuticals [illegible]

Matsuda, Yoshihisa and [illegible] of furosemide modifications" Int. J. [illegible] 60 [illegible]

Mesley, R. J. (1971) "The [illegible]

Milosovich, George (196[illegible]) [illegible] Pharm. [illegible] 53 484-487.

Mitchell, A. G. (1985) [illegible] [illegible]lopramide" Pharm. Pharmacol. 37 [illegible]

Miyamae, Akira, Shigetaka Koda, [illegible] [illegible]yoshi Morimoto (1990) "X-ray crystallographic [illegible] [illegible]carbonylamino-6-methylbenzyloxy)-2-methyl[illegible] 79 189-[illegible]

Molecular Simulations, Inc. [illegible]

Moustafa, M. A., A. R. [illegible] [illegible]methoxydiazine crystal forms" J. Pharm. Pharmacol. [illegible] 23 [illegible]

Munshi, Mavank V. (197[illegible]) [illegible] Thesis, University of Michigan [illegible]

Nirmala, K. A., and D. S. [illegible] Crystallogr., Sect. B: Struct. [illegible]

O'Conner, B. H. and E. N. Maslen (1965) "The crystal structure of α-sulfanilamide" *Acta Crystallogr.* **18** 363–366.

Pearson, J. T. and G. Varney (1969) "Crystal growth studies involving phase transitions in aqueous drug suspensions" *J. Pharm. Pharmacol., Suppl.* **21** 60S–96S.

Perrin, M. and P. Michel (1973a) "Polymorphism of *p*-chlorophenol. I. Crystal structure and morphology of the stable form" *Acta Crystallogr., Sect. B., Struct. Sci.* **B29** 253–258.

Perrin, M. and P. Michel (1973b) "Polymorphism of *p*-chlorophenol. I. Crystal structure of the metastable form (β-form) at low temperature" *Acta Crystallogr., Sect. B., Struct. Sci.* **B29** 258–263.

Pfeiffer, Ralph R., Gary L. Engel, and Dennis Coleman (1976) "Stable antibiotic sensitivity disks" *Antimicrob. Agents Chemother.* **9** 848–851.

Phillips, D. C. (1956) "The crystallography of acridine. II. The structure of acridine III" *Acta Crystallogr.* **9** 237–250.

Phillips, D. C., F. R. Ahmed, and W. H. Barnes (1960) "The crystallography of acridine. III. The structure of acridine II" *Acta Crystallogr.* **13** 365–377.

Rambaud, J., R. Roques, S. Alberola, and F. Sabon (1980) "Crystallographic structure of 3-(4-aminobenzenesulfonamido)-5-methylisoxazole" *Bull. Soc. Chim. Fr.* **1980** 56–60.

Richardson, Mary Frances, Quing-Chuan Yang, Elisabeth Novotny-Bregger, and Jack D. Dunitz (1990) "Conformational polymorphism of dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate. II. Structural, thermodynamic, kinetic and mechanistic aspects of phase transformations among the three crystal forms" *Acta Crystallogr., Sect. B* **B46**, 653–660.

Robertson, J. Monteath and J. G. White (1947) "The crystal structure of the orthorhombic modification of 1,2,5,6-dibenzathracene. A quantitative X-ray investigation" *J. Chem. Soc.* **1947** 1001–1010.

Robertson, J. Monteath and J. G. White (1956) "The crystal structure of the monoclinic modification of 1,2,5,6-dibenzanthracene. A quantitative X-ray investigation" *J. Chem. Soc.* **1956** 925–931.

Rowe, Englebert L. and Bradley D. Anderson (1984) "Thermodynamic studies of tolbutamide polymorphs" *J. Pharm. Sci.* **73** 1673–1675.

Saindon, Patricia J., Nina S. Cauchon, Paul A. Sutton, C.-j. Chang, Garnet E. Peck, and Stephen R. Byrn (1993) "Solid-state nuclear magnetic resonance (NMR) spectra of pharmaceutical dosage forms" *Pharm. Res.* **10** 197–203.

Schulenberg, John W. (1968) "Isolation of crystalline keto-enol tautomers. Conversion into indoles and oxindoles" *J. Am. Chem. Soc.* **90** 7008–7014.

Shafizadeh, Fred and Ronald A. Susott (1973) "Crystalline transitions of carbohydrates" *J. Org. Chem.* **38** 3710–3715.

Shefter, Eli and Takeru Higuchi (1963) "Dissolution behavior of crystalline solvated and nonsolvated forms of some pharmaceuticals" *J. Pharm. Sci.* **52** 781–791.

Shenouda, Latif S. (1970) "Various species of sulfathiazole Form I" *J. Pharm. Sci.* **59** 785–787.

Shieh, Tiee-Leou, Chung-Tang Lin, Ann T. McKenzie, and Stephen R. Byrn (1983) "Relationship between the solid-state and solution conformations of β-(benzylamino)crotonate" *J. Org. Chem.* **48** 3103–3105.

Simmons, D. L., R. J. Ranz, N. D. Gyanchandani, and P. Picotte (1972) "Polymorphism in pharmaceuticals. II. Tolbutamide" *Can. J. Pharm. Sci.* **7** 121–123.

Simmons, D. L., R. J. Ranz, and N. D. Gyanchandani (1973) "Polymorphism in pharmaceuticals. III. Chlorpropamide" *Can. J. Pharm. Sci.* **8** 125–127.

Small, Lyndon F. and Erich Meitzner (1933) "Metathebainone" *J. Am. Chem. Soc.* **55** 4602–4610.

Smith, Jay, Ernesto MacNamara, Daniel Raftery, Thomas Borchardt, and Stephen Byrn (1998) "Application of two-dimensional ^{13}C solid-state NMR to the study of conformational polymorphism" *J. Am. Chem. Soc.* **120** 11710–11713.

Stephenson, G. A., T. B. Borchardt, S. R. Byrn, J. Bowyer, C. A. Bunnell, S. V. Snorek, and L. Yu (1995) "Conformational and color polymorphism of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile" *J. Pharm. Sci.* **84** 1385–1386.

Sunwoo, Chimin and Henry Eisen (1971) "Solubility parameter of selected sulfonamides" *J. Pharm. Sci.* **60** 238–244.

Sutton, Paul Allen (1984) "Crystal packing effects on the photochemical oxidation and solid state carbon-13 NMR chemical shifts of several anti-inflammatory steroids" Ph.D. Thesis, Purdue University, West Lafayette, IN 47907-1330.

Szabó-Révesz, Piroská, I
Kala, and U. Wenzel
IV. The influence o
phenobarbitone tablet

Weintraub, H. J. R. and
solution by empirical
tions" *Int. J. Quantu*

Williams, P. P. (1973)
phenylbarbituric acid

Williams, P. P. (1974) "I
Acta Crystallogr., Se

Yang, Shiu Shiang and J.
26–40.

Yang, Qing-Chuan, Mary
phism of dimethyl 3,6
parameters between
312–323.

Yu, Lian (1998) Personal

Szabó-Révész, Piroská, Klárá Pintye-Hódi, Máriá Miseta, B. Selmeczi, G. Kedvessy, J. Traue, H. Kala, and U. Wenzel (1987) "Investigations about polymorphism of drugs in powders and tablets. IV. The influence of the polymorphism of drugs on the physical properties and drug release of phenobarbitone tablets" *Pharmazie* **42** 179–181.

Weintraub, H. J. R. and A. J. Hopfinger (1975) "*CAMSEQ* [conformational analysis of molecules in solution by empirical and quantum mechanical techniques] software system in drug design calculations" *Int. J. Quantum Chem., Quantum Biol. Symp.* **1975** 203–208.

Williams, P. P. (1973) "Polymorphism of phenobarbitone: the crystal structure of 5-ethyl-5-phenylbarbituric acid monohydrate" *Acta Crystallogr., Sect. B., Struct. Sci.* **B29** 1572–1579.

Williams, P. P. (1974) "Polymorphism of phenobarbitone. II. Crystal structure of modification III" *Acta Crystallogr., Sect. B., Struct. Sci.* **B30** 12–17.

Yang, Shiu Shiang and J. Keith Guillory (1972) "Polymorphism in sulfonamides" *J. Pharm. Sci.* **61** 26–40.

Yang, Qing-Chuan, Mary Frances Richardson, and Jack D. Dunitz (1989) "Conformational polymorphism of dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate. I. Structures and atomic displacement parameters between 100 and 350 K for three crystal forms" *Acta Crystallogr., Sect. B* **B45** 312–323.

Yu, Lian (1998) Personal communication; Eli Lilly and Company: Indianapolis, IN 46285–0001.

Analysis of Organic Polymorphs
A Review

Terence L. Threlfall,
Chemistry Department, University of York, Heslington, York, UK YO1 5DD

Summary of Contents

Keywords: *Polymorphism; phase transitions; amorphous materials; solvates; microscopy; thermal analysis; infrared spectroscopy; Raman spectroscopy; solid-state nuclear magnetic resonance spectroscopy; X-ray diffraction*

Introduction and Definition of Polymorphism

Polymorphism[1–7] in the chemical sense of the word* is a phenomenon of the solid state, associated with the structure of the solid. It has proved difficult to define precisely although the basic concept is readily understood. The definitions which have been offered vary in breadth but the implication of all of them is that polymorphs involve different packings of the same molecules in the solid.[4] The question of how similar the same molecules must be and of how dissimilar the different packing arrangements must be in order to qualify as polymorphs is more than a matter of semantics but goes to the root of our understanding of the organic molecular solid state.

McCrone has defined a polymorph as 'a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state' and has listed those types of solid phenomena which are excluded from this definition.[1] Later writers who have accepted this definition have tended to substitute their own list of exclusions,[5] if they have addressed the matter at all. Buerger's tentative definition[3] 'ideally, two polymorphs are different forms of the same chemical compound which have distinctive properties' is broader and appears not to accept the need for separate phases and to include amorphous forms. The nature of the amorphous state[8,9] will be discussed later.

Polytypism[10] is one-dimensional polymorphism, referring to different stacking of the same layers. It is most familiar in inorganic systems, particularly silicon carbide, but has been recognized in organic crystals, both as ordered[11–13] and as disordered stacking.[14] There is no special term for two-dimensional polymorphism, although some liquid crystal systems display it. Liquid crystals are notorious for their ability to exist in different phases both in the mesomorphic and in the solid state[15–17] and this has led to the suggestion that the term polymorphism should apply to liquids as well as solids,[18] but it is only the solid dimensions of liquid crystals which can adopt distinct packing arrangements. Liquid-crystal polymorphism will not be dealt with specifically in this review except where it is related to the polymorphism of solids. The long standing question[19] of whether allotropy and polymorphism are distinct[20] is not an issue in the case of organic compounds. Inorganic polymorphs have been excluded because the extended structures of which most inorganic crystals are composed raise concepts not discussed here.[21,22] Protein polymorphism usually refers to minor molecular sequence changes[23,24] rather than to packing, but different crystal packing of protein molecules is also known.[25] Polymorphism of thin films[26,27] and polymers, both of biological[28,29] and of synthetic[30] origin, although of the same nature as the concept of polymorphism considered here, will not be discussed.

There is a profusion of words in the English language for the phenomena discussed in this review, yet not enough because of the overlapping usage. 'Polymorph' (dimorph, trimorph) 'form' and 'modification' are all used to describe polymorphic phases, but 'form' and 'modification' are also used in reference to crystal habit. 'Polymorph' and 'form' have been used to describe solvates, whilst 'pseudopolymorph' doubles for both solvates and for those solids which are otherwise not considered true polymorphic forms. The term 'pseudopolymorphic solvate' applied to crystals losing solvent molecules without change of crystalline form offers yet another source of confusion in terminology. Genetic polymorphism which is now the major use of the term is often described as 'polymorphisms' but this is occasionally seen also in chemical senses. In view of the almost universal use of 'polymorphic' as the appropriate adjective, the word 'polymorphous' seems superfluous despite dictionary support. There is an urgent need for consistent usages so as to be able to delineate the phenomena under consideration.

There is no clear choice as to the best method of designating polymorphs. Arbitrary systems are to be discouraged, but numbering based either on order of melting point or of room temperature stability have been recommended. Both are susceptible to change as a result of later identification of new polymorphic forms. Numbering based on order of discovery is unchangeable, but requires a knowledge of the history of the compound. The addition of the crystal class, as has been suggested for minerals[31] is not very practicable, since crystallographic classes are rarely determined from optical microscopic or X-ray powder diffraction studies for organic compounds. The assignment of a space group is even less realistic.

* An on-line search of Chemical Abstracts will reveal more than 47000 entries under 'polymorphism'. Over 90% of these relate to genetic polymorphism, which at least in its origins can claim the true etymology of the word. Some selectivity between biological and chemical uses can be achieved, but there is no certain searching strategy. Searching under 'phase transition' and related concepts will generate a further 44000 entries, most of which refer to inorganic systems, and cannot be easily disentangled. Nevertheless, these represent only a proportion of the papers containing information on polymorphs and polymorphism. Hence it is not possible to state how many publications relate to those aspects of polymorphism described here.

In any case the distribution of organic molecules amongst crystal classes and space groups is extremely limited, as is discussed later.[32,33] The addition of a melting or upper transition point to a Roman numeral is probably the best compromise,[1] although care must be taken to distinguish the melting point of the polymorph and that of the transformed product.

Significance of Polymorphism

The continuing investigation of polymorphism by the Innsbruck school (Kofler, Kuhnert–Brandstätter, Burger) over more than half a century has shown that around one-third of organic substances show crystalline polymorphism under normal pressure conditions.[34,35] A further third are capable of forming hydrates and other solvates.

Much of the literature on the polymorphism of organic compounds relates to pharmaceutical products.[1,36–40] The incentive for this interest in polymorphism began with the need to satisfy regulatory authorities in various countries as to the bioavailability of formulations of new chemical entities.[36,37] Of the several contributory factors to the bioavailability of finished products, the inherent solubility and rate of dissolution of the drug substance itself are of major importance. The solubility is dependent on the polymorphic state, as different polymorphs have different energies and therefore different solubilities.[40] It has been pointed out, particularly by Burger,[36] that the difference in solubility between polymorphs is likely to result in significant bioavailability differences, in practice, only in exceptional cases. Although some may think that this represents an extreme view, the consequences of polymorphism on bioavailability are commonly overstated. Chloramphenicol palmitate, over which the original concerns were voiced,[41] is unique in that the solubility is related to the rate of enzymic attack on the solid.[42] This and novobiocin,[43] which involves consideration of the amorphous state, are among the handful of examples of marketed products showing major bioavailability differences as a result of polymorphism.

As formulations have become more sophisticated and as the tolerances on products have become tighter, the need to identify polymorphic behaviour at an early stage of development has become important in the pharmaceutical industry as a means of ensuring reliable and robust processes[44] and conformity with good manufacturing practice. The aim is to avoid, *inter alia*, tabletting problems and subsequent tablet failure,[45,46] crystal growth in suspensions[47,48] and resultant caking, precipitation from solutions and problems with suppositories,[49] as well as chemical production problems such as filtrability[1] and to ensure analytical reproducibility. By extension such considerations relate to the control of quality in manufacture and product reliability in any industry by ensuring that the processes are well understood and under control so that unpleasant surprises do not occur.[50] This point is most dramatically illustrated in the explosives industry, where the wrong polymorph can have greatly increased sensitivity to detonation.[51,52] Pigment colour and solubility are polymorph dependent,[53–59] as are photographic and photolithographic sensitizers.[60] The performance of industrial products, particularly those based on natural fats and waxes[61,62] and derived soaps,[63] and on petroleum products[64,65] is in many cases related to polymorphic composition and degree of crystallinity. The same is true of the processing, acceptability and deterioration of foods and confectionery containing fats,[66,67] sugars,[68–72] polysaccharides[73] and other constituents.[74–75] A comprehensive summary of the solid-state properties of lipids has recently appeared.[76]

It is also worth establishing the polymorphic behaviour of a compound for the sake of good order in documentation so that reference works, for example, pharmacopoeias, do not contain conflicting data[34,77] such as a spectrum of one polymorph, but the melting point of another.

A major incentive to the study of polymorphism in the pharmaceutical industry during development has become strikingly apparent recently in the use of subsidiary patents on desirable polymorphic forms[78] to prolong the patent life of major products. Much recent pharmaceutical patent litigation has concerned polymorphs and particular interest has been taken in Glaxo's patent on the polymorph of ranitidine[79] (Zantac) which if held valid will extend the patent protection from 1995 to 2002 in many countries.[80] For a compound with annual sales of over 2 400 million pounds sterling,[81] the financial incentives to investigate polymorphs are obvious.

Finally, the very existence of polymorphism tells us something about the solid-state. Investigation of polymorphic systems, especially those with a large number of forms can help in understanding solid-state and molecular behaviour and intermolecular interactions[82] and the relationship between crystal structure, crystal growth and crystal habit[83] and their influence on bulk properties. Apart from knowledge for its own sake, this is of clear application in the development of organic electronic[84,85] and other specialty products[86–88] and in understanding the function of biological membranes.[89]

Distinction From Related Phenomena

At one time polymorphism was regarded only as different arrangements of rigid molecules in the solid state.[90,91]* A clear dichotomy existed between this and arrangements of molecules in different forms, such as could be imagined would occur with isomeric, tautomeric, zwitterionic and chiral structures and later with different conformers.[92] The early crystallographic studies on rigid aromatic molecules tended to reinforce the distinction. This simple division could only be maintained whilst details of the rich variety of solid-state structures were inaccessible. The early examples of dynamic isomerism and tautomerism were few[93,94] and the proposition that they could not be part of polymorphism was copied by reviewers until even the examples were forgotten.[95] A quoted example of a tautomeric solid-state structure, that of 3,5-dichloro-2,6-dihydroxy dimethyl terephthalic acid was shown in 1972 not to be tautomeric, but to involve conformational change with hydrogen bonding differences.[96] One would have expected examples of tautomerically related solid structures to be exceedingly numerous, since the molecular energetic requirements can easily be fulfilled as is shown by the widespread occurrence of tautomerism in solution.[97] Tautomeric polymorphism is surprisingly rare, but a well investigated example is now known, that of 2-amino-3-hydroxy-6-phenylazopyridine.[98]

There are a few papers in the literature either where tautomeric polymorphism is invoked[99–105] or where examination of the IR spectra is suggestive of forms whose difference resides in transfer of hydrogen between one part of the molecule and another.[106] The instances of 1,3-cyclohexadienone and squaric acid (3,4-dihydroxy-3-cyclobutene-1,2-dione are more difficult to place unambiguously in the category of tautomeric polymorphism. Proton transfer between donor and acceptor oxygen sites results in little change in over-all structure.[107]

Both tautomeric equilibrium and the neutral $\longleftrightarrow$ zwitterionic equilibrium formally involve such an intramolecular hydrogen transfer. The nominal difference is that a charge separation is produced in zwitterions which cannot be extinguished intramolecularly by a double-bond rearrangement cascade. The difference may be even smaller in practice because charge stabilization of zwitterions can occur intermolecularly, for example, in solution through solvation, whilst tautomeric structures can retain a substantial part of their charge as shown by dipole moment and IR spectroscopic studies.[108,109] Anthra-

* Earlier literature can be accessed *via* references 1, 2 and 10.

nilic acid exists as two metastable forms containing only uncharged molecules and a form stable at room temperature, half the molecules of which have been shown from crystallographic studies to be zwitterionic and half uncharged.[110] A related phenomenon is the changing of allegiance of hydrogen-bonded hydrogens between electron donor atoms, which is a prolific source of polymorphism.[111] The role of hydrogen-bonding networks in determining crystal structure has been discussed extensively.[112] Conformational differences between molecules of different structures have been admitted, perhaps reluctantly, and distinguished by the title conformational polymorphism.[113] The original examples form one extremity where molecules in distinctive conformations pack similarly,[92] but it is now obvious from the plethora of crystal structures, as could always have been deduced from elementary considerations of energy minimization, that any change of packing will cause geometrical change in molecules and conversely that any change in geometry will invite different packing of the molecules.[82] The extent will depend on the rigidity of the molecules. Although some floppy ring systems maintain their shape in different forms[114,115] even nominally rigid structures such as the ring systems of steroids[116] can show substantially different conformations in different polymorphs. Heteroaromatic[117–121]* and benzoquinone[122] planes are frequently bent and even benzene rings[123] may be. Thus it seems pragmatic to accept conformational polymorphism as a normal sub-set of polymorphism and the term will only be used here when it is necessary to distinguish cases of substantial conformational change.

The distinction between polymorphism and chirality is made in most accounts of polymorphism; yet it has recently been pointed out that if conformational polymorphism is accepted, then racemates and conglomerates of rapidly interconverting chiral systems are in fact polymorphs.[5] Such systems are generally ones with an easy conformational change where the trivial distinguishing feature from other conformational polymorphism is that the result of such a change is a reflection of an asymmetrical structure across a mirror plane. Although this seems difficult to accept, the dextrorotatory and laevorotatory forms of such systems are then equally polymorphs.[124] The narrow line of demarkation between polymorphism, conformational polymorphism and chirality first seems to have been recognized by Eistert *et al.*.[125] Examples of rapidly interchanging enantiomers in solution capable of independent existence in the solid state are known[126,127] but uncommon.

A further extension of the concept of conformational polymorphism is to be found where there is rapid interconversion between isomers.[128] As in the chiral examples, one molecular species or the other becomes exclusively incorporated in the crystal because the mechanism of crystal growth acts as such an exquisitely discriminatory process.[129]

Since a hydrate and an anhydrous form are constitutionally distinct, they cannot bear a strictly polymorphic relationship on the basis of any definition. However, the observation of material of different melting point or other properties during recrystallization may be due (apart from chemical reaction with solvent or decomposition) to solvation or polymorphism and the methods of examination are similar in either case. Hence the term 'pseudopolymorphism' has become common[130] particularly in the pharmaceutical industry. The term seems unnecessary and could lead to confusion[131] with its use to describe all other phenomena related to polymorphism[1] and so will not be used here. It must be emphasized, however, that the distinction between solvates and polymorphs is not as clear-cut as might be imagined, either conceptually or practically.

* In the case of phenothiazines[121] the point of interest is not that the ring system is bent, but that the heteroatoms are out of the plane of the aromatic rings and in the opposite sense to expectation.

The traditional narrow view of polymorphism, rigidly excluding chirality and isomerism, has caused considerable difficulty[128] to the investigators of the systems described above and it is suggested that the way to avoid these problems is to adopt the gloss originally proposed by McCrone and co-workers[1,37] on his definition of polymorphism, namely that the criterion is that the component molecules must have the same structure in solution irrespective of the polymorph from which they were derived; but, as has been suggested by Dunitz,[5] without excluding tautomerism, isomerism or conformers *per se*. Thus, rapidly interconverting species would be accepted, whilst slowly interconverting species would be excluded, as was surely within the original contemplation. Despite appearances, this proposal is likely to multiply examples of polymorphism very little and it avoids what otherwise must be artificial situations of accepting phases as polymorphs based on impeccable polymorph behaviour until their crystal structure reveals excluded molecular forms.[98,110,132] If, as asserted, the transition between polymorph I and polymorph II of 1,3-cyclohexadiene occurs by transfer of hydrogen from one oxygen to another, then this is nominally an example of tautomeric polymorphism.[107] If, on the other hand, the same change occurs or can be made to occur by a movement of the whole molecule then it is an example of regular polymorphism. The boundaries between the various alternative solid structural concepts are too subtle and too vague to be used to define polymorphism.

Although the requirement of the same structure in solution has been canvassed above, one-component phase diagrams are constructed on the basis of equilibrium with vapour, rather than liquid. It is just in the instance of conformational, configurational or hydrogen mobility that molecular differences between vapour,[133,134] melt, solution[126,135] and solid are found. The mobilities are inevitably of different magnitudes in different states. We shall be increasingly obliged to decide where to draw the boundaries of polymorphism as more comparative studies involving polymorphs and molecular structure in different states are undertaken.

One negative consequence of accepting the wider view of polymorphism should be noted, namely that the thermodynamic relationships discussed later are likely to be less certain for the wider polymorphic family.[90]

Stability of Polymorphs

Polymorphs, or strictly dimorphs where only two forms are under consideration, may be in an enantiotropic or monotropic relationship.[19,136] An enantiotropic relationship implies that each form has a range of temperature over which it is stable with respect to the other and a transition point at which the forms are equistable and in principle interconvertible.[137] Above that temperature the thermodynamic tendency is to the formation exclusively of the form stable at the higher temperature. Below the transition temperature the low- temperature form is the only stable one with respect to the other, although there is usually a greater tendency for the high temperature form to become frozen-in than for a low- temperature form to persist beyond its stability range.[8] Forms outside their range of stability are described here as metastable[138]. In the case of a monotropic relationship one form is metastable with respect to another at all temperatures. There is no observable transition point, although the thermodynamic description implies a theoretical transition point above the melting point which is therefore unattainable.[139] The use of the terms enantiotropic or monotropic in reference to a phase, as opposed to a transition, is ambiguous and likely to lead to confusion, since a polymorph can have a monotropic relationship to a second polymorph, but be enantiotropic in relation to a third polymorph. Flufenamic acid provides such an example.[140] The distinction between thermodynamic and kinetic transition points also needs to be drawn.[141]

Polymorphs only exist in the solid state: melting or dissolution destroys any distinctions. It is therefore important in examining polymorphs analytically not to submit them to conditions under which they melt, dissolve or are rendered more likely to interconvert. Heating and grinding[142–144] are obviously potentially hazardous operations in this context, but often cannot be avoided. The presence of solvent, even one in which the substance appears insoluble, will speed up the interconversion.[145] Trace moisture, acid or alkali on vessels can be similarly effective in interconverting polymorphs or in catalysing competing and confusing phenomena such as ring-opening reactions, for example, in 3,5-dihydroxy-3-methylvaleric acid derivatives,[146], or group transfer reactions.[147]

It might be supposed that a transition during grinding would always be from less stable polymorph to the polymorph more stable at that temperature, but in our experience, as well as from the literature,[145] this is not always true, presumably because the transformation takes place at a local temperature generated by the grinding and the unstable form becomes frozen-in by rapid cooling outside the immediate area of grinding.[148] This can only occur in cases in which the transition temperature does not lie too far above ambient. There may be alternative explanations, namely interconversion *via* amorphization or that a less stable polymorph may become the more stable one when in the form of small crystallites, as a result of surface effects. The latter phenomenon has been observed and investigated theoretically in the case of phthalocyanine pigments.[149] The possibility of growing unstable forms in microdrop conditions has been known for some time,[34] but recently the value of emulsions for this purpose has been suggested.[150] Although it would be desirable to have more compelling evidence than that obtained by differential scanning calorimetry (DSC) alone to establish the relationship between forms grown in this way, it does appear that new forms can be produced as well as metastable ones which are otherwise only accessible *via* the melt. The product of a polymorphic transition can also depend on particle size.[151,152]

Mnyukh and Petropavlov, in extensive studies of the transformation of individual crystals, observed that strict orientation of axes between mother and daughter phases was not preserved upon transformation.[153] They have concluded that only reconstructive transitions, *i.e.*, those involving the growth of new crystals in place of the old, take place for organic compounds. Even rapid transitions, described as atypical, were observed to follow the same patterns. No displacive (martensitic, co-operative) mechanism involving concerted structural change is therefore possible for organic compounds in Mnyukh's scheme. Whilst it would now appear that the reconstructive mechanism is the usual one, there are many examples involving preservation of axial orientation at phase transitions[4] some of which appear to be topotactic rather than only epitaxial.[154–157].

Irrespective of the mechanism and the rate of conversion at the point of transition, the stability in practice of a metastable polymorph at room temperature varies enormously,[158] from examples where the transformation is so rapid that the only evidence of the transient existence of a polymorph is its pseudomorphic outline,[1] to those which can be kept indefinitely and indeed refuse to transform in the absence of heat, high humidity or solvents.[152] The majority of systems are in fact quite robust to handling. It may therefore be thought that some of the present work presents over-concern with the possibility of transforming polymorphs during analytical examination. However, the modifications of some compounds show extraordinary sensitivity to handling in so many different ways. For example, with octakisphenylthionaphthalene, pressure on a cover-slip causes the yellow form to change to red;[159] with ethylenediamine hydrochloride, mere contact with KBr is stated to cause transformation;[160] with D,l-pantolactone 2,4-dihydroxy-3,3-dimethylbutyric acid γ-lactone, absorption of IR radiation in the spectrometer is sufficient for transformation;[161] and with meprobamate, high humidity may rapidly transform an otherwise indefinitely stable polymorph.[162] The problem is that this sensitivity may not be apparent until after the measurements have been made and then only if the analyst is alert, so that it is not possible to be too careful at the outset. Three of the commonest methods, IR spectroscopy, X-ray powder diffraction and differential scanning microscopy are unreliable for comparison of identity unless the sample is examined as a fine powder, but grinding can mislead into belief of identity if it induces transformation. This is why optical microscopy is so valuable for the initial examination. On the other hand, where transformation is sluggish, solubility determinations will be of more value than instrumental measurements for establishing the stability relationships.[34]

The existence of enantiotropically related polymorphs is indicative of the fact that the relative stabilities and therefore the Gibbs energies of the forms are very similar.[163,164] For this reason the empirical forecasting of polymorphism of a given compound is unlikely to be reliable.[88,165] Despite this, groups of compounds such as sulfonamides, barbiturates and steroids are known to be extraordinarily susceptible to polymorph formation.[39] Around 70% of these are now known to be polymorphic. Other examples include theophylline derivatives,[35] coumarins,[87] alkanes,[64,65] fatty acids and their derivatives[61,62] molecules which form liquid crystals,[15–17] and molecules which pack badly.[166] With the advent of molecular modelling techniques for crystal growth prediction, interest has been generated in the computer prediction of polymorphism.[87] The task is difficult because of the lacunae in our understanding of polymorph structure.

Methods for the Examination of Polymorphs

Polymorphs can be sought deliberately by cooling or quenching of melts, by condensation of vapour, or by crystallization under different conditions, although they are often encountered by chance. In the process of crystallization from solution, the expected effect of crystallization temperature may be overshadowed by other factors, particularly deliberate or adventitious seeds.[167] The importance of crystallization control during process development and the attitudes when unexpected polymorphic forms are encountered has been described by Bavin:[42] 'the process of crystallization is taken for granted by most chemists and it takes a reaction vessel clogged with an unstirrable mass to provoke serious thought'.

All the solid-state properties of the different polymorphic modifications of a compound will be different, but often only marginally so, to the point of instrumental indistinguishability. For this reason, it is important to look at potentially polymorphic systems by a variety of techniques to avoid erroneous conclusions. Failure to recognize a polymorph is the more obvious situation but it is also possible to identify polymorphs where none exist, if reliance is placed on too few techniques.[168] Substances with multiple forms can require substantial effort for their complete elucidation, especially when previous studies have characterized the forms inadequately.[142,148,151,169,170]

The techniques which have been available for a long time for the examination of polymorphs include those listed in Table 1. Which are the commonest methods depends to some extent on the area of interest, but in industrial practice, microscopy, IR spectroscopy, DSC, X-ray powder diffraction, solubility and density measurements have been the most widely used techniques. Within the past decade several new techniques and instrumental accessories have become widely available. These ease the manipulation of polymorphs and so lessen the danger of interconversion, or enable new properties to be investigated and allow measurements to be made which would have formerly

been impossible on the specimen under examination because of its size or microcrystallinity, for example. These developments are listed in Table 2. In general, the application of these newer techniques to polymorphism has not been adequately reviewed. Much of this article will therefore be devoted to a description of these methods in relation to examples taken from the literature on polymorphism. Some attention will also be devoted to aspects of the traditional techniques which have been given surprisingly little coverage in the reviews. Apart fom the techniques discussed below, there have of course been many other methods applied to particular aspects of polymorphism and solid–solid phase transitions. Examples include scanning tunnelling microscopy,[64] electron diffraction,[53] atomic force microscopy,[171] crystal etching,[172] electron microscopy[64,173] and thermobarometric measurements.[174]

The analytical strategy in approaching a polymorphism study will be dictated by the availability of instrumentation, time and material. At the beginning of a study, the fact that minimal quantities of a compound are required by IR spectroscopy, DSC and, particularly microscopy can be a significant consideration. Since thousands of compounds are put into pre-development in the pharmaceutical industry for each successful marketed product[175]* the cost of extensive investigation of polymorphism also needs to be borne in mind.

Microscopy

Although a theme of this review is that no one technique should be used in isolation, hot-stage microscopy has been often so used and remains the outstanding method for the examination and generation of polymorphs.[1] In the hands of experts, surprisingly comprehensive accounts of polymeric behaviour have been generated from microscopy alone,[37,39,140,176] but it is a technique which requires experience for rapid study and the drawing of confident conclusions. A preliminary examination under a binocular microscope will enable the overall characteristics of the sample to be ascertained. Temperature cycling and melt and solvent recrystallization experiments with a polarizing microscope equipped with a hot-stage[177–179] will allow the identification of transition points, the distinguishing of monotropic and enantiotropic relationships, estimation of the tendency of melts and individual phases to supercool, the generation of stable and unstable polymorphs and the recording of their optical properties.[140,180,181] The identification of solvates and the observation of sublimates and of any tendency to decompose are added information.[175] This can be carried out with minute amounts of material. The field has been excellently and comprehensively reviewed in the past,[1,37–39,178,179] and for that reason only the developments since then will be considered in detail here. The basic hot-stage methods have changed little in the intervening years, although there have been considerable improvements in the design of microscopes in terms of greater stability, versatility, ease of use and optical excellence. The availability of phase[182,183] and differential interference contrast (Nomarski) methods[184] and of interference microscopy has enabled precise refractive indices to be more readily determined.[185]

Several designs of hot-stage have been developed and are commercially available. Unfortunately, convenience is often sacrificed to temperature precision and many are unsatisfactory in maintaining temperature control whilst allowing for the manipulation of the specimen since the housings restrict access to the specimen. In fact in some designs, access cannot be gained at all whilst the stage is in position on the microscope. Recourse to a more open design, such as the Kofler stage, a graduated hot-stage[186–188] or a purpose-built heated microscope slide[189] will be necessary for such a requirement. The simplest rotating needle stages[177,185] are similarly more useful in practice than four-axis or five-axis Federov stages, because of the open access.

Although the determination of refractive indices and optic axis angles on birefringent specimens is time-consuming,[190] these optical measurements are critically distinctive of phases[140] especially when variation methods can be justified,[177,191,192] and such measurements ought to be more widely considered when doubt remains as to whether different specimens represent different phases. Such doubt is of more frequent occurrence than is ever suggested in the literature. This is owing, at least partly, to our inadequate understanding of the molecular solid state, and the relationship of that state to its properties. X-ray crystallographic studies have shown that hot-stage microscopic investigations have tended to overestimate the number of polymorphs,[193] presumably because crystal habits have been judged as modifications and because samples of different melting or transition points have been assumed necessarily to represent distinct forms. In fairness to the early investigators it is by no means clear how samples of the same polymorph, for example, can have the same unit cell yet melt 19 °C apart where purity considerations can be excluded.[146] Crystal strain which has been invoked in other,[179] less extreme cases, seems to be a rationalization rather than an explanation.

A major advance in microscopy for the analyst confronted with potential polymorphism has been the availability of video recording.[5] A change in a specimen or perhaps only in a few crystals of the specimen under examination is often only noticed after it has occurred. The ability to replay the video and re-observe the changes, perhaps in slow motion and to compare the timing of the changes in different crystals of the specimen can be exceedingly useful in making judgements of whether sample

Table 1 Techniques which have been available for many years for the examination of polymorphs

Hot-stage microscopy

Thermal methods—
- DTA
- DSC
- Thermogravimetric analysis

Solution calorimetry
Infrared spectroscopy
Solubility measurements

Density measurements—
- Flotation
- Pyknometry
- Dilatometry

X-ray powder diffraction
X-ray single-crystal diffraction

Table 2 Techniques of particular value for the examination of polymorphs which have become readily or more widely available within the past decade

Solid-state NMR
Diffuse-reflectance IR spectroscopy
Near-IR spectroscopy
Raman spectroscopy
Area detectors on diffractometers

Combined techniques including—
- Hot-stage IR spectroscopy
- IR microscopy
- Video recording on the microscope

* According to Lumley and Walker[172] '5000–10000 candidate substances have to be synthesized and screened for every one new medicine that reaches the market'.

homogeneity is in question, in determining transition temperatures or temperature ranges, in recording events in systems displaying irreproducible, erratic behaviour and in sorting out sequential but nearly concurrent events that sometimes occur. For example, a melting followed by resolidification of the low-temperature form will often accompany the transition without melting,[194], individual crystals or crystal domains within the field of view behaving independently.[110,122] A particularly valuable use is in distinguishing the movement of boundaries between domains or phases[178,195] and so distinguishing polymorphic changes from related behaviour such as crystal strain effects.[179]

A more elaborate arrangement has been described[196] in which a differential scanning calorimeter and a hot-stage microscope are linked through video recording. Commercial hot-stages with associated thermal sensors are also available which enable the optical changes and the associated changes in thermal properties to be examined simultaneously. There is a compromise[197] between optical and thermal excellence, versatility and convenience so that it is best regarded as a supplement for a microscope plus a calorimeter rather than a substitute. Close transitions or meltings are better resolved by microscopy than by DSC.[198] There are transitions which are seen by microscopy and not by DSC[106,199] and *vice versa*. The different behaviour of ethyl morpholine $HCl \cdot 2H_2O$ under the microscope and in DSC is particularly striking.[200] Thermomicrophotometry has been recommended and shown to be effective in detecting phase transitions that were not detected either by microscopy or DSC.[201]

A triple system of DSC–microscopy–microphotometry has also been described.[202] The combination of microscopes with other instruments is discussed in the following sections.

Infrared Spectroscopy

The first intimation of polymorphism not previously noticed as a melting point discrepancy or sought deliberately by hot-stage microscopy is often from inconsistencies in solid-state IR spectra. Infrared spectroscopy has had, of course, enormous exposure in the literature through books,[203] reviews[204] and papers but there are surprisingly few descriptions of the precautions to be taken when recording or interpreting the IR spectra of polymorphs. For example, in the case of non-matching spectra, a wide variety of causes might be suspected, including mis-labelling of a homologue,[205*] sample purity, crystal size,[206,207] crystal habit and orientation,[208,209] instability to comminution,[210] formation or partial decomposition of a salt,[211] solubility in the mulling medium, hydration,[212] dehydration[213] or other solvent loss under vacuum, level of impurities in the mulling or disk medium and instrumental variables[214] including the inadequate elimination of background peaks. The latter can be more of a problem with the Fourier transform instruments now in almost universal use, because of the high (often unnecessarily high) resolution which can be achieved in routine use. Experience of the expected levels of instrument and sample reproducibility is the best prophylactic against the discovery of non-existent polymorphs or the disregard of actual polymorphs.

The choice of routine sample presentation methods now includes mulls[215–217], disks[215–219], diffuse reflection[220,221] and attenuated total reflection (ATR).[222,223] All present hazards particularly for amorphous forms and for crystals of limited stability. The running of solution spectra is, of course, excluded for distinguishing between polymorphs, but can be used to check the molecular identity and purity of the specimens and so distinguish polymorphism from solvation, isomerism and other phenomena. The key factor in determining the sample procedure is simply the stability of the polymorph to the chosen conditions. Disks or mulls are usually most appropriate for routine use, but diffuse reflectance spectra are particularly suited for preliminary examination because the preparation technique will minimize polymorphic interconversion in most cases. For particularly sensitive compounds, the choice between ATR, photoacoustic spectroscopy or microspectroscopy will probably be determined by the availability of the appropriate accessories. Interconversion depends on the nature of the compound as well as the vigour of the preparatory stages of the examination. It is desirable to establish the sensitivity of the forms to grinding at an early stage of the investigation, but it is rarely indicated in the literature that this is ever considered.

In general the preparation of a mull is less likely to produce polymorphic changes than that of a disk,[224,225] presumably because the heat of grinding is carried away more efficiently by a liquid than by a solid. However, Nujol itself can cause polymorphic change.[128,143] There is also the belief that the pressure itself during disk formation can bring about polymorphic transitions.[226,227] KCl and KI have been recommended in place of KBr for various reasons,[206,211] but KBr is now most commonly used. It is softer than KCl[228] and so safer for this reason. On the other hand, it is less neutral and so can cause salt formation. Ethylenediamine dihydrochloride is so sensitive to KBr that merely placing a Nujol mull in contact with a KBr disk causes transformation, as previously noted, although a KCl disk is inert in the same circumstances.[160] Different alkali halides have different refractive indices.[204,228] Although not often a problem with organic materials, mismatch of refractive index of medium and sample can cause distorted spectra due to the Christiansen filter effect,[229] which in extreme cases also produces an apparent band shift to lower frequencies. Sometimes, with strong bands, substantial shifts in the opposite direction result[204] a phenomenon which has never been satisfactorily explained. This reinforces the importance of always comparing spectra run under the same conditions.

The use of a grinding or dispersion promoter such as acetone for disk making is excluded, as polymorphic changes are catalysed by solvents.[145] This raises the caveat that non-polar polymorphic systems should not be examined as paraffin mulls.[128,143] In an extreme case, there is the possibility of observing the solution spectrum of the compound being mulled. The further problem with mulls is that they are less quantitatively reproducible and parts of the spectra are obscured owing to the bands of the mulling agent which makes comparison of spectral identity or differences more difficult.[230] For this reason, the use of alternative mulling agents such as hexachlorobutadiene or Fluorolube[98] may be attractive if only the high-frequency region of the spectrum is of interest. This is only likely to be the case for hydrogen-bonded molecules. The most pronounced band shifts are, however, often to be found below 800 cm^{-1} and into the far IR (FIR) region.[231,232]

In the diffuse reflectance (DRIFTS)[233,234] technique the substance to be examined is dispersed in a matrix of a powdered alkali halide and placed in a sample cup in the diffuse reflectance accessory. The sample is illuminated by a wide cone of radiation and the reflected radiation collected over a wide angle. The effects of multiple scatter and multiple reflection within the sample over a wide range of permutations of angles of incidence and reflection tend to reduce orientation effects accompanying insufficient grinding of needle or platey crystals. The observed spectrum results primarily from the transmission of radiation through crystals rather than from reflection from individual faces. Acceptable spectra of polymorphs can generally be obtained by this technique, with much gentler grinding than either for disks or for mulls. For this reason it is to be regarded as the presentation method of choice[146,226,234] for the initial examination of the IR spectra of polymorphs. KCl has

* The fact that a homologue and a polymorph can produce similar degrees of difference was first noted by Jones as quoted by Rosenkrantz and Zablow.[205]

been recommended as the best diluent.[226] For quantitative work, it may be necessary to grind the sample thoroughly, but this may be avoidable for an initial examination. Care must be taken to ensure reproducible dispersion and packing of the sample in the sample cup.[235–237] The use of diffuse reflection is now becoming more commonly reported for the examination of polymorphic systems and the reader is referred to the literature[226,234] for details of the preparation of samples.

In ATR spectroscopy, also called frustrated total reflection or internal reflection spectroscopy, the evanescant wave that penetrates the low refractive index medium under total internal reflectance conditions at a high refractive index/low refractive index boundary is minutely absorbed. This is because the depth of penetration is only of the order of magnitude of the wavelength of the radiation or less. In practice IR radiation is directed through a thallium bromide iodide crystal which represents the high refractive index medium against which the sample is pressed. ATR spectroscopy is widely used for the examination of materials which present problems when examined by other methods. It is particularly valuable for samples which are strongly absorbing or which must be examined *in situ* or at least neat. ATR would thus appear at first sight to be the ideal way of obtaining the IR spectra of polymorphs[238-240] which is possibly why it has been preferred by some of the pharmacopoeias and authorities, for example, in Australia. In principle neither grinding nor any preparation other than possibly sprinkling the sample on to transparent sticky tape is required. However, ATR spectra are particularly susceptible to packing and crystal orientation problems. This, combined with the difficulty in obtaining sufficiently strong and acceptably reproducible spectra, without finely grinding the sample and pressing it to the face of the ATR crystal, makes the technique less attractive and it is rarely used in polymorphism studies. The potential presence of a dispersion component superimposed on the absorption component can also make the comparison of subtle differences less certain.[241] Nevertheless, if a sample proves susceptible to grinding, as in the case of phenylbutazone[239] or sulfathiazole,[242] ATR spectroscopy may be a valuable resort.

Sulfathiazole is one of the few substances in the literature for which spectra run as KBr disks,[243] Nujol mulls[169] and ATR[242] are displayed. The differences in scale make comparisons difficult. Therefore, in Fig. 1 a set of spectra of sulfathiazole polymorph III is displayed, to highlight typical differences. These are mostly in the background and in intensity variation; the position of bands, except those associated with hydrogen bonding, remain at the same wavelengths. Diffuse reflectance spectra of sulfathiazole forms are illustrated in Fig. 2 to give an idea of typical spectral differences between polymorphs. Comparison with spectra in the literature[169,242,243] reveal differences due, apart from the variation in sample presentation technique, to the possibility of interconversion during preparation for spectral examination and to the difficulty in producing pure polymorphs or even reproducible specimens. The spectra of III and IV show only minute differences. This is a consequence of the inherent similarity of the crystal structures and is reflected in the ease of conversion of IV to III. The largest spectral differences between polymorphs I and III are in the NH stretching region, reflecting the substantially different hydrogen bonding networks. Despite the curious appearance of the spectrum of polymorph II above 1700 cm^{-1}, all the features are genuine, but have become exaggerated because of the crystallinity of the sample. This illustrates the dilemma in examining polymorphs. Grinding would improve the appearance of the spectrum but at the risk of promoting a transition. The IR spectra of polymorph III shown[243] or implied[169] in the two most carefully conducted studies in the literature are those of an approximately (1 + 1) mixture of polymorphs III and IV, as are some samples of the commercial material. By near IR difference measurements (see below) the specimen of polymorph III used here was estimated to contain 8% of IV and the specimen of IV to contain 9% of III. The polymorphs of sulfathiazole must be

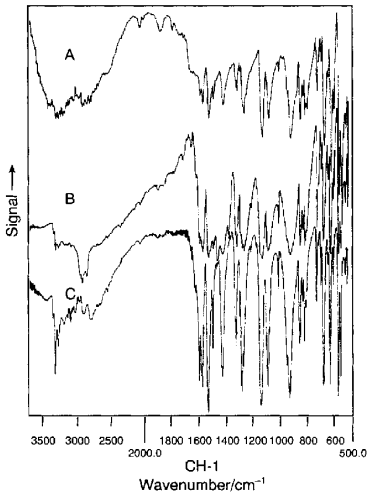


Fig. 1 The IR spectrum of polymorph III of sulfathiazole A, by attenuated total reflection; B, as a Nujol mull; and C, as a KBr disk, for comparison with the diffuse reflection spectrum, Fig. 2. Polymorph III is believed to be stable to grinding, hence any differences are due to orientation effects or to the optical differences inherent in the sample presentations. The intensity differences along the wavelength scale are due to the change in depth of radiation penetration.

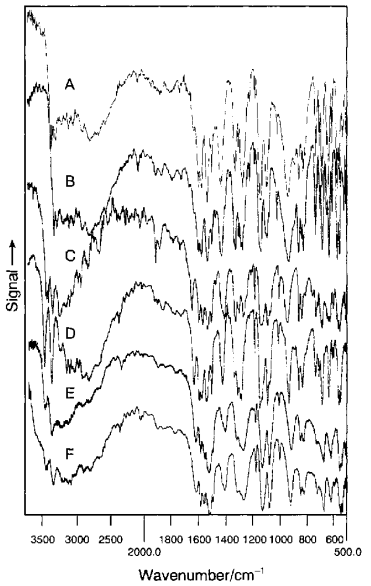


Fig. 2 Diffuse IR spectra of forms of sulfathiazole, admixed into a KBr matrix using minimal grinding. A, polymorph IV prepared inadvertantly; B, polymorph III, commercial sample; C, polymorph II by boiling an aqueous saturated solution to dryness; D, polymorph I by heating polymorph III above 175 °C; E, melt; and F, amorphous form produced by quenching the melt in liquid nitrogen. The spectrum of the melt (in a KBr matrix) is shown for comparison with the amorphous form.

regarded as amongst the most difficult to make and keep as pure specimens, as the number of papers on this topic reflect.[243]

Photoacoustic spectroscopy (PAS) relies on the detection of the acoustic signals generated by the absorption of modulated radiation[244,245] and is therefore not subject to the blacking out effect that occurs when IR spectra of too strongly absorbing samples are recorded by any other technique. Hence spectra can be obtained from neat samples and as such it might be expected to have been more widely explored for polymorphic systems.[246] Control of particle size is, however, important in ensuring reproducibility.[247] PAS has been used to obtain IR spectra of 2*R*,4*S*-6-fluoro-2-methylspiro(chroman-4,4′-imidazoline)-2′,5-dione because the forms were too sensitive to grind.[248] Comparisons of DRIFTS and PAS have been made.[249–251]. There is a difference in the over-all intensity relationship with wavelength between these techniques and transmission methods related to the variation of depth of penetration with wavelength and this needs to be taken into account in comparing spectra obtained by the different methods.

Spectra at low temperatures are more highly resolved and so more characteristic than those at room temperature, owing to suppression of the thermal motion. Low temperature spectra have been recommended for the examination of antibiotics.[252] The relative ease of obtaining spectra at −196 °C has been stressed and the technique has been applied to polymorphic steroids to achieve greater resolution and distinguishability.[116]

The absorption of polarized radiation is dependent on molecular orientation and therefore potentially of value in examining packing modes of molecules,[253] but appears to have been little explored for enhancing the distinguishability of polymorphs. The transformation of polymorphs of fatty acids has, however, been recently investigated. Monoclinic phases of fatty acids pack in layers with oblique orientation of the hydrocarbon chains within a layer. An orthorhombic polytypic phase of both the B and the E forms is known, in which alternate layers have the contrary orientation.[254] Polarized IR spectroscopic studies have been used in establishing the relationship between the orientation of crystal axes in crystals undergoing transformation.[255]

Recording the IR spectra on thin films made by rapid cooling of melts between salt plates or pressed KBr disks is a valuable way of investigating polymorphic propensities.[256,257] Ostwald's principle[257] predicts that the form involving the least loss of Gibbs energy, that is, the modification least stable at low temperatures will be first formed on cooling and if it can be trapped by rapid cooling, it may be possible to follow a whole series of polymorphic changes with time and temperature by IR spectroscopic examination of the film. This can be achieved by warming the centre of the disk with a hot rod,[258] although it is more elegantly carried out on a hot-stage. This technique of making thin films can only be used for substances stable at moderate melting temperatures because of the possibility of fracture of the salt plates from thermal shock.[230]

Commercial heated stages for IR spectrometers have been available for some time, but have not always had sufficient temperature control or insulation to enable differential scanning calorimetric or hot-stage microscopic observations, for example, to be matched with the spectral changes. An alternative is to adapt a hot-stage to fit the IR cell compartment. The expectation of sharp changes in the spectrum at the transition points is not always borne out in practice,[259] because the degradation of the resolution and signal-to-noise ratio at high temperatures may obscure the small changes being sought. Thermal emissivity, convection currents and change in focus may be the main causes of the problem. Detailed studies have established generally the decrease in intensity of IR bands of condensed phases with temperature[260] and a sudden decrease at transition points for alkanes.[261] It is important to make allowances for these variations when comparing spectra taken at different temperatures, as may be necessary when the polymorphs interconvert readily and so cannot be examined outside their range of stability. To overcome these problems and render small changes more visible, it was advantageous to record difference spectra,[262] but now chemometric methods have been brought to bear.[263] Gu[264] has used Malinowski's criteria of number of components to determine the number of transitions and temperature of transition points for glycerides. Two-dimensional correlation plots applied to variable temperature DRIFTS have also been used to pair-up bands in the spectra and so identify the spectroscopic components of the different phases.[265] Partial least squares computation has also been used in conjunction with variable temperature DRIFTS.[234]

The most exciting development in the application of IR spectroscopy to the study of polymorphism has been that of the IR microscope.[208,253,266–269] Normally a single crystal or crystalline powder of sufficient area to fill the sample aperture of an IR spectrometer cannot be examined by transmission because of excessive absorption and can be examined only with difficulty by reflectance because of the mixture of diffuse and specular reflectance components. Although there are techniques and computer programs for the transformation based on the Kronig–Kramers relationship[241] (Hilbert transformation[270,271]) the residual uncertainties make the technique unsatisfactory for comparing subtly differing spectra. With an IR microscope, however, individual small crystals can be examined directly in transmission. The pigment naphthazarin (5,8-dihydroxy 1,4-naphthoquinone) has been examined in this way.[225] Thicker crystals can be examined by seeking thinner areas of acceptable absorptivity near the edges.[272] Apart from the virtue of minimizing polymorphic transformation and of allowing measurements to be made on minimum sample quantities, the difference in the spectra of individual crystals can be ascertained, since it is not unknown for a crystallization to produce a mixture of polymorphs.[85,199,273] Microphases can also be examined.[274] Naturally a great deal more time and manipulation is required for IR microscopy, so in the usual instance, in which sufficient sample is available, an IR macro spectrum would normally be taken first under standard conditions.

Despite all the potential problems, many of which have been discussed above, in most cases IR spectroscopy provides a simple and reliable tool for the investigation of polymorphism. The distinction between spectra of different phases is rarely large, although there are exceptions.[160,275–277] Small changes in peak positions, peak shapes, and absence or presence of a few bands may be all that can be distinguished. This may be enough to characterize a whole series of polymorphs, for example all nine polymorphs and solvates of phenobarbitone prepared by Mesley *et al.* were clearly distinguishable by IR spectroscopy.[151] On the other hand, IR spectra of polymorphs have been frequently reported as virtually identical.[116,160,277–281] In some instances such indistinguishability may be an artefact[282] of interconversion. Reports of identity or difference in IR spectra and in X-ray diffraction patterns in many publications are not borne out upon examination of the accompanying spectra or diffractograms where these have been reproduced at sufficient size to make an informed comparison.

A valuable application of IR spectra (and X-ray diffractograms) of polymorphs is as the basis of a patent claim.[78,80] The use of the NH and OH stretching band positions in establishing stability relationships in hydrogen bonded polymorphic systems is discussed in the section on solubility and density measurement.

Near IR (NIR) spectra due to overtone and combination bands[283] are less resolved than spectra in the fundamental region in the mid-IR. The multivariate methods which are routinely used in this region[284,285] minimize this disadvantage and enable small differences between spectra to be distinguished. The spectra are also much less intense, but provided

that sufficient sample is available, this is an advantage, because saturation of the absorption will not occur and so neat samples can be used. NIR microscopy has also been tried[286] and should show the same advantages for polymorph investigation as IR microscopy. For the normal macro technique, the same problems of reproducible packing and effects of crystal size and orientation as discussed under diffuse reflection apply, but are reduced because of the larger illuminated area. The absence of diluent also removes three variables: the distribution of the analyte, the particle size of the carrier; and the bands due to the carrier or its impurities,[287] particularly moisture. The question of the particle size and reproducible packing discussed above for the mid-IR region are equally important here, although chemometric methods have been applied to try to minimize their effects.[288,289] Since the bands in the NIR region are due to OH, NH and CH stretching vibrations, it would be expected that the spectral changes would be most noticeable in hydrogen-bonded systems[290] and in conformational polymorphism. The published reports[291] are too few to confirm this, although the NIR spectra of many pharmaceutical polymorphs have been recorded. Therefore Fig. 3 shows the NIR spectra of a typical set of polymorphs of a substance, sulfathiazole, in which hydrogen-bonding networks play a significant role. Note that the differences in the spectra of polymorph III and polymorph IV, for example, are greater in the NIR region than in the mid-IR region, in line with the expectations expressed above. The technique is non-invasive, these spectra being obtained by placing a fibre optics probe on the outside of the glass tubes containing the samples. A further advantage of NIR spectra is the ease with which data manipulation, such as spectral differences, can be performed without generating unrealistic results.

Raman Spectroscopy

The Raman effect depends on the inelastic scattering, with loss of vibrational energy, of radiation in the near-UV, visible or NIR region of the spectrum.[292–294] It is inherently very weak and needs an intense, monochromatic excitation source and good filters to remove the excitation line from the collected radiation.[295]

Although commercial Raman spectrometers have been available for a long time, visible excitation sources tend to produce swamping fluorescence from many compounds.[296,297] Where this is due to impurities it may be possible to burn them out,[298] but otherwise the Raman spectrum is difficult or impossible to record against the background. In this case also there is a tendency to char the sample.[299]. There have been numerous mechanical[293] and electronic devices[299] proposed to minimize these effects, but they all have disadvantages. It is only since the advent of NIR Fourier transformation Raman (NIR–FT Raman) spectrometers using the Nd. YAG laser source at 1064 nm with efficient cut-off filters to remove Rayleigh scattering from the laser line,[300] that routine Raman spectra have become reliably available from most organic solids.[296] Although the spectra obtained are broadly similar to IR spectra, the difference in selection rules makes the information complementary.[294,301] Polar groups such as carbonyl and hydrogen-bonded hydroxy groups which are strongly apparent in the IR, are weak in Raman, whereas non-polar symmetrical or nearly symmetrical bonds such as carbon–carbon single and double bonds are strong in Raman.[292] Furthermore, the Raman effect, being a polarizability, falls off as the sixth power of the distance, whereas IR coupling, being a polarization, falls off only as the cube of the distance.[302] Therefore Raman spectra of molecular organic solids in the bond stretching and bending region would be expected to show little influence from neighbouring molecules. The effect is enhanced because the typical organic molecule consists of a non-polar backbone with polar groups on the periphery, so minimizing further the coupling of Raman active bands.

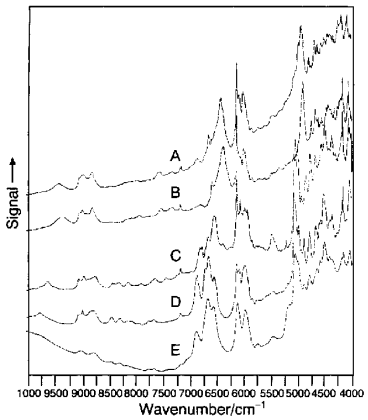


Fig. 3 Near IR spectra of sulfathiazole forms. A, Polymorph IV; B, polymorph III; C, polymorph II; D, polymorph I; and F, amorphous. The spectral differences appear larger than in the mid-IR region because NIR spectroscopy is insensitive to ring and chain modes and records only the XH modes, in this case particularly the NH stretchings.

The effect of this is firstly that Raman spectra of solids tend to have narrower bands than IR spectra. In one polymorphic set that we examined, the typical bands in the IR in the 700–1500 cm^{-1} region had bandwidths at half height of about 15 cm^{-1}, whereas the equivalent Raman bandwidth was about 11 cm^{-1}. Secondly, IR spectra are influenced by neighbouring molecules both directly by hydrogen bonding[303,304] and indirectly by the above spatial distance effect. One would therefore expect that conformational polymorphism would show up more distinctly in Raman spectroscopy and that packing effects especially of hydrogen-bonded molecules would show up most clearly in the IR spectra. There is little in the literature to test this, but we have encountered examples which support this contention. For rigid, non-hydrogen bonded molecules, the largest differences would be expected to occur in the region of the low-frequency lattice modes.[231,232] Comparison of coincidences in IR and Raman bands of symmetrical molecules can lead directly to a decision between alternative structures. The possible centrosymmetric structures for polymorphs B and C of naphthazarin were eliminated in this way.[305] This study shows that the Raman spectra of even deeply coloured solids can be obtained with NIR–FT Raman spectroscopy.[306]

The chief advantage of Raman spectroscopy is that no sample manipulation is required[294] and therefore in the case of polymorphs which are, or are suspected to be, susceptible to transformation, the spectra can be obtained with complete certainty of the identity of the sample under examination. The multiple scattering taking place in powder samples[307] tends to eliminate orientation effects in the same way as occurs in DRIFTS. Because glass is transparent to the excitation and emitted radiation and gives no interfering bands, spectra can even be obtained without removal of the specimen from the sample tube. Consequently, Raman spectra of polymorphs are now actually easier to obtain than IR spectra and deserve to be more widely recorded than the handful of papers[169,233,308,309] in the literature would indicate.

A disadvantage of the NIR–FT Raman system is that commercial instruments do not allow spectra to be recorded to very low frequencies, so that the region where the greatest difference between polymorphs might be expected to be seen,[231,232,310,311] is inaccessible. As this region is also outside

the range of most IR instruments, recourse must be made to conventional Raman spectrometers. As a result, there are few examples in the literature of the examination of organic polymorphs in this low-frequency region,[312–314] reflecting the difficulty of measurement.

Raman microscopy offers in principle even greater advantages than IR microscopy because the theoretical limit of resolution, related to the wavelength of the incident radiation, allows samples of an area less than 1 μm^2 to be examined.[296,297,315] The limit for IR is in the region of 50 μm^2 dependent on the wavelength range of interest.[316] However, in practice, the optical throughput due to the instrumental aperture characteristics, render it difficult to reach the theoretical limit of resolution with FT–NIR systems.[296,297] Conventional instrumentation with argon-ion laser sources at 488 nm, which can be used to examine smaller areas, produce the problems for organic compounds mentioned earlier of fluorescence and charring. The latter is particularly troublesome because of the high intensity at the focus of the beam. Even when charring is not observed, the possiblity of phase transition due to local heating needs to be taken into account.

Ultraviolet and Fluorescence Spectroscopy

Although electronic reflection spectroscopy has been rarely invoked for the examination of polymorphs, it has long been known that different polymorphs of coloured compounds[317–319] including certain dyes and pigments,[58,59] in particular, phthalocyanines,[149,320–323] display different hues. Bandshifts of up to 170 nm in the solid state as a result of packing differences of the molecules have been reported.[324–326] Furthermore, it is remarkable how many organic crystals deepen in colour on transformation to a higher melting polymorph,[98,122,155,159] so it must be presumed that many, probably most, uninvestigated colourless polymorphs would also show a spectral change in the UV region on transformation. The information that can be extracted from UV reflection is less than from the techniques whose spectral characteristics are more readily related to structure, and the measurements are more difficult. The electronic spectrum may, however, be recording more subtle solid-state changes. It has been recently ascertained that the yellow to red transformation of pyridinium picrate which has been known since 1929 does not occur at the temperature of the only transition point recorded by variable temperature X-ray diffraction studies.[327] The use of polarized near-normal UV spectral reflectance from different faces of single crystals has been applied to the conformational polymorphism of dichlorobenzylidene anilines to relate solution and crystal properties and to elucidate the relationship between molecular conformation and electronic properties.[4] The origin of these colour differences has been discussed only briefly, but must be presumed to be due to intermolecular charge-transfer effects.

Ultraviolet spectra of solids can also be obtained by transmission from the mull or KCl disk technique[328] (KCl is transparent to shorter wavelengths than KBr), provided that a thinner matrix is used and account is taken of the vast difference in molar absorption coefficients in the IR and UV regions. The UV spectra of polymorphs of 2(2-methyl-3-chloroanilino)nicotinic acid have been investigated by diffuse reflectance from Nujol mulls.[132]. A detailed comparison of the relative merits of photoacoustic spectroscopy and diffuse reflectance in the UV, visible and NIR regions has been made.[329]

The colour of cyanine dyes is related to the aggregated state in solution, concentrated solutions yielding the more deeply coloured solid-state forms containing the more extensive molecular aggregates.[330] The absorption spectra, the fluorescence spectra and the electronic properties of solid cyanines[331] display marked differences between the polymorphs. The fluorescence spectral differences in this and other cases[332] have been ascribed to a type of excimer formation. Fluorescence spectra have otherwise been little reported although they have been investigated for possible quantitative analysis of polymorph content.[333] Polymorphs may also differ in their thermoluminescent characteristics.[334,335]

Solid-state Nuclear Magnetic Resonance and Nuclear Quadrupole Resonance Spectroscopy

An NMR spectrum on a solid run under similar conditions to those used for solutions will result only in a broad hump of extremely low signal intensity. For the investigation of melting phenomena or of order–disorder transitions representing the onset of molecular rotation or libration this is advantageous: the phase yielding signals of moderate width as a result of orientational, positional or configurational freedom can be measured with little interference from the signals generated from the rigid solid phase.[336,337] For detailed observation and interpretation of the molecular structure, however, it is necessary to narrow the signals.[338,339]

The breadth and low sensitivity of the solid state signals in ^{13}C NMR spectroscopy is due to three separate effects, each of which must be minimized.[340–342] The lines are broadened firstly by anisotropic dipole–dipole coupling and the quadrupole field gradient. Secondly, the chemical field anisotropy which is normally averaged to zero in liquids cannot be averaged out by molecular tumbling in solids. Finally, the extremely long spin–lattice relaxation times require long pulse repetition times to build up the signal. The chemical field anisotropy can be averaged by magic-angle spinning (MAS) in which the sample is rotated at speeds of 4–15 kHz.[340–342] The dipolar and quadrupolar field effects can be removed by high-power heteronuclear decoupling. Finally, the spin–lattice relaxation time is reduced by cross-polarization involving pulse sequences which transfer energy between nuclei, thus involving the 1H nucleus in the mechanism of relaxation. The net result is that NMR spectra of solids are now routinely available of acceptable signal-to-noise ratio which show adequate resolution for structural interpretation,[343–345] although longer acquisition times than for solution spectra are necessary. The detail and information content of NMR spectra should be particularly valuable in distinguishing polymorphs and in understanding the sources of their differences.[64,313,342–345] The use of NMR spectra for examination of dosage forms has been canvassed.[345,346] In practice, relatively few descriptions of the NMR spectra of polymorphs are available in the literature and in several cases where phases which have proved to be very similar by other techniques have been examined, they have also proved to show few differences by NMR spectroscopy.[5,169,281,347] This illustrates that very small packing differences are sometimes characteristic of phases or polymorphs. The interpretation of the spectra in terms of molecular structure is normally by comparison with the solution spectrum, but the assignment of carbon type can be made in the solid state with the use of appropriate pulse-sequence techniques.[348] A promising use of solid-state NMR spectra is in investigating amorphous forms.[28,349,350] The amorphous form of testosterone was assumed to have ordered packing but disordered molecular orientation from examination of the features in the NMR spectrum associated with the different portions of the molecules.[116] Conclusions could therefore be drawn as to the probable mechanism of solidification. It is not clear why a solid with positional order but rotational freedom behaves as an amorphous phase rather than a disordered one. Solid-state NMR signals can sometimes be observed to be doubled as a result of non-equivalent crystallographic molecules in the unit cell.[116,340,351]

Nuclear quadrupole resonance spectroscopy[352] (NQR) is not troubled by the broadening effects encountered by NMR spectroscopy and has been widely used particularly for the examination of inorganic systems. It relies on the detection of the electric quadrupolar effects and is confined to those nuclei with suitable spins. For organic compounds these are principally ^{2}H, ^{14}N, ^{17}O, ^{19}F, ^{35}Cl, ^{37}Cl, ^{79}Br and ^{81}Br. It is relatively insensitive so large quantities of material are required. Chlorine and bromine can be detected by conventional radiofrequency spectroscopy but ^{14}N, which is probably the most generally useful nucleus for organic compounds,[353] requires sensitivity enhancement. Cross-relaxation experiments, similar to the cross-polarization experiments discussed above, are appropriate. ^{2}H and ^{17}O studies require isotopic enrichment. All these nuclei have been used to study phase transitions, particularly in relation to mechanism and molecular dynamics.[354,355] The use of ^{17}O to study order–disorder phenomena is discussed later. Phase transitions are detected by changes in relaxation times, couplings or multiplicity with temperature. Malononitrile[356,357] is particularly interesting, because the change in multiplicity of the ^{14}N NQR signals at −132 and 22 °C heralds a new phase in between those temperatures, although the phase below the lower temperature appears to be the same as that above the higher one. It can be seen from Fig. 4 that the Gibbs energy values for the two polymorphs are constrained to follow very similar paths. As might be expected from this, the intermediate phase has a structure which is only marginally different from the surrounding phase.

X-ray Crystallography

X-rays are reflected from crystals only when the angle between the ray and the planes in the crystal fulfil the Bragg condition $n\lambda = 2a\sin\theta$, where θ is the angle between the ray and the plane, λ is the wavelength of the radiation, a is the interplanar spacing and n is an integer. There is an infinite number of possible planes through the crystal, but only a limited number which give reflections within the accessible range $2 < \theta/\text{degrees} < 180$. With a single-crystal brought into all orientations with respect to the beam, a series of spots is generated on the surface of a sphere centred on the crystal. In the case of a powder sample a set of concentric cones is generated which can be recorded as a series of arcs on a photographic strip or as a diffraction trace *via* a detector.[358] Every molecular repetition will give a unique set of reflections and so generate a unique pattern. Any change in crystal packing will lead to changes in the form of the molecular repetition. In principle, then, any polymorph will give a distinctive X-ray powder pattern. X-ray powder crystallography is therefore of great value for distinguishing and identifying polymorphs.[359]

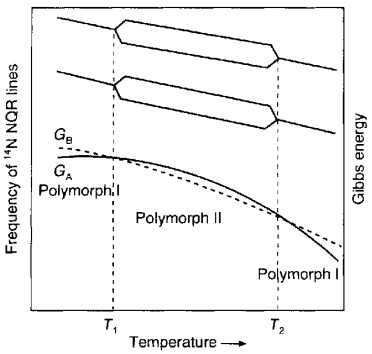


Fig. 4 Interpretation of the phase transitions of malononitrile in terms of Gibbs energy. The upper part of the diagram is a schematic representation of the variation of the ^{14}N NQR spectrum of malononitrile with temperature. T_1 and T_2 are the transition points at −132 and 22 °C, respectively. The lower part of the diagram represents the Gibbs energy situation. Instead of crossing once as in the enantiotropic system in Fig. 7, the Gibbs energy curves G_A and G_B (for polymorphs I and II, respectively) must cut twice (see text).

X-ray single-crystal diffraction is, of course, even more descriptive and in principle can lead to unique definition of the packing of the molecule, the molecular interconnectivity and the three-dimensional conformation of the molecule in the crystal. However, it often proves difficult in practice to grow crystals of sufficient size and perfection for an X-ray structural analysis to be carried out whereas a powder pattern can nearly always be obtained.[73] The difficulties which may be encountered in growing crystals of the polymorph stable at room temperature are much magnified when unstable polymorphs and enantiomeric polymorphs are required and particularly when crystals of unstable polymorphs of enantiomers are involved.[248,360–363] The evidence for this packing prejudice against optically active molecules has been undermined by a detailed comparison of the density measurements recorded in the literature for racemates and enantiomers and a consideration of the statistical bias,[124] but it remains a matter of common observation during crystallization experiments that optical isomers are difficult to produce as good crystals.[364] The problems with metastable forms are easy to understand as owing to the presence of crystal strain and defects. Some crystals show such a large change in volume on transition that they generate enough strain to shatter or move violently and are therefore sometimes characterized[275,312,347,365–367] as 'jumping crystals'. Variable-temperature X-ray diffractometers[368,369] are helpful and, of course, essential for the examination of polymorphs which have no existence at room temperature but the required apparatus is infrequently available in laboratories where polymorphs are encountered. It is good practice to look at a sample under the polarizing microscope for homogeneity and for appearance of individual crystals as single and perfect, free from twinning or unusual features, before submission for single crystal X-ray examination. Occasionally, even the most beautiful and transparent crystals may be twisted, too thin to produce an adequate signal, multiply twinned, polycrystalline or otherwise defective and hence fail to give an interpretable diffraction pattern.[370] Even if the diffraction pattern is too poor for a complete structural analysis, the unit cell dimensions are a criterion for the existence of distinctive phases and the derived density a further critical reference value for the polymorph. Regrettably, crystallographers often fail to record minimum physical characteristics of specimens of polymorphs such as melting point, range of stability or relative stability[371,372] or even origin[373,374] thus limiting the usefulness of their results. For this reason it proved impossible, by examination of the Cambridge Structural Database (Cambridge Crystallographic Data Centre), to check the reliability of the rule that the polymorph stable at higher temperature has the more symmetrical structure. The structure of over a thousand pairs of organic polymorphs has been recorded, but only a small portion have adequate accompanying physical information. The theoretical basis of the rule has been described by Kitaigorodski[375] and Desiraju.[376] The total energy of a crystal is the sum of the lattice energy and the vibrational energy. Close packing minimizes the lattice energy but interferes with vibrational motion increasingly at higher temperatures. The loss of lattice energy stabilization in a more open lattice can be compensated by the entropy gain resulting from the more symmetrical structure. The close packing requirement means that the majority of organic crystal structures reside in very few space groups ($P2_1/c$, $P\bar{1}$, $C2/c$, $P2_1$, $P2_12_12_1$).[32,33] The combined effect of the vibrational and close packing requirements on organic polymorphs is that

one of the commonest patterns for a dimorphic system on transition is monoclinic at low temperature to orthorhombic ($P2_12_12_1$) at higher temperatures. Higher symmetry space groups are adopted by disordered states.[275]. Plastic crystals generally adopt cubic space groups in the disordered phase,[8,377] reflecting the requirements for the molecular motions.

The development of area detectors for diffractometers for small molecule work means that crystals previously too small to examine can be successfully tackled, or areas of otherwise unsatisfactory crystals can be chosen.[378] This can be very effective in conjunction with the use of synchroton radiation.[312,379–382] Although there are occasional reports of incorrect conclusions being drawn from X-ray data[5,327,383,384] the most likely source of error in studying polymorphs is picking the wrong crystals.[385] As mentioned above, metastable forms often crystallize badly and in a sample of such a product it is not uncommon for the only satisfactory crystals to be interlopers of the stable polymorph. Computation of the correlation of X-ray single-crystal diffraction patterns with powder patterns is now possible and should capture such error at an early stage.[142,169,386] The contrary process, converting powder patterns of complex molecular crystals to structural information,[387] although an exciting prospect, is not yet applicable to sufficiently large molecules to be of general interest for studying polymorphs of commercially interesting compounds.

However, for the ordinary laboratory environment an X-ray powder diffractometer is of more general value. It will sometimes identify differences between samples which are too subtle to be detected up by thermal analysis[5,313] microscopy or IR spectroscopy,[388], although a few contrary examples are known.[312] One such general instance is where water or other small[389,390] molecules fill voids in a structure in a random fashion without altering the crystal packing itself as in the examples of antibiotics such as cefaloglycin and cefalexin.[391] A mixture of crystalline and amorphous material will be indistinguishable from a pure sample of the crystalline material except in absolute intensity which is rarely measured in normal use. There are other cases which are not so easy to explain.[282] For example, the X-ray patterns of the forms of D,l-norleucine are virtually identical, although the IR spectra are easily distinguishable.[160,392] Examination of the IR spectra excludes the possibility that a neutral $\longleftrightarrow$ zwitterionic transformation is involved.

A more common problem with X-ray powder diffraction is in the examination of samples consisting of larger crystals. These may produce a spotty pattern which is difficult to reduce to a series of line intensity measurements and is impossible to compare satisfactorily with diffractograms from other samples.[358] If the crystals are not roughly isometric, particularly if they are needles or platey, the pattern may show distinctive features from crystal orientation effects[169] as is shown in Fig. 5. Grinding is appropriate providing that the polymorph is stable. For soft crystals an inert powder may be mixed in,[393] in order to facilitate grinding. An alternative approach is the use of the Gandolfi camera which can be made to generate a simulated powder pattern from a single crystal. The orientational bias for platey crystals of polymorphs III and IV of sulfathiazole was eliminated in this way.[169] The calculation of powder patterns from single-crystal data mentioned above has been recommended by several groups as a means of obtaining the best reference X-ray powder pattern.[142,169,387,394]

Neutron diffraction, although of less general value than X-ray diffraction, has the advantage that the scattering factors for atoms vary little with atomic number.[395,396] Light atoms can therefore be detected and located accurately in the presence of heavy atoms, in contrast to X-ray studies. As such, it is of potential value in examining polymorphic systems for their hydrogen bonded networks[82,84,111,122,397] and in investigating tautomeric or zwitterionic polymorphism. The naphthazarin C polymorphs have been examined by neutron diffraction to establish their hydrogen-bonding characteristics and the order–disorder transition.[398] The deduced centrosymmetric structure, in contrast to the Raman results mentioned earlier, is the result of the averaging of the structure over a substantial time-scale. This factor also applies to X-ray structures[399] and needs to be borne in mind when comparing these with NMR and vibrational data. The comparative rarity of sources and the need for relatively large crystals means that neutron diffraction is likely to be infrequently used for investigation of polymorphs.

X-ray crystallography is well supported by texts at all levels, both for single-crystal work[400–404] and powder methods.[358,395,405,406]

Thermal Analysis

Although the term thermal analysis is sometimes considered to include hot-stage microscopy, it is convenient to deal with these methods separately. Microscopy is concerned with qualitative visual observations whilst instrumental thermal analysis is capable of giving quantitative measurements, but without necessarily identifying the nature of the processes responsible. Thus the techniques are complementary and best used in conjunction.[407] The main thermal techniques considered will be thermogravimetric analysis (TGA) and differential thermal analysis (DTA)/ DSC.[408] TGA measures the change in mass of a sample with temperature and is therefore particularly valuable in examining solvent loss from crystals and in identifying sublimation and decomposition processes. As it is recording dynamic processes, not only the temperature at which changes occur will vary with procedure but the very occurrence of those processes may depend on sample environment and heating conditions. The subtleties of thermal analysis are often overlooked. In the vivid words of Garn,[409] 'The apparent simplicity of the technique leads the uninformed to assume that satisfactory data may be obtained, for example, by sticking a pair of thermocouples into a sample and reference and lighting a fire under them.'

DSC and DTA are alternative ways of measuring heat capacity changes in a sample.[196,410] Although they may occasionally give significantly different thermal traces,[411] the term DSC will be used here without implying the method of acquisition of the data. Any compound will absorb heat in acquiring a higher temperature. During a transition, heat will be absorbed or emitted in effecting a change of phase. The remarks

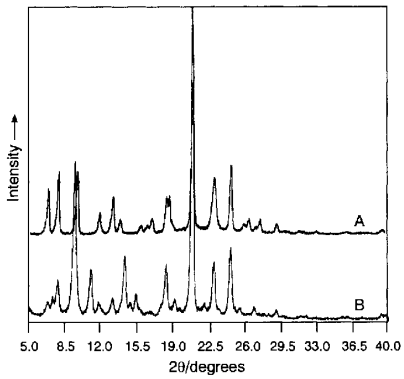


Fig. 5 Crystal orientation effects in X-ray powder diffraction. Traces due to A, the platey and B, acicular habits of the same polymorph of RP 54275 are shown. At high values of 2θ, the traces are similar, but at low values they are different. Reproduced with permission of Rhône-Poulenc Rorer Ltd.

made above regarding the dynamic nature of TGA apply equally to DSC. In most cases where the forms are stable to grinding and the transitions are rapid the resulting curves will be sensibly reproducible. In other cases, the thermograms obtained may depend on the heating rate,[412,413] sample packing,[414] crystal size,[415,416] the ambient atmosphere[417] and encapsulation[239,367,407,418] and interpretation needs appropriate care. In particular, it is often overlooked that the history of a polymorphic crystal may be critical, for example, a later run may differ because of tempering on standing with loss or gain of seed nuclei of other forms.[200,313,367,419–421] Many instruments now run TGA and DSC simultaneously. This is valuable in that it enables a clear distinction to be made between processes involving solvent loss, sublimation and decomposition on one hand and pure phase changes on the other. The principles of thermal analysis have been set out recently in a book[422] and in an introductory video.[423]

The features to be seen in a DSC trace (Fig. 6) are endotherms, representing absorption of heat, exotherms representing the emission of heat and the so-called second-order transitions representing a change in the heat capacity without either absorption or emission of heat. A sloping baseline could represent a continually changing heat capacity, but is often due to imbalance between sample and reference, or slow loss of mass from the sample during heating. During a heating cycle endothermic processes are the most common ones. Melting and sublimation are always endothermic as are transitions involving enantiomorphs at or above transition points. Desolvation is usually endothermic and chemical reactions can be, especially at lower temperatures. Monotropic transitions, crystallization and most decomposition reactions are exothermic. On cooling, crystallization and enantiotropic transitions are exothermic, so cooling cycles normally contain only exotherms. Despite this there is often value in running the sample under both heating and cooling modes.[414] Although this has long been recommended, it is rarely indicated in the thermal analysis literature on small molecules that this has been considered.[208] By contrast it is common in lipid and polymer work to run both heating and cooling curves.[89] If it is intended to identify the material at room temperature after a phase transition, it is imperative to check on the cooling cycle that no reverse change has occurred. Heats of transformation and melting can be evaluated from the area under a DSC curve,[424,425] although not, of course, as satisfactorily as from a precision adiabatic calorimeter.[426] Conditions need to be chosen carefully in order to obtain reliable results. The greatest difficulty is in determining the most suitable base line.[427]

It is common for a polymorph to show a transition to a higher melting polymorph at the appropriate transition temperature when heated slowly, but to overshoot and melt at its own melting point under more rapid heating conditions.[194] This is often followed immediately by re-solidification to the higher melting polymorph giving a characteristic curve shape (Fig. 6, c). The polymorph thus produced may or may not be the same as that resulting from the transition at the proper transition point and in other instances the re-solidification may be delayed.[224] Dependent on the complexity of the polymorphic set, a whole series of such events may take place. Finally, the form with the highest melting point will melt if it has not previously decomposed. Several meltings may take place in the case of a

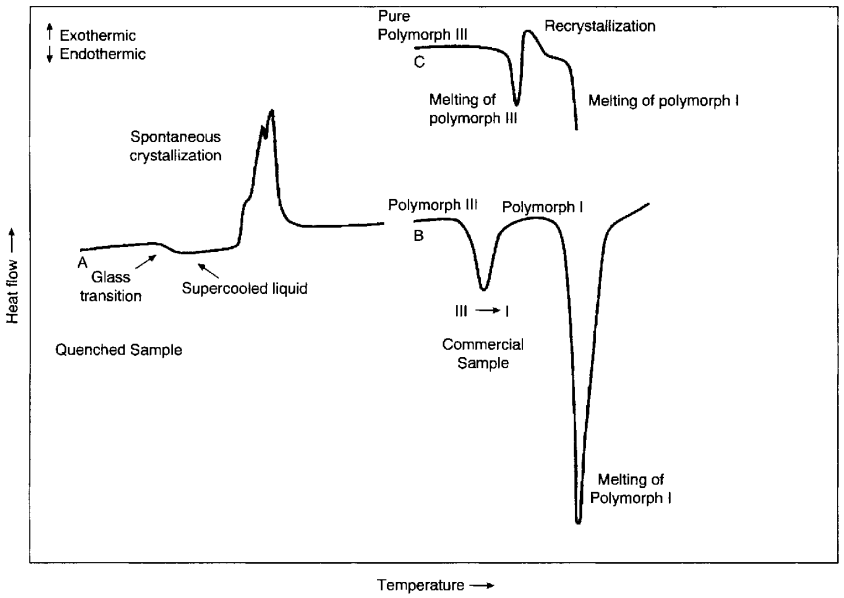


Fig. 6 Typical features in the DSC of a polymorphic system. A, Quenching the melt of sulfathiazole gives an amorphous solid, which on heating undergoes a second-order transition (glass transition) to a supercooled liquid (see refs. 422, 542–544). In a second order transition no heat is evolved or absorbed and only the heat capacity alters. This is seen as a drop in the base line. A supercooled liquid always represents an unstable phase and on heating spontaneous crystallization of this can occur. In this case it happens suddenly, causing the rapid movement away from this new base line. Irreversible processes are exothermic, but the complex exotherm which follows is unusual and probably represents several overlapping transitions. As described by Ostwald's Principle (see refs. 258 and 436) this is a cascade of transitions to successively more stable forms at that temperature. The resulting phase must be polymorph I, since it melts at 201 °C without further thermal events occurring, B, a specimen of polymorph III shows an endotherm due to the transition from polymorph III to polymorph I, followed by melting. The fact that it is endothermic indicates that polymorph I and polymorph III are enantiotropic. This endotherm always occurs around 150–175 °C although it is known that the true transition point lies many degrees below this; and C, a specimen of polymorph III which is free from seeds of polymorph I (see refs. 194 and 242), may overshoot the transition point and melt at its own melting point. This is often followed immediately by recrystallization, which is an exothermic process, of the higher melting polymorph I giving the characteristic trace shown.

compound with liquid crystal phases, but finally a clear melt will form.

The literature on the investigation of the behaviour of phenylbutazone[239,428–432] provides an instructive example of the role of thermal analysis in polymorphism. Early work produced the not untypical situation of conflicting data on the number and properties of polymorphs.[239,428] Subsequent application of thermogravimetric analysis showed that two of the reported polymorphs were in fact solvates.[429] In a substantial re-investigation, five polymorphs were identified and characterized.[430] The IR spectra were not very useful for differentiating between the crystal forms because of their similarity.[430] The X-ray diffractograms were also reported as somewhat similar, although the earlier work[429] had relied on these to distinguish forms. The published patterns look distinguishably different[239,429,431] but it is reported that phenylbutazone shows orientation effects and is sensitive to grinding,[239] which is undoubtedly the reason for the reported similarity of the IR spectra. Dissolution rate data were also acquired, but in the absence of surface area information (see later) they cannot be regarded as definitive evidence for polymorphism. Distinction between the polymorphs relies then in this study[430] on thermal analysis. The temperatures of peak maxima are quoted for all polymorphs as well as onset temperatures of melting, the latter agreeing closely with the melting point as determined on a hot-stage microscope. The two highest melting polymorphs, A and B, show only a single peak due to melting at all heating rates, with onset temperatures of 105 and 103 °C, respectively. The remaining three polymorphs, C, D and E, each show a single melting endotherm at 96, 94 and 92.5 °C under rapid heating rate conditions of 32 °C min^{-1}. At lower heating rates they all display a melting endotherm adjacent to a recrystallization exotherm (similar to that shown in Fig. 6, c) followed by a melting endotherm at 105 °C. This was interpreted as the formation of polymorph A from the melt. Grinding or compressing the polymorphs C, D and E caused an increase in the area under this higher melting peak and a small reduction in the observed temperature of all the endotherms. In view of this and the closeness of the melting points it is difficult to be sure that A and B do not represent only one polymorph and C, D and E another, although there is some evidence of a third endotherm in some of the thermograms and evidence from the other papers of at least four forms. Subsequent studies have identified other forms[431] and confirmed the sensitivity of the results to the thermal history of the sample.[432]

By contrast, the melting points of the three polymorphs of gepirone hydrochloride[433] are substantially different and the conclusions from thermal analysis about the relationship between them unambiguous. Under slow heating conditions, samples of the low melting polymorph (mp 180 °C) showed an endotherm due to the transformation to the higher melting polymorph. At faster heating rates, a melting endotherm followed immediately by an exotherm representing re-solidification of the higher melting polymorph was observed. The higher melting polymorph then melted at 220 °C. This interpretation of the DSC measurements was confirmed by hot-stage microscopy. By prolonged heating of the lower melting polymorph it could be converted entirely to the higher melting form. The sample then showed a single endotherm at 220 °C. The endotherms of mixtures showed the disproportionate effect of small quantities of the higher melting form. The third polymorph could only be produced by crystallization as a minor component of a mixture. From DSC supported by thermomicroscopy the melting endotherm could be identified at 212 °C. Consideration of the relative thermal stabilities allowed small samples of the pure polymorph to be produced by heat treating mixtures in the calorimeter; the pure polymorph so produced showed only a single endotherm at 212 °C whereas the mixture had shown endotherms at all three melting points. From these experiments it was possible to decide on the relative thermal stabilities of the polymorphs and to calculate their heats of fusion.

The most important advance in understanding of the thermodynamic relationships between polymorphs and in interpretation of DSC curves has been through the formulation of Burger's rules.[136,434] Two of these will be discussed here and the other two in Solubility and Density Measurement. Burger's heat of transition rule implies that (*i*) if an endothermic transition is observed at a certain temperature on heating, then there must be an enantiotropic transition point at or below that temperature; but (*ii*) if an exothermic transition is observed, then the transition point must lie above that temperature, or the two forms are related monotropically.

Burger's heat of fusion rule is of value when the heat of transition cannot be observed, owing to the failure of the polymorphs to transform readily. This states that the higher melting polymorph will have the lower heat of fusion if the polymorphs are in an enantiomorphic relationship, otherwise they are monotropically related. Because of the misunderstanding of these rules which is apparent from the literature, and because of the insight into the stability relationships between polymorphs which they yield, a simplified derivation will be given here.

Fig. 7(*a*) and (*b*) are representations of the Gibbs–Helmholtz equation for enantiotropic and monotropic cases, respectively. The shape of the H (enthalpy) curves is determined by $H = H_o + \int c_p dT$. Since the specific heat C_p is always positive, they must slope upwards at an increasing rate with temperature, as shown. G, the Gibbs energy, is related to the negative summation of all the entropies, S. The value of S is again dependent on C_p. The value of S must be positive, therefore the G curves must slope increasingly downwards, again as shown. At absolute zero, $H = G$ and the curves meet. The lowest energy crystalline structure at absolute zero will have the strongest intermolecular bonds. Strong bonds imply high lattice vibration frequencies (phonon modes[396,435]) which make the smaller contribution to C_p. Therefore, the angle of divergence of the G and H curves of the polymorph most stable at low temperatures will be less than that of the less stable polymorph. Hence the G curves will tend to cross, but the H curves will not. The heat of transformation rule can be ascertained by concentrating on the H curves and noting the enthalpy consequences on going from H_a to H_b or *vice versa*, remembering that this is only possible by lowering the Gibbs energy, *i.e.*, ΔG must be positive. Hence processes which are exothermic on raising the temperature are spontaneous ones and are irreversible at or below that temperature, and *vice versa* for endothermic processes. The heat of fusion rule depends on the enthalpy curves for the polymorphs and the liquid phase being approximately parallel over the relevant region, so that the differences in C_p do not obscure differences in the heats of transition. These rules are extra-thermodynamic, in that they involve structural considerations, so they are not 100% certain. It is not clear whether there are any exceptions in practice as re-evaluation of the literature data has eliminated many of the apparent exceptions.[42]

These rules, as already implied, can be helpful in sorting out DSC results. The concept of enantiotropism as reversibility needs to be approached with caution. Mirror image curves cannot be expected on heating and cooling. Apart from Ostwald's rule[257,436] and hysteresis due to high energy barriers,[194,434] leading to offset of heating and cooling events, consider the energy–temperature diagram for a trimorphic enantiotropic system, Fig. 8(*a*). The heating cycle might produce transformations at A, B and C whilst the cooling cycle might proceed *via* any of the many paths on the diagram. A form such as polymorph II in Fig. 8(*b*) which is metastable at any temperature would be most unlikely to form on heating, but could well be the product of cooling the melt.

For investigation of melting by DSC, small samples are usually appropriate and the temperature of melting is taken as either the peak maximum, or more precisely as a peak maximum corrected for heat flow,[425] or as the extrapolation of the leading edge back to the base line.[437] Because solid–solid transformations are often sluggish[157,438] and may reflect very small enthalpy changes, the use of larger quantities of compacted sample has been recommended, together with low heating rates and the assignment of the first discernible movement away from the base-line as the transition temperature.[197] The appropriateness of this may depend on the thermal stablity of the material under examination. Similar treatment of cooling curves then yields a transition range dependent on the hysteresis of the system. Organic compounds may be more appropriate calibrants than the almost universally used indium, as they are likely to have conductivity characteristics similar to the sample.[197,439]

It is often implied in accounts of the determination of purity by DSC that the true melting endotherm of a pure substance will be infinitely sharp,[440] but of course this cannot be so for organic powders. Apart from practical considerations of thermal conductivity, edges and surfaces are less stable than bulk and will melt first and so small crystals will melt before larger ones.[441] Melting normally starts at crystal defect sites. The observed melting will also be affected by a polymorphic transition very near to the melting temperature or decomposition at the melting point and, of course, impurities. Although it was generally thought that the melting temperature could not be exceeded without melting occurring, there are scattered reports of slow melting[442,443] and superheating[444] and increasing acceptance of the existence of this phenomenon.[445] In addition there are instrumental factors. Different instruments (DSC, DTA, melting point apparatus, hot stages, thermal photometers) measure different manifestations of the melting process and so will not necessarily give the same value.[196,199] All these factors apply also to solid-solid transformations. Even after the elimination of the possible effects, there still remain unexplained examples of anomalous melting behaviour. For obvious reasons most of these never appear in the literature but there are a few[446–449] and further examples are known to the author. Note that whilst examples of curious melting and transition behaviour ought to be carefully checked, they are not necessarily the result of inaccurate observation.

A large endotherm followed by a small melting endotherm is characteristic of the formation of a disordered phase in which the positional order of the crystal is retained, but the orientational order is lost.[8,275,426,438] This may be due to random orientation of molecules, but is most often associated in organic systems with the onset of 'free' rotation. Molecules of roughly spherical shape are particularly likely to show an order–disorder transition to a plastic crystal state.[8,224,426,450,451] At lower temperatures, crystals of such molecules sometimes show a glass transition in the crystalline state.[452,453] Order–disorder transitions have been regarded as second-order transitions,[154,180,454] but organic examples are not characterized by 'second-order' DSC traces. Although second-order transitions are widely discussed in the literature, the concept presents certain difficulties as has been well addressed by West.[154] On the whole the term is better avoided, except in reference to glass transitions, in considering the inter-relationships of organic polymorphs.

From a study involving a selection of appropriate techniques it should be possible in most cases to acquire a reliable listing of the polymorphs, their relative stabilities and their transition points, which is as far as present day economics of industry may allow. However, a study is incomplete without the drawing of a semi-schematic energy–temperature or the equivalent pressure–temperature diagram.[433] If all the relevant data have been assembled such a figure takes, except in complicated cases, only a few minutes to prepare. The discipline of setting out the results in this form leads to a great confidence that the system is understood and avoids the erroneous descriptions of polymorphic systems sometimes presented in the literature.[35] Whilst the unwelcome appearance of a further polymorph at a late stage of investigation cannot thereby be excluded, it is rendered less likely.

A development which offers greater sensitivity as well as enabling overlapping spontaneous and reversible processes to be separated is oscillating, alternating or modulated DSC.[455] The superposition on the temperature ramp of a periodic temperature function allows a computational separation *via* a Fourier transform. Although the rate of modulation in commercial instrumentation is too slow for many polymorphic transitions, it is already being found useful in pharmaceutical investigations.

Thermosonimetry[456] is a relatively unexplored technique owing to the lack of convenient instrumentation and the dearth of applicable theory. It is mentioned here because it would appear to have considerable potential for the identification of phase changes and possibly for the understanding of the crystal structure changes accompanying these. The frequency spectra of the sonic emission of solids on heating are very rich, although it is only possible to use these at present as a signature.[457,458] Phase changes are accompanied by increased activity and a change in the spectrum.

Solubility and Density Measurement

These are two of the measurements traditionally used to identify polymorphic behaviour. They remain important today: solubility because that is often the target property which is required of the polymorph in practice: and density because of its reliability and theoretical linkage with crystal structure and with stability. A pigment which bleeds, a solution of an agrochemical* which is liable to precipitate and block spray nozzles or a suspension of any product which cakes[47–49,461] during storage is probably unmarketable. The solubility also has an important thermodynamic feature: it is inversely related to the stability of the polymorph such that the most stable polymorph is always the least soluble at a given temperature.[19,34] At a transition point, the interconverting polymorphs are equally soluble. There is an implicit assumption behind these assertions that the solutions prepared from either of the polymorphs are identical. There is limited evidence against this in some cases. For example, in the case of sulfonamides the polymorph crystallizing from solution is dependent on that dissolved.[462] In principle then, the determination of the solubility over a temperature range for two or more forms of a substance will readily establish the transition points and thermodynamic stabilities.[463] It is the author's experience, however, that the measurement of solubility gives rise to more difficulty and more erroneous data than any other connected with polymorphism. The problem is threefold.

(i) The attainment of equilibrium is often slow, particularly with poorly soluble or poorly wettable substances,[464] for which several days' agitation may be required to establish a consistent value. Either through system instability, lack of awareness or time constraints this is often not done and the measured solubility is then effectively a dissolution rate measurement. This latter, whilst related to solubility *via* the Noyes–Whitley equation[465] and so roughly parallelling it in many cases, is also a direct function of surface area and therefore of particle size.[36,466] If particle size is checked only instrumentally

* Examples of polymorphs of agrochemicals in the open literature are few, *e.g.*, Borka.[459] Instability of formulations is more often related to supersaturation than to polymorphism and problems are often solved pragmatically. However, the more sophisticated formulations now being introduced demand attention to polymorphism.[460]

(Coulter counter, Malvern analyser) over-all aggregate size rather than individual grain size may well be measured.[467] Any differences in grain and aggregate size can then result in erroneous solubility comparisons. A preliminary microscopic examination will give forewarning of such a situation, but may not indicate how to solve it. Intrinsic dissolution measurements[464,468] may provide a surrogate solution to the problem. 'Surrogate' because there are both practical and theoretical reasons why the intrinsic dissolution rate ratio of polymorphs will only approximate the relative solubilities. (For an example see Table 1 in the study by Buxton, *et al.*[469]). Wettability differences can totally destroy any correlation.[470,471] Nor can slow equilibrium be overcome by working at higher temperatures followed by cooling, because the temperature–solubility hysteresis usually determines an even longer equilibration time. The second factor is the susceptibility of the polymorphs to transformation when examined outside their stability ranges.[472] As indicated earlier, the presence of a solvent can be particularly efficacious at promoting a polymorphic transition. It is often possible to measure the solubility of a polymorph below its lower transition point, but rarely many degrees above its upper one.

(ii) The possibility of a transformation to a solvate,[473] or hydrolysis[146] or other chemical reaction. Sometimes the shape of a solubility–time curve will indicate whether a transformation is occurring, but whether or not this is so depends on the relative kinetics of the dissolution and transformation processes. One solution is to measure the solubility of the polymorphs in an inert solvent and then measure the partition coefficient rapidly.[474]

(iii) There are the consequences of pH variation in the measurement of the solubility of ionizable species.[463,475] The self-buffering capacity of organic acids and bases can often make a dramatic difference to the observed solubility. The need to match buffer capacity to the expected solubility is rarely considered.[476] Trace ionic[477] or other (oxygen, carbon dioxide) contamination can occasionally present a source of error. If the solubilities are being measured spectrophotometrically the effect of pH or complexation on the absorption spectrum also needs to be taken into account.[36,478]

When the solubilities cannot be determined in the region of the supposed transition point, it is possible to extrapolate from other temperatures using the van't Hoff isochore. This procedure needs to be applied with caution as the experimental inaccuracies and theoretical assumptions are often not appreciated.[77,162,463,479]

For molecular solids in which hydrogen bonding is not a structural feature, the stability of a form is nearly always closely related to the density. Although this relationship, as a consequence of the rapid reduction of intermolecular attractive forces with distance, has been understood for a long time, the structural implications were first explored in detail by Kitaigorodski.[480] Dipole–dipole interactions can contribute to the structural stability (surprisingly, however, they do not appear to contribute to the preferential formation of polymorphs[481]), but the only common and significant attractive force other than van der Waal's forces is hydrogen bonding. This can produce more open structures in which the loss of polarizability energy is matched by favourable disposition of the strong hydrogen bonds. This is the basis of the other two of Burger's rules,[136] namely the density rule 'the more stable polymorph at absolute zero will possess the highest density' and the IR rule 'the highest frequency OH or NH stretching band will be associated with the form least stable at absolute zero'. The highest frequency OH or NH stretching will be associated with the weakest hydrogen bond. Juxtaposition with the heat of transformation and heat of fusion rules will usually allow the deductions to be generalized to working temperatures. Consideration of the circumstances pertinent to these rules could lead to the expectation of exceptions. It is found in practice that whilst there is a small proportion of exceptions to each rule, their complementarity makes the concurrent failure of both rules less likely.[42]

Density can be measured by flotation,[482,483] by volumenometry, or by pyknometry.[483] All are time consuming. Alternatively the true density* can be calculated from the unit cell dimensions.[485] The latter must always be marginally greater than the measured density, as the crystal voids and other defects always lower the overall density of the crystals. Any discrepancy is a warning of solvates or other incorrectly assumed molecular structure. Generally, the measured density will increase marginally on grinding as a result of cracking occurring preferentially at crystal pores and defects, but on prolonged grinding it may begin to decrease owing to increased surface area and amorphization.[42,486] An attempt to check Burger's density rule against the true densities by using the Cambridge Crystallographic Data Centre data base for X-ray structures failed for the reasons mentioned earlier.

The air comparison pyknometer represents an instrumental method of measuring densities with enhanced sensitivity. Flotation is best carried out with centrifugation and it may detect the presence of interloper crystals of a different polymorph in a specimen. The main problems with flotation are in finding a liquid mixture of suitable density that does not dissolve the sample and in maintaining that density through adequate temperture control. The first requirement is particularly critical for organic polymorphs.

Solvates

Hydrates or other solvates often produce a further level of complexity in a polymorphic system.[487,488] There is the expectation of a monohydrate or monosolvate but, in fact, the accommodation in a unit cell for a small molecule can produce multiple,[489,490] fractional,[282] irrational[412] or variable[469,491] molar ratios. Amongst the polymorphs of a molecule some can be hygroscopic and others stable to water or water vapour.[489] Different hydrates can be produced from different polymorphs.[45] This is probably related to the 'stuffing' effect of impurities described by Buerger.[3] Where there are two or more hydrates of the same composition, these are in a polymorphic relationship with each other.[138] In practice it may be difficult to interconvert polymorphic solvates, because of the likelihood of preceding desolvation.[389,469] The desolvation of a solvate can sometimes produce a polymorph not obtainable in any other way.[138,389] A detailed study of celiprolol hydrochloride has shown that the hydrate is not a true one in the usual sense but appears to be a solid solution of the drug in water.[492] This leads to speculation about the exact nature of the crystal structure involved.

Thermomicroscopy in silicone oil will reveal desolvation on heating by bubble formation.[178] DSC will show features corresponding to solvent loss, but such features are notoriously sensitive to heating rate, crystal size, mass of sample, sample packing, and to the use of open as against closed or sealed pans or even pan shape.[427] When the transitions are accompanied by inhomogeneous melting (dissolution) or a mixture of inhomogeneous and homogeneous melting[282] or when the desolvation overlaps the normal melting or a phase transition, the DSC can become difficult on interpret. Another phenomenon which leads to confusion when the DSC trace is viewed in isolation is stepwise loss of solvent, especially when this occurs in irrational proportions.[492] A simultaneous TGA is of unique

* The term 'true density' is used by other authors in contrast with bulk density to describe what is here called the 'measured density'. For a discussion of different measures of density, see Lowell and Shields.[484]

value in these cases in pinpointing the temperature or temperatures of solvent loss in the particular run. It cannot be necessarily assumed that the form resulting from recrystallization from an 'anhydrous' solvent will be the anhydrate.[494] In contrast, the anhydrous form III of cortisone acetate is reported as only obtainable in the presence of water, whilst the hemihydrate is produced from wet solvents and the monohydrate from dry solvents.[488] Erythromycin dihydrate is said to dehydrate when heated in water at lower temperatures than in air.[417,487]

Whilst X-ray powder diffraction patterns will distinguish a solvate except for the rare examples discussed earlier, they do not display any characteristic features of the solvent as such. By contrast, all of the common solvents have strong and distinct bands in the IR spectrum which generally reappear at the same or similar wavelengths in the solvate.[495] Those bands sensitive to hydrogen bonding will shift, but these shifts are again very characteristic. It could be supposed that except for very low molar ratios of solvent or high molecular mass compounds, IR spectra would be a totally reliable reflection of the presence of a solvate. The bands due to water are often difficult to distinguish from those due to hydrogen-bonded hydroxy groups in the host molecules and there are occasional reports of the indistinguishability of IR spectra of hydrates and other solvates.[365,430,496,497] There is the danger of pumping off the solvent if the sample is prepared as a KBr disk, or of rehydration.[365] Some of the literature reports may well reflect this. Hydrates have occasionally been mistaken for enolic tautomers[498] and frequently for simple polymorphs. A microanalysis, Karl–Fischer or mass loss determination will avoid such misinterpretation. Quantitative DSC has also been used to determine the degree of hydration, based on assumptions of the energy of binding of the water molecules.[499] Solid-state ^{13}C NMR spectra will show bands due to solvate guest molecules but not, of course, to water. The presence of the latter will affect the positions of other signals,[349,500] except presumably in those cases where X-ray diffraction shows no change in packing. In one such case of spectral indistinguishability, resort was made to differences in spin–lattice relaxation times.[346]

The solubility of a hydrate in water or a solvate in its own solvent is always less than that of the unsolvated form, for thermodynamic reasons. On the other hand, the solubility of the hydrate in ethanol or of an ethanolate in water will be always greater than that of the unsolvated form.[463] The vacuum microbalance which measures the mass of a sample under different pressure and humidity conditions is a valuable way of quantifying the stepwise loss and gain of solvent.[501]

Quantitative Aspects

The requirement of analytical control implies reliable methods of detecting, distinguishing and quantifying polymorphs. All the caveats in the examination of polymorphs referred to previously apply with greater force when quantification is required. A method needs to be selected in which the differences between the polymorphs is maximal, yet unlikely to be interfered with by the presence, in particular, of other potential polymorphs or solvates. X-ray powder crystallograpy,[359,393,502] IR,[234,469] NIR[291] and Raman[308] spectroscopy, DSC[234] and DTA[503] have all been investigated for the determination. They have a common feature, namely that the transfer of energy to and through the powdered sample is one of the critical factors with respect to the precision of the measurement. Whilst solution transmission properties are capable of being dealt with theoretically, powder absorption can only be tackled when simplifying assumptions are made.[251,504] The critical features are the particle size and shape of the sample and of the diluent, if one is present, and the homogeneity.[505] It is therefore necessary to grind, and to grind reproducibly. The sample then needs as a minimum requirement to be stable under the grinding conditions. Again microscopy comes into play to check whether the sample is dispersed. Care must be taken to ensure that the sample is quantitatively transferred with the matrix powder, rather than left coating the vessel.[505] This applies particularly to greasy, low melting or plastic crystals. Each compound will present its own problems. It is unlikely that any one technique will prove universally suitable. Because of the small differences that are commonly encountered, realistic limits of quantification even with the use of chemometric methods will probably be 1–10%, dependent on the individual problem. The few examples in the literature on the determination of polymorphic mixtures support most of these contentions. The precautions needed to obtain reliable results in DRIFT spectra have been explored in detail in the case of sulfamethoxazole[234] and of a new anti-inflammatory drug.[226] The potential of X-ray methods have been explored on a model system.[394] Although it has a long history,[359] quantitative X-ray analysis has often been used without attention to possible sources of error. The α-inosine content of mixtures of α- and β-inosine has been investigated by both X-ray powder diffraction and IR spectroscopy.[393] The limit of detection by the X-ray method was decidedly superior to that by IR spectroscopy, but the IR spectra display some curious features. X-ray diffraction has also been used for the detection of α-prasosin in γ-prasosin. Using a profile fitting analysis, a detection limit of 0.5% was achieved.[506] Possible interference from other polymorphs was not considered. The polymorphic composition of cortisone–acetate mixtures and of a candidate hypolipidaemic drug have been determined by Raman spectroscopy,[309] as has chlorpropamide.[507] DTA was found to be superior to X-ray powder diffraction for the determination of fatty acid polymorphs.[503]

If the enthalpy of solution of two polymorphs is sufficiently different, then solution calorimetry can be used for their determination in a mixture.[508,509] The solution obtained by dissolution of one polymorph must be the same by definition, as that obtained from another polymorph of the same substance.[19,462] The difference in heat (enthalpy) of solution therefore determines the relative enthalpies of the polymorphs.[463] the polymorph stable at lower temperatures will have the lower enthalpy (see Fig. 7). The determination can be made indirectly from solubility measurements over a temperature range with the application of the van't Hoff isochore or preferably, directly by measuring the heat of solution in an adiabatic calorimeter.[463] The enthalpy difference will be the same whatever solvent is chosen: therefore it is possible to select one in which adequate solubility is shown. The occurrence of polymorphic change during dissolution will not affect the calorimetric result, as the heat of transition will be summed in the measured heat of dissolution.[463] X-ray powder studies are most commonly used to determine the degree of crystallinity.[510] Solution calorimetry has also been applied to the determination of degree of crystallinity of partly amorphous antibiotics, proving more reliable than X-ray powder methods.[512] The values of crystallinity determined by the two methods were substantially different. The polymorphic composition of phenobarbitone[411] and phenylbutazone[512] by X-ray powder diffraction and by DSC have also been reported to be different, but no explanation of either of these observations has been offered.

Amorphous and Crystalline Solids

There are different schools of thought as to whether amorphous states ought or ought not to be included in the definition of polymorphism.[513] Crystalline solids are distinguished by the presence of periodic pattern repetition in three dimensions

leading to long-range order*: this can be defined as the expectation of finding an identical pattern repeated at regular intervals in any direction throughout the solid.[514] Isotropic liquids and amorphous solids, on the other hand, have no long-range order so the most that can be said about the structure is that the probability of finding a particle distant from any point is given by the particle density.

The neatness of this distinction has been obscured firstly by the existence of liquid crystals[515] with one- or two-dimensional long-range order and incommensurate phases[516] and more recently by the discovery of quasicrystals[517,518] with long-range non-periodic order,[519] often characterized by pseudo five-fold crystallographic axes,[520,521] some of which enjoy greater stability than the equivalent crystalline state.[522] The term non-crystalline therefore does not imply total randomness and there is an increasing awareness of the possibility of different amorphous structures.[523–524] For example, the amorphous and liquid state are generally considered to represent the same phase, yet there are substances which exist in two amorphous forms separated by what appears to be a phase transition.[131,524] Different amorphous structures may arise from different processes of production.[525,526] In practice many of the organic materials usually described as amorphous are the 'meringues' produced by evaporation of solvent from solutions of substances which do not crystallize readily, or the powders produced by precipitation, transition,[487] freeze drying,[527] spray drying[259,528] or grinding,[449] although the terms microcrystalline or colloidal might be more appropriate, dependent on the size of the crystalline volume.

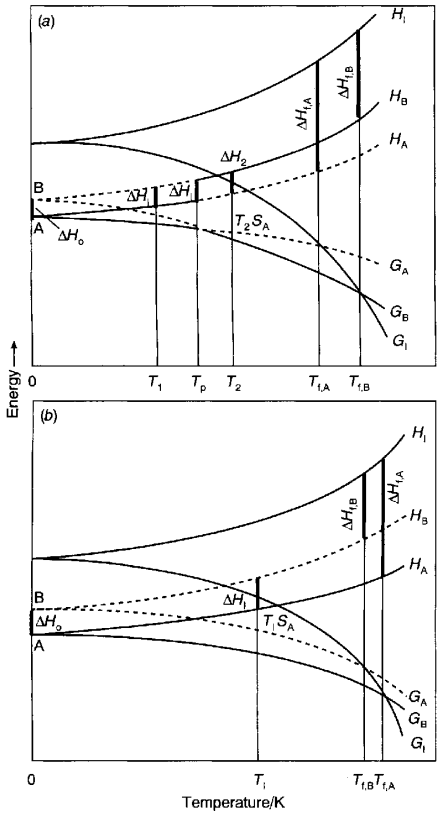


Fig. 7 Energy–temperature diagrams of dimorphic systems. Reproduced from Burger, A., and Ramberger, R., *Mikrochim. Acta*, 1979, **II**, 261 by permission of Springer–Verlag, Vienna (*a*) Enantiotropic systems and (*b*) monotropic systems. (T_p, transition point; T_f, fusion point; H, molar enthalpy; G, molar free energy; S, molar entropy; A, B: crystalline modifications; l, liquid phase).

The concept of an amorphous solid as microcrystallite clusters rather than as a continuous random network or dense random packing has fallen into disfavour, but most of the work has been done with semiconductor materials, and the conclusion may not apply to organic molecular solids. Quasicrystal clusters or 'amorphons' may need to be considered for organic states.[8,9,529] However, there is limited possibility with the analytical tools presently at our disposal of deciding the nature of the detailed structure of amorphous materials. X-ray crystallography has been the most used technique for establishing structure both in terms of long- and short-range order,[9,358,530], although calorimetric methods, vibrational spectroscopy, and increasingly NMR spectroscopy[531,532] provide structural information. Solid-state ^{13}C NMR spectroscopy can show, for example, conformational preferences of molecules even when there is no discernable X-ray pattern.[28,349] Despite this, there has been an almost total neglect of the study of organic amorphous materials. When they are reported they are usually characterized inadequately, if at all. It is not always possible even to ascertain if the reported lack of crystallinity is derived from visual examination, polarized light microscopy or X-ray examination. The significant advances in our understanding of the amorphous solid-state have come recently not in the area of structure but in recognizing the entropic relationships between liquids, crystals and the amorphous state.[533–537]

The most investigated amorphous materials are polymers[364] and inorganic glasses formed by cooling silicate melts[538] although amorphous metals and semiconductors have become the subject of intense research activity in recent years.[320,539] The solids most typically and traditionally regarded as amorphous are those produced by cooling a liquid in the absence of crystallization. During this process the material passes by continual change from a liquid state though the glass transition to a solid state, *via* a more viscous, possibly rubbery or malleable state.[540,541] The term 'supercooled liquid' gives rise to some confusion.[542] A solid is usually arbitrarily defined as a material whose shear viscosity exceeds $10^{14.6}$ poise ($10^{13.6}$ N s m^{-2}).[515] Amorphous materials have therefore been described as having the rheological properties of a solid but the structure of a liquid.[543] Given the limited knowledge of the structure of either liquids or amorphous materials, it may be felt that the latter half of that statement is ambitious. The glass transition temperature is the point at which the melt sets, accompanied by changes in many other properties. There are several methods of investigating the glass transition, including DSC.[544,545] In the idealized case, the DSC trace shows no peak, but only a step representing a change in the heat capacity. This occurs only when the heating rate is the same as the cooling rate which has produced the glass. If the heating rate is faster than the cooling rate, an exotherm is superimposed and if the cooling rate is faster, the usual case, an endotherm is superimposed.[546] These effects are due to strain as a result of the structure failing to reach equilibrium within the experimental time-scale.[9,531,540] In either case the underlying heat capacity change can be

* More precisely, the definition of a crystalline array is given by:

$$\lim | x - x' | \to \infty < \rho(x)\,\rho(x') > = F(x - x')$$

Where $< \rho(x)\,\rho(x') >$ is the density-density correlation between two points x and x' related by a basis factor. Isotropic liquids and amorphous solids, on the other hand, have no long-range order, so the probability of finding a particle distant from x is given by

$$\lim | x - y' | \to \infty < \rho(x)\,\rho(x') > \approx \bar{\rho}^2,$$

where $\bar{\rho}$ is the average particle density.

obscured. The temperature of the glass transition is not fixed, but is lower the slower the cooling and heating rates.[422,546] Amorphous solids are always less stable than crystalline forms and so on heating will normally show an exothermic transition to a crystalline phase, although this may be preceded by a glass transition.[242,422] There are a few compounds which, as solids, are only known in the amorphous state and these display only a step corresponding to the glass transition.[547]

Many organic materials can be prepared as glasses by rapid cooling.[162] Molecules with myriad conformational possibilities, particularly polysaccharides and synthetic polymers, tend to occur as amorphous forms. Molecules whose shape precludes a packing density, that is, the ratio of the volume occupied by the molecules as such to the volume of the space in which they reside, of at least 0.60 also solidify most easily as glasses.[85,548] Directed bonds favour the more open structure implied by these low densities, so that multiply hydrogen-bonded molecules, for example, carbohydrates, are notoriously difficult to crystallize.[73,549,540]

The industrial significance of amorphous organic materials has increased enormously. Polymers are, of course, ubiquitous. In the pharmaceutical industry there are compounds, particularly antibiotics, which have long been used in that form because of the difficulty of crystallization and solubility

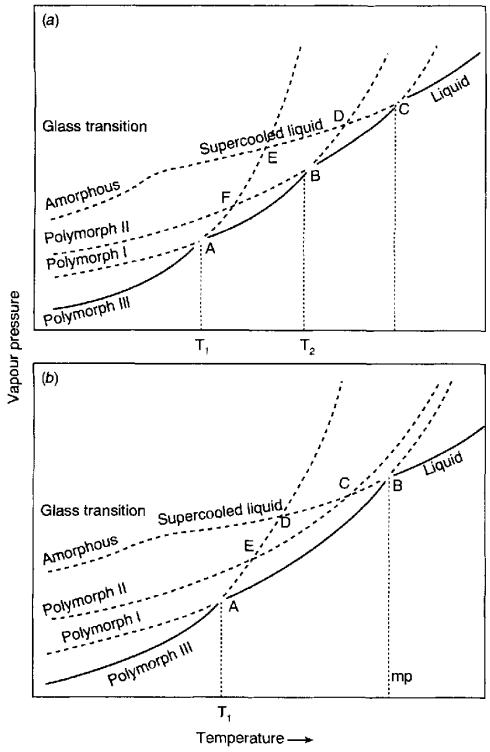


Fig. 8 Vapour pressure–temperature diagrams for trimorphic systems showing that heating and cooling curves can follow different paths *via* different polymorphs. Dashed lines represent metastable equilibria and full lines stable equilibria. The heating cycle in the system shown in (*a*) will probably proceed *via* A, B and C (but see ref. 194 and the caption to Fig. 6 whilst any propensity to undercool might give routes to polymorph III *via* CBF, CDB or CEA. In addition the paths may well end at the amorphous form or polymorphs I or II. Similarly in (*b*) heating will probably proceed *via* A and B, but cooling could follow several paths. In either case spontaneous transitions (vertical drops) are also possible.

problems of the crystalline forms.[43,512,551] More recently attention has been paid to the deliberate use of amorphous forms with a crystallization inhibitor as a means of more rapid drug delivery.[521] Interest in amorphous forms relates not only to active ingredients but to excipients including sugars[550,552] and polymers. In the food industry, carbohydrates often need to be used in amorphous forms and many food constituents exist naturally in an amorphous state.[66–73,553,554]

Amorphous material may result from grinding[449,555], deliberately or inadvertently. The effect of comminution of a crystal is to reduce the long-range periodicity and broaden the signals in X-ray diffraction patterns until in the limit the pattern is so diffuse as to be indistinguishable from that of an amorphous form produced from the melt.[524] On this argument there is no break between a crystalline and an amorphous form. If by contrast, one cools a melt so as to produce a glass, then by this process there is no break between the liquid state and the amorphous form. There may be distinction between the products of the two processes. It may be possible in principle, or in practice in favourable cases, to distinguish between limitingly small crystalline domains and large non-crystalline domains, for example by analysis of the shapes of X-ray powder diffraction lines,[358,405,556] but it would be very artificial to draw the boundaries of the coverage of this review between the two, especially as their properties for all practical purposes are likely to be identical. On balance then, the wider definition is adopted here, intended to allow the reader to decide on the inclusion of amorphous states or otherwise in the term polymorphism. On this wider definition, McCrones' view[1] that every system will be discovered to be polymorphic if studied enough, comes much nearer to verification.

The author thanks numerous colleagues for their help in locating references. The IR spectra in Figs. 1 and 2 and DSC measurement in Fig. 6 were provided by P. Elliott and S. Taramer, University of York. I am grateful to G. Nichols of Pfizer, Sandwich, and Dr. B. Slater of Rhône–Poulenc Rorer, Dagenham, for suggestions about the manuscript and I am particularly indebted to Professor M. Hursthouse, University of Wales, Cardiff, for his comments on crystallographic aspects of the manuscript and for help in so many ways over many years.

References

1 McCrone, W. C. in *Physics and Chemistry of the Organic Solid State*, ed. Fox, D., Labes, M. M., and Weissberger, A., Interscience, New York, 1965, vol. II, p. 725.
2 Deffet, L., *Répertoire des Composés Organiques Polymorphes*, Desoer, Liege, 1942.
3 Buerger, M. J., *Trans. Am. Crystallogr. Assoc.*, 1971, **7**, 1.
4 Bernstein, J. in *Organic Crystal Chemistry*, ed. Garbarczyk, J. B. and Jones, D. W., International Union of Crystallography, Oxford University Press, 1991.
5 Dunitz, J. D., *Pure Appl. Chem.*, 1991, **63**, 177.
6 Bayard, F., Decoret, C., and Royer, J., *Stud. Phys. Theort. Chem.*, 1990, **69**, 211.
7 Rao, C. N. R., and Rao, K. J., *Phase Transitions in Solids*, McGraw–Hill, New York, 2nd edn., 1978.
8 Ubbelhohde, A. R., *The Molten State of Matter*, Wiley, Chichester, 1978.
9 Elliott, S. R., *The Physics of Amorphous Materials*, Longmans, Harlow, 2nd edn., 1990.
10 Verma, A. R., and Krishna, P., *Polytypism and Polymorphism in Crystals*, Wiley, New York, 1966.
11 Amelinkx, S., *Acta Cryst.*, 1955, **8**, 53.
12 Amelinkx, S., *Acta Cryst.*, 1955, **9**, 16.
13 Amelinkx, S., *Acta Cryst.*, 1955, **9**, 217.
14 Dunitz, J. D., *Pure Appl. Chem.*, 1991, **63**, 177.
15 Maliniak, A., Greenbaum, S., Poupko, R., Zimmermann, H., and Lutz, Z., *J. Chem. Phys.*, 1993, **97**, 4832.

16 Bhide, V. G., Agrihotri, S. A., and Chaudra, S., *Indian J. Pure Appl. Phys.*, 1981, **19**, 821.
17 Gruger, A., Romain, F., and Le Calvé, N., *Thermochim. Acta*, 1984, **116**, 57.
18 Reinke, H., Heinz, D., and Hans, M., *J. Chem. Ed.*, 1993, **70**, 101.
19 Campbell, A. N. and Smith, N. O., *Alexander Findlay's The Phase Rule*, Dover, New York, 9th edn., 1951.
20 Sharma, B. D., *J. Chem. Ed.*, 1987, **64**, 404.
21 Sirota, N. N., *Cryst. Res. Technol.*, 1987, **22**, 1343.
22 Sirota, N. N., *Cryst. Res. Technol.*, 1982, **17**, 661.
23 Doyle, B. B., Hukins, D. W. L., Hulnes, J. S., Miller, A. and Woodhead–Galloway, J., *J. Mol. Biol.*, 1975, **91**, 79.
24 Oxford, G. S., and Rollinson, D., *Protein Polymorphism: Adaptive and Taxonomic Significance*, Academic Press, London, 1983.
25 Jackson, A. P., Maxwell, A., and Wigley, D. B., *J. Mol. Biol.*, 1991, **217**, 15.
26 Knobler, C. M., and Desai, R. C., *Annu. Rep. Phys. Chem.*, 1992, **43**, 207.
27 Chapman, D., Urbino, J. and Keough, K. M., *J. Biol. Chem.*, 1974, **249**, 2512.
28 Saito, H., *Yuki Gosei Kagaku Kyokaishi*, 1992, **50**, 488.
29 Burden, C. H., PhD Thesis, University of Leeds, 1987.
30 Corradini, P. and Guerra, G., *Adv. Polymer Sci.*, 1992, **100**, 182.
31 *CRC Handbook of Chemistry and Physics*, ed. Weast, R. C., CRC Press, Cleveland, 61st edn., 1981, p. B-69.
32 Wilson, A. J. C., *Acta Cryst., Sect. A*, 1988, **44**, 715.
33 Wilson, A. J. C., *Acta Cryst., Sect. A*, 1990, **A46**, 742.
34 Kuhnert-Brandstätter, M. and Riedmann, M., *Mikrochim. Acta*, 1987, **II**, 107.
35 Burger, A., *Acta Pharm. Tech.*, 1979, **Suppl. 7**, 107.
36 Burger, A., in *Topics in Pharmaceutical Sciences*, ed. Bremer, D. D., and Speiser, P., Elsevier, Amsterdam, 1983, p. 347.
37 Halebian, J. K., and McCrone, W. C., *J. Pharm. Sci.*, 1969, **58**, 911.
38 Halebian, J. K., *J. Pharm. Sci.*, 1975, **64**, 1269.
39 Kuhnert-Brandstätter, M., *Thermomicroscopy in the Analysis of Pharmaceuticals*, Pergamon Press, Oxford, 1974.
40 Byrn, S. R., *Solid State Chemistry of Drugs*, Academic Press, New York, 1982.
41 Aguiar, A. J., Krc, J., Kinkel, A. W., and Samyn, J. C., *J. Pharm. Sci.*, 1967, **56**, 847.
42 Burger, A., *Pharm. Int.*, 1982, **3**(5), 158.
43 Mullins, J. D. and Macek, T. J., *J. Pharm. Sci.*, 1960, **49**, 245.
44 Bavin, M., *Chem. Ind.*, 1989, 527.
45 Nakamachi, H., Yamaoka, T., Wada, Y. and Miyaka, F., *Chem. Pharm. Bull.*, 1982, **30**, 3685.
46 Chan, H. K., and Doelker, E., *Drug Dev. Ind. Pharm.*, 1985, **11**, 315.
47 Macle, C. H. G., and Grant, D. J. W., *Pharm. Int.*, 1986, **September**, 233.
48 Thoma, K., and Serno, P., *Deut. Apotek. Z.*, 1984, **124**(43), 2162.
49 Liversidge, G. G., Grant, D. J. W., and Padfield, J. M., *Anal. Proc.*, 1982, 549.
50 Woodard, G. D., and McCrone, W. C., *J. Appl. Crystallog.*, 1975, **8**, 342.
51 Kohlbeck, J. A., *Microscope*, 1982, **30**, 249.
52 Teetsov, A., and McCrone, W. C., *Microscope*, 1965, **15**, 13.
53 Kendall, D. N., *Anal. Chem.*, 1952, **24**, 382.
54 Susich, G., *Anal. Chem.*, 1950, **22**, 425.
55 Ebert A. A., and Gottlieb, H. B., *J. Am. Chem. Soc.*, 1952, **74**, 2806.
56 Whitaker, A., *J. Soc. Dyers Colour*, 1992, **108**, 282.
57 Thomas, A., and Ghode, P. M., *Paintindia*, 1989, **39**, 25.
58 Kuhnert-Brandsttter, M. and Riedmann, M., *Mikrochim. Acta*, 1989, **I**, 373.
59 Warwicker, J. O., *J. Text. Inst.*, 1959, **50**, T443.
60 Etter, M. C., Kress, R. B., Bernstein, J., and Cash, D. J., *J. Am. Chem. Soc.*, 1984, **106**, 6921.
61 *The Physical Chemistry of Lipids*, ed. Small, D., Plenum, New York, 1986.
62 *Crystallization and Polymorphism of Fats and Fatty Acids*, ed. Garti, N. and Sato, K., Marcel Dekker, New York, 1988.
63 Gupta, S., *J. Am. Oil Chem. Soc.*, 1991, **94**, 450.
64 Srivastara, S. P., Handoo, J., Agrawal, K. M., and Joshi, G. C., *J. Phys. Chem. Solids*, 1993. **54**, 639.
65 Ungar, G., *J. Phys. Chem.*, 1983, **87**, 689.
66 Cebula, D. J., and Ziegleder, G., *Fett Wiss. Technol.*, 1993, **95**, 340.
67 deMan, L., Shen, C. F., and deMan, J. F., *J. Am. Oil Chem. Soc.*, 1991, **68**, 70.
68 Saltmarsh, M., and Labuza, T. P., *J. Food Sci.*, 1980, **45**, 1231.
69 Roos,Y., and Karel, M., *Int. J. Food Sci. Technol.*, 1991, **26**, 55.
70 Herrington, T. M. and Branfield, A. C., *J. Food Technol.*, 1984, **19**, 427.
71 Cammenga, H. K., and Steppuhn, I. D., *Thermochim. Acta*, 1993, **229**, 253.
72 Siniti, M., Carré, J., Bastide, J. P., Létoffé, J. M., and Claudy, P., *Thermochim. Acta*, 1993, **224**, 105.
73 Imberty, A., Buleon, A., Vihn, T., and Perez, S., *Starch/Staerke*, 1991, **43**, 375.
74 Bothe, H., and Cammenga, H. K., *J. Therm. Anal.*, 1979, **16**, 267.
75 Pirttimäki, J., Laine, E., Ketolainen, J., and Parrien, P., *Int. J. Pharm.*, 1993, **95**, 93.
76 Gunstone, F. D., Harwood, J. L., and Padley, F. B., *The Lipid Handbook*, Chapman and Hall, London, 2nd edn., 1994.
77 Burger, A., and Ramberger, R., *Mikrochim. Acta*, 1980, **I**, 17.
78 Bavin, P. M. G., Sly, J. C. P., Tovey, G. D., and Ward, R. J., *Ger. Offenlegung* 1978, **742**, 2, 531.
79 Cholerton, T. J., Hunt, J. H., Klinkert, G., and Martin-Smith, M., *J. Chem. Soc., Perkin Trans. 2*, 1984, 1761.
80 Crookes, D. L., *UK Pat.* 2084580B, 1982.
81 *Guardian*, September 9, 1994.
82 Reutzel, S. M., and Etter, M. C., *J. Phys. Org. Chem.*, 1992, **5**, 44.
83 Hammond, R. B., Roberts, K. J., Singh, D., and York, P., in preparation.
84 Bernstein, J., *J. Phys. D; Appl. Phys.*, 1993, **26**, 1366.
85 Bernstein, J., and Chosen, E., *Mol. Cryst. Liquid Cryst.*, 1988, **164**, 213.
86 Sato, K., *J. Phys. D; Appl. Phys.*, 1993, **26**, B77.
87 Desiraju, G. R., *Crystal Engineering*, Elsevier, Amsterdam, 1989.
88 Gavezzotti, A., *Acc. Chem. Res.*, 1994, **27**, 309.
89 Mannock, D. A., Lewis, R. N. A. H., Sen, A. and McElhaney, R. N., *Biochemistry*, 1988, **27**, 6852.
90 Hartshorne, N. H., and Stuart, A., *Crystals and the Polarising Microscope*, Edward Arnold, London, 4th edn., 1970, p. 20.
91 Stobbe, H., *Ber. Deut. Chem. Ges.*, 1905, **44**, 2732.
92 Bernstein, J., and Hagler, A. J., *J. Am. Chem. Soc.*, 1978, **100**, 673.
93 Bancroft, *J. Phys. Chem.*, 1898, **2**, 143.
94 Bancroft, *J. Phys. Chem.*, 1899, **3**, 44.
95 Rao, B. R., Rao, G. R., and Avadharmlu, A. B., *J. Sci. Ind. Res.*, 1987, **46**, 450.
96 Byrn, S. R., Curtin, D. Y., and Paul, I. C., *J. Am. Chem. Soc.*, 1972, **94**, 890.
97 Elguero, J., Marzin, C., Katritzki, A. R., and Linda, P., *The Tautomerism of Heterocycles*, Academic Press, London, 1966.
98 Desiraju, G. R., *J. Chem. Soc., Perkin Trans. 2*, 1983, 1025.
99 Gassim, A. E. H., Takla, P. G., and James K. C., *Int. J. Pharm.*, 1986, **34**, 23.
100 Costakis, E., Canone, P., and Tsala, G., *Can. J. Chem.*, 1969, **47**, 4483.
101 Annese, M., Corradi, A. B., Forlani, L., Rizzoli, C., and Sgarabotto, P., *J. Chem. Soc., Perkin Trans. 2*, 1994, 614.
102 Terol, A., Pauvert, B., Bouasseb, A., Chevallet, P., and Cassaneus, G., *J. Therm. Anal.*, 1992, **38**, 1545.
103 Kehrmann, F., and Matusinsky, Z., *Ber. Deut. Chem. Ges.*, 1912, **45**, 3498.
104 Elguero, J., Marzin, C., Katritzki, A. R., and Linda, P., *The Tautomerism of Heterocycles*, Academic Press, London, 1966, p. 57.
105 Cleverly, B., and Williams, P. P., *Tetrahedron*, 1959, **7**, 277.
106 Kuhnert-Brandstätter, M., and Sollinger, H. W., *Mikrochim. Acta*, 1990, **III**, 247.
107 Katrusiak, A., *J. Mol. Struct.*, 1992, **269**, 329.
108 Elguero, J., Marzin, C., Katritzki, A. R., and Linda, P., *The Tautomerism of Heterocycles*, Academic Press, London, 1966, p. 5.
109 Threlfall, T. L., PhD Thesis, University of London, 1972.
110 Ojala, W. H., and Etter, M. C., *J. Am. Chem. Soc.*, 1992, **114**, 10288.
111 Bernstein, J., *Acta Cryst Sect. B*, 1991, **47**, 1004.

112 Bernstein, J., *Acta Cryst Sect. C*, 1988, **44**, 900; Etter, M. C., *Acc. Chem. Res.*, 1990, **23**, 120; Aakeroy, C. B. and Seddon, K. R., *Chem. Soc. Rev.*, 1993, **22**, 397.
113 Bernstein, J., in *Organic Solid State Chemistry, Studies in Organic Chemistry, Vol. 32*, ed. Desiraju, G. R., Elsevier, Amsterdam, 1987.
114 Duax, W. L., *J. Chem. Ed.*, 1988, **65**, 502.
115 Blake, A. J., Gould, R. O., Halerow, M. A., and Schroeder, M., *Acta Cryst., Sect. B*, 1993, **49**, 773.
116 Fletton, R. A., Harris, R. K., Kenwright, A. M., Lancaster, R. W., Packer, K. J., and Sheppard, N., *Spectrochim. Acta, Part A*, 1987, **43**, 1111.
117 Phillips, D. C., *Acta Cryst.*, 1956, **9**, 237.
118 Senge, M. O., Hope, H., and Smith, K. M., *J. Chem. Soc., Perkin Trans. 2*, 1993, 11.
119 Barikigia, K. M., Renner, M. W., Furentio, L. R., Medforth, C. J., Smith, K. M., and Fajer, J., *J. Am. Chem. Soc.*, 1993, **115**, 3627.
120 Williams, P. P., *Acta Cryst., Sect. B*, 1974, **30**, 12.
121 McDowell, J. J. H., *Acta Cryst., Sect. B*, 1977, **33**, 5.
122 Desiraju, G. R., Paul, I. C., and Curtin, D. Y., *J. Am. Chem. Soc.*, 1977, **99**, 1594.
123 Perrin, R., Lamartine, M., Perrin, R., and Thozet, A., in *Organic Solid State Chemistry, Studies in Organic Chemistry, Vol. 32* ed. Desiraju, G. R., Elsevier, Amsterdam, 1987.
124 Brock, C. P., Schweizer, W. B., and Dunitz, J. D., *J. Am. Chem. Soc.*, 1991, **113**, 9811.
125 Eistert, B., Weygand, F., and Csenides, E., *Chem. Ber.*, 1952, **85**, 164.
126 Okada, Y., Takebayashi, T., Mashimoto, M., Kasiga, S., Sato, S., and Tamura, C., *J. Chem. Soc., Chem. Commun.*, 1983, 784.
127 Wilson, K. R., and Pincock, R. E., *Can. J. Chem.*, 1977, **55**, 889.
128 Matthews, T. H., Paul, I. C., and Curtin, D. Y., *J. Chem. Soc., Perkin Trans. 2*, 1991, 113.
129 McBride, J. M., *Angew. Chem., Int. Ed. Eng.*, 1989, **28**, 377.
130 David, R., and Giron, D., *Handbook of Powder Technology*, 1994, **9**, 193.
131 Stezowski, J. J., Biedermann, P. U., Hildenbrand, T., Dorsch, J. A., Eckhardt, C. J., and Agranat, I., *J. Chem. Soc. Chem. Commun.*, 1993, 213.
132 Takasuka, M., Nakei, H. and Shiro, M., *J. Chem. Soc., Perkin Trans. 2*, 1982, 106.
133 Zhang, Z., Rettig, S. J. and Orvig, C., *Can. J. Chem.*, 1992, **70**, 763.
134 Nelson, W. O., Karpishin, T. B., Rettig, S. J., and Orvig, C., *Can. J. Chem.*, 1988, **66**, 123.
135 Kessler, H., Zimmermann, G., Foerster, H., Engel, J., Oepen, G., and Sheldrick, W. S., *Angew. Chem., Int. Ed. Eng.*, 1981, **20**, 1053.
136 Burger, A., and Ramberger, R., *Mikrochim. Acta*, 1979, **II**, 259.
137 Mnyukh, Y. U., and Panfilova, N. A., *J. Phys. Chem. Solids.*, 1973, **34**, 159.
138 McCauley, J. A., Varsolona, R. J., and Levorse, D. A., *J. Phys. D; Appl. Phys.*, 1993, **26**, B85.
139 Westrum, E. R. and McCullough, J. P., in *Physics and Chemistry of the Organic Solid State*, ed. Fox, D., Labes, M. M., and Weissberger, A., Interscience, New York, 1963, vol. 1, p. 76.
140 Krc, J., *Microscope*, 1977, **28**, 25.
141 Gunning, S. R., Freeman, M., and Stead, J. A., *J. Pharm. Pharmacol.*, 1976, **28**, 758.
142 Bar, I., and Bernstein, J., *J. Pharm. Sci.*, 1985, **74**, 255.
143 Cleverley, B., and Williams, P. P., *Chem. Ind.*, 1959, 49.
144 Smakula, E., Gori, A., and Wotiz, H. H., *Spectrochim. Acta*, 1957, **9**, 346.
145 Burger, A., and Ramberger, R., *Mikrochim. Acta*, 1979, **II**, 271.
146 Threlfall, T. L., and Slater, B. J., in preparation.
147 Sukenik, C. N., Bonapace, J. A., Mandel, N. J., Land, P. Y., Wood, G., and Bergin, R. J., *J. Am. Chem. Soc.*, 1977, **99**, 851.
148 Katritsky, A. R., and Lagowski, J. M., *Adv. Heterocyclic Chem.*, 1963, **1**, 382.
149 Iwatsu, F., *J. Phys. Chem.*, 1988, **92**, 1678.
150 Dumas, J. P., Tounsi, F., and Babin, L., *J. Dispersion Sci. Technol.*, 1987, **8**, 29.
151 Mesley, R. J., Clements, R. L., Flaherty, B., and Goodhead, K., *J. Pharm. Pharmacol.*, 1968, **20**, 239.
152 Kuhnert-Brandstätter, M., and Moser, I., *Mikrochim. Acta*, 1979, **I**, 125.
153 Mnyukh, Y. V., and Petropavlov, N. N., *J. Phys. Chem. Solids*, 1972, **33**, 2079.
154 West, A. R., *Solid State Chemistry and its Applications*, Wiley, Chichester, 1984.
155 Theocharis, C. R., and Jones, W., *J. Chem. Soc. Chem. Commun.*, 1984, 369.
156 Theocharis, C. R., Jones, W., and Rao, C. N. R., *J. Chem. Soc. Chem. Commun.*, 1984, 1291.
157 Jones, W., Thomas, J. M., and Williams, J. O., *Philos. Mag.*, 1975, **32**, 1.
158 Kuhnert-Brandstätter, M., and Sollinger, H. W., *Mikrochim. Acta*, 1990, **III**, 233.
159 Barbour, R. H., Freer, A. A., and MacNichol, D. D., *J. Chem. Soc., Chem. Commun.*, 1983, 362.
160 Kuhnert-Brandstätter, M., and Moser, I., *Mikrochim. Acta*, 1981, **I**, 421.
161 Kuhnert-Brandstätter, M., and Friedl, L., *Mikrochim. Acta*, 1979, **II**, 97.
162 Burger, A., and Schulte, K., *Arch. Pharm.*, 1981, **314**, 398.
163 Carter, P. W., and Ward, M. D., *J. Am. Chem. Soc.*, 1994, **116**, 769.
164 Royer, J., Decoret, C., Tinland, B., Perrin, M., and Perrin, R., *J. Phys. Chem.*, 1989, **93**, 3393.
165 Etter, M., Britton, D., and Reutzel, S. M., *Acta Cryst., Sect. C*, 1991, **47**, 556.
166 Di, L., and Small, D. L., *J. Lipid Res.*, 1993, **34**, 1611.
167 Dunitz, J. D., and Bernstein, J., *Acc. Chem. Res.*, 1995, **28**, 193.
168 Pfeiffer, R. R., *J. Pharm. Pharmacol.*, 1971, **23**, 75.
169 Anwar, J., Tarling, S. E., and Barnes, P., *J. Pharm. Sci.*, 1989, **78**, 337.
170 Harris, R. K., Kenwright, A. M., Say, B. J., Yeung, R. R., Fletton, R. A., Lancaster, R. W. and Mangrove, G. L., *Spectrochim. Acta, Part A*, 1990, **46A**, 927.
171 Snévity, D., Vancso, J., and Rutledge, G. C., *Macromolecules*, 1992, **25**, 7037.
172 Kaneko, F., Sakashita, H., Kobayashi, M., and Suzuki, M., *J. Phys. Chem.*, 1994, **98**, 3801.
173 Jones, W., and Thomas, J. M., *Prog. Solid State Chem.*, 1980, **12**, 101.
174 Lourdin, D., Roux, A. H., Grolier, J. P. E., and Butsin, J. M., *Thermochim. Acta*, 1992, **204**, 99.
175 Lumley, C. E. and Walker, S. R., in *Medicines: Regulation, Research and Risk*, ed. Griffin, J. P., Greystone, Antrim, 1989, p. 157.
176 Kofler, L., and Kofler, A., *Thermomikromethoden*, Wagner, Innsbruck, 1952.
177 Hartshorne, N. H., and Stuart, A., *Crystals and the Polarising Microscope*, Edward Arnold, London, 4th edn., 1970.
178 Kuhnert-Brandstätter, M., in *Comprehensive Analytical Chemistry*, ed. Svehla, G., Elsevier, Amsterdam, 1982, vol. XVI.
179 McCrone, W. C., *Fusion Methods in Chemical Microscopy*, Interscience, New York, 1957.
180 Bloss, F. D., *Crystallography and Crystal Chemistry*, Holt, Reinhart and Winston, New York, 1971.
181 Jordan, D. D., *J. Pharm. Sci.*, 1993, **82**, 1269.
182 Ojena, S. M., and DeForest, P. R., *J. Forensic Sci. Soc.*, 1972, **12**, 315.
183 Ojena, S. M., and DeForest, P. R., *J. Forensic Sci.*, 1972, **17**, 409.
184 Holik, A. S. and Taylor, D. F., *Microscope*, 1977, **28**, 265.
185 Bloss, F. D., *The Spindle Stage*, Cambridge University Press, 1981.
186 Hartshorne, N. H., *Microscope*, 1975, **23**, 177.
187 Hartshorne, N. H., *Microscope*, 1976, **24**, 102.
188 Hartshorne, N. H., *Microscope*, 1976, **24**, 215.
189 McCrone, W. C., *Microscope*, 1991, **39**, 43.
190 Watanabe, A., Tanaku, Y. and Tanaku, Y., *Chem. Pharm. Bull.*, 1977, **25**, 2239.
191 Saylor, C. P., *Anal. Chem.*, 1975, **47**, 1114.
192 Chao, E. C. T., *Am. Mineral.*, 1976, **61**, 212.
193 Craven, B. M., and Vizzici, E. A., *Acta Cryst., Sect. B*, 1971, **27**, 1917.
194 Kuhnert-Brandstätter, M., *Thermomicroscopy in the Analysis of Pharmaceuticals*, Pergamon Press, Oxford, 1974, p. 19.
195 McCrone, W. C., *Discuss. Faraday Soc.*, 1949, **5**, 158.
196 Wiedermann, H. G., and Bayer, G., *J. Therm. Anal.*, 1985, **30**, 1273.
197 Burger, A., *Pharm. uns. Zeit*, 1982, **11**, 177.

198 Kuhnert-Brandstätter, M., and Sollinger, H. W., *Mikrochim. Acta*, 1990, **III**, 137.
199 Richardson, M. F., Yang, Q. C., Novotny-Bregger, E., and Dunitz, J. D., *Acta Cryst., Sect. B*, 1990, **46**, 653.
200 Kuhnert-Brandstätter, M., and Proell, F., *Mikrochim. Acta*, 1983, **III**, 287.
201 Reffner, J. A., and Ferrillo, R. G., *J. Therm. Anal.*, 1988, **34**, 19.
202 Cammenga, H. K., and Hemminger, W. F., *Labo*, 1990, **21**, 7.
203 Willis, H. A., van der Maas, J. H., and Miller, R. G. J., *Laboratory Methods in Vibrational Spectroscopy*, Wiley, Chichester, 3rd edn., 1987.
204 Duyckaerts, G., *Analyst*, 1959, **84**, 201.
205 Rosenkrantz, H., and Zablow, L., *Anal. Chem.*, 1953, **25**, 1025.
206 Baker, A. W., *J. Phys. Chem.*, 1957, **61**, 450.
207 Sharpless, N. E. and Gregory, D. A., *Appl. Spectrosc.*, 1963, **17**, 47.
208 Griesser, U. J., and Burger, A., *Sci. Pharm.*, 1993, **61**, 113.
209 Kobayashi, M., Matsumoto, Y., Ishida, A., Ute, K., and Hatada, K., *Spectrochim. Acta, Sect. A*, 1994, **50**, 1605.
210 Farmer, V. C., *Spectrochim. Acta*, 1957, **8**, 374.
211 Stewart, J. E., *J. Chem. Phys.*, 1957, **26**, 248.
212 Kuhnert-Brandstätter, M., and Riedmann, M., *Mikrochim. Acta*, 1989, **I**, 81.
213 Burger, A., and Ramberger, R., *Mikrochim. Acta*, 1979, **II**, 271.
214 Free, M. L., and Miller, J. D., *Appl. Spectrosc.*, 1994, **48**, 891.
215 De Faubert Maunder, M. J., *Practical Hints on Infrared Spectroscopy*, Adam Hilger, London, 1971.
216 Potts, W. F., *Chemical Infrared Spectroscopy*, Wiley, New York, 1963, vol. 1.
217 Bradley, K. B., and Potts, W. J., *Appl. Spectrosc.*, 1958, **12**(3), 77.
218 Roberts, G., *Anal. Chem.*, 1957, **29**, 911.
219 White, R. G., *Handbook of Industrial Infrared Analysis*, Plenum, New York, 1964.
220 Fuller, M. P., and Griffiths, P. R., *Anal. Chem.*, 1978, **50**, 1906.
221 Krishnan, K., and Ferraro, J. R. in *Fourier Transform Infrared Spectroscopy*, ed. Ferraro, J. R. and Basile, L. J., Academic Press, New York, 1982, vol. 3, p. 149.
222 Harrick, N. J., *Internal Reflection Spectroscopy*, Wiley, New York, 1967.
223 Mirabella, F. M., *Internal Reflectance Spectroscopy*, Marcel Dekker, New York, 1992.
224 Kuhnert-Brandstätter, M., and Riedmann, M., *Mikrochim. Acta*, 1989, **II**, 173.
225 Schutte, C. J. H., and Paul, S. O., *S. Afr. Tydskr. Chem.*, 1986, **39**, 252.
226 Roston, D. A., Walters, M. C., Rhinebarger, R. R., and Ferro, L. J., *J. Pharm. Biomed. Anal.*, 1993, **11**, 293.
227 Barker, S. A., Bourne, E. J., Weigl, M., and Whiffen, D. H., *Chem. Ind.*, 1956, 318.
228 Ford, M. A., and Wilkinson, G. R., *J. Sci. Instr.*, 1954, **31**, 338.
229 Price, W. C., and Tetlow, K. S., *J. Chem. Phys.*, 1948, **16**, 1157.
230 Kuhnert-Brandstätter, M., and Bachleitner-Hoffman, F., *Spectrochim. Acta, Part A*, 1971, **27**, 191.
231 Kirov, N., Fontana, M. P., and Cavatorte, F., *J. Mol. Struct.*, 1980, **59**, 147.
232 Gruger, A., Romain, F., and le Calvé, N., *Thermochim. Acta*, 1984, **116**, 85.
233 Neville, G. A., Beckstead, H. D., and Shurvell, H. F., *J. Pharm. Sci.*, 1992, **81**, 1141.
234 Hartauer, K. J., Miller, E. S., and Guillory, J. K., *Int. J. Pharm.*, 1992, **85**, 163.
235 Yeboah, S. A., Wong, S-H., and Griffiths, P. R., *Appl. Spectrosc.*, 1984, **38**, 259.
236 Brimmer, P. J., and Griffiths, P. R., *Appl. Spectrosc.*, 1988, **42**, 242.
237 TeVrucht, M. L. E., and Griffiths, P. R., *Appl. Spectrosc.*, 1989, **43**, 1492.
238 Marabella, L. J., *Appl. Spectrosc. Revs.*, 1985, 21, 45.
239 Ibrahim, G., Pisano, F., and Bruno, A., *J. Pharm. Sci.*, 1977, **66**, 669.
240 Hartauer, K. J., and Guillory, J. K., *Pharm. Res.*, 1989, **6**, 608.
241 Katon, J. E., and Sommers, A. J., *Anal. Chem.*, 1992, **64**, 931A.
242 Lagas, M., and Lerk, C. F., *Int. J. Pharm.*, 1981, **8**, 11.
243 Burger, A., and Dialer, R. D., *Pharm. Acta Helv.*, 1983, **58**, 72.
244 Vidine, D. W., in *Fourier Transform Infrared Spectroscopy* ed. Ferraro, J. R., and Basile, L. J., Academic Press, New York, 1982, vol. 3.
245 Graham, J. A., Grim, N. M., and Fateley, W. G., in *Fourier Transform Infrared Spectroscopy*, ed. Ferraro, J. R. and Basile, L. J., Academic Press, New York, 1985, vol. 4, p. 346.
246 Belton, P. S., Saffron, A. M., and Wilson, R. H., in *Analytical Applications of Spectroscopy*, ed. Creaser, C. S. and Davies, A. M. C., The Royal Society of Chemistry, London, 1988.
247 Rockley, N. L., Woodard, M. K., and Rockley, M. G., *Appl. Spectrosc.*, 1984, **38**, 329.
248 Ashizawa, K., *J. Pharm. Sci.*, 1989, **78**, 256.
249 Griffiths, P. R., and Fuller, M. P. in *Advances in Spectroscopy*, ed. Clark, R. J. H., and Hester, R. E., 1982, **9**, 63.
250 Huvenne, R., Depecker, C., and Legrand, P., *S.T.P. Pharma*, 1989, **5**, 350.
251 Chalmers, J. M., and Mackenzie, M. W. in *Advances in Applied Fourier Transform Infrared Spectroscopy*, ed. Mackenzie, M. W., Wiley, New York, 1988.
252 Brickell, W. S., *Proc. Anal. Div. Chem. Soc.*, 1978, 343.
253 Yano, J., Ueno, S., Arishima, T., Sagi, N., Kaneko, K., and Kobayashi, M., *J. Phys. Chem.*, 1993, **97**, 12967.
254 Kaneko, F., Sakashita, H., and Kobayashi, M., *Acta Cryst., Sect. C*, 1994, **50**, 245, 247.
255 Kaneko, K., Shirai, O., Miyamoto, H., Kobayashi, M., Kitagawa, Y., Matsuura, Y., and Sasaki, M., *J. Phys. Chem.*, 1994, **98**, 2185.
256 Kuhnert-Brandstätter, M., and Junger, E., *Spectrochim. Acta, Part A*, 1976, **23**, 1453.
257 Ostwald, W., *Z. Phys. Chem.*, 1897, **22**, 306.
258 Cocks, G. G., and Jelley, E. E., in *Physical Methods of Chemistry*, ed. Weissberger, A., and Rossiter, B. W., Wiley, New York, 1972, p. III
259 Matsuda, Y., and Tatsumi, E., *Int. J. Pharm.*, 1990, **60**, 11.
260 George, W. O., Hassid, D. V., and Maddams, W. F., *J. Chem. Soc., Perkin Trans. 2*, 1973, 957.
261 Snyder, S. G., Maroncelli, S., and Hallmark, V. M., *J. Phys. Chem.*, 1986, **90**, 5623.
262 Chapman, D., *J. Chem. Soc.*, 1958, 3186.
263 Rao, G. R., and Zerbi, G., *Appl. Spectrosc.*, 1984, **38**, 795.
264 Gu, W., *Anal. Chem.*, 1993, **65**, 827.
265 White, R. L., *Appl. Spectrosc.*, 1993, **47**, 1492.
266 Bergin, F. J., *Appl. Spectrosc.*, 1989, **43**, 511.
267 Humecki, H. J., *Practical Guide to Infrared Microspectrometry*, Marcel Dekker, New York, 1988.
268 Nguyen, N. A. T., Ghosh, S., Gatlin, L. A., and Grant, D. J. W., *J. Pharm. Sci.*, 1993, **83**, 1116.
269 *The Design, Sampling, Handling and Application of Infrared Microscopes*, ASTM Special Technical Publication 9494 , ed. Roush, P. B., American Society for Testing and Materials, Philadelphia, 1987.
270 Marshall, A. G., *Fourier, Hadamard and Hilbert Transformations in Chemistry*, Plenum, New York, 1982.
271 Marshall, A. G., *Chemom. Intell. Lab. Syst.*, 1988, **3**, 261.
272 Turner, P. M., *Anal. Proc.*, 1986, **23**, 268.
273 Okada, Y., Takebayashi, T., and Sato, S., *Chem. Pharm. Bull.*, 1989, **37**, 5.
274 Kellner, R., Kuhnert-Brandstätter, M., and Malissa, H., *Mikrochim. Acta*, 1988, **III**, 153.
275 Kuhnert-Brandstätter, M., and Moser, I., *Mikrochim. Acta*, 1980, **II**, 333.
276 Todori, K., Sano, K., and Mori, Y., *Spectrochim. Acta, Part B*, 1994, **50**, 1201.
277 Geiger, W., *Spectrochim. Acta*, 1963, **10**, 655.
278 Kuhnert-Brandstätter, M., Wurian, I., and Geiler, M., *Sci. Pharm.*, 1982, **50**, 91.
279 Kuhnert-Brandstätter, M., and Wurian, I., *Sci. Pharm.*, 1982, **50**, 3.
280 Borka, L., *Acta Pharm. Suec.*, 1977, **14**, 205.
281 Bettinetti, G., Giordiano, F., Fronza, G., Italia, A., Pellegrata, R., Villa, M., and Ventura, P., *J. Pharm. Sci.*, 1990, **79**, 470.
282 Burger, A., and Lettenbichler, A., *Pharmazie*, 1993, **48**, 262.
283 Kaye, W., *Spectrochim. Acta*, 1954, **6**, 257.
284 Osborne, B. G., Fearn, T., and Hindle, P. H., *Practical NIR Spectroscopy*, Longmans, Harlow, 2nd edn., 1993.
285 Mark, H., *Principles and Practice of Spectroscopic Calibration*, Wiley, Chichester, 1991.
286 Smith, H. J., and Carl, R. T., *Appl. Spectrosc.*, 1989, **43**, 865.
287 Ollinger, J. M., and Griffiths, P. R., *Anal. Chem.*, 1988, **60**, 2427.

288 Barnes, R. J., Dhanoa, M. S. and Lister, S. J., *Appl. Spectrosc.*, 1989, **43**, 772.
289 Aucott, L. S., Garthwaite, P. H., and Buckland, S. T., *Analyst*, 1988, **113**, 1849.
290 Miller, C. E., and Honigs, D. E., *Spectroscopy*, 1989, **4**, 44.
291 Gimet, R., and Luong, A. T., *J. Pharm. Biomed. Anal.*, 1987, **5**, 205.
292 Colthup, N. B., Daly, L. H., and Wiberley, S. E., *Introduction to Infrared and Raman Spectroscopy*, Academic, New York, 2nd edn., 1975.
293 Grasselli, J. G., and Bulkin, B. J., *Analytical Raman Spectroscopy*, Wiley, New York, 1991.
294 Hendra, P. J., Jones, C., and Warnes, J., *Fourier Transform Raman Spectroscopy*, Ellis Horwood, 1991.
295 Hirschfeld, T., and Chase, B., *Appl. Spectrosc.*, 1986, **40**, 133.
296 Bergin, F. J., and Shurvell, H. F., *Appl. Spectrosc.*, 1989, **43**, 516.
297 Messerschmidt, R. G., and Chase, B., *Appl. Spectrosc.*, 1989, **43**, 11.
298 Schrader, B., Hoffman, A., and Keller, S., *Spectrochim. Acta, Part A*, 1991, **47**, 1135.
299 Loewenschuss, A., and Moss, A., *Appl. Spectrosc.*, 1982, **36**, 183.
300 Chase, B., *Appl. Spectrosc.*, 1994, **48**, 14A.
301 Cutmore, E. A., and Skett, P. W., *Spectrochim. Acta, Part A*, 1993, **49**, 809.
302 Wright, J. D., *Molecular Crystals*, Cambridge University Press, Cambridge, 1987.
303 Cannon, C. F., *Spectrochim. Acta*, 1958, **10**, 341.
304 Schuster, P., Zundel, G., and Sandorfy, C., *The Hydrogen Bond*, North Holland, Amsterdam, 1976.
305 Paul, S. O., Schutte, C. J. H., and Hendra, P. J., *Spectrochim. Acta, Part A*,, 1990, **46**, 323.
306 Zimba, C. G., Hallmark, V. M., Swalen, J. D. and Rabolt, J. F., *Appl. Spectrosc.*, 1987, **41**, 721.
307 Waters, D. N., *Spectrochim. Acta, Part A*, 1994, **50**, 1833.
308 Deeley, C. M., Spragg, R. A., and Threlfall, T. L., *Spectrochim. Acta, Part A*, 1991, **47**, 1217.
309 Tudor, A. H., Davies, M. C., Melia, C. D., Lee, D. G., Mitchell, R. C., Hendra, P. J., and Church, S. J., *Spectrochim. Acta, Part A*, 1991, **47**, 1389.
310 Kobayashi, M., Kobayashi, T., Itoh, Y., and Sato, K., *J. Chem. Phys.*, 1984, **80**, 2897.
311 Ishii, K., Kawahara, M., Yakasaki, Y., Hibino, Y., and Nakayana, H., *J. Phys. D: Appl. Phys.*, 1993, **26**, B193.
312 Davey, R. J., Maginen, S. J., Andrews, E. J., Black, S. N., Buckley, A. M., Cotties, D., Dempsey, P., Plowman, R., Rout, J. E., Stanley, D. R., and Taylor, A., *J. Chem. Soc., Faraday Trans.*, 1994, **90**, 1003.
313 Ip, D. P., Brenner, G. S., Stevenson, J. M., Lindenbaum, S., Douglas, A. W., Klein, S. D., and McCauley, J. A., *Int. J. Pharm.*, 1986, **28**, 183.
314 Kaneko, F., Yamazaki, K., Kobayashi, M., and Sato, K., *Spectrochim. Acta, Part A*, 1995, **50**, 1589.
315 Sawatzki, J., *Bruker Applications Note, Fourier Transform Raman Microspectroscopy*, 1990.
316 Messerschmidt, R. G., in *The Design, Sampling, Handling and Application of Infrared Microscopes*, ASTM Special Technical Publication 9494, ed. Roush, P.B., American Society for Testing and Materials, Philadelphia, 1987, p. 12.
317 Cohen, M. D., Schmidt, G. M. J., and Flavian, S., *J. Chem. Soc.*, 1964, 2041.
318 Pfeiffer, P., Braude, S., Kleber, J., Marcon, G., and Wittkop, P., *Ber. Deut. chem. Ges.*, 1915, **48**, 1777.
319 Desiraju, G. R., Paul, I. C., and Curtin, D. Y., *J. Am. Chem. Soc.*, 1977, **99**, 1594.
320 Qian, R., *Mol. Cryst. Liq. Cryst.*, 1988, **171**, 117.
321 Enokida, T., and Enashi, S., *Chem. Lett.*, 1988, 179.
322 Takano, S., Enokida, T., Kakuta, A., and Mori, Y., *Chem. Lett.*, 1984, 2073.
323 Cook, M. J., in *Advances in Spectroscopy*, ed. Clark, J. H., and Hester, R. E., 1993, **22**, 87.
324 Klebe, G., Graser, F., Haedicke, E., and Berndt, J., *Acta Cryst., Sect. B*, 1989, **45**, 69.
325 McKerrow, A. J., Buncel, E., and Kazmeier, P. M., *Can. J. Chem.*, 1993, **71**, 390.
326 Loutfy, R. O., Hor, A. M., Kazmaier, P., and Tam, M., *J. Imaging Sci.*, 1989, **33**, 151.
327 Botoschanski, M., Herbstein, F. H., and Kapon, M., *Acta Cryst., Sect. B*, 1994, **50**, 191.
328 Everett, A. J., personal communication.
329 Childers, J. W., Rohl, R., and Palmer, R. A., *Anal. Chem.*, 1986, **58**, 2629.
330 Daehnen, S., Bornowski, B., Grimm, B., Kulpe, S., Leopold D., and Naether, M., *J. Signalaufzeichnungsmater.*, 1977, **5**, 277.
331 Morel, D. L., Strogryn, E. L., Ghosh, E. K., Feng, T., Purwin, P. E., Shaw, R. F., Fushman, C., Bird, G. R., and Piechowski, A. P., *J. Phys. Chem.*, 1984, **88**, 923.
332 Becker, H.-D., Hall, S. R., Skelton, B. W., and White, A. H., *Aust. J. Chem.*, 1984, **37**, 1313.
333 Sanchez-Felix, M., personal communication.
334 Chandra, B. P., and Zink, J. I., *Phys. Rev. B, Condens. Matter*, 1980, **21**, 816.
335 Hardy, G. E., Kaska, W. C., Chandra, B. P., and Zink, J. I., *J. Am. Chem. Soc.*, 1981, **103**, 1074.
336 Lynch, L. J., Webster, D. S., and Barton, W. A., *Adv. Mag. Res.*, 1988, **12**, 285.
337 Dosseh, G., Fressigne, C., and Fuchs, A. H., *J. Phys. Chem. Solids*, 1992, **53**, 203.
338 Gavezzoti, A., and Simonetta, M., in *Organic Solid State Chemistry*, ed. Desiraju, G. R., Elsevier, Amsterdam, 1987.
339 Chirlian, L. E., and Opella, S. J., *Adv. Magn. Res.*, 1990, **14**, 183.
340 Harris, R. K., *Chem. Br.*, 1993, 601.
341 Bruker CXP *Applications Note, High Resolution NMR in Solids*, 1983.
342 Bugay, D. E., *Pharm. Res.*, 1993, **10**, 317.
343 Fletton, R. A., Lancaster, R. W., Harris, R. H., Kenwright, A. M., Parker, K. J., Waters, D. N., and Yeadon, A., *J. Chem. Soc., Perkin Trans. 2*, 1986, 1705.
344 Byrn, S. R., Pfeiffer, R. R., Stevenson, G., Grant, D. J. W., and Gleason, W. B., *Chem. Mater.*, 1994, **6**, 1148.
345 Saindon, P. J., Cauchon, N. S., Sutton, P. A., Chang, C. J., Peck, G. E., and Byron, S. R., *Pharm. Res.*, 1993, **10**, 197.
346 Suryanaryanan, R., and Wiedman, T.S., *Pharm. Res.*, 1990, **7**, 184.
347 Steiner, T., Hinrichs, W., Saenger, W., and Gigg, R., *Acta Cryst., Sect. B*, 1993, **49**, 708.
348 Opella, S. J., and Frey, H. M., *J. Am. Chem. Soc.*, 1979, **101**, 5854.
349 Byrn, S. R., Gray, G., Pfeiffer, R. R., and Frye, J., *J. Pharm. Sci.*, 1985, **74**, 565.
350 Fyfe, C. A., *Solid State NMR for Chemists*, CFC, Guelph, Ontario, 1984.
351 Etter, M., Jahn, D. A., and Urbanczyk-Lipkowska, Z., *Acta Cryst., Sect. C*, 1987, **43**, 260.
352 Smith, J. A. S., *Chem. Soc. Rev.*, 1986, **25**, 225.
353 Gourdji, M., Guibé, L., Kaplan, A., and Péneau, A., *J. Mol. Struct.*, 1983, **111**, 371.
354 Rao, C. N. R., in *Organic Solid State Reactions*, ed. Desiraju, G. R., Elsevier, Amsterdam, 1987.
355 van Driel, H. M., Wiszniewska, M., Moores, B. M., and Armstrong, R. L., *Phys. Rev.*, 1972, **6B**, 1596.
356 Dove, M. T., and Rae, A. I. M., *Faraday Discuss. Chem. Soc.*, 1980, **69**, 98.
357 Rae, A. I. M., and Dove, M. T., *J. Phys. C.*, 1983, **16**, 3233.
358 Klug, M. P., and Alexander, L. E., *X-ray Diffraction Procedures for Polycrystalline and Amorphous Materials*, Wiley, New York, 2nd edn., 1974.
359 Takahashi, H., Takenishi, T., and Nagashima, N., *Bull. Chem. Soc. Japan*, 1962, **35**, 925.
360 Azibi, M., Draguet-Brughmans, M., Bouche, R., Tinant, B., Germain, G., Declercq, J.-P., and van Meersche, M., *J. Pharm. Sci.*, 1983, **72**, 322.
361 Forni, A., Moretti, I., Torre, G., Brueckner, S., Malpezzi, L., and DiSilvestro, G., *J. Chem. Soc., Perkin Trans. 2*, 1984, 791.
362 Fuhrup, J. H., Krull, M., and Bueldt, G., *Angew. Chem., Int. Ed. Eng.*, 1987, **26**, 698.
363 Goldberg, I., and Becker, Y., *J. Pharm. Sci.*, 1987, **76**, 255.
364 Tiers, G. V. D., *Thermochim. Acta*, 1993, **226**, 317.
365 Kuhnert-Brandstätter, M., and Lehner, G., *Sci. Pharm.*, 1984, **52**, 267.
366 Kuhnert-Brandstätter, M., and Sollinger, H. W., *Mikrochim. Acta*, 1990, **III**, 137.
367 Kuhnert-Brandstätter, M., and Vollenklee, R., *Sci. Pharm.*, 1987, **55**, 13.

368 Epple, M., and Cammenga, H. K., *Ber. Bunsenges. Phys. Chem.*, 1992, **96**, 1774.
369 Epple, M., and Cammenga, H. K., *J. Therm. Anal.*, 1992, **38**, 619.
370 Lloyd, L. F., Bruk, P., Mei-Ehe, L., Chagen, N. E., and Blow, D. G., *J. Mol. Biol.*, 1991, **217**, 19.
371 Manor, P. C., and Saenger, W., *J. Am. Chem. Soc.*, 1974, **86**, 3630.
372 Lindler, K., and Saenger, W., *Acta Cryst., Sect. B*, 1982, **38**, 1982.
373 Polishchuk, A. P., Kulishov, V. I., Antipin, M. Y., Gerr, R. G., and Struchov, Y. T., *Cryst. Struct. Commun.*, 1981, **10**, 895.
374 Polishchuk, A. P., Kulishov, V. I., Antipin, M. Y., and Struchov., Y. T., *Cryst. Struct. Commun.*, 1289.
375 Kitaigorodski, A. I., *Molecular Crystals and Molecules*, Academic Press, New York 1973, p. 36.
376 Desiraju, G. R., *Crystal Engineering*, Elsevier, Amsterdam, 1989, p. 42ff.
377 Petrouslas, V., Lemmon, R. M., and Christensen, A., *J. Chem. Phys.*, 1978, **68**, 2243.
378 Hursthouse, M., in *Encyclopaedia of Advanced Materials*, ed. Bloor, D., Brook, R. J., Flemming, M. C. and Majahu, S., Pergamon, Oxford, 1995.
379 Harding, M. M., *Chem. Br.*, 1990, 956.
380 Rizkullah, P. J., Harding, M. M., Lindsey, P. F., Aiger, A., and Bauer, A., *Acta Cryst., Sect. B*, 1990, **46**, 262.
381 King, H. E., Sirota, E. B., Shao, H., and Singer, D. M., *J. Phys. D: Appl. Phys.*, 1993, **26**, B137.
382 Sato, K., *J. Phys. D: Appl. Phys.*, 1993, **26**, B77.
383 Harmon, K. M., and Avci, G. F., *J. Mol. Struct.*, 1986, **140**, 261.
384 Marsh, R. E., *Appl. Cryst., Sect. C*, 1993, **49**, 193.
385 Aakeroy, C. B., and Seddon, K. R., *Chem. Soc. Rev.*, 1993, **22**, 397.
386 Harris, K. D. M., and Patterson, L. J., *J. Chem. Soc., Perkin Trans. 2*, 1994, 1201.
387 Lightfoot, P., Tremayne, M., Harris, K. D. M., and Bruce, P. G., *J. Chem. Soc., Chem. Commun.*, 1992, 1012.
388 Yang, S. S., and Guillory, J. K., *J. Pharm. Sci.*, 1972, **61**, 26.
389 Kitamura, S., Chang, L.-C., and Guillory, K. J., *Int. J. Pharm.*, 1984, **101**, 127.
390 Brenner, G., Roberts, F. E., Hoinowski, A., Budvari, J., Powell, B., Hinkley, D., and Schoenewaldt, E., *Angew. Chem., Int. Ed, Eng.*, 1969, **8**, 975.
391 Pfeiffer, R. R., Yang, K., and Tucker, M. A., *J. Pharm. Sci.*, 1989, **78**, 337.
392 Mynukh, Y. V., Panfilova, N. A., Petropavlov, N. N., and Uchvatova, N. S., *J. Phys. Chem. Solids*, 1975, **36**, 127.
393 Doff, D. H., Brownen, F. L., and Corrigan, O. I., *Analyst*, 1986, **111**, 179.
394 Kidd, W. C., Varlashin, P., and Li, C., *Powder Diffr.*, 1993, **8**, 180.
395 Dent Glasser, L. S., *Crystallography and its Applications*, Van Nostrand Reinhold, 1977.
396 Hall, H. E., *Solid State Physics*, Wiley, London, 1974.
397 Grindley, T. B., McKinnon, M. S., and Wasylishen, R. E., *Carbohydrate Res.*, 1990, **197**, 41.
398 Herbstein, F. H., Capon, M., Reisner, G. M., Lehmann, M. S., Kress, R. B., Shiau, W. I., Duesler, E. N., Paul, I. C., and Curtin, D. Y., *Proc. R. Soc. A*, 1985, **399**, 295.
399 Ermer, O., *Angew. Chem., Int. Ed. Eng.*, 1987, **26**, 782.
400 Bunn, C. W., *Chemical Crystallography*, Oxford University Press, 2nd edn., 1961.
401 Nyburg, S. C., *X-Ray Analysis of Organic Structures*, Academic Press, New York, 1961.
402 Giaccovazzo, G., *Fundamentals of Crystallography*, International Union of Crystallography, Oxford, 1992.
403 Dunitz, J. D., *X-ray Analysis and the Structure of Organic Molecules*, Cornell University Press, Ithica, 1979.
404 Rossi, M., and Berman, H. M., *J. Chem. Ed.*, 1988, **6**, 472.
405 *Modern Powder Diffraction*, ed. Bish, D. L., and Post, J. E., Reviews in Mineralogy, vol. 2, Mineralogical Society of America, 1989.
406 Azároff, L. V., and Buerger, M. J., *The Powder Method in X-ray Crystallography*, McGraw–Hill, New York, 1958.
407 Shafizadeh, F., and Susott, R. A., *J. Org. Chem.*, 1973, **38**, 3710.
408 Perrenot, B., and Widman, G., *Thermochim. Acta*, 1994, **234**, 31.
409 Garn, P. D., *Thermoanalytical Methods of Investigation*, Academic Press, New York, 1965, p. 21.
410 Voress, L., *Anal. Chem.*, 1994, **66**, 1035A.
411 Kopp, S., Beyer, C., Graf, E., Kubel, F., and Doelker, E., *Acta Pharm. Technol.*, 1988, **34**, 213.
412 Burger, A., and Lettenbichler, A., *Eur. J. Pharm. Biopharm.*, 1993, **39**, 64.
413 Chataing, G., and Vergnaud, J. M., *Thermochim. Acta*, 1985, **94**, 379.
414 Kuhnert-Brandstätter, M., and Seidel, D., *Mikrochim. Acta*, 1982, **I**, 243.
415 Van Dooren, A. H., and Muller, B. W., *Thermochim. Acta*, 1983, **66**, 161.
416 Kuhnert-Brandstätter, M., and Heindle, W., *Sci. Pharm.*, 1976, **44**, 18.
417 Allen, P. V., Rahn, P. D., Sarapu, A. C., and Vanderwielen, A. J., *J. Pharm. Sci.*, 1978, **67**, 1087.
418 Kuhnert-Brandstätter, M., and Proell, F., *Mikrochim. Acta*, 1983, **II**, 463.
419 Kuhnert-Brandstätter, M., Geiler, M., and Wurian, I., *Mikrochim. Acta*, 1983, **I**, 221.
420 Giron-Forest, D., Goldbrunn, C., and Piechon, P., *J. Pharm. Biomed. Anal.*, 1989, **7**, 144.
421 Kuhnert-Brandstätter, M., and Vollenklee, R., *Sci. Pharm.*, 1987, **55**, 27.
422 Haines, P., *Thermal Analysis*, Blackie, London, 1995.
423 *Thermal Analysis: an Introduction to Principles and Practice*, ed. Hodgson, A., University of York, York.
424 Takahashi, Y., *Thermochim. Acta*, 1985, **88**, 199.
425 McNaughton J. L., and Mortimer, C. T., *Differential Scanning Calorimetry*, Perkin–Elmer, Norwalk, Connecticut.
426 Westrum, E. R., and McCullough, J. P., in *Physics and Chemistry of the Organic Solid State*, ed. Fox, D., Labes, M. M., and Weissberger, A., Interscience, New York, 1963, vol. 1.
427 Daniels, T., *Thermal Analysis*, Halsted Press, New York, 1973.
428 Matsunaga, J., Nambu, N., and Nagai, T., *Chem. Pharm. Bull.*, 1976, **24**, 1169.
429 Muller, B. W. W., *Pharm. Acta Helv.*, 1978, **53**, 333.
430 Taludar, M. D., Carless, J. E., and Summers, M. P., *J. Pharm. Phamacol.*, 1983, **35**, 208.
431 Matsumoto, T., Ichikawa, J., Kaneniwa, N., and Otsuka, M., *Chem. Pharm. Bull.*, 1988, **36**, 1074.
432 Forni, F., Coppi, G., Iannuccelli, V., and Cameroni, R., *J. Therm. Anal.*, 1990, **36**, 35.
433 Behme, R. J., Brooke, D., Farney, R. F., and Kensler, T. T., *J. Pharm. Sci.*, 1985, **74**, 1041.
434 Burger, A., and Ramberger, R., *Mikrochim. Acta*, 1979, **II**, 273.
435 Prasad, P. N., in *Organic Solid State Chemistry*, ed. Desiraju, G. R., Elsevier, Amsterdam, 1989.
436 Ostwald, W., *Z. Physik. Chem.*, 1897, **22**, 306.
437 Wentlandt, W. W., *Thermal Methods of Analysis*, Interscience, New York, 1964.
438 Kuhnert-Brandstätter, M., and Sollinger, H. W., *Mikrochim. Acta*, 1989, **III**, 125.
439 Sarge, S., and Cammenga, H. K., *Thermochim. Acta*, 1985, **94**, 17.
440 Barell, E. M., *Thermochim. Acta*, 1973, **5**, 377 quoted by Ford, J. L., and Timmins, P., *Pharmaceutical Thermal Analysis*, Ellis Horwood, Chichester, 1989, p. 27.
441 Harbury, L., *J. Phys. Chem.*, 1946, **50**, 190.
442 Kuhnert-Brandstätter, M., and Heindl, W., *Sci. Pharm.*, 1975, **43**, 112.
443 Kuhnert-Brandstätter, M., and Lindler, R., *Mikrochim. Acta*, 1976, **I**, 513.
444 Ubbelhohde, A. R., *The Molten State of Matter*, Wiley, Chichester, 1978, p. 317.
445 Cahn, R. W., *Nature (London)*, 1992, **356**, 108.
446 Docherty, C., and York, P., *Int. J. Pharm.*, 1988, **47**, 141.
447 Serpinet, J., *Nature (London) Phys. Sci.*, 1971, **232**, 42.
448 Serpinet, J., and Robin, J., *C.r. Acad. Sci. Paris.*, 1971, **272C**, 1765.
449 Florence, A. T., and Salole, E. G., *J. Pharm. Pharmacol.*, 1976, **28**, 637.
450 Sherwood, J. N., *The Plastically Crystalline State*, Wiley, New York, 1979.
451 Aston, J. G., in *Physics and Chemistry of the Organic Solid State*, ed. Fox, D., Labes, M. M., and Weissberger, A., Interscience, New York, 1963, vol. I.

452 Adachi, K., Suga, H., and Seki, S., *Bull. Chem. Soc. Japn.*, 1970, **43**, 1916.
453 Westrum, E. R., and McCullough, J. P., in *Physics and Chemistry of the Organic Solid State*, ed. Fox, D., Labes, M. M., and Weissberger, A., Interscience, New York, 1963, vol. 1, p. 83.
454 Staveley, L. A. K., *Quart. Rev.*, 1949, **3**, 65.
455 Reading, M., *Trends in Polym. Sci.*, 1993, **1**, 248.
456 Ford, J. L., and Timmins, P., *Pharmaceutical Thermal Analysis*, Ellis Horwood, Chichester, 1989.
457 Clark, G. M., *Anal. Proc.*, 1986, **23**, 393.
458 Wenzell, P. D., and Wade, A. P., *Anal. Chem.*, 1989, **61**, 2638.
459 Borka, L., *Acta Pharm. Suec.*, 1974, **11**, 413.
460 Bergman, E., Hoff, E. E., Lefiles, J. H., McKinney, L. J., and Misselbrook, J., *Eur. Pat.* 380325.
461 Pearson, J. T., and Varney, G., *J. Pharm. Pharmacol.*, 1969, **21**, 60S.
462 Mesley, R. J., and Houghton, E. E., *J. Pharm. Pharmacol.*, 1967, **19**, 295.
463 Grant, D. J. W., and Higuchi, T., *Solubility Behaviour of Organic Compounds*, Techniques in Chemistry, Vol. XXI, Wiley, New York, 1990.
464 Mader, W.J., and Grady, L. T., in *Physical Methods of Organic Chemistry*, ed. Weissberger, A., and Rossiter, B. W., Wiley, New York, 1971, vol. 1, pt. V.
465 Florence, A. T., and Attwood, D, *Physicochemical Principles of Pharmacy*, Macmillan, London, 1981.
466 Doughty, D. G., *Drug Dev. Ind. Pharm.*, 1989, **15**, 2455.
467 Windram, V. A., and Threlfall, T. L., *Anal. Proc.*, 1992, **29**, 108.
468 Abdou, H. M., *Dissolution, Bioavailablity and Bioequivalence*, Mack, Easton, 1989, p. 126.
469 Buxton, P. C., Lynch, I. R., and Roe, J. M., *Int. J. Pharm.*, 1988, **42**, 135.
470 Murthy, K. S., Turner, N. A., Nesbitt, R. U., and Fawzi, M. B., *Drug Dev. Ind. Pharm.*, 1986, **12**, 665.
471 Martínez-Oharriz, M. C., Martín, C., Goñi, M. M., Rodríguez-Espinosa, C., Tros de Ilarduya-Apadaza, M. C., and Sánchez, M., *J. Pharm. Sci.*, 1994, **83**, 174.
472 Higuchi, T., *J. Pharm. Sci.*, 1969, **56**, 200.
473 Kuhnert-Brandstätter, M., and Linsmeyer, L., *Sci. Pharm.*, 1986, **54**, 1.
474 Beall, H. D., Getz, J. J., and Sloane, K. B., *Int. J. Pharm.*, 1993, **93**, 37.
475 Albert, A., and Sargeant, E. P., *The Determination of Ionisation Constants*, Chapman and Hall, London, 3rd edn., 1984.
476 Perrin, D. D., and Dempsey, B., *Buffers for pH and Metal Ion Control*, Science Paperbacks, London, 1979.
477 Stearns, E. I., *The Practice of Absorption Spectroscopy*, Wiley, New York, 1969, p. 75.
478 Perkampus, H. H., *UV-VIS Spectroscopy and its Applications*, Springer, Berlin, 1992.
479 Burger, A., *Acta Pharm. Technol.*, 1982, **28**, 1.
480 Kitaigorodski, A. I., *Organic Chemical Crystallography*, Consultants Bureau, New York, 1961.
481 Whitesell, J. K., Davis, R. E., Saunders, L. L., Wilson, R. J., and Feagin, J. P., *J. Phys. D: Appl. Phys.*, 1993, **26**, B56.
482 Andreev, G. A., and Hartmanová, M., *Phys. Status Solidi. A*, 1989, **116**, 457.
483 Bauer, N., and Lewin, S. Z., in *Physical Methods of Organic Chemistry*, ed. Weissberger, A., and Rossiter, B. W., Wiley, New York, 1972, vol. 1, pt. IV.
484 Lowell, S., and Shields, J. E., *Powder Surface Area and Porosity*, Chapman and Hall, London, 3rd edn., 1991.
485 Dent Glasser, L. S., *Crystallography and its Applications*, Van Nostrand Reinhold, 1977, p. 111–114.
486 Orr, C., and Dallevalle, J. M., *Fine Particle Measurement*, Macmillan, New York, 1959.
487 Fukumori, Y., Fukuda, T., Yamamoto, Y., Shigitami, Y., Hanyu, Y., Takeuchi, Y., and Sato, N., *Chem. Pharm. Bull.*, 1983, **31**, 4029.
488 Carless, J. E., Moustafa, M. A., and Rapson, H. D. C., *J. Pharm. Pharmacol.*, 1966, **18**, 190S.
489 Botha, S. A., Caira, M. R., Guillory, J. K., and Lötter, A. P., *J. Pharm. Sci.*, 1988, **77**, 444.
490 Otsuka, M., and Kanemiwa, N., *Chem. Pharm. Bull.*, 1983, **31**, 1021.
491 Chapman, J. H., Page, J. E., Parker, A. C., Rogers, D., Sharp, C. J., and Staniforth, S. E., *J. Pharm. Pharmacol.*, 1968, **20**, 418.
492 Burger, A., Ratz, A. W., and Zolss, G., *Acta Pharm. Technol.*, 1988, **34**, 147.
493 Michel, G., in *Analytical Profiles*, vol. 6., ed. Florey, K., Academic Press, New York, 1977, vol. 6.
494 Kuhnert-Brandstätter, M., *Pharm. Ind.*, 1977, **39**, 377.
495 Pouchert, C. J., *Aldrich Library of Infrared Spectra*, Aldrich, Milwaukee, 3rd edn., 1981.
496 Bjaen, A. K. B., Nord, K., Furuseth, S., Agren, T., Tonneson, H. H., and Karlsen, J., *Int. J. Pharm.*, 1993, **92**, 193.
497 Chauvet, A., Masse, J., Ribet., J. P., Bigg, D., Autin, J. M., Maurel, J. L., Patoneau, J. F., and Jans, J., *J. Pharm. Sci.*, 1992, **81**, 836.
498 Williams, P. P., *Acta Cryst., Sect. B*, 1973, **29**, 1572.
499 Khankhari, R. J., Law, D., and Grant, D. J. W., *Int. J. Pharm.*, 1992, **82**, 117.
500 Harris, R. K., Say, B. J., Yeung, R. R., Fletton, R. A., and Lancaster, R. W., *Spectrochim. Acta, Part A*, 1989, **45**, 465.
501 Hendricksen, B. A., Preston, M. S., and York, P., in the press.
502 Chrzanowski, F. A., Fegley, B. J., Sisco, W. R., and Newton, M. P., *J. Pharm. Sci.*, 1984, **73**, 10.
503 Garti, N., Sarig, S., and Wellner, E., *Thermochim. Acta*, 1980, **37**, 131.
504 Hirshfeld, T., in *Fourier Transform Infrared Spectroscopy*, ed. Ferraro, J. R., and Basile, L. J., Academic Press, 1979, vol. 2.
505 Hamadah, L. M., Yeboah, S. A., Turnbull, K. A., and Griffiths, P. R., *Appl. Spectrosc.*, 1984, **38**, 486.
506 Tanninen, V. P., and Yliruusi, J., *Int. J. Pharm.*, 1992, **81**, 169.
507 Tudor, A. M., Church, S. J., Hendra, P. J., Davies, M. C., and Melia, C. D., *Pharm. Res.*, 1993, **10**, 1771.
508 Guillory, J. K., and Erb, D. M., *Pharm. Manuf.*, 1985, **2**(9), 28.
509 Lindenbaum, S., and McGraw, S. E., *Pharm. Manuf.*, 1985, **2**(1), 273.
510 Crocker, L. S., and McCauley, J. A., *J. Pharm. Sci.*, 1995, **84**, 226.
511 Pikal, M. J., Lukes, A. L., Lang, J. E., and Gaines, K., *J. Pharm. Sci.*, 1978, **67**, 676.
512 Matsuda, Y., Tatsumi, E., Chiba, E., and Miwa, Y., *J. Pharm. Sci.*, 1984, **73**, 1453.
513 Jenkins, E. W., *The Polymorphism of Elements and Compounds*, Methuen Educational, London, 1973.
514 Rosenberg, H. M., *The Solid State*, Oxford University Press, 3rd edn., 1988.
515 De Gennes, P. G., and Prost, J., *The Physics of Liquid Crystals*, Clarendon, Oxford, 1993.
516 Janner, A., and Janssen, T., *Phys. Rev. B: Condens Matter*, 1977, **13**, 643.
517 Stevens, P. W., and Goldman, A. T., *Sci. Am.*, 1991, **261**(April), 24.
518 Janot, C., Dubois, J.M., and de Boisseau, M., *Amer. J. Phys.*, 1989, **57**, 972.
519 Nelson, D. R., *Sci. Am.*, 1986, **255**(August), 32.
520 Ronchetti, M., *Philos. Mag.*, 1987, **56**, 237.
521 Goldman, A. I., and Kelton, R. F., *Rev. Mod. Phys.*, 1993, **65**, 213.
522 Holzer, J. C., and Kelton, R. F., in *Crystal-Quasicrystal Transitions*, ed. Yacaman, M. J., and Torres, M., Elsevier, Amsterdam, 1993.
523 Finney, J. L., *Stud. Phys. Theor. Chem.*, 1981, **13**, 439.
524 Mayer, E., and Pletzer, R., *NATO ASI Ser., Ser. 3*, 1985, **156**, 81.
525 Samwer, K., *Phys. Rep.*, 1988, **161**, 1.
526 Sandman, D. J., Elman, B. S., Hamill, G. P., Velazquez, C. S., and Samuelson, L. A., *Mol. Cryst. Liq. Cryst.*, 1986, **134**, 89.
527 Halebian, J. K., Koda, R. T., and Biles, J. A., *J.Pharm. Sci.*, 1971, **60**, 1485.
528 Corrigan, O. I., and Holohan, E. M., *J. Pharm. Pharmacol.*, 1984, **36**, 217.
529 Parthasathy, R., Rao, K. J., and Rao, C. N. R., *Chem. Soc. Rev.*, 1984, 361.
530 Hukins, D. W. L., *X-Ray Diffraction by Ordered and Disordered Systems*, Pergamon Press, Oxford, 1981.
531 Elliott, S. R., *Nature (London)*, 1991, **354**, 445.
532 Atalla, R. H., Gast, J. C., Sindorf, D. W., Bartuska, V. G., and Maciel, G. E., *J. Am. Chem. Soc.*, 1980, **102**, 3249.
533 Fecht, H. J., *Nature (London)*, 1992, **365**, 133.
534 Fecht, H. J., and Johnson, W. L., *Nature (London)*, 1988, **334**, 50.
535 Cahn, R. W., *Nature (London)*, 1988, **334**, 17.
536 Cahn, R. W., *Nature (London)*, 1992, **356**, 108.
537 Tallon, J. L., *Nature (London)*, 1989, **342**, 658.

538 Zarzicki, J., *Glasses and the Vitreous State,* Cambridge University Press, 1982.
539 Chauhadri, P., Giessen, B. C., and Turnbull, D., *Sci. Am.,* 1980, **242**(April), 84.
540 Kauzmann, W., *Chem. Rev.,* 1948, **43**, 219.
541 Jaeckle, J., *Rep. Prog. Phys.,* 1986, **49**, 17.
542 Randall, J. T., *The Diffraction of X-rays and Electrons by Amorphous Solids, Liquids and Gases,* Chapman and Hall, London, 1934.
543 Jaeckle, J., *Philos. Mag. B,* 1987, **56**, 113.
544 Wunderlich, B., *Thermal Analysis,* Academic, New York, 1990.
545 Sichina, W. J., *Int. Laboratory,* 1994, **March**, 20.
546 van der Plaats, G., *The Practice of Thermal Analysis,* Mettler, Greifensee, Switzerland.
547 Westrum, E. R., and McCullough, J. P., in *Physics and Chemistry of the Organic Solid State*, ed. Fox, D., Labes, M. M., and Weissberger, A., Interscience, New York, 1963, vol. 1, p. 43.
548 Kitaigorodski, A. I., *Molecular Crystals and Molecules,* Academic Press, New York, 1973, p. 18.
549 Partington, J. R., *The Properties of Solids, Advanced Treatise on Physical Chemistry, vol. III,* Oxford University Press, 1952, p. 519.
550 Saleki-Gerhardt, A., Stowell, J. G., Byrn, S. R., and Zografi, G., *J. Pharm. Sci.,* 1995, **84**, 318.
551 Burger, A., and Ratz, A. W., *Sci. Pharm.,* 1990, **58**, 69.
552 van Skoik, K. G., and Carstensen, J. T., *Int. J. Pharm.,* 1990, **58**, 185.
553 White, G. W., and Cakebread, S. H., *J. Food Technol.,* 1966, **1**, 73.
554 Talbot, G., in *Industrial Chocolate Manufacture and Use,* ed. Beckett, S.T., Blackie, London, 2nd edn., 1993.
555 Suryanarayanan, R., and Mitchell, A. G., *Int. J. Pharm.,* 1986, **32**, 213.
556 James, R. W., *The Optical Principles of the Diffraction of X-Rays,* Bell, London, 2nd edn., 1962.

Paper 5/01094B
Received February 23, 1995
Accepted July 6, 1995

Guidance for Industry

ANDAs: Pharmaceutical Solid Polymorphism

Chemistry, Manufacturing, and Controls Information

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 2007
OGD

Guidance for Industry

ANDAs: Pharmaceutical Solid Polymorphism

Chemistry, Manufacturing, and Controls Information

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 2007
OGD

TABLE OF CONTENTS

Contains nonbinding recommendations

Guidance for Industry[1]

ANDAs: Pharmaceutical Solid Polymorphism Chemistry, Manufacturing, and Controls Information

This guidance, represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternate approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this document.

I. INTRODUCTION[2]

Chemistry, manufacturing, and controls (CMC) information must be submitted to support the approval of an abbreviated new drug application (ANDA).[3] This guidance is intended to assist applicants with the submission of ANDAs when a drug substance[4] exists in polymorphic forms.[5] Specifically, this guidance provides:

- FDA recommendations on assessing *sameness*[6] when the drug substance exists in polymorphic forms.
- Decision trees that provide recommendations on monitoring and controlling polymorphs in drug substances and/or drug products.[7]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

---

[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Office of Pharmaceutical Science (OPS), Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] Although issues relating to polymorphic forms may be relevant to new drug applications (NDAs), this guidance only addresses polymorphic forms in the context of ANDA approvals.

[3] See 21 CFR 314.94 (a)(9); see also section 505(j)(4)(A) of the Federal Food, Drug, and Cosmetic Act (the Act).

[4] For the purposes of this guidance the terms *drug substance* and *active ingredient* are used interchangeably.

[5] The terms *polymorphic forms* and *polymorphs* are synonymous and are used interchangeably in this guidance.

[6] Refer to Section IV for more information.

[7] This guidance is intended to help industry with the most common types of polymorphs. A drug substance may exist in many polymorphic forms, but some forms may be rare and not likely to form. For example, in one approved drug product, the drug substance can exist in at least twenty polymorphic forms, but in reality only a subset of polymorphic forms has the potential to develop under the process conditions used to manufacture the drug substance and drug product. Therefore, we recommend that you consider only those polymorphs that are likely to form during manufacture of the drug substance, manufacture of the drug product, or while the drug substance or drug product is in storage.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DEFINITION OF TERMS: POLYMORPHIC FORMS AND POLYMORPHISM

We recommend that ANDA applicants investigate whether the drug substance in question can exist in polymorphic forms. Polymorphic forms in the context of this guidance refer to crystalline and amorphous forms as well as solvate and hydrate forms, which are described below.[8]

- Crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice.
- Amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice.
- Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent.[9] If the incorporated solvent is water, the solvate is commonly known as a hydrate.

When a drug substance exists in polymorphic forms, it is said to exhibit polymorphism.

III. GENERAL PRINCIPLES OF PHARMACEUTICAL SOLID POLYMORPHISM

A. Importance of Pharmaceutical Solid Polymorphism

Polymorphic forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility,[10] dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties can have a direct effect on the ability to process and/or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, polymorphism can affect the quality, safety, and efficacy of the drug product.

B. Characterization of Polymorphs

There are a number of methods that can be used to characterize polymorphs of a drug substance.[11] Demonstration of a nonequivalent structure by single crystal X-ray diffraction is

---

[8] Guidance for industry, Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances,* International Conference on Harmonisation (ICH), December 2000.
[9] SR Byrn, RR Pfeiffer, and JG Stowell. *Solid-State Chemistry of Drugs.* 2nd Edition, SSCI, Inc., West Lafayette, Indiana, 1999.
[10] Apparent solubility refers to the concentration of material at apparent equilibrium (supersaturation). Apparent solubility is distinct from true thermodynamic solubility, which is reached at infinite equilibrium time.
[11] H Brittain. "Methods for the characterization of polymorphs and solvates." In HG Brittain (ed.) *Polymorphism in Pharmaceutical Solids.* Marcel Dekker, Inc., New York, 1999, pp. 227-278.

currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g., differential scanning calorimetry, thermal gravimetric analysis, and hot-stage microscopy), and spectroscopy (e.g., infrared [IR], Raman, solid-state nuclear magnetic resonance [ssNMR]) are helpful to further characterize polymorphic forms.

C. Influence of Polymorphism On Drug Substance And Drug Product

1. Influence on Solubility, Dissolution, and Bioavailability (BA) and Bioequivalence (BE)

The solid-state properties of a drug substance can have a significant influence on the apparent solubility of the drug substance. Since polymorphic forms differ in their internal solid-state structure, a drug substance that exists in various polymorphic forms can have different aqueous solubilities and dissolution rates.[12] When there are differences in the apparent solubilities of the various polymorphic forms, we recommend that you focus on the potential effect such differences can have on drug product bioavailability (BA) and bioequivalence (BE).[13]

Whether drug product BA/BE can be affected by the differences in apparent solubilities of the various polymorphic forms depends on the various physiological factors that govern the rate and extent of drug absorption including gastrointestinal motility, drug dissolution, and intestinal permeability. In this context, the Biopharmaceutics Classification System (BCS)[14, 15] provides a useful scientific framework for regulatory decisions regarding drug substance polymorphism.

For a drug whose absorption is only limited by its dissolution, large differences in the apparent solubilities of the various polymorphic forms are likely to affect BA/BE. On the other hand, for a drug whose absorption is only limited by its intestinal permeability, differences in the apparent solubilities of the various polymorphic forms are less likely to affect BA/BE. Furthermore, when the apparent solubilities of the polymorphic forms are sufficiently high and drug dissolution is rapid in relation to gastric emptying, differences in the solubilities of the polymorphic forms are unlikely to affect BA/BE.

---

[12] HG Brittain and DJW Grant. "Effect of polymorphism and solid-state solvation on solubility and dissolution rate." In HG Brittain (ed.) *Polymorphism in Pharmaceutical Solids.* Marcel Dekker, Inc., New York, 1999, pp. 279-330.

[13] Bioavailability (BA) is defined in 21 CFR 320.1(a) as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action." Bioequivalence (BE) is defined in 21 CFR 320.1(e) as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

[14] GL Amidon, H Lennernas, VP Shah, and JR Crison. "A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability," *Pharm. Res.* 12:413-420, 1995.

[15] LX Yu, GL Amidon, JE Polli, H Zhao, M Mehta, DP Conner, VP Shah, LJ Lesko, M-L Chen, VHL Lee, and AS Hussain. "Biopharmaceutics Classification System: The scientific basis for biowaiver extension." *Pharm. Res.* 19:921-925, 2002.

Upon demonstration of in-vivo bioequivalence between the generic drug product[16] and the reference listed drug (RLD),[17] in-vitro dissolution testing is then used to assess the lot-to-lot quality of the generic drug product. Drug product dissolution testing frequently provides a suitable means to identify and control the quality of the product from both the bioavailability and physical (stability) perspectives. In particular, inadvertent changes to the polymorphic form that may affect drug product BA/BE can often be detected by drug product dissolution testing.

2. Influence on Manufacturing of the Drug Product

Drug substance polymorphic forms can also exhibit different physical and mechanical properties, including hygroscopicity, particle shape, density, flowability, and compactibility, which in turn may affect processing of the drug substance and/or manufacturing of the drug product. Since an ANDA applicant should demonstrate that the generic drug product can be manufactured reliably using a validated process, we recommend that you pay close attention to polymorphism as it relates to pharmaceutical processing.[18]

The effect of polymorphism on pharmaceutical processing also depends on the formulation and the manufacturing process.[19] For a drug product manufactured by direct compression, the solid-state properties of the active ingredient will likely be critical to the manufacture of the drug product, particularly when it constitutes the bulk of the tablet mass. On the other hand, for a drug product manufactured by wet granulation, the solid-state properties of the active ingredient are often masked by the resultant granulation, and the solid-state properties of the active ingredient are less likely to affect the manufacture of the drug product. In the context of the effect of polymorphism on pharmaceutical processing, what is most relevant is the ability to consistently manufacture a drug product that conforms to applicable in-process controls and release specifications.

Polymorphic forms of the drug substance can undergo phase conversion when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray-drying, and compaction. Exposure to environmental conditions such as humidity and temperature can also induce polymorph conversion. The extent of conversion generally depends on the relative stability of the polymorphs, kinetic barriers to phase conversion, and applied stress.[20] Nonetheless, phase conversion generally is not of serious concern, provided that the conversion occurs consistently, as a part of a validated manufacturing process where critical manufacturing process variables are well understood and controlled, and when drug product BA/BE has been demonstrated.

---

[16] The term *generic drug product* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[17] See 21 CFR 314.3 (b) (providing that *reference listed drug* means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application).

[18] Section 505(j)(4)(A) provides that FDA must approve an ANDA if, among other things, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity.

[19] DA Wadke, ATM Serajuddin, and H Jacobson. "Preformulation testing." In HA Lieberman, L Lachman, and JB Schwartz (eds.) *Pharmaceutical Dosage Forms: Tablets* (Vol. 1). Marcel Dekker, Inc., New York, 1989, pp. 1-73.

[20] SR Vippagunta, HG Brittain, DJW Grant. "Crystalline solids," *Adv. Drug Del. Rev.* 48:3-26, 2001.

3. Influence on Stability

Polymorphs can have different physical and chemical (reactivity) properties. The most thermodynamically stable polymorphic form of a drug substance is often chosen during development based on the minimal potential for conversion to another polymorphic form and on its greater chemical stability. However, a metastable form can be chosen for various reasons, including bioavailability enhancement. Since an ANDA applicant must demonstrate that the generic drug product exhibits adequate stability,[21] we recommend that you focus on the potential effect that a polymorphic form can have on drug product stability. Nonetheless, because drug product stability is affected by a multitude of other factors, including formulation, manufacturing process, and packaging, it is the stability of the drug product and not stability of the drug substance polymorphic form that should be the most relevant measure of drug quality.

IV. POLYMORPHISM AND *SAMENESS* IN ANDAs

Section 505(j)(2) of the Act specifies that an ANDA must contain, among other things, information to show that the active ingredient in the generic drug product is the "same as" that of the RLD. Under section 505(j)(4) of the Act, FDA must approve an ANDA unless the agency finds, among other things, that the ANDA contains insufficient information to show that the active ingredient is the same as that in the RLD. FDA regulations implementing section 505(j) of the Act provide that an ANDA is suitable for consideration and approval if the generic drug product is the "same as" the RLD. Specifically, 21 CFR 314.92(a)(1) provides that the term "same as" means, among other things, "identical in active ingredient(s)." The drug substance in a generic drug product is considered to be the same as the drug substance in the RLD if it meets the same standards for identity.[22]

When a United States Pharmacopeia (USP) monograph exists for a particular drug substance, standards for identity generally refer to the definition (e.g. chemical name, empirical formula, molecular structure, description) at the beginning of the monograph. However, FDA may prescribe additional standards that are material to the *sameness* of a drug substance.[23]

Polymorphic forms of a drug substance differ in internal solid-state structure, but not in chemical structure. In the context of *sameness* of active ingredient(s) in the preamble to the 1992 final rule, FDA specifically rejected a proposal that would have required an ANDA applicant to show that the active ingredient in its generic drug product and the active ingredient in the RLD "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process and that the stereochemistry characteristics and solid state forms of the drug have not been altered."[24] Therefore, differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals within the meaning of the Act and FDA regulations.

---

[21] See footnote 18.
[22] See preamble to the 1992 final rule (57 FR 17958; April 28, 1992).
[23] See footnote 22.
[24] See footnote 22.

In addition to meeting the standards for identity, each ANDA applicant is required to demonstrate that, among other things, the drug product exhibits sufficient stability and is bioequivalent to the RLD.[25] While the polymorphic form can affect drug product stability and bioequivalence, these performance characteristics are also dependent on the formulation, the manufacturing process, and other physicochemical properties (e.g., particle size, moisture) of both the drug substance and formulation excipients. Using a drug substance polymorphic form that is different from that of the RLD may not preclude an ANDA applicant from formulating a generic drug product that exhibits bioequivalence and stability, and the drug substance in the generic drug product need not have the same polymorphic form as the drug substance in the RLD.

Over the years, FDA has approved a number of ANDAs in which the drug substance in the generic drug product had a different polymorphic form from the drug substance in the respective RLD (e.g., warfarin sodium, famotidine, and ranitidine). FDA also has approved some ANDAs in which the drug substance in the generic drug product differed in solvate or hydrate forms from the drug substance in the corresponding RLD (e.g., terazosin hydrochloride, ampicillin, and cefadroxil).

V. CONSIDERATIONS FOR POLYMORPHISM IN ANDAs

The decision trees shown in Attachments 1 to 3 provide ANDA applicants with a suggested process for evaluating the importance of and approaches to setting specifications for polymorphic forms in solid oral drug products and oral suspensions. Although the conceptual framework adopted by these decision trees is based primarily on the potential for polymorphic forms to affect drug product BA/BE, we recommend that you still consider the influence polymorphic forms may have on the ability to manufacture the drug product and on the stability of the drug product.

The following sections describe each of the decision trees.

A. Investigating the Importance of Setting Specifications for Polymorphs

Decision Tree 1 provides recommendations on when specifications for polymorphic form(s)[26] for the drug substance and/or the drug product may be appropriate. Polymorphs are unlikely to have a significant effect on BA/BE when all forms have the same apparent solubilities or all forms are highly soluble.

ANDA applicants are expected to have adequate knowledge about drug substance polymorphs. Information on polymorphism can come from the scientific literature, patents, compendia, other references, or in some cases, polymorph screening.

B. Setting Specifications for Polymorphs in Drug Substances

[25] See 505(j)(4) of the Act and 21 CFR 314.127.
[26] See footnote 7.

Decision Tree 2 provides an approach for setting specifications for polymorphs in the drug substance when at least one form is known to have low solubility based on the BCS. If relevant and adequate specifications for polymorphs are included in the USP, ANDA applicants may adopt these specifications for the drug substance polymorphic form. Otherwise, we recommend that a new specification for the drug substance polymorphic form be established.

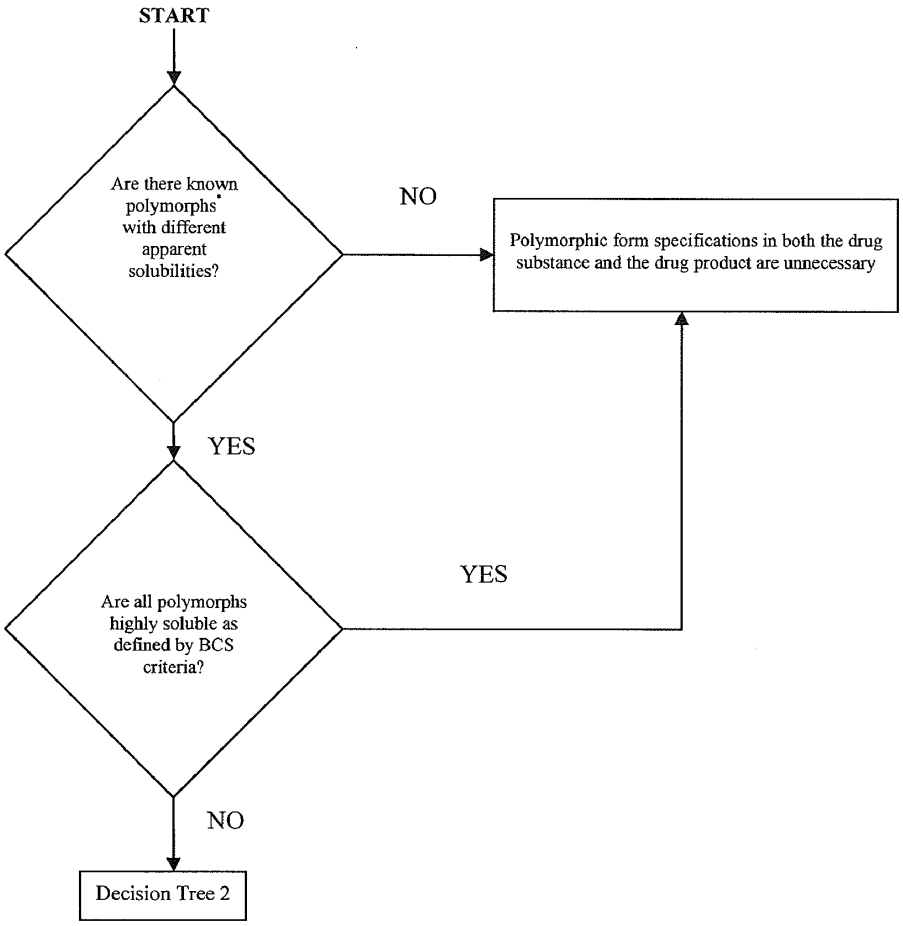
C. Investigating the Importance of Setting Specifications for Polymorphs in Drug Products

Decision Tree 3 provides an approach when considering whether to set specifications for polymorphs in the drug product. Generally, specifications for polymorphs in drug products are not necessary if the most thermodynamically stable polymorphic form is used or if the same form is used in an approved product of the same dosage form. However, since manufacturing processes can affect the polymorphic form, we recommend that you use caution if a metastable form is used.

Drug product performance testing (e.g., dissolution testing) can also generally provide adequate control of polymorph ratio changes that can influence drug product BA/BE for poorly soluble drugs. In such instances, setting specifications for polymorphs in the drug product would generally not be considered important for ensuring adequate product performance. Only in rare cases would we recommend setting specifications for polymorphic forms in drug products.

ATTACHMENT 1 – DECISION TREE 1

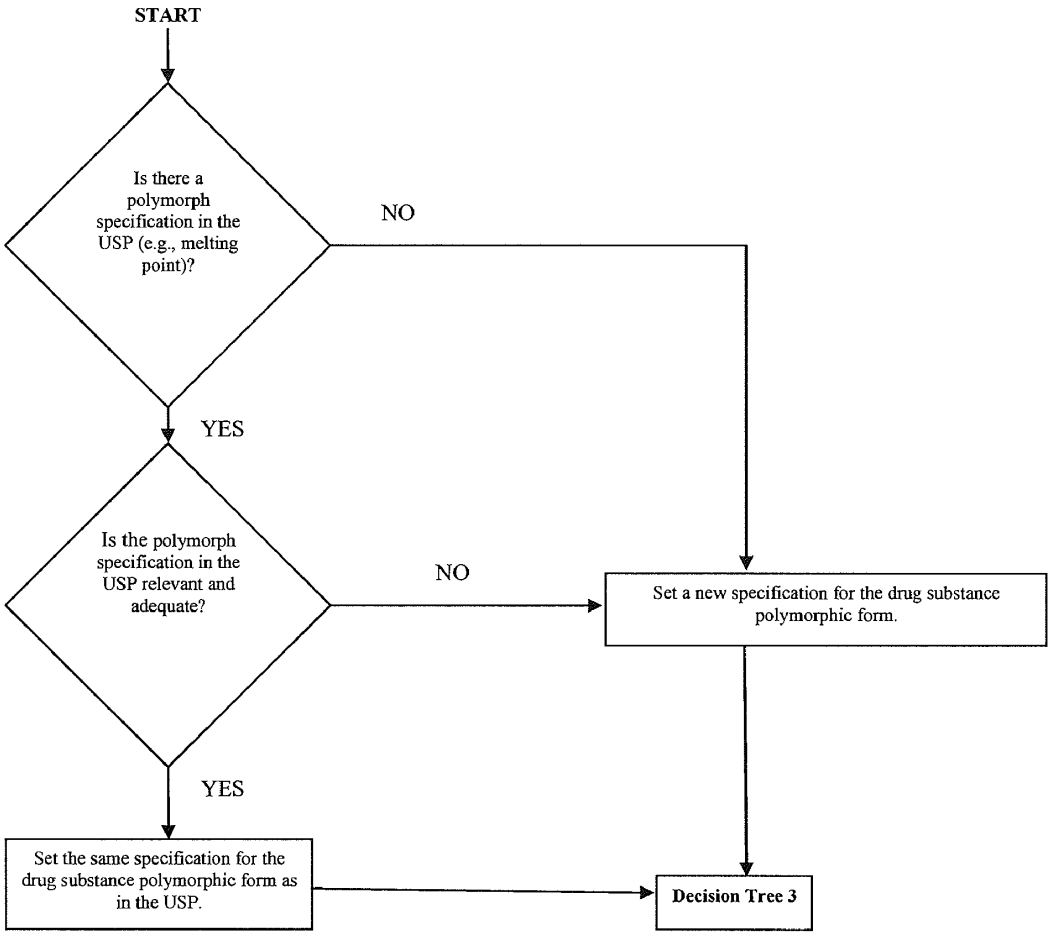
Decision Tree 1 Investigating whether to set specifications for polymorphs for solid oral and suspension dosage form products.



*We recommend that you consider only those polymorphs that are likely to form during manufacture of the drug substance, manufacture of the drug product, or while the drug substance or drug product is in storage. See footnote 7 in this guidance document.

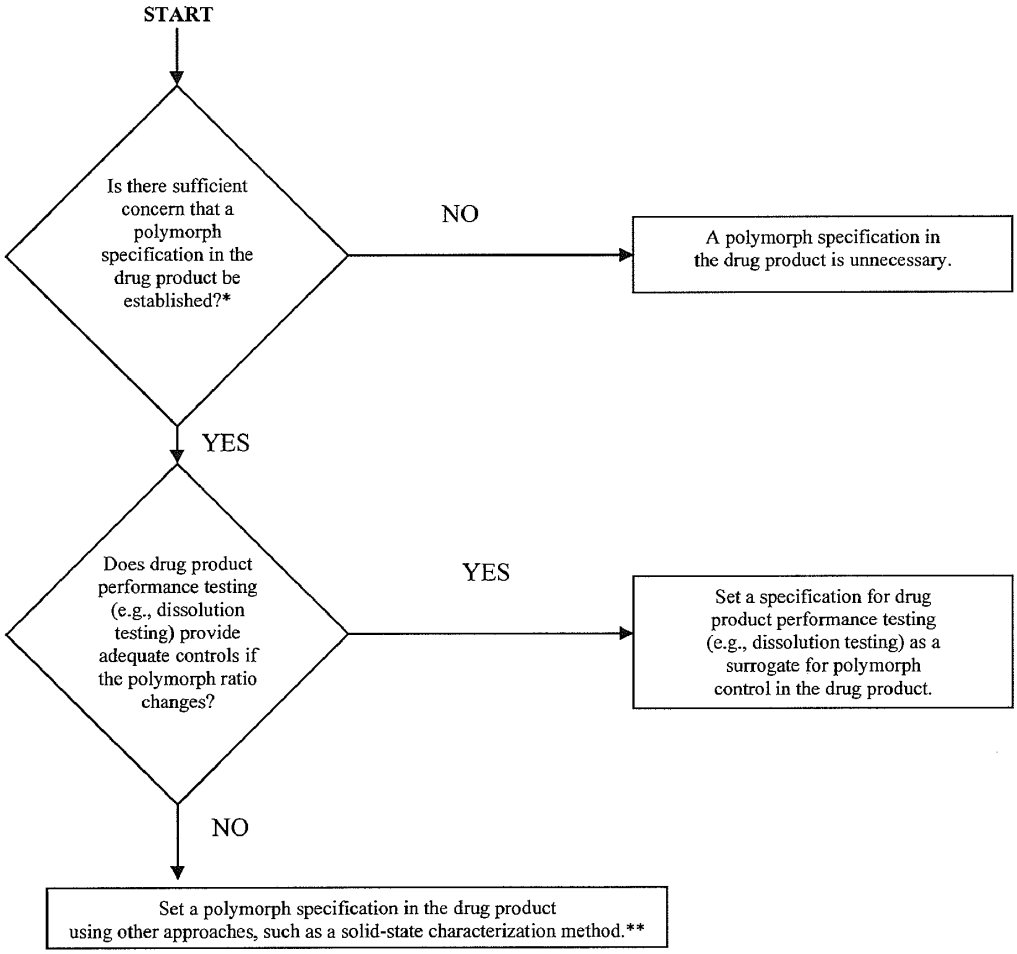
ATTACHMENT 2 – DECISION TREE 2

Decision Tree 2 Setting specifications for polymorphs in drug substances for solid oral and suspension dosage form products.



ATTACHMENT 3 – DECISION TREE 3

Decision Tree 3 Investigating whether to set specifications for polymorphs in drug products for solid oral and suspension dosage form products.



*In general, there may not be a concern if the most thermodynamically stable polymorphic form is used or the same form is used in a previously approved product of the same dosage form.

**Drug product performance testing (e.g., dissolution testing) can generally provide adequate control of polymorph ratio changes for poorly soluble drugs, which may influence drug product BA/BE. Only in rare cases would polymorphic form characterization in the drug product be recommended.

Solid-State Chemistry of Drugs

SECOND EDITION

Stephen R. Byrn
Ralph R. Pfeiffer
Joseph G. Stowell

SSCI, Inc. · West Lafayette, Indiana
www.ssci-inc.com

5

Thermal Methods of Analysis

Thermal analysis generally refers to any method involving heating the sample and measuring the change in some physical property. The most important thermal methods for the study of solid-state chemistry are **thermogravimetric analysis** (TGA), **differential scanning calorimetry** (DSC), and thermal microscopy (discussed in Section 4.4). Thermogravimetric analysis measures the change in the mass of sample as the temperature is changed. Differential scanning calorimetry involves measuring the difference between the temperature of the sample and a reference compound as the temperature of the system is changed, thus providing information on the enthalpy change of various solid-state processes. Thermal methods of analysis are important analytical tools for characterizing pharmaceutical solids. The use of TGA and DSC in conjunction with thermal microscopy (Section 4.4) can elucidate many behaviors of solids.

5.1 THERMOGRAVIMETRIC ANALYSIS (TGA)

Basically, a thermogravimetric instrument consists of a microbalance connected to a sample compartment situated in a small oven with computer-controlled temperature programming. A dry nitrogen atmosphere is most commonly used, however, other gases can be employed (the compostion and flow dynamics of the gas are important perameters.) This method measures the change in mass with temperature and is often used to study the loss of solvent of crystallization or other solid $\rightarrow$ solid + gas reactions. A typical TGA trace is shown in Figure 5.1. In studies of solid-state chemistry, TGA is usually performed in one of three modes:

1. **Isothermal mode**—the temperature is kept constant.
2. **Quasi-isothermal mode**—the sample is heated to a constant mass through a series of increasing temperatures.
3. **Dynamic mode**—the temperature is raised at a known rate, typically linear.

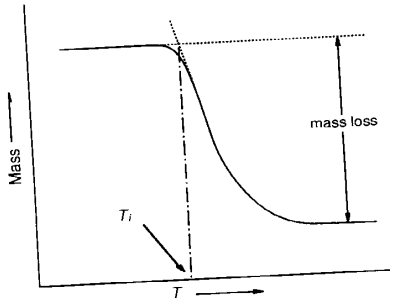


Figure 5.1 A typical TGA trace for a single-state mass loss with T_i (the transition temperature) marked. The temperature corresponding to the point at which tangents to the original baseline and to the slope of the tracing represents the transition temperature T_i.

The last approach uses high heating rates in temperature regions where no weight changes are occurring and slow rates in regions where weight changes do occur, thus avoiding transition temperature overshoot and blurring of peaks from overlapping transitions.

There are a number of factors or conditions that affect TGA curves including the heating rate, atmosphere, geometry of the sample holder (pan), particle size of the sample, nature of the reaction, treatment of the sample, thermal conductivity of the sample, and sample weight. The effect of the heating rate has been extensively studied (Wendlandt, 1974). In general, as the heating rate is increased, the apparent starting temperature of the thermal event (T_i) increases. However, this condition can sometimes be corrected by decreasing the sample size.

The atmosphere can have a dramatic effect on the TGA curve. For example, an atmosphere already containing the product gas can increase T_i or stop the reaction completely. In addition, the atmosphere can change the course of the reaction, particularly if the atmospheric gas reacts with either the products or the reactant. Knowledge of how the substance responds to changes in relative humidity (RH) is essential to proper handling of the sample before the scan is started. For these reasons, it is a prudent practice to use an atmosphere of dry nitrogen when performing a study.

Although dependent on the reaction mechanism, the particle size of the sample has a predictable effect on the TGA curve in general. The smaller the particle size, the faster the reaction and the lower the value of T_i. This is because the smaller particle sizes allow more rapid escape of the product gas. Obviously, the nature of the reaction affects T_i which will be lower for more facile reactions.

In addition, the treatment of the sample, and in particular the extent of compression of the sample, will obviously affect the T_i. For example, increased compression will increase T_i since the product gas will have less opportunity to escape.

Finally, the thermal conductivity of the sample will influence T_i. Anomalous effects may be obtained if the temperature of the sample is not uniform because of poor thermal conductivity.

The rates of reactions of the type shown in Equation 5.1 can be determined using

TGA. Obvious
reaction and the
time. These plot
also been used
general, the kine
thermogravimetr
desolvation of cr

5.2 DIFFEREN

Differential scan
energy (heat flu
DSC sample cor
The result c

Figure 5.2 Cros
are p

5.3 A hyp
sampl

TGA. Obviously, isothermal TGA traces can be used to determine the rate of the reaction and the rate law governing the reaction by simply plotting weight loss versus time. These plots can then be analyzed as described in Chapter 3. Dynamic TGA has also been used to determine the rates of such gas-evolving reactions. However, in general, the kinetic data thus obtained should be substantiated by other data. Isothermal thermogravimetric analysis has been used extensively in our laboratory to study the desolvation of crystal solvates (Chapter 16).

$$A_{solid} \longrightarrow B_{solid} + C_{gas} \tag{5.1}$$

5.2 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) is a method which measures the difference in energy (heat flux or heat flow) between a reference (R) and a sample (S). A typical DSC sample compartment is shown in Figure 5.2.

The result of a DSC analysis is a thermogram, a plot of $\Delta T = T_s - T_r$ (temperature

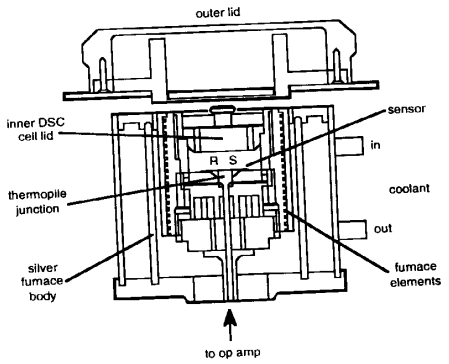


Figure 5.2 Cross section of a Cahn® DSC 4000 cell. The sample pan (S) and the reference pan (R) are positioned in the sensor (Cahn Instruments, 1996).

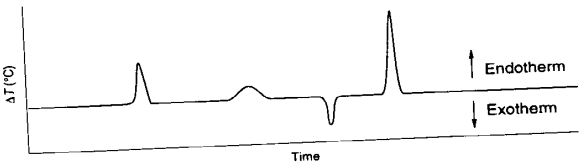


Figure 5.3 A hypothetical DSC thermogram showing the changes that might occur upon heating a sample.

difference) versus T. Figure 5.3 shows an idealized DSC trace. The endotherms represent processes in which heat is absorbed, such as solvent loss, phase transitions, or melting. The exotherms represent processes such as crystallization or chemical reactions where heat is evolved. In addition, the area under a peak is proportional to the heat change involved. Thus this method, with proper calibration, can be used to determine the enthalpies (ΔH)) of the various processes. The method can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

$$T_s = T_0 - \frac{T_0^2 R X_i}{F \Delta H_f} \tag{5.2}$$

where T_s is the sample temperature, T_0 is the melting point of the pure compound, R is the gas constant, X_i is the mole fraction of the impurity, F is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus $1/F$ should give a straight line whose slope is proportional to X_i (Brittain *et al.*, 1991). However, the equation appears to fail when purity is less than 97%. Application of this equation is illustrated by the DSC thermograms shown in Figure 5.4.

There are a number of factors other than purity that can affect the DSC curve including heating rate, atmosphere, sample holder, particle size, and sample packing. In general, a greater heating rate will cause a shift of the peaks to higher temperatures. A decreased heating rate also usually causes endotherms and exotherms to become sharper. The shape of the sample holder and whether it is open, totally sealed, or contains a pin prick to vent gases can also affect a DSC curve. When a DSC experiment is performed in a closed pan, the resulting atmosphere within the sample holder can greatly affect the resulting DSC curve. Obviously, a tightly sealed sample holder would not allow vapor to escape, thereby changing the behavior or mechanism of a

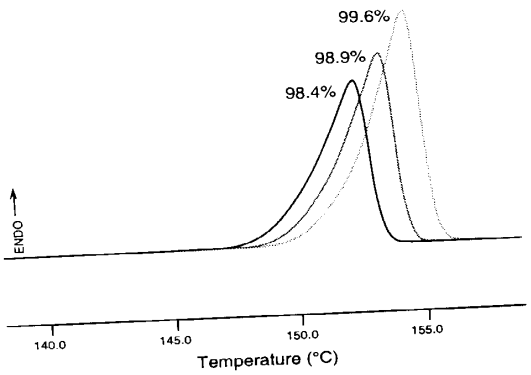


Figure 5.4 DSC thermograms of three ethoxycarbonyl-3-phenylpropyl-L-alanine samples of varying purity from different manufacturers (Giron, 1990).

desolvation processes. As with TGA, the particle size and packing of the sample has an important influence on reactions especially those of desolvation type. Any changes that affect the rate of heat transfer should also be taken into account. Thus a sample that has sublimed or melted and then recrystallized may show somewhat different DSC properties upon reheating.

Two definitions are often used to describe the relationship between the relative energies of polymorphs at different temperatures: **monotropic** and **enantiotropic**. In a monotropic system, one form is the thermodynamically stable form regardless of the temperature. In an enantiotropic system, one form is more stable below a certain (transition) temperature but another form is more stable above that temperature. Thus, high temperature recrystallization may lead to one form, whereas recrystallization at room temperature could lead to the other form. Enantiotropic systems can sometimes cause confusion and problems with crystallization. In general, to determine whether a system is enantiotropic or monotropic it would be helpful to construct an energy-termperature diagram. Burger and Ramberger (1979a–b) have constructeded two reliable rules which assist in determining whether a system is enantiotropic or monotropic using thermoanalytical results:

1. The **heat** (or **enthalpy**) **of transition rule** states that (a) if an endothermic transition is observed between the forms at some temperature it may be assumed that the two forms are related enantiotropically and (b) if an exothermic transition is observed between the forms at some temperature it may be assumed that the two forms are related monotropically.
2. The **heat** (or **enthalpy**) **of fusion rule** states that if the higher melting form has the lower heat of fusion then the two forms are related enantiotropically, otherwise they are related monotropically.

Based on this work, Grunenberg *et al.* (1996) expanded these rules with the **entropy of fusion rule** (particularly necessary for polymorphs with very different melting points but similar ethalpies of fusion) and a **heat capacity rule**. Since only about forty energy-temperature diagrams for pharmaceutical systems have been published, much more work needs to be done. In related studies, Behme and Brook (1991) calculated the heat of fusion of the lower melting of an enantiotropically related pair of polymorphs(based on the heat of transition and the heat capacities) and demonstrated the applicability of thermodynamic calculations.

DSC is also useful for studies of polymorphic mixtures. Figures 5.5 and 5.6 show the DSC scans of propyphenazone. Figure 5.5 shows the DSC scans of batches containing mixtures of Forms I and II indicating that DSC can detect as little as 5% of the higher melting form in the mixtures (Giron-Forest *et al.*, 1989). Trace A in Figure 5.6 shows pure Form I, trace B shows a mixture of Forms I and II, and trace C shows this same mixture after heating at 100°C for two days indicating that the higher melting form is converted to the lower melting form under these conditions. In a more extensive study of mixtures, (Giron, 1986) showed that DSC could be used to quantitate mixtures of polymorphs as shown in Figure 5.7. The left panel in Figure 5.7 shows the DSC thermograms of Forms I and II of a pharmaceutical; the right panel shows that DSC can be used to analyze mixtures of these two forms (Giron, 1986).

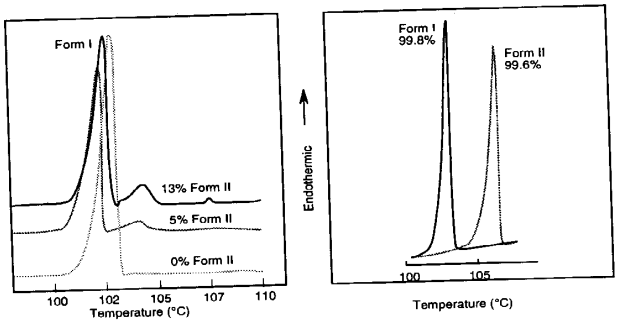


Figure 5.5 Melting behavior of batches containing propyphenazone which are mixtures of Form I with a small amount of Form II (Giron-Forest *et al.*, 1989).

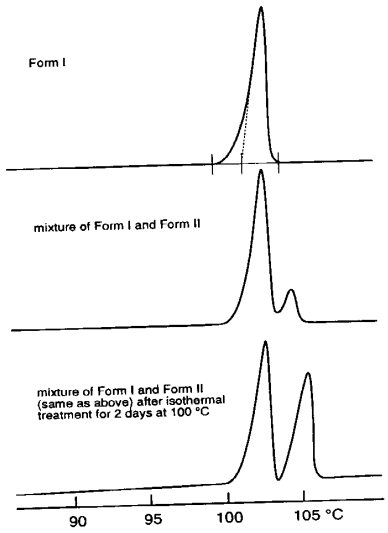


Figure 5.6 DSC scans of propyphenazone pure Form I and mixtures of Form I and Form II before and after isothermal treatment (Giron-Forest *et al.*, 1989).

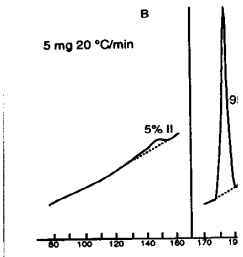
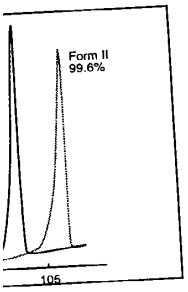


Figure 5.7 Determination of

Thermal methods have
ity (Giron, 1990). In this
varying between 10:1 and
of the heated samples is us
and the results are compar
should reflect the actual p
determine incompatibilities
the DSC thermograms of
formation; thus, a change
tive of a stability problem
One advantage of DS
thus, a study over a wid
however, will have to be
useful in the study of solic
combined with other tech
HPLC.

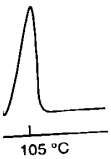
5-3 MICROCALORIMET

Microcalorimetry is a ver
given off or taken up by v
try is used, for example,
every transformation, eith
of heat, this method has si
baum and McGraw (1985
different crystal forms ha
However, the difference b
solvents should remain t
difference is the heat of tr

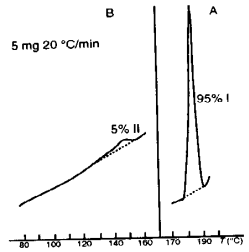


nperature (°C)

zone which are mixtures of Form I
1989).



d mixtures of Form I and Form II before
al., 1989).



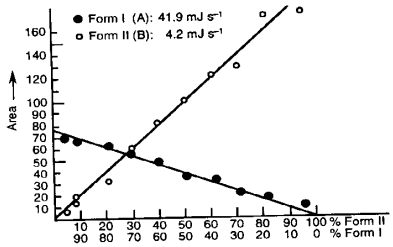


Figure 5.7 Determination of ratios of Forms I and II of a pharmaceutical (Giron, 1986).

Thermal methods have been successfully used to study drug-excipient compatibility (Giron, 1990). In this procedure, drug and excipient are intimately mixed in ratios varying between 10:1 and 1:10 and each mixture is analyzed by DSC. HPLC analysis of the heated samples is used to interpret any changes in the DSC profile of the mixture and the results are compared with those of the pure components. The ratios analyzed should reflect the actual proportions in the formulation; however, it is instructive to determine incompatibilities at other concentrations as well. It is important to note that the DSC thermograms of mixtures will show some changes simply from eutectic formation; thus, a change in DSC melting point for a drug and excipient is not indicative of a stability problem by itself.

One advantage of DSC is that the sample is subjected to different temperatures; thus, a study over a wide temperature range can be rapidly carried. Most results, however, will have to be confirmed by using other methods. Thermal methods are useful in the study of solids but the power of these methods is greatly enhanced when combined with other techniques such as X-ray powder diffraction, microscopy, and HPLC.

5.3 MICROCALORIMETRY

Microcalorimetry is a very sensitive calorimetric technique that determines the heat given off or taken up by various processes. For pharmaceutical solids, microcalorimetry is used, for example, to measure heats of solution and degradation rates. Since every transformation, either chemical or physical, occurs with evolution or absorption of heat, this method has significant potential for the study of transformations. Lindenbaum and McGraw (1985) have used microcalorimetry to study drug forms. Because different crystal forms have different structures, they have different heats of solution. However, the difference between the heats of solution of two polymorphs in different solvents should remain the same (Table 5.1) if there is no solvate formation. This difference is the heat of transition between the forms at that temperature.

Table 5.1 Heats of Solution of Sodium Sulfathiazole

Solvent	ΔH_s Form I (kJ/mol, 25 °C)	ΔH_s Form II (kJ/mol, 25 °C)	ΔH_{trans} (kJ/mol, 25 °C)
Acetone	11.94	5.144	6.798
DMF	−4.659	−11.47	6.810

Lindenbaum and McGraw, 1985.

Studies by Ip *et al.* (1986) on enalapril maleate give similar results showing that the heats of transition between the two forms determined by subtraction of the heats of solution in two different solvents are within the experimental error. With suitable calibration of known mixtures, this phenomenon can sometimes be the basis for analyzing mixtures of polymorphs or crystalline and amorphous forms of a compound. Of course these comparisons apply only to solids with the same composition (*i.e.*, when the resulting solutions are identical). Also, a hydrate and an anhydrate cannot be compared since the heat of the solution of water will be different in different solvents and thus the ΔH_{trans} will be different.

Isothermal microcalorimetry has also been used to determine the crystallinity of mixtures of amorphous and crystalline antibiotics as shown in Figure 5.8 (Thompson *et al.*, 1994). DSC could not be used since the samples decomposed prior to melting. In contrast to studies by Osawa and coworkers (1988) as well as Pikal and coworkers (1978), it was found that the heat of solution was not dependent on water content. The importance of initial water content is probably greatest when dealing with hydratable ionic species since sodium and quaternary ammonium salts have very high heats of hydration (see Figure 5.9).

Several important papers on the use of microcalorimetry for stability determinations have appeared. Hansen *et al.* (1989) studied the kinetics of decomposition of lovastatin and other HMG-CoA reductase inhibitors using **heat conduction calorimetry** (the response of the instrument is directly proportional to the rate of heat produced in the sample cell). Heat conduction calorimetry has a substantial advantage over

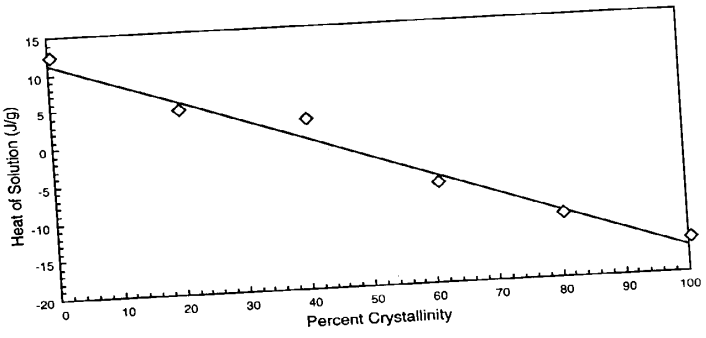


Figure 5.8 Heat of solution of antibiotic BO2669 in 0.02 *M* Na_2HPO_4 at 35 °C as a function of percent crystallinity (Thompson *et al.*, 1994).

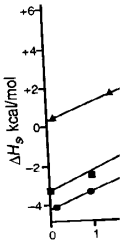


Figure 5.9 The effect of w

conventional microcalor
μW) can be detected. T
determined after only a
urement of degradation
temperature. The rate
calorimeters can also b
excipients and stabilize
rimetry to establish that
atmospheres only a sn
under oxygen atmosph
atmospheres. Further
change was about –40
oxidation. Bond ener
group would produce
tion microcalorimetry,
area of the sample has
experiments, they sh
produced under identi
oxygen than others.
that a single measuren
used to predict the tot
conduction microcalo
cases and appears to

REFERENCES

Behme, Robert J. and Da
of carbamazepine th
analysis" *J. Pharm.*

Brittain, Harry G., Susa
Ann W. Newman
963–973.

Burger, A. and R. Raml
crystals. I. Theory

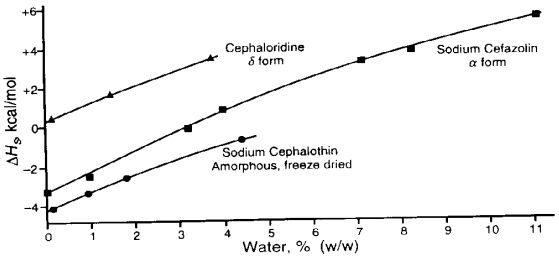


Figure 5.9 The effect of water content on the heats of solution of antibiotics (Pikal *et al.*, 1978).

conventional microcalorimetric methods in that extremely small outputs of heat (±0.1 μW) can be detected. The heat of decomposition and the kinetics of the process can be determined after only a very small percentage of reaction. This then allows the measurement of degradation of the material in the early stages of the reaction even at room temperature. The rate law and the activation energy can also be determined. These calorimeters can also be used to study freshly formulated materials and the effects of excipients and stabilizers on degradation. Hansen *et et al.* (1989) also used microcalorimetry to establish that oxygen was required for degradation of lovastatin since in inert atmospheres only a small amount of heat was produced whereas the heat produced under oxygen atmosphere was 20–90 times greater than that produced under inert atmospheres. Furthermore, they used the heat produced to estimate the enthalpy change was about –400 kJ mol^{-1} which is consistent with what one might expect for oxidation. Bond energy calculations show that reaction of oxygen with a methylene group would produce an enthalpy change of about –600 kJ mol^{-1}. Using heat conduction microcalorimetry, Hansen and coworkers were also able to show that the surface area of the sample has an effect on the rate of oxidation, as might be expected. In other experiments, they showed that there was significant lot-to-lot variation in the heat produced under identical conditions. Some lots showed much greater reactivity with oxygen than others. One of the most significant results of this study was the finding that a single measurement of the heat produced per gram of drug for each lot could be used to predict the total degradation of that lot under conventional stability testing. Heat conduction microcalorimetry has been shown to have predictive capability in some cases and appears to be an important addition to other stability studies.

REFERENCES

Behme, Robert J. and Dana Brooke (1991) "Heat of fusion measurement of a low melting polymorph of carbamazepine that undergoes multiple-phase changes during differential scanning calorimetry analysis" *J. Pharm. Sci.* **80** 986–990.

Brittain, Harry G., Susan J. Bogdanowich, David E. Bugay, Joseph DeVincentis, Geoffrey Lewen, and Ann W. Newman (1991) "Physical characterization of pharmaceutical solids" *Pharm. Res.* **8** 963–973.

Burger, A. and R. Ramberger (1979a) "On the polymorphism of pharmaceuticals and other molecular crystals. I. Theory of thermodynamic rules" *Mikrochim. Acta* **11** 259–271.

Burger, A. and R. Ramberger (1979b) "On the polymorphism of pharmaceuticals and other molecular crystals. II. Applicability of Thermodynamic rules" *Mikrochim. Acta* **11** 273–316.

Cahn Instruments (1996) 5225 Verona Road, Bldg. 1, Madison WI 53711-4418.

Giron, D. (1986) "Applications of thermal analysis in the pharmaceutical industry" *J. Pharm. Biomed. Anal.* **4** 775–770.

Giron, Daniele (1990) "Thermal analysis in pharmaceutical routine analysis" *Acta Pharm. Jugosl.* **40** 95–157.

Giron-Forest, D., Ch. Goldbronn, and P. Piechon (1989) "Thermal analysis methods for pharmacopocial materials" *J. Pharm. Biomed. Anal.* **7** 1421–1433.

Grunenberg, A., J.-O. Henck, and H. W. Siesler (1996) "Thcoretical deviation and practical application of energy/temperature diagrams as an instrument in performulation studies of polymorphic drug substances" *Int. J. Pharm.* **129** 147–158.

Hansen, Lee D., Edwin A. Lewis, Delbert J. Eatough, Robert G. Bergstrom, and Damaris DeGraft-Johnson (1989) "Kinetics of drug decomposition by heat conduction calorimetry" *Pharm. Res.* **6** 20–27.

Ip, Dominic P., Gerald S. Brenner, James M. Stevenson, Siegfried Lindenbaum, Alan W. Douglas, S. David Klein, and James A. McCauley (1986) "High resolution spectroscopic evidence and solution calorimetry studies on the polymorphs of enalapril maleate" *Int. J. Pharm.* **28** 183–191.

Lindenbaum, Siegfried and Scott E. McGraw (1985) "The identification and characterization of polymorphism in drug solids by solution calorimetry" *Pharm. Manufacturing* 27–30.

Pikal, Michael J. and Karen D. Dellerman (1989) "Stability testing of pharmaceuticals by high-sensitivity isothermal calorimetry at 25 °C: cephalosporins in the solid and aqueous solution states" *Int. J. Pharm* **50** 233–252.

Pikal, M. J., A. L. Lukes, John E. Lang, and K. Gaines (1978) "Quantitative crystallinity determinations for β-lactam antibiotics by solution calorimetry: correlations with stability" *J. Pharm. Sci.* **67** 767–773.

Osawa, Takashi, Madhav S. Kamat, and Patrick P. DeLuca (1988) "Hygroscopicity of cefazolin sodium: application to evaluate the crystallinity of freeze-dried products" *Pharm. Res.* **5** 421–425.

Thompson, Karen C., Jcrome P. Draper, Michael J. Kaufman, and Gerald S. Brenner (1994) "Characterization of the crystallinity of drugs: BO2669, a case study" *Pharm. Res.* **11** 1362–1365.

Wendlandt, Wesley W. (1974) *Thermal Methods of Analysis*, 2nd ed.; John Wiley and Sons: New York, NY; pp 9–13.

6

Solubilit Testing

The rate of disso important aspe and solubility same drug can obvious necessary for both pure have the proper dissoluti 1991; Banakar, 1992). dissolution testing and *USP-NF* (United States

6.1 TESTING

Dissolution tests are sp individual drugs. For e specification that 80% carbamazepine tablets m be dissolved in 60 m laboratories now measu variations. For dissolu variables (*e.g.*, time pr chosen carefully.

Dissolution tests a potential for bioequival are usually compounds disperse. Examples i digoxin, diphenylhyd quinidine, and warfarin. to ensure that the Unite

Kawakami

treprostinil

In The United States Patent And Trademark Office

Before The Patent Trial And Appeal Board

U.S. Patent No. 8,497,393 Case No. IPR 2016-00006

SteadyMed Ltd.

Petitioner

v.

United Therapeutics Corporation

Patent Owner

November 29, 2016

SteadyMed THERAPEUTICS

Topics

1 Legal Concepts

2 Key Scientific Concepts

3 Overview

4 Anticipation

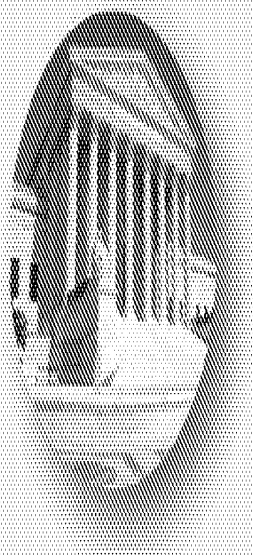
5 Obviousness

- Phares and Moriarty
- Kawakami and Moriarty
- Dependent Claims 6, 10, 21 & 22

6 Claim Construction

1 Legal Concepts

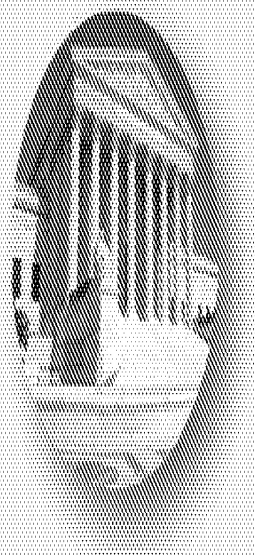
Legal Concepts



We have clearly stated that "[i]n determining validity of a product-by-process claim, the focus is on the product and not the process of making it." ... "That is because of the ... longstanding rule that an old product is not patentable even if it is made by a new process."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016) (cites and internal quotations omitted)

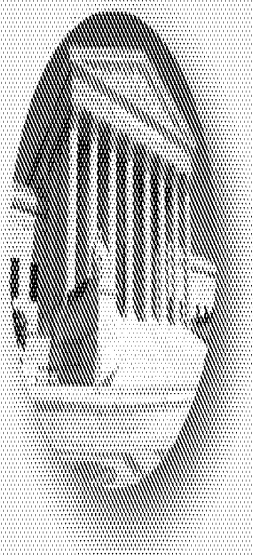
Legal Concepts



"If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985)

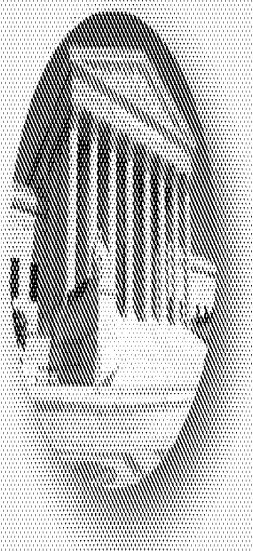
Legal Concepts



"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step.... One need not know that the 14–hydroxy was derived from 8α as opposed to 8β to answer that question."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

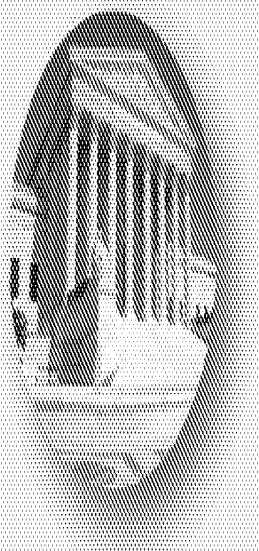
Legal Concepts



"[T]he fact that the 14–hydroxy is derived from 8α imparts no structural or functional differences in the low-ABUK [impurity] hydrocodone API as compared to the prior art products. Thus, the court did not err in disregarding the process limitation in its obviousness determination."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016)

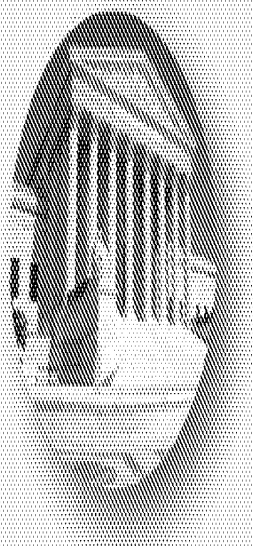
Legal Concepts



"Cases involving the "purification" of a natural substance employ similar analysis. Our predecessor court recognized that merely purifying a naturally occurring substance does not render the substance patentable unless it results in a marked change in functionality. *In re Merz*, 25 CCPA 1314, 97 F.2d 599, 601 (1938) (holding that there was no right to a patent on a purer version of ultramarine, but recognizing that if a claimed article is "of such purity that it differs not only in degree but in kind it may be patentable") ...."

Ass'n for Molecular Pathology v. USPTO, 689 F. 3d 1303, 1353-54 (Fed. Cir. 2012) (emphases added).

Legal Concepts



"[I]f the process by which a product is made imparts 'structural and functional differences' distinguishing the claimed product from the prior art, then those differences 'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'"

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016) (cites and internal quotations omitted) (emphasis added)

2 Key Scientific Concepts

Key Scientific Concepts

Recrystallization

Q: How long has crystallization been around as a method of purification?

A: I don't know how long it's been around.

Q: Before 2007?

A: Oh, yes.

Q: Did you learn about it when you were in college at the university?

A: Yes, I did. [...]

Q: And when did you go to college?

A: In 1968 I started. In 1968.

* * *

Q: ... But how far back does doing that process you just described, how far back does that go?

The Witness: Decades.

(Ex. 2058, 175:19-176:22, 179:11-17)

Key Scientific Concepts

Melting Point

The method [of differential scanning calorimetry] can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

$$T_s = T_0 - \frac{T_0^2 R X_i}{F \Delta H_f} \qquad (5.2)$$

where Ts, is the sample temperature, T_0 is the melting point of the pure compound, R is the gas constant, X_i, is the mole fraction of the impurity, F is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus $1/F$ should give a straight line whose slope is proportional to X_i (Brittain *et al.*, 1991).

Stephen R. Byrn et al., Solid-State Chemistry of Drugs, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027, at 84.)

Key Scientific Concepts

Melting Point

Figure 18

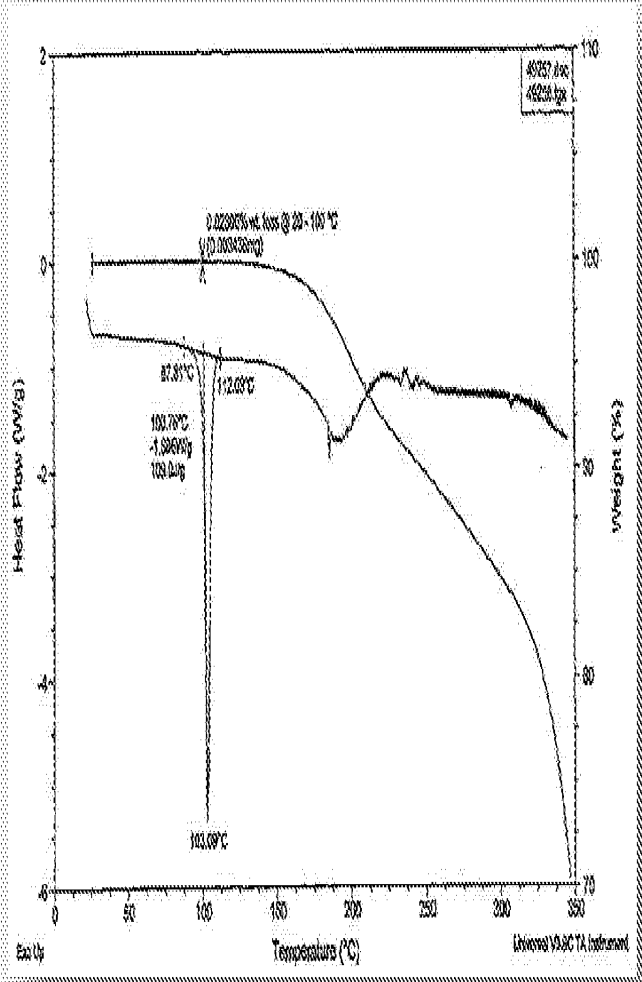
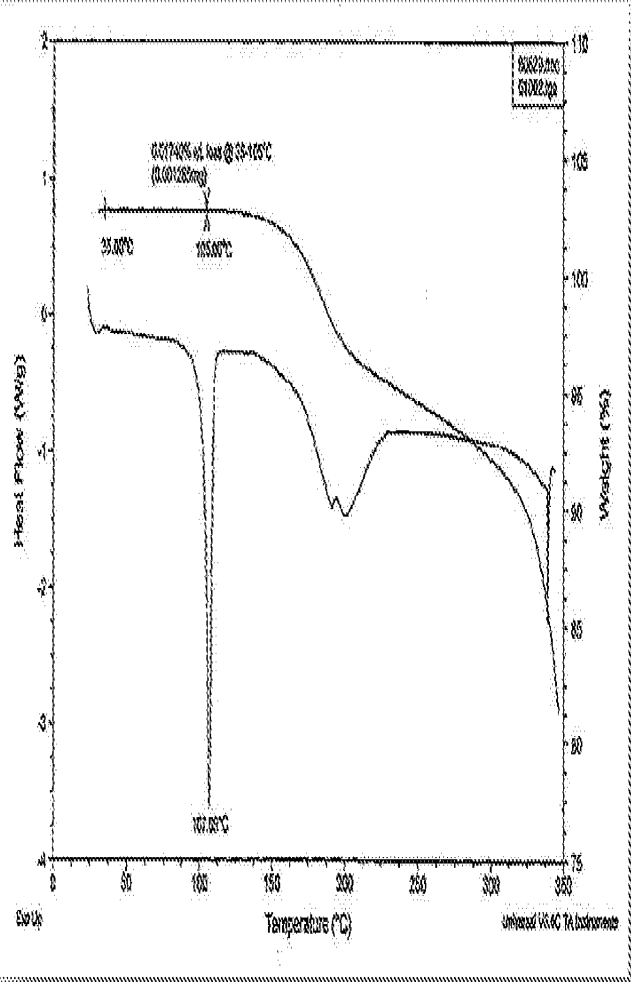


Figure 21



Ex. 1005 ("Phares"), Figures 18 and 21.

Key Scientific Concepts

Melting Point

The method [of differential scanning calorimetry] can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

$$T_s = T_0 - \frac{T_0^2 R X_i}{F \Delta H_f} \qquad (5.2)$$

where Ts, is the sample temperature, T_0 is the melting point of the pure compound, R is the gas constant, X_i, is the mole fraction of the impurity, F is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus $1/F$ should give a straight line whose slope is proportional to X_i (Brittain *et al.*, 1991).

Stephen R. Byrn et al., Solid-State Chemistry of Drugs, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027, at 84.)

Key Scientific Concepts

HLPC and Purity

Analytical data on and Treprostinil Diethanolamine Salt (1:1)

Test	Batch 1	Batch 2
IR	Conforms	Conforms
Residue on Ignition (ROI)	<0.1% w/w	<0.1% w/w
Water content	0.1% w/w	0.0% w/w
Melting point	105.0-106.5° C.	104.5-105.5° C.
Specific rotation $[\alpha]^{25}_{589}$	+34.6°	+35°
Organic volatile impurities		
Ethanol	Not detected	Not detected
Ethyl acetate	Not detected	<0.05% w/w
Heptane	<0.05% w/w	<0.05% w/w
HPLC (Assay)	100.4%	99.8%
Diethanolamine	Positive	Positive

Ex. 1001, '393 Patent col.13, ll.50-65

Ex. 1001 ("393 Patent") at 9

Key Scientific Concepts

HLPC and Purity

During the initial analytical method validation for the treprostinil assay, the results indicated that there is about 2% variability in the assay. Our specifications of 97.0-101.0% were centered at 99% purity for the API. When the process for the manufacture of treprostinil was instituted in Silver Spring, it was observed that the purity of the treprostinil improved to close to 100%. From a statistical stand-point, an analytical variability of 2% in the assay may result in an OOS on the high side (considering a two sigma range) when the upper limit of the specification is 101.0%. Scientifically, an API cannot have a purity of greater than 100%. If an API is 100% pure, 2% variability in the assay may result in an OOS at specifications of 97.0-101.0%. During development in Silver Spring, it was observed that there were

Ex. 2006 at 3

3 Overview

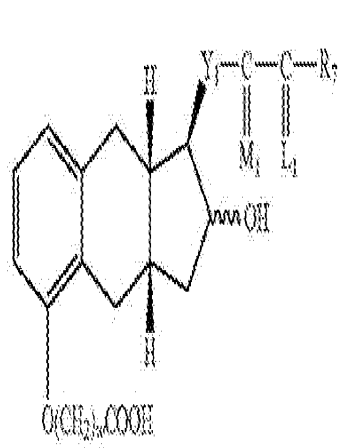
Overview

Independent Claims

Claim 1

What is claimed is:

1. A product comprising a compound of formula I

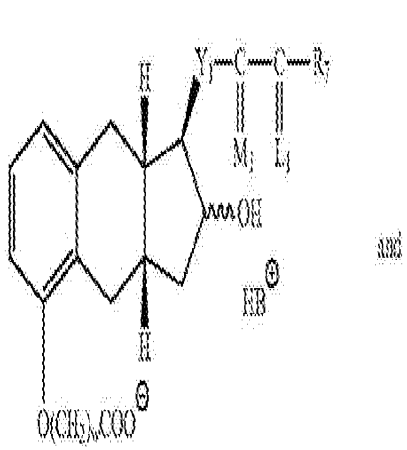


or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,

(b) hydrolyzing the product of formula III of step (a) with a base,

(c) contacting the product of step (b) with a base B to form a salt of formula I_s,



and

(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

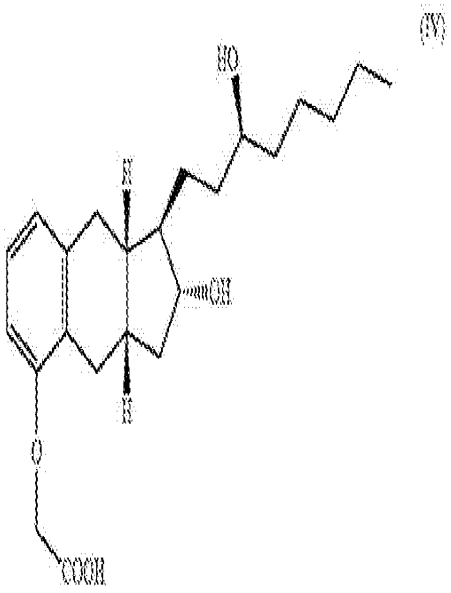
Ex. 1001 ("393 Patent") at 11-12

Overview

Independent Claims

Claim 9

9. A product comprising a compound having formula IV

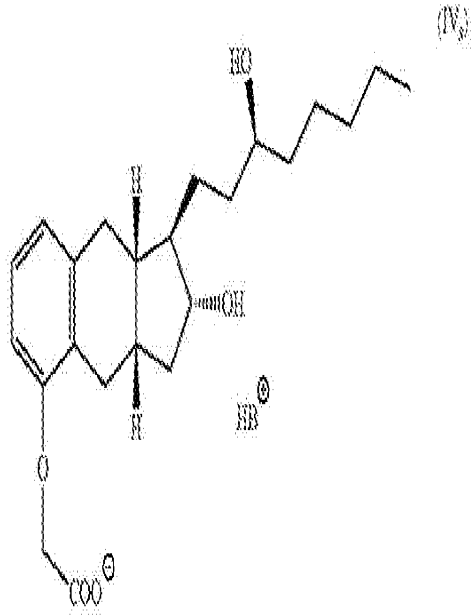


or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,

(b) hydrolyzing the product of formula VI of step (a) with a base,

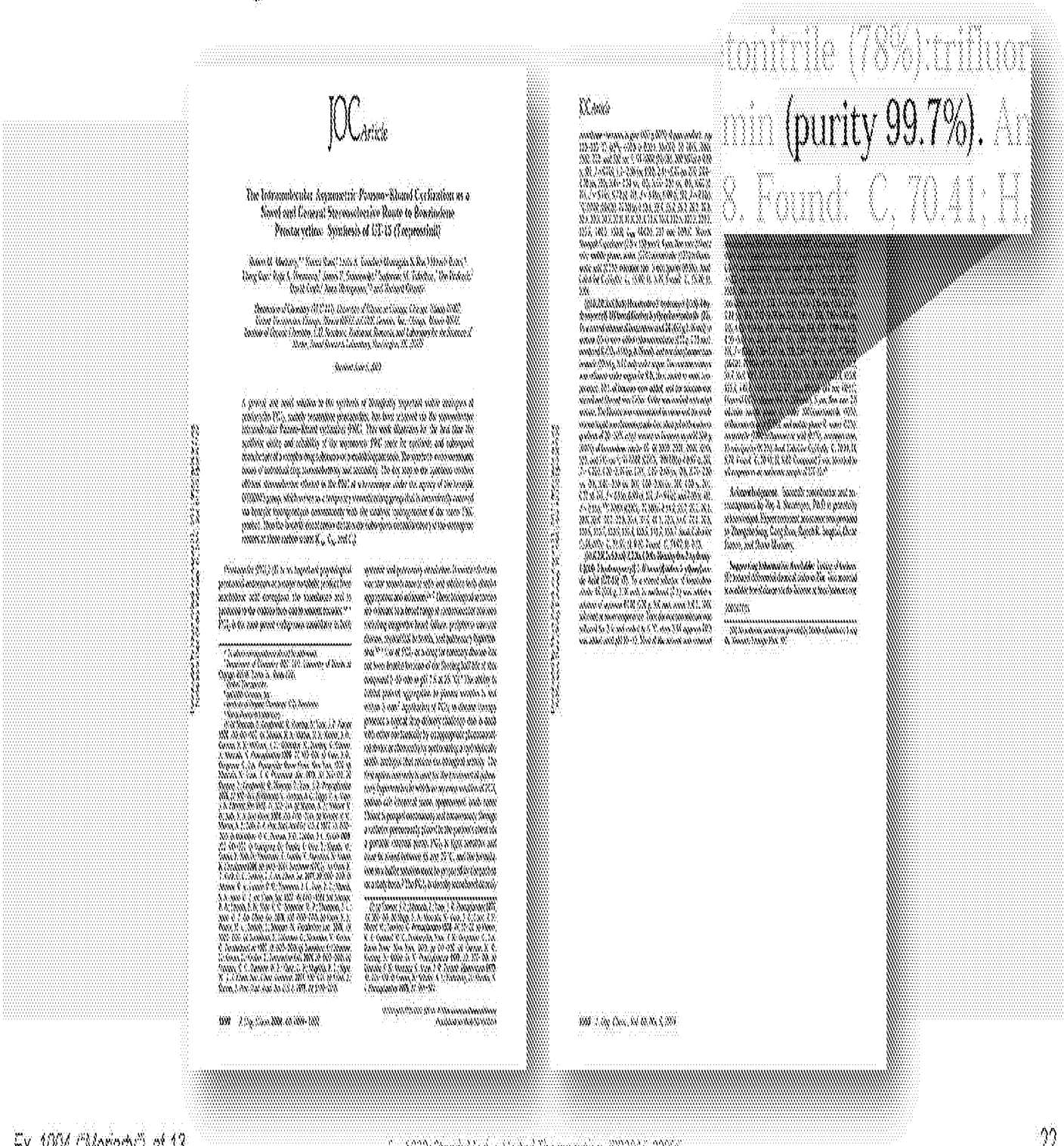
(c) contacting the product of step (b) with a base B to form a salt of formula IV_a, and



(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

Overview

Prior Art: Moriarty



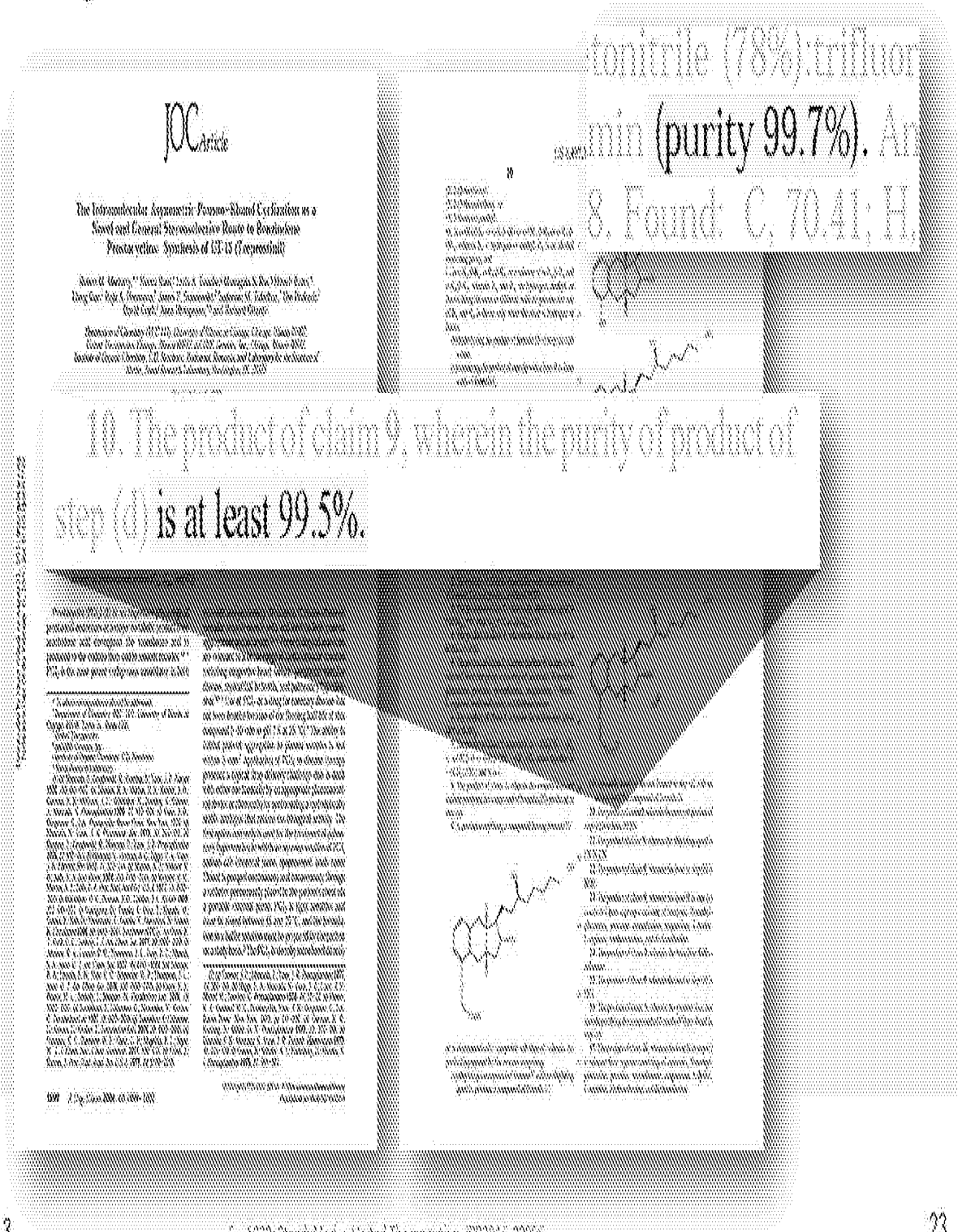
JOC Article

The Intramolecular Asymmetric Pauson–Khand Cyclization as a Novel and General Stereoselective Route to Bicyclooctane Prostacyclins: Synthesis of UT-15 (Treprostinil)

tonitrile (78%):trifluor
min (purity 99.7%). An
8. Found: C, 70.41; H,

Overview

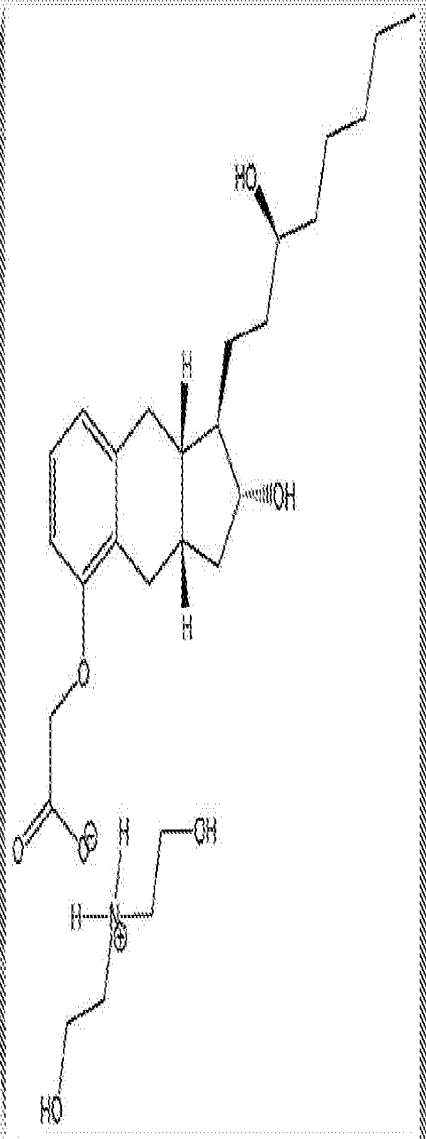
Prior Art: Moriarty



Overview

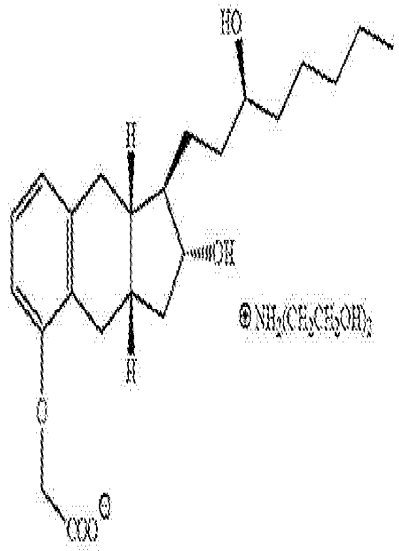
Prior Art: Phares

Ex. 1005



Ex. 1001

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



(d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

Ex. 1005 ("Phares") at 99 (Claim 49); Ex. 1001 at 6 ('393 Patent) col.8 ll. 47-65.

Overview

Phares and Melting Point

The method [of differential scanning calorimetry] can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

$$T_s = T_0 - \frac{T_0^2 R X_i}{F \Delta H_f} \qquad (5.2)$$

where Ts, is the sample temperature, T_0 is the melting point of the pure compound, R is the gas constant, X_i, is the mole fraction of the impurity, F is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus $1/F$ should give a straight line whose slope is proportional to X_i (Brittain *et al.*, 1991).

Stephen R. Byrn et al., Solid-State Chemistry of Drugs, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027, at 84.)

Overview

Prior Art: Phares

Ex. 1005

The thermal data for Form B are shown in Figure 21. The DSC thermogram (Sample ID 1557-17-01) shows a single endotherm at 107 °C that is consistent with a melting event (as determined by hotstage microscopy). The TG shows minimal weight loss up to 100 °C.

At this stage, if melting point of the treprostinil diethanolamine salt is more than 104° C., it was considered polymorph B. There is no need of recrystallization. If it is less than 104° C., it is recrystallized in EtOH-EtOAc to increase the melting point.

Data on Treprostinil Diethanolamine Salt (1:1)

Batch No.	Wt. of Benzindene Triol (g)	Wt. of Treprostinil Diethanolamine Salt (1:1) (g)	Yield (%)	Melting point (°C.)
1	1250	1640	88.00	104.3-106.3
2	1250	1528	82.00*	105.5-107.2

Ex. 1001

Ex. 1005 ("Phares") at 91; Ex. 1001 at 8 ('393 Patent) col 12, ll. 43-58.

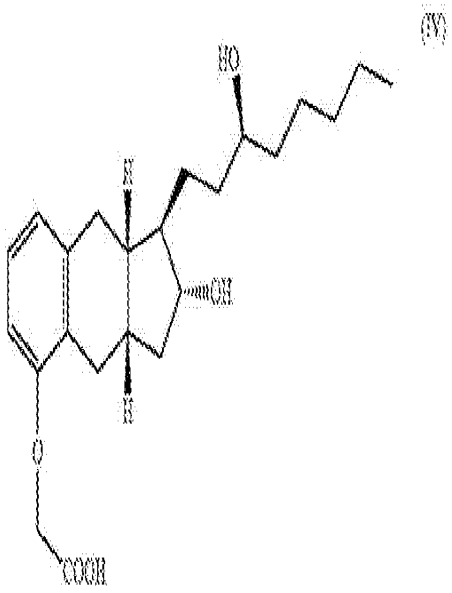
4 Anticipation

Anticipation

Independent Claims

Claim 9

9. A product comprising a compound having formula IV

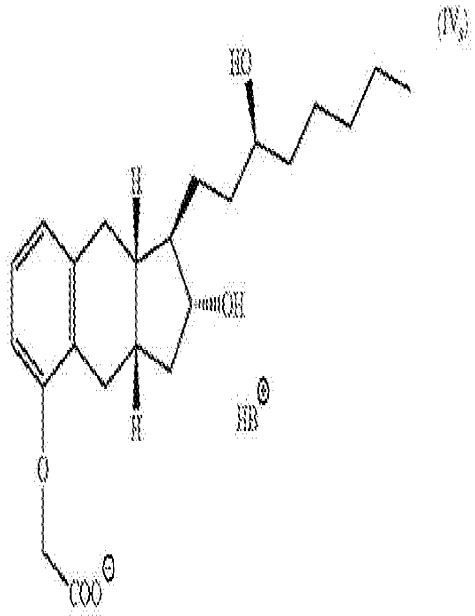


or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,

(b) hydrolyzing the product of formula VI of step (a) with a base,

(c) contacting the product of step (b) with a base B to form a salt of formula IV_a, and

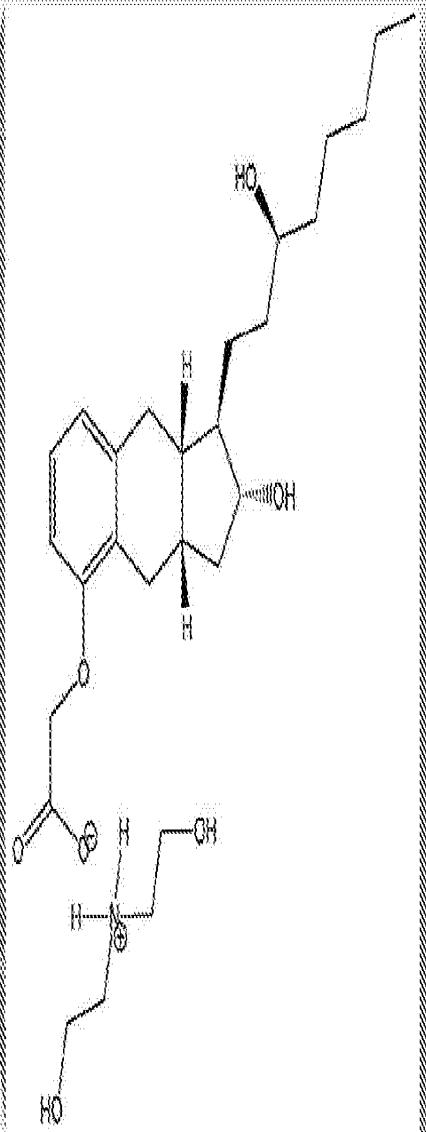


(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

Anticipation

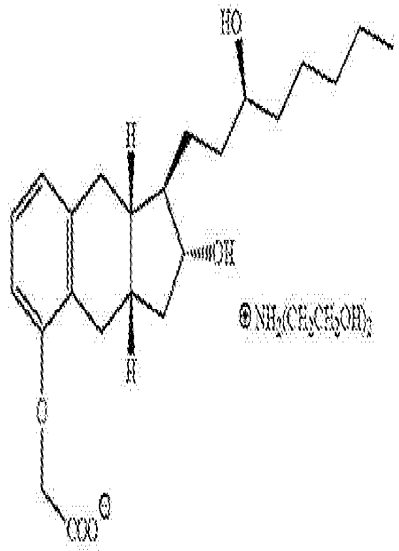
Prior Art: Phares

Ex. 1005



Ex. 1001

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



(d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

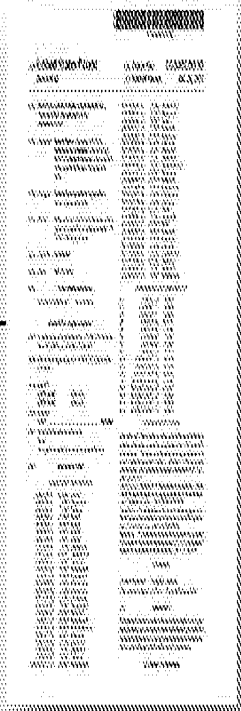
In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

Ex. 1005 ("Phares") at 99 (Claim 49); Ex. 1001 at 6 ('393 Patent) col.8 ll. 47-65.

Anticipation

'393 Patent/Phares Melting Points

Ex. 1001: '393 Patent



Example 3

Batch 1: 104.3-106.3 °C

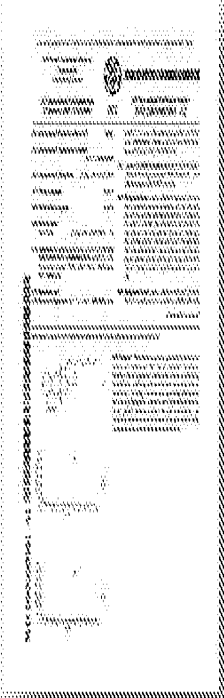
Batch 3: 104.7-106.6 °C

Example 4

Batch 1: 105.0-106.5 °C

Batch 2: 104.5-105.5 °C

Ex. 1005: Phares



"The DSC thermogram (Sample ID 1557-17-01) shows a single endotherm at 107 °C that is consistent with a melting event (as determined by hotstage microscopy)."

Ex. 1005 at 91

Figure 21: "107.06 °C"

Ex. 1005 at 121

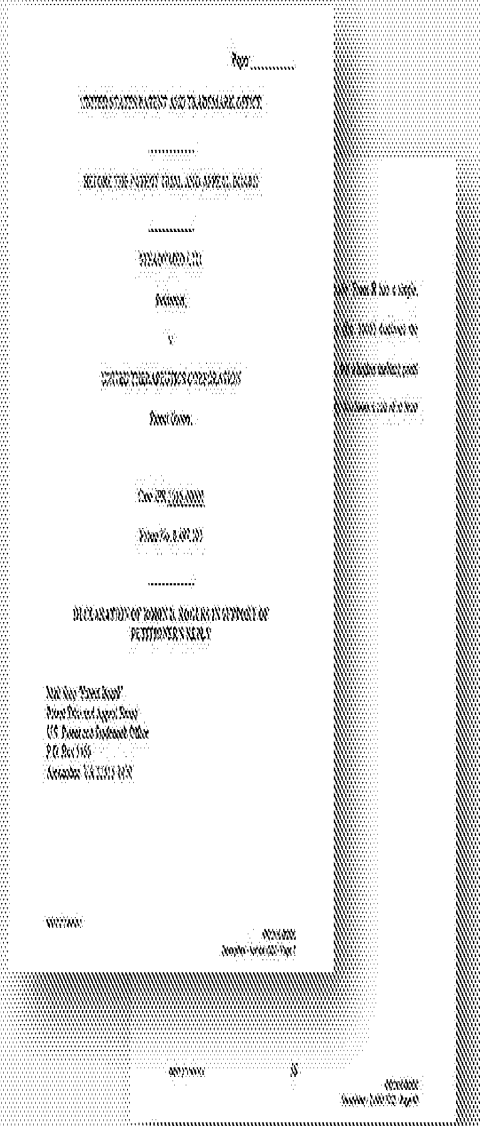
Ex. 1001 at 8-9 ('393 Patent) col 12-13; Ex. 1005 ("Phares") at 91, 121

Anticipation

Prior Art: Phares

IX. CONCLUSION

88. In summary, no matter how Form B is made, Form B has a single, defined melting point, and since the Phares Reference (Ex. 1005) discloses the same Form B crystal form as the '393 Patent (Ex. 1001), but a higher melting point than most of the '393 Patent examples, Phares necessarily discloses a salt of at least equal purity to the salt in the '393 Patent, if not higher.



Anticipation

Prior Art: Phares

Dr. Williams declared identical polymorphs might have different melting points, depending on how they were made.

THE WITNESS: Yeah. So I'm not a polymorph expert.

Ex. 2059 (Williams Dep.) 158:17-18

Q. Do you consider yourself an expert on crystal forms of organic molecules?

A. No.

Ex. 2059 (Williams Dep.) 156:25-157:2

Ex. 2059 ("Williams Deposition Transcript") at 156-58

Anticipation

Prior Art: Phares

Dr. Williams relied on "Adhiyaman reference" (Ex. 2030), which he initially believed showed different melting points for same crystal form.

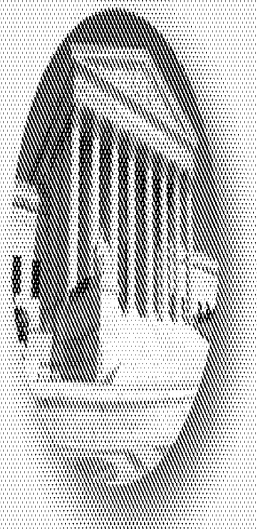
Q. Okay. So each of these is really a different crystal form of the same drug; is that fair?

A. I think that's fair."

Ex. 2059 (Williams Dep.) 180:17-20

Anticipation

Process can be Different

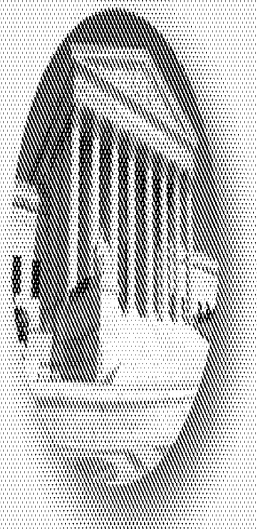


"If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985)

Anticipation

Starting Material Irrelevant

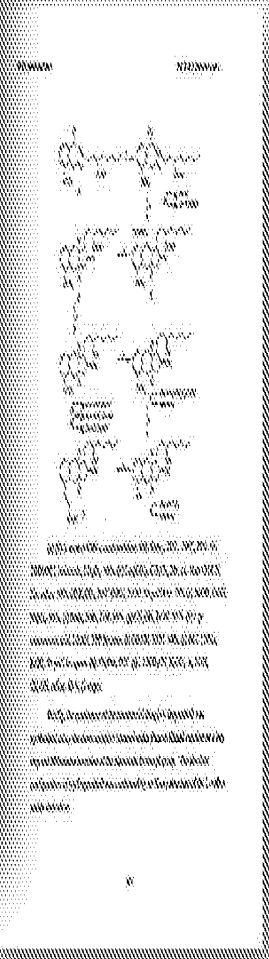


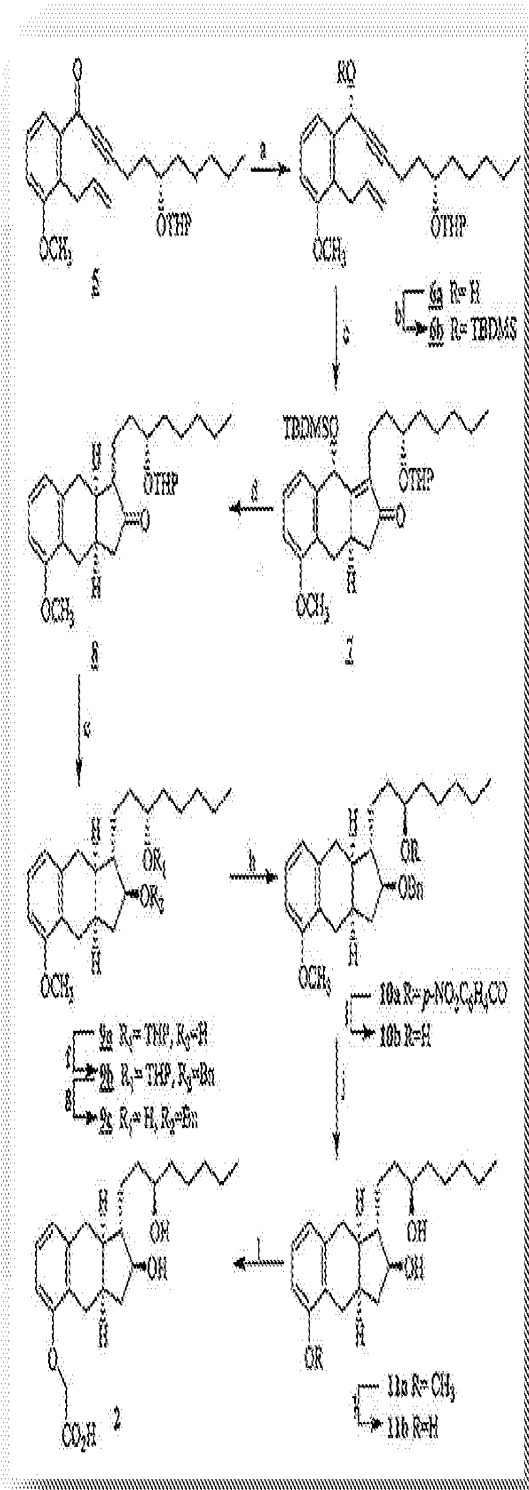
"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step.... One need not know that the 14-hydroxy was derived from 8α as opposed to 8β to answer that question."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

Anticipation

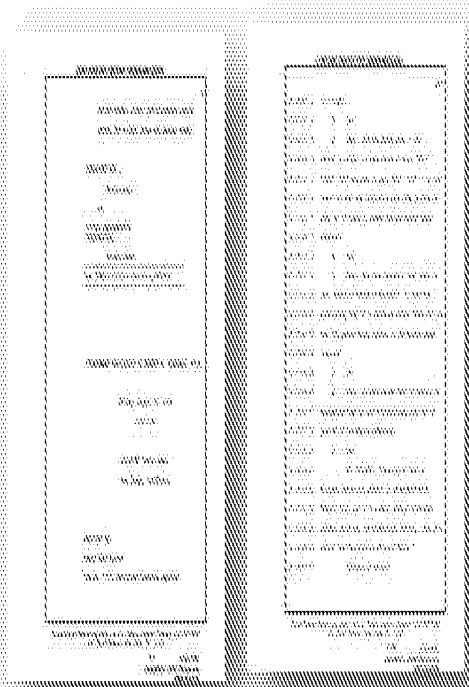
Prior Art: Phares





Anticipation

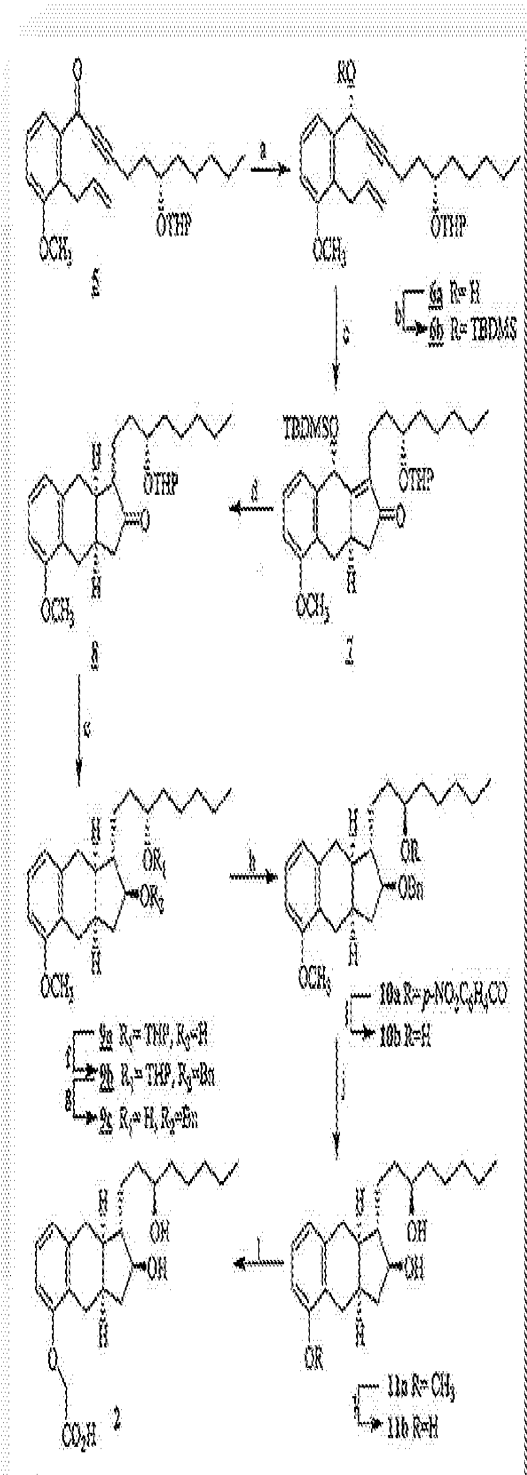
Prior Art: Phares



Q. Okay. So what we see here is there's an alkylating step (a) and hydrolyzing step (b) on page 42 of the Phares reference.

A. Yes.

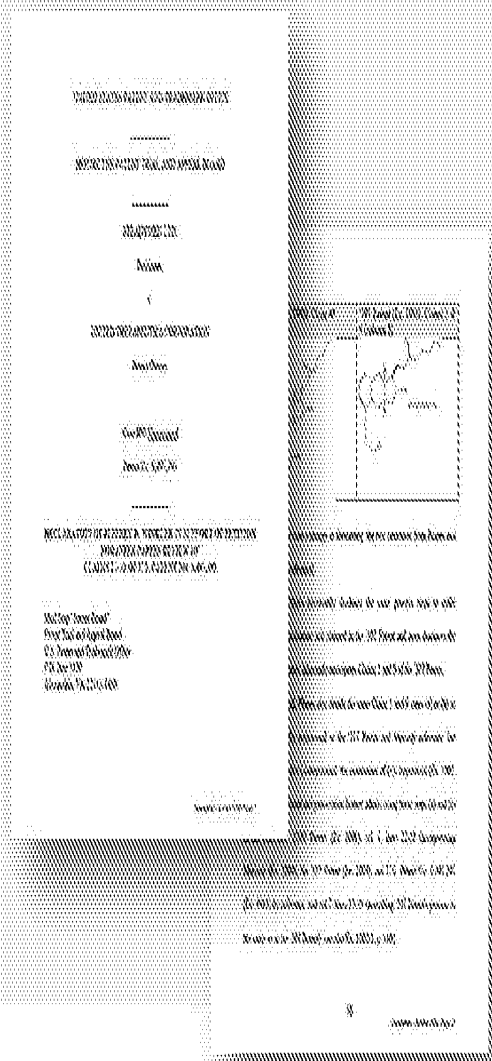
Ex. 2059 (Williams Dep.) 190: 16-19



Ex. 1005 ("Phares") at 42; Ex. 2059 (Williams Deposition Transcript) at 190.

Anticipation

Prior Art: Phares



55. Second, Phares also details the same Claim 1 and 9 steps (a) or (b) as were used to make treprostinil in the '117 Patent and Moriarty reference, but applies them to make (-)-treprostinil, the enantiomer of (+)- treprostinil (Ex. 1005, p. 42). The '393 Patent and prosecution history admits using these steps (a) and (b) in the prior art. ('393 Patent, (Ex. 1001), col. 1, lines 22-28 (incorporating Moriarty (Ex. 1004), the '117 Patent (Ex. 1003), and U.S. Patent No. 6,441,245 (Ex. 1013) by reference, and col.7, lines 17-20 (describing '245 Patent's process as the same as in the '393 Patent); *see also* Ex. 1002-1, p. 109).

Ex. 1009 (Winkler Decl.) ¶ 55 at 21

Anticipation

Starting Material Irrelevant

"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step.... One need not know that the 14-hydroxy was derived from 8α as opposed to 8β to answer that question."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

Anticipation

Impurity Profile Irrelevant

"[T]he fact that the 14–hydroxy is derived from 8α imparts no structural or functional differences in the low-ABUK [impurity] hydrocodone API as compared to the prior art products. Thus, the court did not err in disregarding the process limitation in its obviousness determination."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016)

Anticipation

Impurity Profiles Not Different

Ex. 1004: Moriarty

TEST/REFERENCE	SPECIFICATIONS	RESULTS
Chromatographic Purity (HPLC) NB 1, LDR 68 - 72		
1AU90	Not more than 0.5%	ND
2AU90	Not more than 0.5%	ND
97W86 (Benzindene Triol)	Not more than 0.2%	ND
3AU90	Not more than 1.0%	0.2%
Treprostinil Methyl Ester	Not more than 0.2%	<0.05%
Treprostinil Ethyl Ester	Not more than 0.6%	0.2%
750W93	Not more than 1.5%	0.07%
751W93	Not more than 1.3%	<0.05%
Unidentified	Not more than 0.1% AUC each	ND

Ex. 2036 at 5

(Prior Art 12/23/2003)

Ex. 1001: '393 Patent

Treprostinil as the free acid prepared according to claims 1 or 10

	Compound	Specifications	
Impurities (HPLC)	1AU90	Not more than 0.40%	ND
	2AU90	Not more than 0.10%	ND
	3AU90	Not more than 1.00%	ND
	750W93	Not more than 0.50%	0.06 % w/w
	751W93	Not more than 0.30%	< 0.05 % w/w
	97W86 (Benzindene Triol)	Not more than 0.20%	ND
	Treprostinil Ethyl Ester	Not more than 0.50%	0.13 % w/w
	Treprostinil Methyl Ester	Not more than 0.20%	ND
Impurities (HPLC) [Unidentified Impurities]	Not more than 0.10% AUC each		ND
Impurities (HPLC) [Total Related Substances]	Not more than 3.00%		0.2 %

Ex. 1002 at 249

(Walsh Declaration)

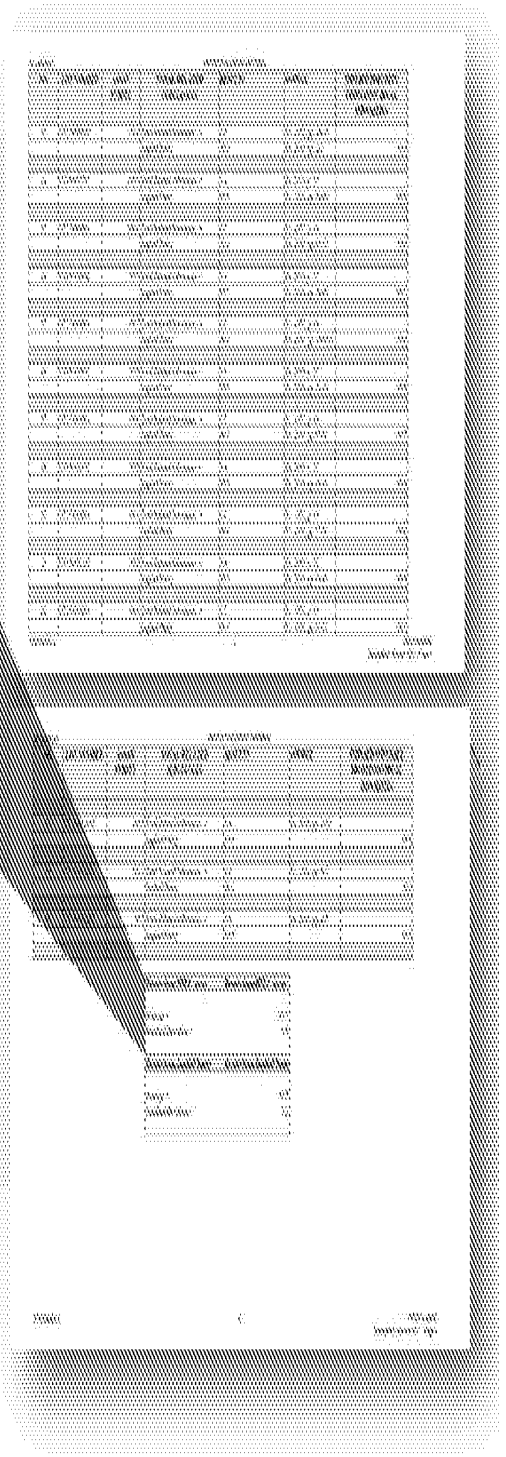
Ex. 2036 ("Phares") at 5; Ex. 1002 at 249 ("393 Patent Prosecution")

Ex. 1038 Sandhu v. United Therapeutics, PR2016-00000

Anticipation

Impurity Profiles Meaningless

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5



99.7±0.5%

Ex. 1021 at 5 (Moriarty, average of 46 samples)

Anticipation

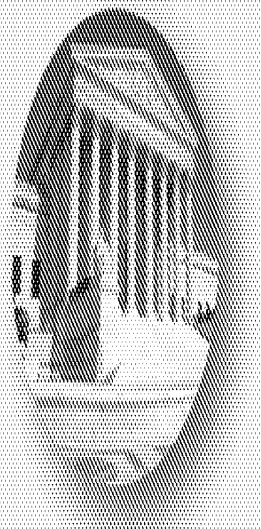
Key Scientific Concepts: HPLC and Purity

During the initial analytical method validation for the treprostinil assay, the results indicated that there is about 2% variability in the assay. Our specifications of 97.0-101.0% were centered at 99% purity for the API. When the process for the manufacture of treprostinil was instituted in Silver Spring, it was observed that the purity of the treprostinil improved to close to 100%. From a statistical stand-point, an analytical variability of 2% in the assay may result in an OOS on the high side (considering a two sigma range) when the upper limit of the specification is 101.0%. Scientifically, an API cannot have a purity of greater than 100%. If an API is 100% pure, 2% variability in the assay may result in an OOS at specifications of 97.0-101.0%. During development in Silver Spring, it was observed that there were

Ex. 2006 at 3

Anticipation

No Functional Differences



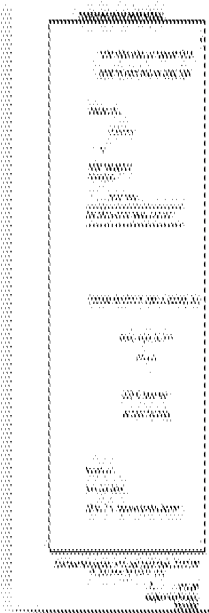
"[I]f the process by which a product is made imparts '**structural** and **functional differences**' distinguishing the claimed product from the prior art, then those differences 'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'"

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016) (cites and internal quotations omitted) (emphasis added)

Anticipation

No Functional Differences

ROBERT M. WILLIAMS, PH.D



Q. Do any of the -- as far as you know, any of these particular impurities have deleterious biological consequences?

THE WITNESS: I'm not a clinician, so I don't know.

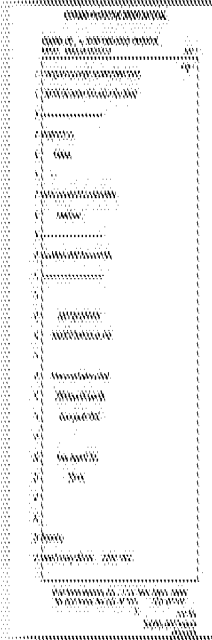
BY MR. POLLACK:

Q. You don't know?

A. I don't know.

Ex. 2059 (Williams Dep.) 47:4-13

ROBERT R. RUFFOLO, PH.D



Q. Do you know if any of these listed chromatographic impurities have any adverse effects in humans?

BY MR. POLLACK:

Q. And if so, what are they?

THE WITNESS: I don't know. What I can tell you is that if you review the FDA label, there are a host of adverse effects produced or observed in patients who are taking treprostinil.

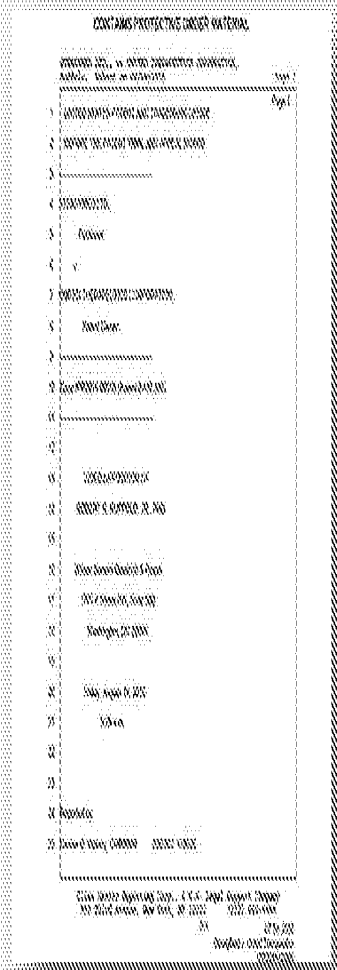
Ex. 2058 (Ruffolo Dep.) 257:22-258:3

Ex. 2059 (Williams Dep. at 47; Ex. 2058 (Ruffolo Dep.) at 66

Ex. 1035, Sandoz v. United Therapeutics, IPR2019-00976

Anticipation

No Functional Differences



ROBERT R. RUFFOLO, PH.D

Q. Okay. And I make another batch of treprostinil API and I measure its HPLC analysis and it's 98.5 percent. Could that batch move on in the process?

THE WITNESS: Yes, with that current level spec, that could move on.

Ex. 2058 (Ruffolo Dep.) 160: 17-24

Q. Is there a difference between the approved Moriarty treprostinil product that was shown clinically that's different from the '393 product?

THE WITNESS: Not – not to my knowledge.

Ex. 2058 (Ruffolo Dep.) 315:5-23

Ex. 2058 (Ruffolo Dep.) at 41, 80

Ex. 1023; Sandoz Inc. v. United Therapeutics; IPR2016-00818

Conclusions

1. No structural differences
2. No functional differences
3. No separate argument for dependent claims
4. Claims 1-5, 7-9, 11-14, 16-20 anticipated

5 Obviousness

Phares and Moriarty

Kawakami and Moriarty

Dependent claims 6, 10, 15, 21, and 22

5 Obviousness

- Phares and Moriarty
- Kawakami and Moriarty
- Dependent claims 6, 10, 15, 21, and 22

Obviousness: Phares & Moriarty

Motivation to Combine

CONTAINS PROTECTIVE ORDER MATERIAL

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2020-00769 (Patent 9,630,903)

DEPOSITION DESIGNATION OF ROBERT A. WILLIAMS, M.D.

Friday, August 21, 2020

9:03 a.m.

12670 El Camino Road

San Diego, California

Reported by:

Cheryl Ann Palmer

CSR No. 7769, Certified Shorthand Reporter

Ex. 2059 (Williams Dep.) at 240:2-7

Q Okay. So a person of ordinary skill in the art in 2005 reading the Phares reference, that person would know the best way to make treprostinil is the Moriarty method, Exhibit 12; right? Is that fair?

A I think that's fair.

Q But, you know, on average, a typical person of ordinary skill in the art, typical graduate student, they would have found the Moriarty paper and used that technique to make treprostinil in 2005?

MS. MASTER: Objection.

THE WITNESS: It was in the literature. It wasn't buried in some obscure journal. So, sure, it was available.

BY MR. POLLACK:

Q That was a "yes" to my question, I think?

A Yes.

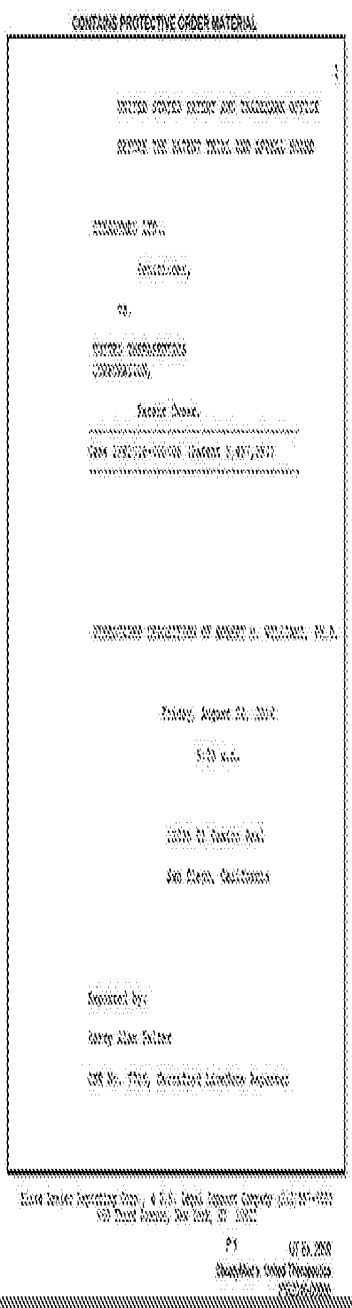
Ex. 2059 (Williams Dep.) 244:10-21

Ex. 2059 (Williams Dep.) at 240, 244

Ex. 1029, Sandoz, Inc. v. United Therapeutics, IPR2019-00939

Obviousness: Phares & Moriarty

Reasonable Expectation of Success



CONTAINS PROTECTIVE ORDER MATERIAL

Q Sure. I understand. I'm not disagreeing with you on that. I'm just saying, you told the Patent Office that these two differed. And one of the ways they differed was one was 99.0 and the other was 99.7. Now we see that both are 99.7. How does that jive with acceptable scientific conduct?

A Well, the -- again, the '393 batches were produced without chromatography. So you could repurify and purify anything you want --

Q Of course.

A -- by chromatography to 99.99999 percent if you wanted to --

Ex. 2059 (Williams Dep.) 94:1-12.

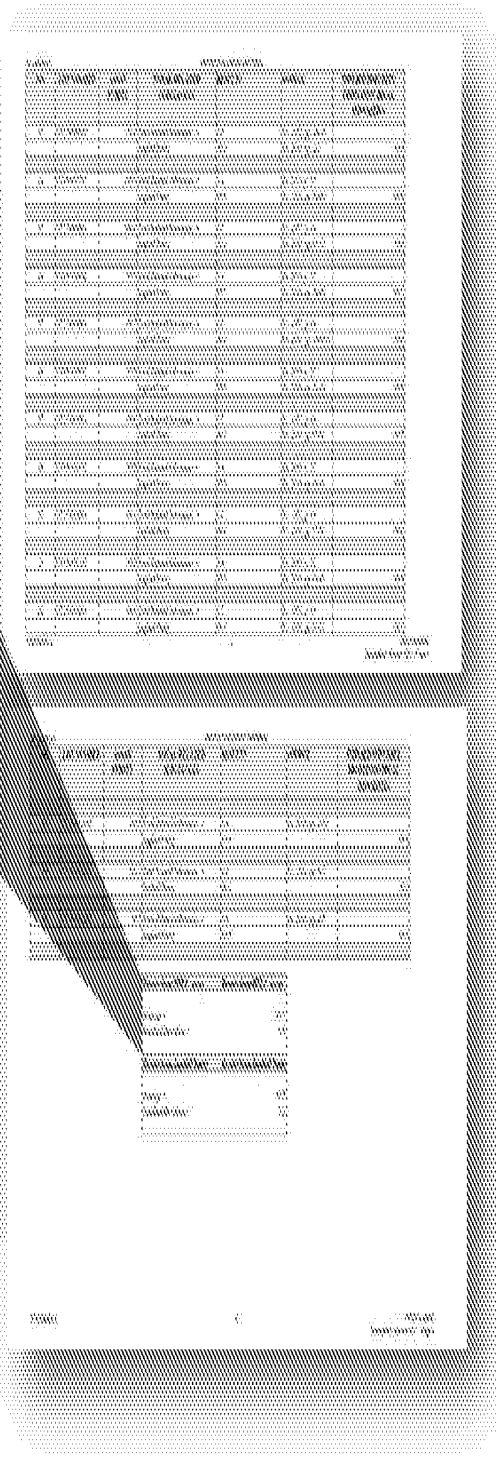
Ex. 2059 (Williams Dep.) at 94

51

Obviousness: Phares & Moriarty

Reasonable Expectation of Success

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5



99.7 ± 0.5 %

Ex. 1021 at 5 (Moriarty, average of 46 samples)

Obviousness: Phares & Moriarty

Reasonable Expectation of Success


tonitrile (78%):trifluor
min (purity 99.7%). An
8. Found: C, 70.41; H,
JOC Article
The Intramolecular Asymmetric Pauson–Khand Cyclization as a Novel and General Stereoselective Route to Bendazlene Prostacyclins: Synthesis of UT-15 (Treprostinil)

5 Obviousness

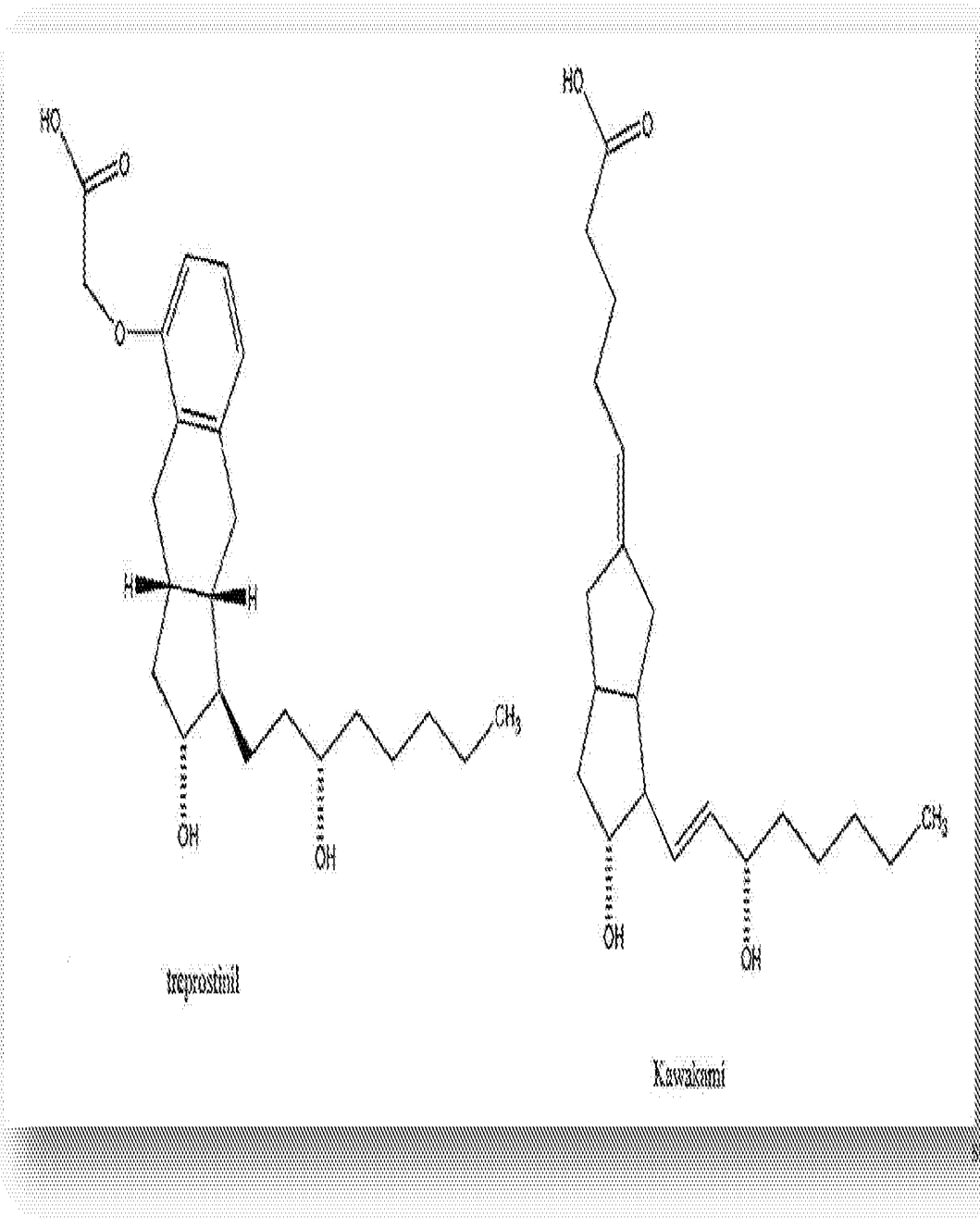
Phares and Moriarty

Kawakami and Moriarty

Dependent claims 6, 10, 15, 21, and 22

Obviousness: Kawakami & Moriarty

Motivation to Combine

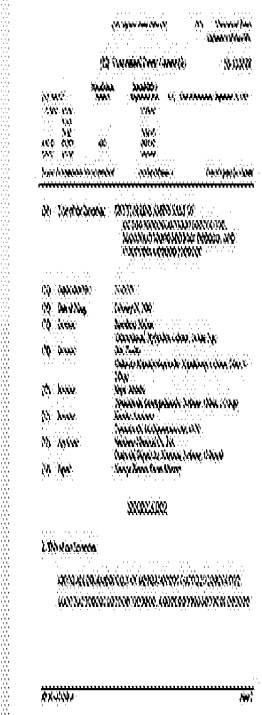


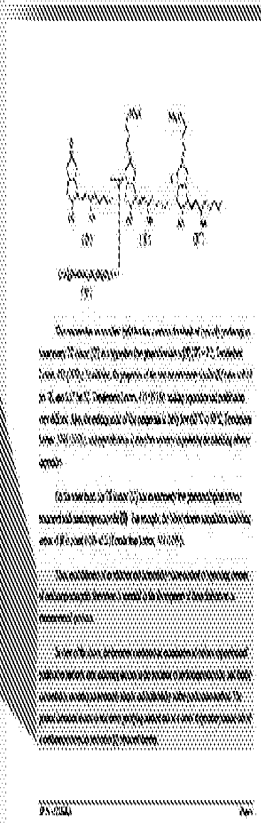
Obviousness: Kawakami & Moriarty

Motivation to Combine

Thus, establishment of an efficient and industrially viable method of separating isomers of methanoprostacyclin derivatives is essential in the development of these derivatives as pharmaceutical products.

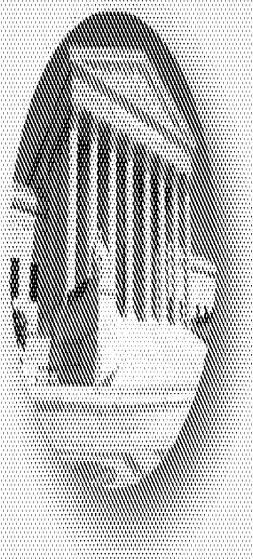
In view of the above, the inventors conducted an examination of various separation and purification methods after achieving success in the synthesis of methanoprostacyclin, and finally succeeded in inventing an extremely simple and industrially viable purification method. The present invention relates to this novel purifying method and to a novel dicyclohexylamine salt of a methanoprostacyclin derivative [I] obtained thereby.





Obviousness: Kawakami & Moriarty

Motivation to Combine

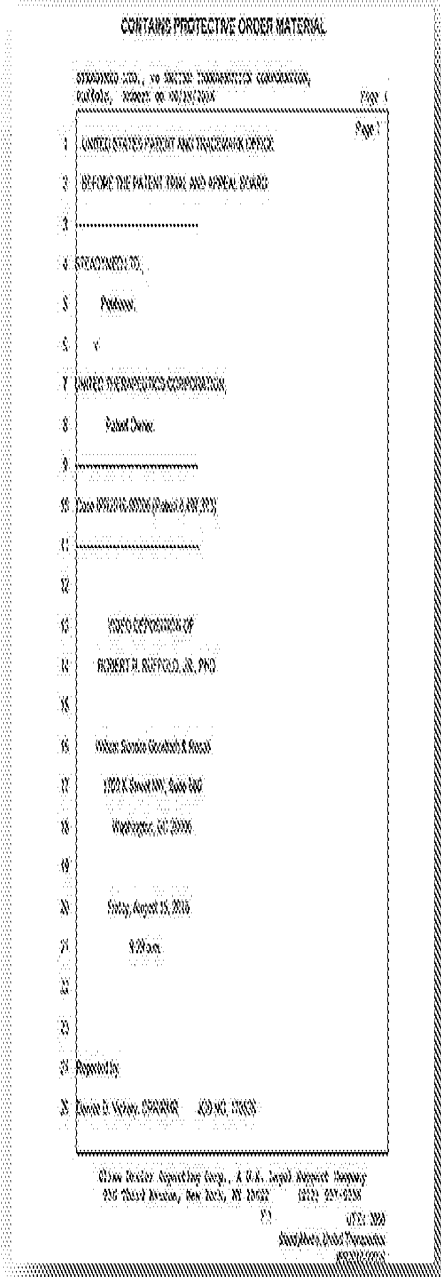


"[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007).

Obviousness: Kawakami & Moriarty

Reasonable Expectation of Success


CONTAINS PROTECTIVE ORDER MATERIAL

Page 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Petitioner,

v.

Patent Owner.

VIDEO DEPOSITION OF

ROBERT H. RUFFOLO, JR., PhD

Friday, August 10, 2018

9:00 a.m.

Reported by:

Q. How long has crystallization been around as a method of purification?

THE WITNESS: I don't know how long it's been around.

Q. Before 2007?

A. Oh, yes.

THE WITNESS: Yes.

Q. Did you learn about it when you were in college at the university?

THE WITNESS: Yes, I did.

Q. What course did you -- in what course did you learn about that?

THE WITNESS: The inorganic chemistry, organic chemistry, physical chemistry, medicinal chemistry, pharmaceutical chemistry, analytical chemistry. Maybe some others.

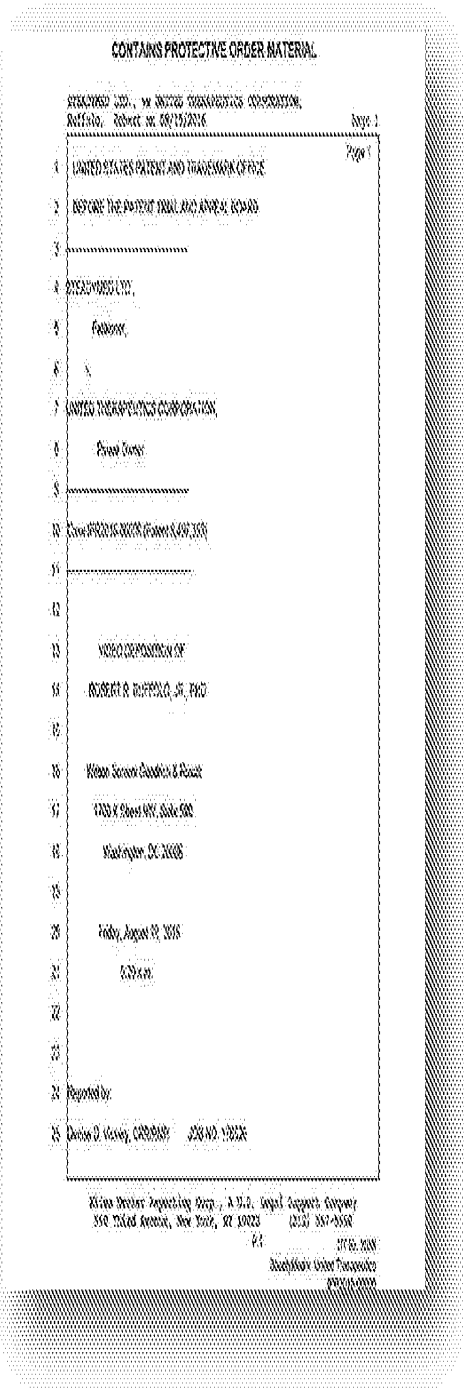
Q. And when did you go to college?

A. In 1968 I started. In 1968.

Ex. 2058 (Ruffolo Dep.) 175:19-176:22

Obviousness: Kawakami & Moriarty

Reasonable Expectation of Success


CONTAINS PROTECTIVE ORDER MATERIAL

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Petitioner,

v.

Patent Owner

Friday, August 19, 2016

Reported by:

Q. Okay. Was -- was there any kind of list of what impurities were in the treprostinil made in the '393 patent?

BY MR. POLLACK:

Q. In the patent itself?

A. Without reading the whole thing, I see primarily purities of the parent compound, which is what I believe the invention is related to. And -- and so I see comparisons between the old process and new process with purities, but -- but I don't see, unless I've missed it, I don't see the impurities.

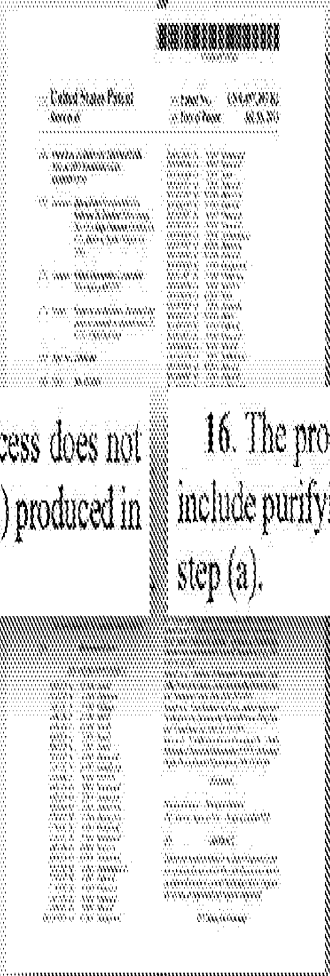
Ex. 2058 (Ruffolo Dep.) 234:25-235:12

Obviousness: Kawakami & Moriarty

Dependent Claims 8 & 16

Claim 8

8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).

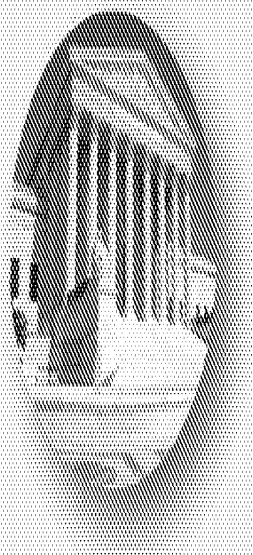


Claim 16

16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).

Obviousness: Kawakami & Moriarty

Dependent Claims 8 & 16



We have clearly stated that "[i]n determining validity of a product-by-process claim, the focus is on the product and not the process of making it." ... "That is because of the ... longstanding rule that an old product is not patentable even if it is made by a new process."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1354 (Fed. Cir. 2016) (cites and internal quotations omitted)

5 Obviousness

Phares and Moriarty

Kawakami and Moriarty

Dependent Claims 6, 10, 15, 21, and 22

Conclusions

1. Motivation to combine conceded by Dr. Williams
2. Reasonable expectation of success since prior-art purity already higher than patent
3. No structural differences
4. No functional differences
5. Processes well-known in the art
6. No separate argument for most dependent claims
7. Claims 8 and 16 do not generate a different product
8. Claims 1-5, 7-9, 11-14, 16-20 obvious

5 Obviousness

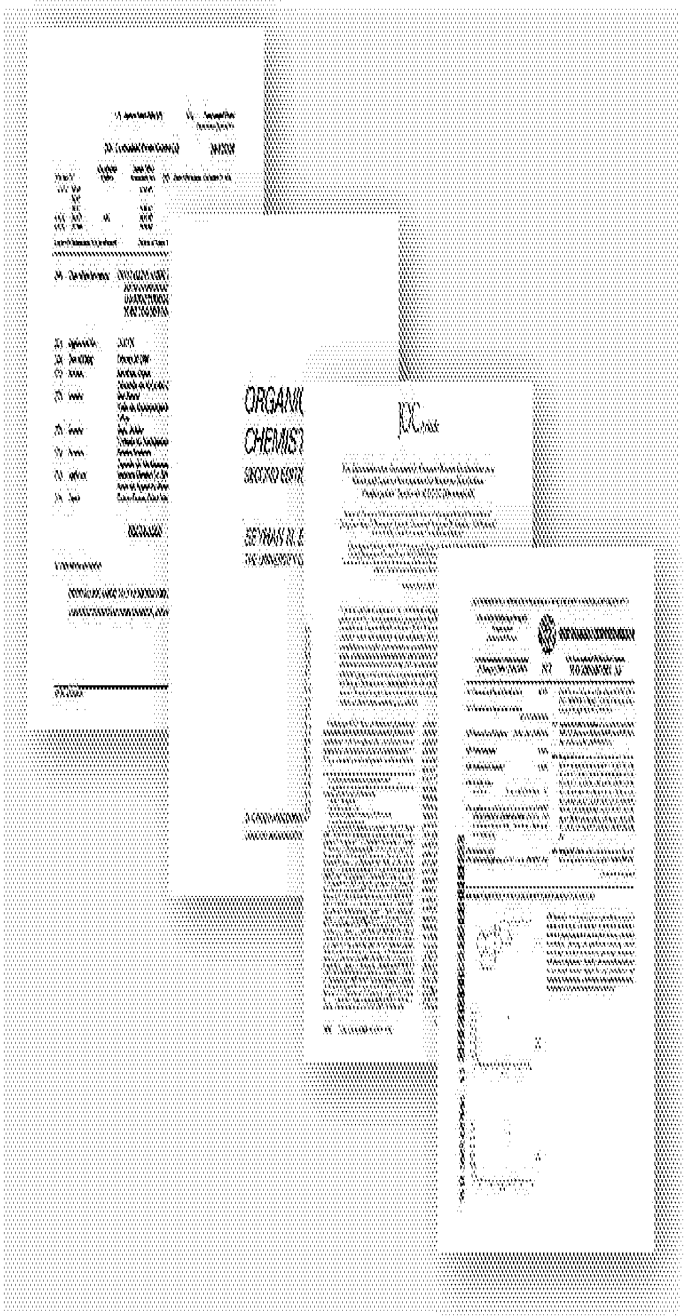
Phares and Moriarty

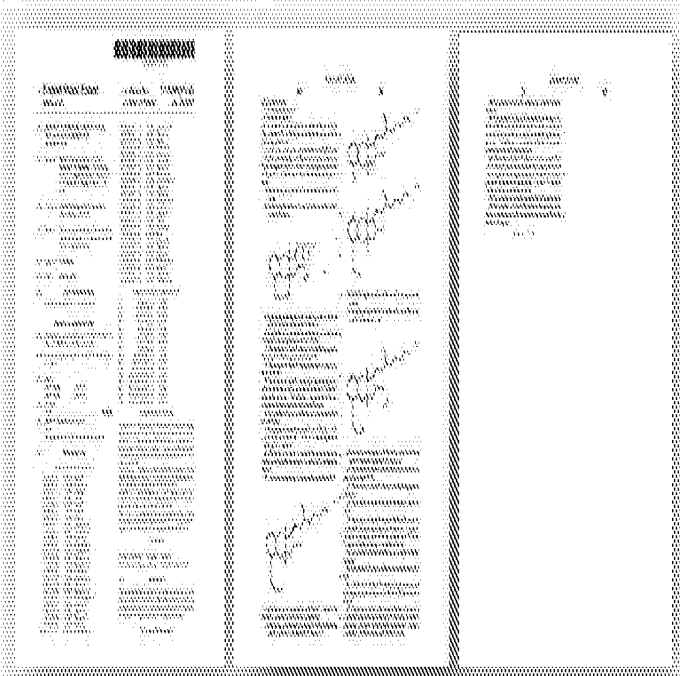
Kawakami and Moriarty

Dependent Claims 6, 10, 15, 21, and 22

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Kawakami with Moriarty, Phares and Ege





6. The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

15. The product of claim 9, wherein the acid in step (d) is HCl.

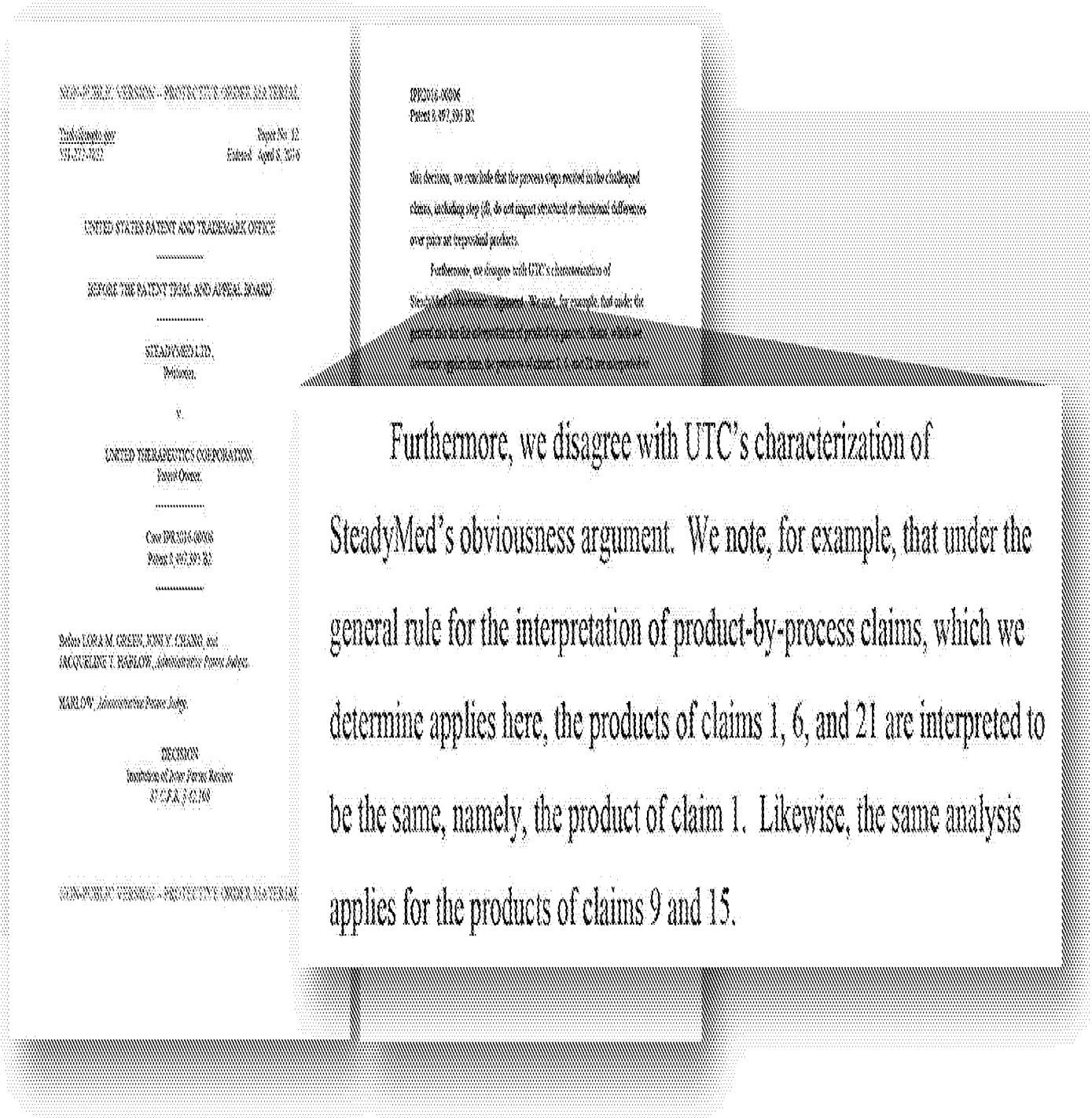
21. The product of claim 1, wherein step (d) is performed.

22. The product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

Ex. 1007 (Kawakami); Ex. 1004; Ex. 1008 (Ege); Ex. 1005 (Phares); Ex. 1001

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Kawakami with Moriarty, Phares and Ege

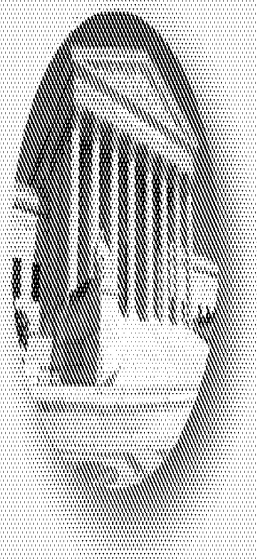


Furthermore, we disagree with UTC's characterization of SteadyMed's obviousness argument. We note, for example, that under the general rule for the interpretation of product-by-process claims, which we determine applies here, the products of claims 1, 6, and 21 are interpreted to be the same, namely, the product of claim 1. Likewise, the same analysis applies for the products of claims 9 and 15.

Institution Decision, Paper No. 12 at 47

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Process Step Irrelevant



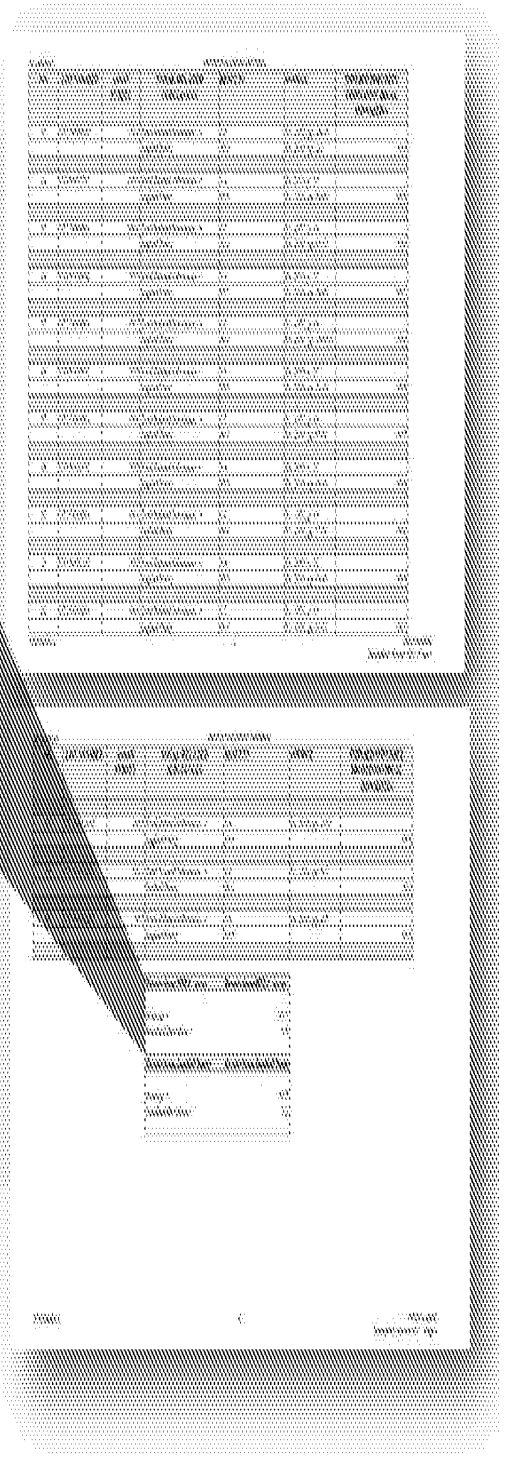
"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step...."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Made Same Product

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5



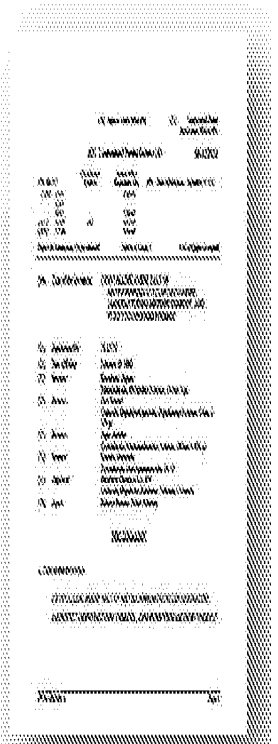
99.7 ± 0.5 %

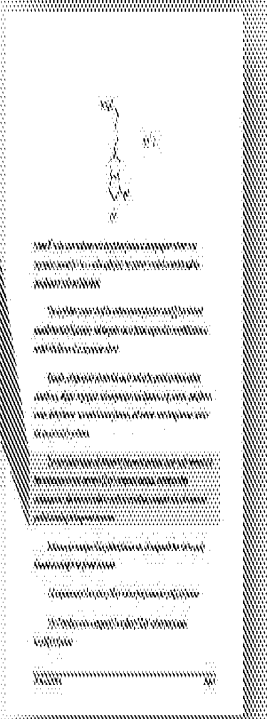
Ex. 1021 at 5 (Moriarty, average of 36 samples)

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Used Same Process

The dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention.

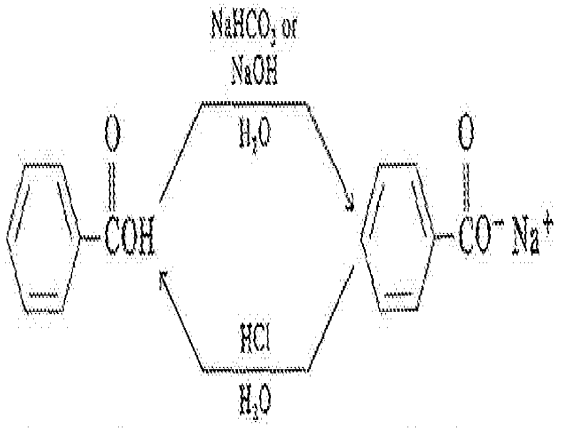




Obviousness: Dependent Claims 6, 10, 15, 21 & 22

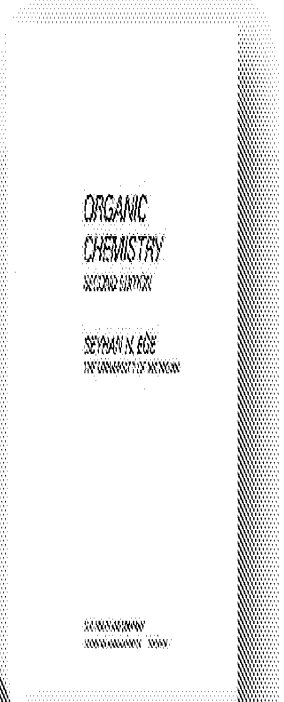
Prior Art Used Same Process

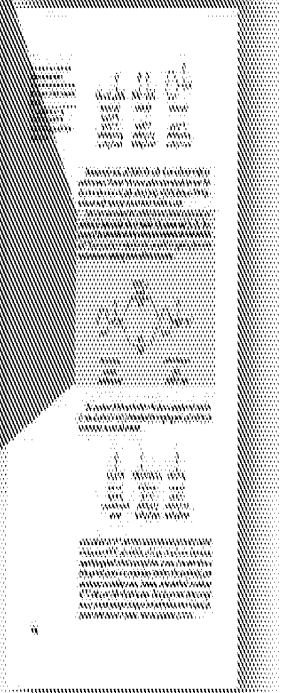
Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base (p. 95). Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.



benzoic acid
covalent,
insoluble in water

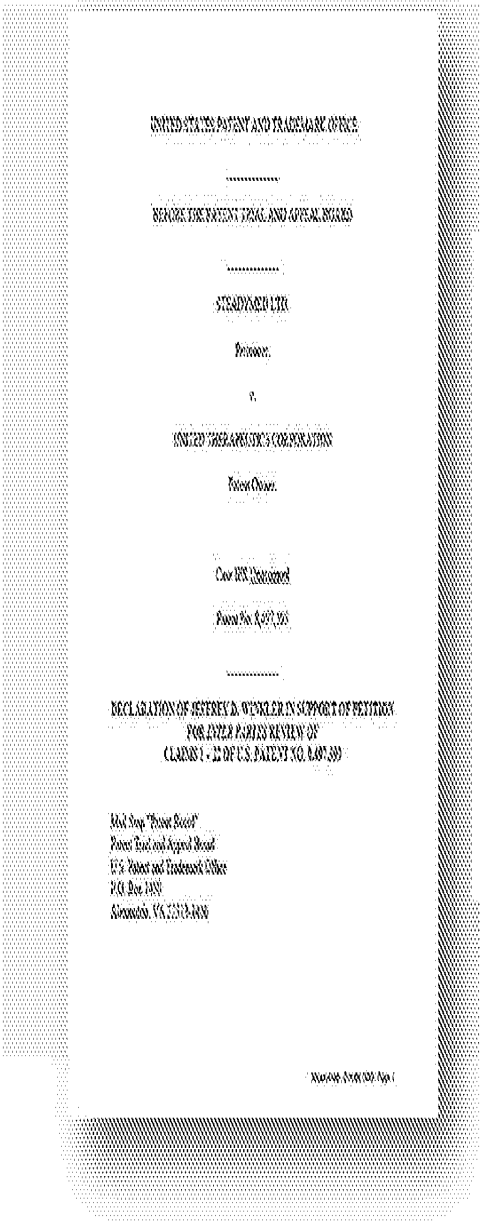
sodium benzoate
ionic,
soluble in water





Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Used Same Process



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR Unassigned

Patent No. 8,497,393

DECLARATION OF STEPHEN D. WINKLER IN SUPPORT OF PETITION FOR INTER PARTES REVIEW OF CLAIMS 1 - 22 OF U.S. PATENT NO. 8,497,393

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Winkler Decl. Exhibit No. 1009 Page 1

40. A person of ordinary skill in the art would recognize that the formation of a carboxylate salt, by the addition of a weak base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in steps (c) and (d), is standard chemistry purification – *i.e.*, organic chemistry 101.

Ex. 1009 (Winkler Decl. at 12) ¶ 40

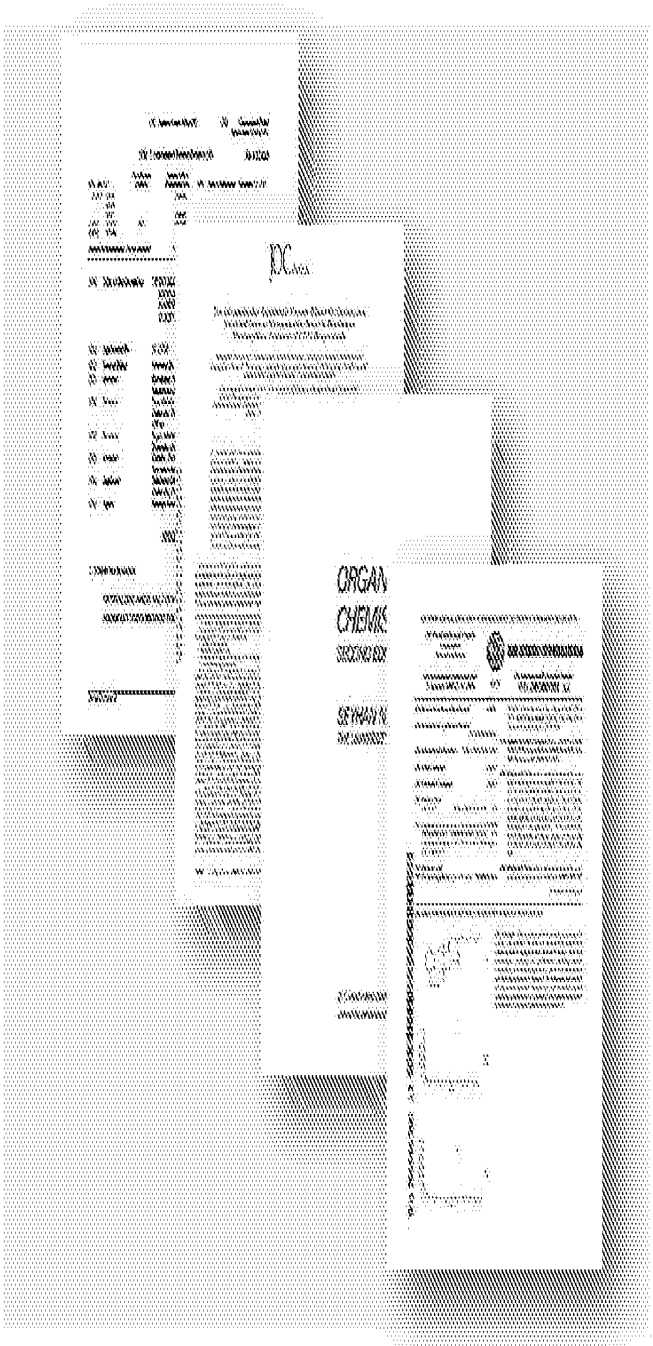
Ex. 1009 ("Winkler Declaration") at 15

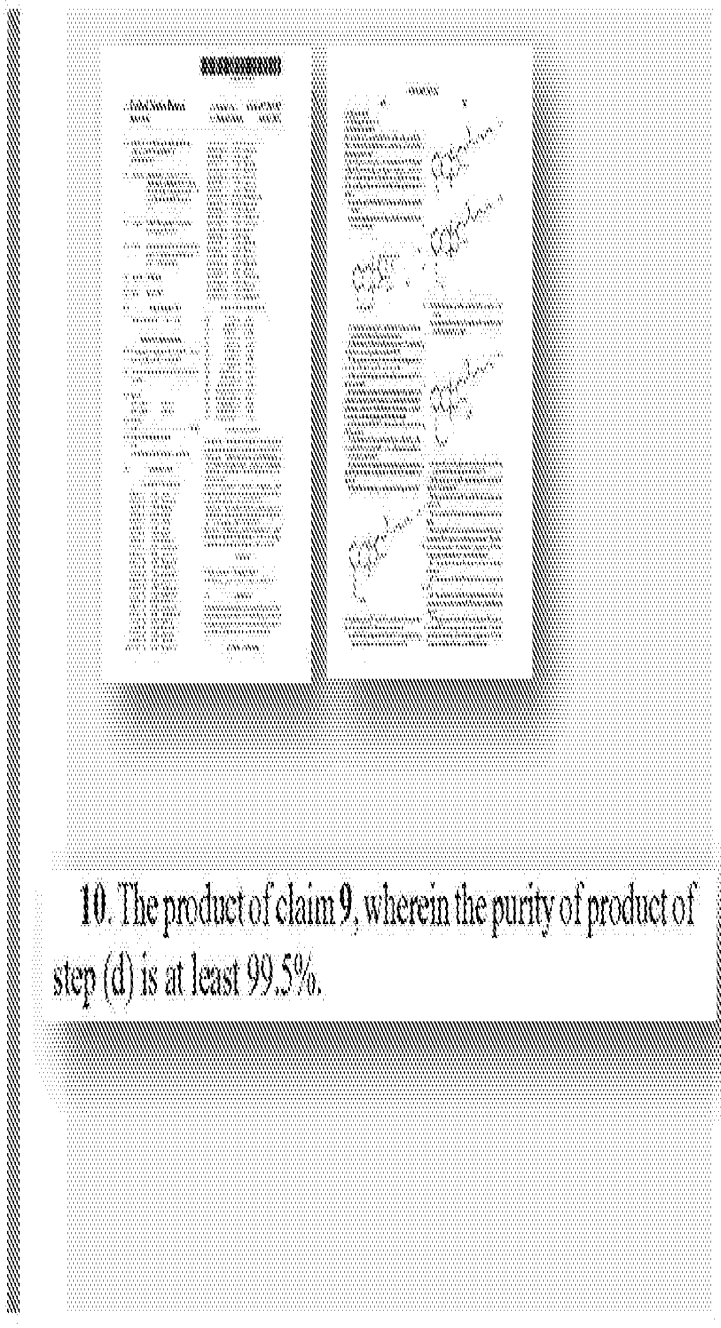
Ex. 1029; SteadyMed v. United Therapeutics; IPR2016-00326

71

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Kawakami with Moriarty, Phares, and Ege





10. The product of claim **9**, wherein the purity of product of step (d) is at least 99.5%.

Ex. 1007 (Kawakami); Ex. 1004, Ex. 1008 (Ege); Ex. 1005 (Phares); Ex. 1001

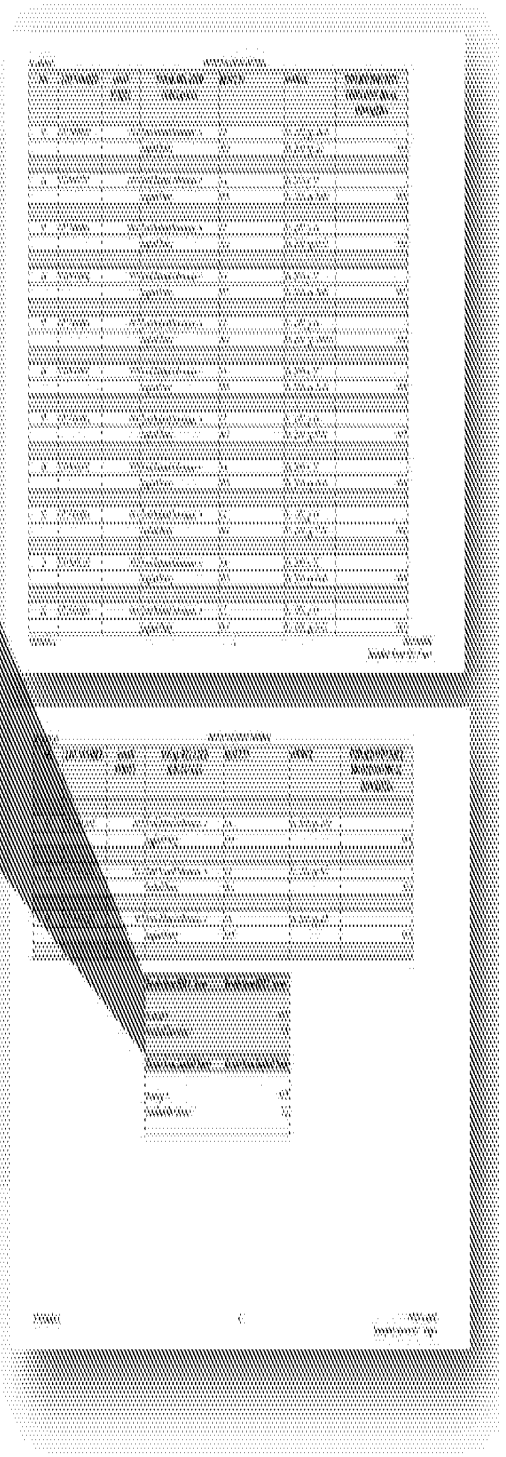
Ex. 1020; Sandoz/Mylan v. United Therapeutics, IPR2019-00665

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Made Same Product

Results from HPLC Assay	Results from HPLC Assay
Average =	99.7
Standard Deviation =	0.5

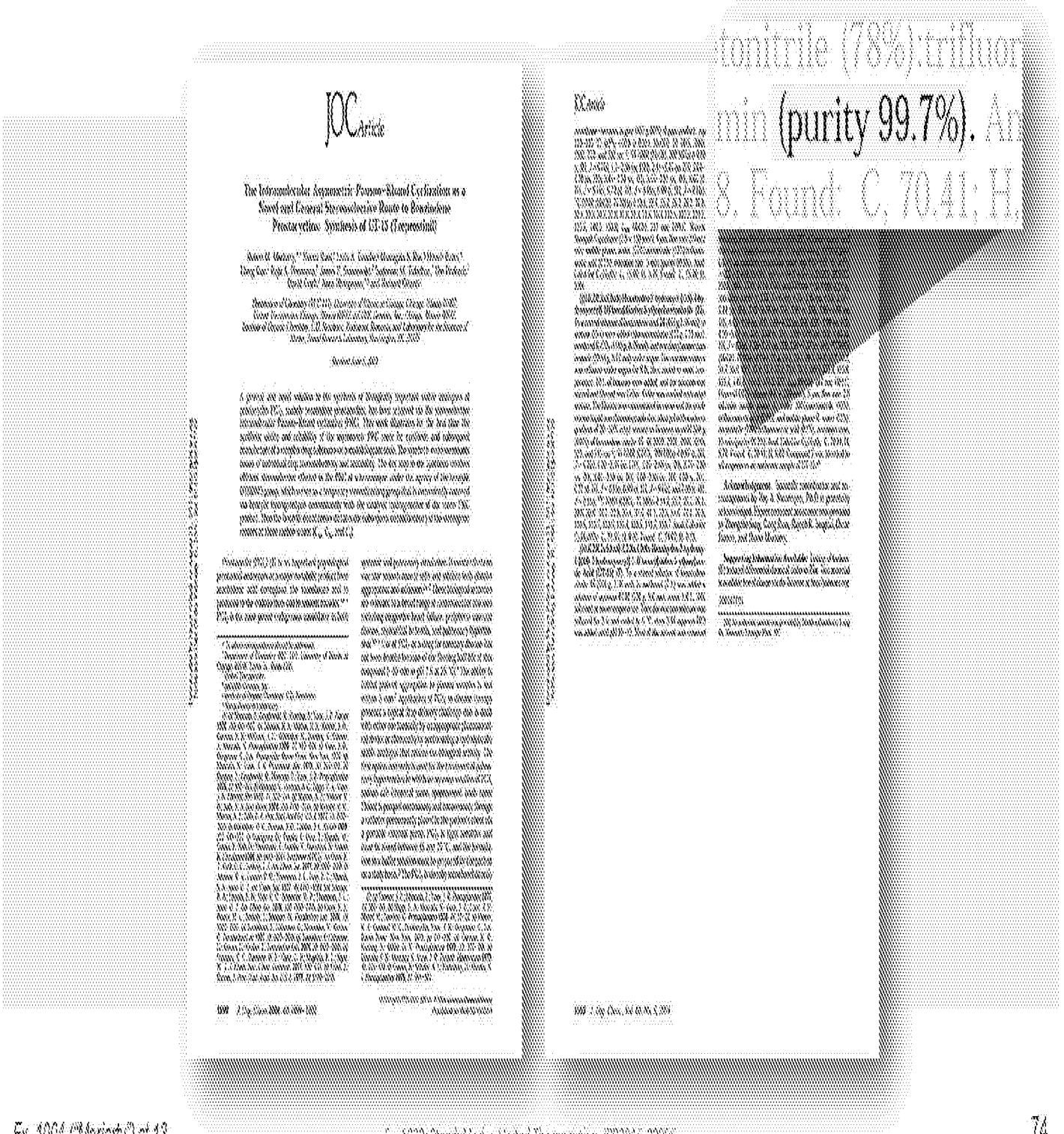
99.7 ± 0.5 %



Ex. 1021 at 5 (Moriarty, average of 46 samples)

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Made Same Product



Obviousness: Dependent Claims 6, 10, 15, 21 & 22

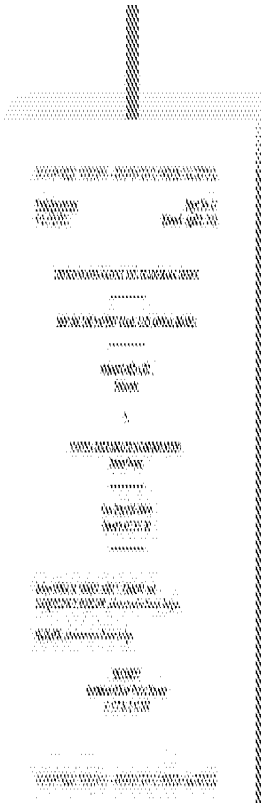
Conclusions

1. No structural differences
2. No functional differences
3. Process of adding acid is "organic chemistry 101"
4. Additional process step makes same product as independent claims
5. Prior art purity > 99.5%
6. Claims 6, 10, 15, 21, & 22 obvious

6 Claim Construction

Claim Construction

Board's Construction



"Comprising"

"including, but not limited to."

Institution Decision, Paper No. 12, at 13

"Product"

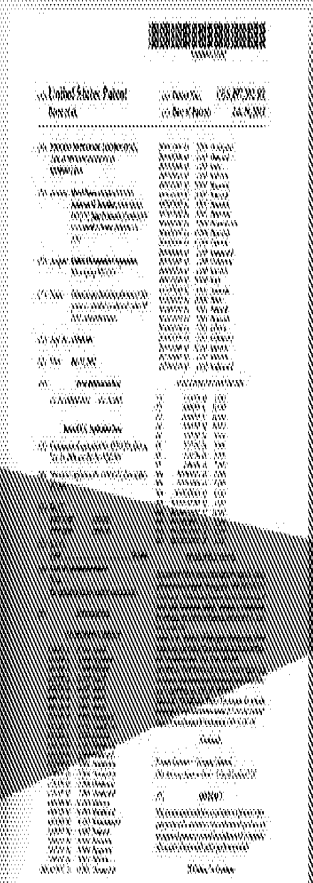
The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by

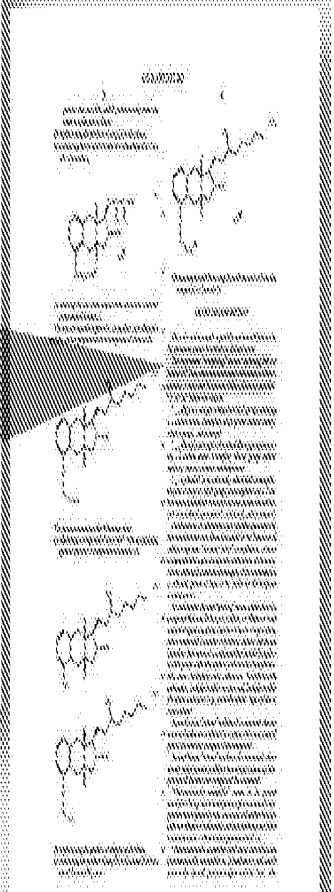
Institution Decision, Paper No. 12, at 12

Claim Construction

"Comprising"

The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

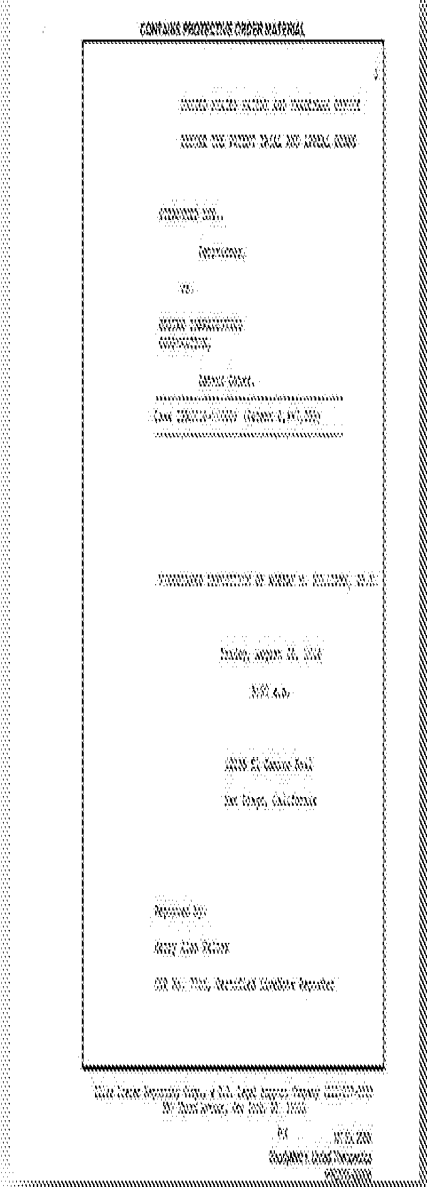




Ex. 1001 at 4

Claim Construction

"Product"



Q. Why not?

A. Because chemists use the word "product" in two different contexts, routinely.

Q. Okay.

A. There's a molecular structural context, okay? So if I said to one of my students, "Show me the product of this reaction on my blackboard." And they'd write a structure like Ecteinascidin-743; okay?

Q. Okay.

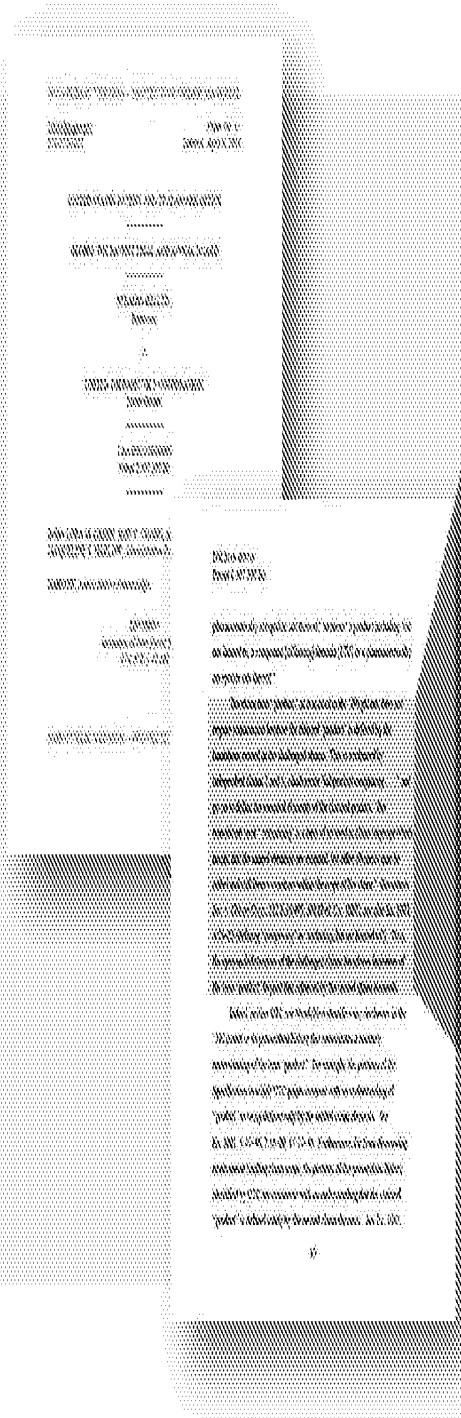
A. And if I said, "Bring me a sample of the product that you just made in the lab," they would bring me a bottle, a flask, a vial of a real-world substance that, hopefully, contains mostly what we were trying to make, and it would also have its characteristic impurities. So there's the molecular structural context, and then there's the real-world substance context of the word "product." And chemists know what you're talking about when you use the word "product" in those two different contexts.

Q. Okay. Let me ask you: In the '393 patent, do you see any place where the '393 patent says: I'm going to define the word "product" for this patent? Do you see that anywhere in there?

A. I don't recall it being defined, other than its plain, ordinary meaning as it's understood, as I just explained.

Claim Construction

"Product"



The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by independent claims 1 and 9, which recite "[a] product comprising . . . ," and go on to define the essential elements of the claimed product. The transitional term "'comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* Ex. 1001, 4:23–25 (defining "comprising" as "including, but not limited to"). Thus, the open-ended structure of the challenged claims forecloses limitation of the term "product" beyond that achieved by the recited claim elements.

Conclusions

Anticipation and Obviousness

Claims 1-5, 7-9, 11-14, 16-20

Conclusions

1. No structural differences
2. No functional differences
3. No separate argument for dependent claims
4. Phares anticipates
5. Moriarty and Phares or Kawakami make obvious

Obviousness

Dependent Claims 6, 10, 15, 21, & 22

Conclusions

1. No structural differences
2. No functional differences
3. Process of adding acid is "organic chemistry 101"
4. Additional process step makes same product as independent claims
5. Prior art purity > 99.5%
6. Kawakami, Moriarty, Phares, Eğe make obvious

CONTAINS PROTECTIVE ORDER MATERIAL Paper _____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-00006
Patent 8,497,393

Patent Owner Response to Petition

4814-0612-4340.3

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Federal Cases

Federal Statutes

Regulations

Other Authorities

I. INTRODUCTION

United Therapeutics Corporation ("UTC") submits this Response in accordance with 35 U.S.C. § 316(a)(8) and 37 C.F.R. § 42.120, responding to the instituted grounds of the Petition for *Inter Partes* Review filed by SteadyMed Ltd. ("SteadyMed") challenging claims 1-22 of U.S. Patent No. 8,497,393 ("the '393 patent"). The Declaration of Dr. Williams ("Ex. 2020") and of Dr. Ruffolo ("Ex. 2022") are filed herewith in support of the Response (Ex. 2020 and Ex. 2022, respectively). The Board should conclude that SteadyMed has failed to prove by a preponderance of the evidence that the instituted claims are unpatentable, as required under 35 U.S.C. § 316(e).

II. SUMMARY OF THE ARGUMENT

SteadyMed's anticipation and obviousness arguments are flawed for two fundamental reasons. First, SteadyMed's arguments rely on Moriarty (Moriarty *et al.*, J. Org. Chem. 2004, 1890-1902; Ex. 1004) and Phares (International Publication No. WO 2005/007081; Ex. 1005), but neither reference discloses the same highly pure treprostinil or treprostinil diethanolamine product claimed by the '393 patent when properly construed, let alone the same synthesis recited in the instituted claims. In fact, the Office considered both references during prosecution of the '393 patent, and the Office construed the claims of the '393 patent in a way that distinguished the product of the '393 patent specifically from the Moriarty

product. Moreover, a person of ordinary skill in the art ("POSA") would not look to either Eğe (Seyhan N. Eğe, Organic Chemistry 543-547 (2d ed. 1989) (Ex. 1008) or Kawakami (JP 56-122328A) (Ex. 1007) as neither reference is relevant to further purification of the complex treprostinil carboxylic acid structure that is at issue in the '393 patent, and a POSA would have no reasonable expectation of success in combining these references with either Moriarty or Phares.

Second, SteadyMed's anticipation and obviousness arguments are flawed because they misunderstand, both the error associated with such measurements and the difference between "assay purity" against a standard and measurements of purity that directly measure the level of impurities. As explained in the Williams and Ruffolo Declarations, this misunderstanding resulted in Petitioner's incorrect assertion that there are inconsistencies between the purity values recited in the '393 specification, the Walsh Declaration, and the Moriarty prior art. Ex. 2020 at ¶¶88-89; Ex. 2022 at ¶¶73-74. Dr. Williams notes that the '393 patent itself expressly refers to assay purity values as "HPLC (assay)" values whenever it uses such measurements, as opposed to other purity values based on measuring amount of impurities. Ex. 2020 at ¶89. Dr. Ruffolo further explains that FDA drug approval system rests on precise measurements of individual impurities that make up a purity "specification" for a drug, which can be reliably determined within the detection limits of HPLC measurements. Ex. 2022 at ¶¶32-35 and 44-50. Dr.

Ruffolo also specifically notes that it is routine to have assay purity values above 100% because it is a relative value measurement. Ex. 2022 at ¶53.

SteadyMed's purported expert, Dr. Winkler, confirmed this misunderstanding. Dr. Winkler acknowledged at his deposition that FDA's purity specification of less than 0.1% for the impurity 2AU90 indicates that precise measurements of impurities are possible: "I would think that the error in the measurement for 2AU90 would be, should be less than 0.1 percent." Ex. 2051 at 64:7-9. Dr. Winkler further acknowledged that he did not know how the treprostinil purity specification adopted by FDA could change from 101% to 102% and stated that he viewed purity levels above 100% as errors: "I think the thing that I am able to conclude from the data that is on page 6 of this, of this letter [Ex. 2006] is that the error in the HPLC assay could be as high as [redacted] percent in the first column and by my analysis could be as high as [redacted] percent in the second column." Ex. 2051 at 86:15-21; 24-25; 87:2-9. As Dr. Williams explained, Dr. Winkler's conclusions on this point appear "to arise from Dr. Winkler's fundamental misunderstanding of how assay purity values are calculated." Ex. 2020 at ¶¶90-92; *see also* Ex. 2022 at ¶¶74. Moreover, Dr. Winkler admitted he did not know what the actual error was associated with the measurements submitted in the Walsh declaration. Ex. 2051 at 62:16-25; 63:2-14. Because Dr. Winkler does not understand the basic differences in types of purity measurements and their related

errors that are used in the '393 patent, discussed in the Walsh Declaration, and which form the basis for FDA's regulation of drug product manufacturing, his declaration should not be credited.

Moreover, the Williams Declaration establishes that there are measurable structural differences between the average impurity profiles of the Moriarty product and the claimed product based on data obtained from 175 batches. Ex. 2020 ¶¶94-99, Appendices A-B; see also Ex. 2005, Ex. 2036, Ex. 2037, Ex. 2052, Ex. 2053. The average impurity profiles show that Moriarty process and the '393 process produce two physically distinct products that contain different total and specific impurities. *Id.* Specifically, the claimed product essentially lacks certain impurities found in the Moriarty product, such as 97W86, 1AU90, and 2AU90. Ex.2020 at ¶¶96-97. The claimed product also contains much smaller amounts of other impurities that are found in the Moriarty product, such as methyl ester, 751W93, 750W93, and 3AU90. *Id.* at ¶96.

Furthermore, based on the same 175 batches, the average purity of the '393 product is 0.7% greater than the average purity of the Moriarty product, thereby corroborating that the Moriarty process and the '393 process produces two physically distinct products that contain measurable and significant structural differences. *Id.* at ¶98.

Finally, the initial claim construction of the preamble "a product… comprising" urged by SteadyMed and adopted by the Board would violate the canon that patent claims may not be construed to encompass material that was clearly disavowed in order to obtain allowance of claims. Even under the broadest reasonable interpretation standard, the Board has found in its own cases that the prosecution history may limit the plain meaning of a limitation in a claim, which otherwise is presumed to apply. The '393 claims were allowed after submission of the Walsh Declaration, which established the differences between the '393 products and the Moriarty product. This disavowal of the Moriarty subject matter is further reinforced by additional intrinsic evidence. The '393 patent includes a side-by-side comparison in Example 6 to show the difference between the Moriarty product and the '393 product and repeatedly references higher purity and different impurity profile compared to Moriarty. In the face of this disavowal, it is improper to construe "a product …comprising" to allow the impurities "without limitation," as such a construction would encompass the impurity profile of Moriarty.

In addition, the Williams Declaration explains why Phares cannot anticipate the claimed products because of the particular conditions used to prepare the Phares product for polymorph screening and because of the uncertain provenance of starting treprostinil used to make the diethanolamine salt.

As to instituted grounds 2 and 3, Dr. Williams also explains why the references in the instituted obviousness grounds would not have been combined in the asserted manner due to lack of motivation and the failure of the references to provide an expectation of success for achieving the purity level and impurity profile of the '393 patent in the specific case of treprostinil. Kawakami teaches away from the selection of diethanolamine, the salt specifically claimed in claims 14 and 18. Lastly, secondary considerations of long-felt need and unexpected results would rebut any case of obviousness as to grounds 2 and 3.

In view of the foregoing, SteadyMed has not met its burden of proving the unpatentability of claims 1-22 by a preponderance of the evidence, as required under 35 U.S.C. § 316(e).

III. STRUCTURAL/FUNCTIONAL DIFFERENCES OF THE CLAIMED PRODUCTS OVER THE CITED ART

The combined Declarations of Dr. Williams and Dr. Ruffolo establish that the '393 product has a different impurity profile than the Moriarty product, and in fact, that the '393 product has higher average purity. These differences matter. FDA uses both overall purity and levels of individual impurities ("purity specification") as a basis to regulate the manufacturing of pharmaceuticals. Batches that fall outside of the purity specification cannot be sold or used to treat

patients. Thus, differences in purity and impurity profile are not merely academic, but critical to the successful manufacture of a clinical product.

A. The Importance of Purity in Pharmaceuticals

As noted by the '393 patent itself, "because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production." Ex. 1001, col. 1:57-61. The invention therefore "provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity." *Id.*, col. 5:47-50. As the treprostinil product is a drug product subject to the rules of FDA, the reduction of impurities is of great importance in the drug. Drug purity is defined by FDA as "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product." See, Ex. 2022 at ¶33; see also 21 C.F.R. §600.3 (r) (2015). The purity of a drug is of such importance to FDA that the purity level of a drug substance must appear in the drug product specification, which is a collection of data about the drug required by FDA. *See*, Ex. 2022 at ¶¶32-34. "Regulatory agencies have also sought to increase levels of purity, and consequently decrease levels of impurities, in order to provide to the maximum extent possible, the highest level of safety to patients." *Id.* at ¶36. This is due to

the fact that even trace amounts of impurities can sometime pose serious health concerns.

For example, the drug penicillin is one of the best known and extensively studied examples of trace impurities that can cause serious, life-threatening adverse events. *Id.* at ¶62. While penicillin is safe and effective for most people, it can cause serious allergic reactions resulting in anaphylaxis and death. *Id.* Because the amount of trace impurity of penicillin needed to cause an allergic reaction is so low, FDA has mandated the production of penicillin active pharmaceutical ingredient (API) and finished product to be made in buildings entirely separate from buildings that manufacture other APIs or finished drug product. *Id.*, *see also* FDA Guidance for Industry, Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination, (2013) (Ex. 2047) at 1-6. The same is true for the drug cephalosporin. Ex. 2022 at ¶63; *see also* Ex. 2047 at 1-6.

Additionally, human insulin is another example. For many years, human insulin was derived from pig pancreases, but then it became possible to produce human insulin in the bacteria *E. coli* using large bioreactors. Ex. 2022 at ¶64. Even though the human insulin derived from *E. coli* was highly pure, it contained very small trace amounts of *E. coli*, a very dangerous bacteria causing reactions (directly from the trace amounts of bacteria, and not due to infection) in some people even in trace amounts. *Id.* As a result, the product needed to be even more

highly purified to further minimize or eliminate the trace bacterial contaminants. *Id.* These examples highlight the importance of drug purity in pharmaceutical formulations and the potential risks to patients between two products that differ in their impurity profile and purity. By having a different impurity profile and overall purity, two products are structurally and functionally different.

B. The '393 Product Has A Different Impurity Profile and a Higher Purity Than Moriarty

As detailed in Dr. Williams' Declaration and supporting exhibits, comparing the average impurity profiles for the '393 product and the Moriarty product using data obtained from over 175 batches reveals measurable structural differences, as the two processes produce physically different products which contain different total and specific amounts of impurities. Ex. 2020 ¶¶94-99 and Appendices A-B; *see also* Ex. 2005, Ex. 2036, Ex. 2037, Ex. 2052, Ex. 2053. The batch reports show that the Moriarty product and the claimed product exhibit different impurity profiles and that the claimed product has a higher average purity than Moriarty's product. *Id.*

Moriarty Process Impurities (Average Percent Detected)								
1AU90	**2AU90**	**3AU90**	**750W93**	**751W93**	**97W86**	**ethyl ester**	**methyl ester**	**Total Related Substance**
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	**0.9545**
'393 patent Process Impurities (Average Percent Detected)								
1AU90	**2AU90**	**3AU90**	**750W93**	**751W93**	**97W86**	**ethyl**	**methyl**	**Total**

						ester	**ester**	**Related Substance**
0.0004	0.0004	0.0455	0.0642	0.0488	0	0.1207	0.005	**0.2936**

In total, the '393 product has 3.25 times fewer impurities than the Moriarty product.[1] Ex. 2020 ¶¶94-95. Additionally, certain specific impurities found in the prior art Moriarty product are essentially eliminated in the '393 product, as the '393 product does not contain detectable amounts of the impurity 97W86, and none of the commercial batches of the '393 product contain detectable amounts of 1AU90 or 2AU90. Ex. 2020 ¶¶94, 96-97. Other impurities, including methyl ester, 751W93, 750W93, and 3AU90, are also greatly reduced in the '393 product as compared to the Moriarty product, while the level of the ethyl ester impurity is slightly increased in the '393 product. Ex. 2020 ¶96. These substantial differences between the impurity profiles of the '393 product and the Moriarty product constitute structural differences between the claimed product and the prior art.

Furthermore, the average purity based on data from over 175 batches is higher for the '393 product than that of Moriarty. As shown above, the average purity of a Moriarty batch was 99.05% while the average purity of a '393 batch

[1] Moriarty Total Related Substances: 0.9545; '393 patent Process Total Related Substances: 0.2936

was 99.71%. Ex. 2020 ¶¶94-99. This is a marked improvement in overall purity. Moreover, the purity analyzed in these batches – the total related substances – is exactly the same type of analysis Dr. Walsh referred to in his declaration when referring to purity of the '393 patent process versus that of the Moriarty process. Thus, this analysis is consistent with how the inventor interpreted the purity of the '393 patent. And this analysis also persuaded the Office to allow the claims.

The Institution Decision cited to the Walsh Declaration for revealing "that each of the impurities detected in [the tested batch of] Moriarty treprostinil was present in an amount below that identified as acceptable in UTC's own specification for treprostinil produced according to the process disclosed in the '393 patent." Paper 12 at 20-21. First, the above data shows that the average amount of each impurity and the average purity is different between Moriarty treprostinil and the '393 product. Second, whether an isolated batch of Moriarty treprostinil does or does not satisfy the new FDA purity specification is not relevant to patentability. The question for patentability is whether or not a given batch of *starting* Moriarty treprostinil (steps a and b of the '393 independent claims) will be physically changed when step (c) is performed *on that batch*. The above averages show that it does change, as do the large scale synthesis examples 4-6 in the '393 patent. While Moriarty treprostinil may show inter-batch variation in overall purity and impurity profiles, the data of record establishes that

performing step (c) *on a given starting batch* of Moriarty treprostinil will lead to a higher purity and a different impurity profile in the end product. Petitioner has not established that any specific batch of Moriarty treprostinil is not physically changed by performing step (c), and all the evidence suggests that it is.

C. The Differences In Impurity Profile And Average Purity Between The '393 Product And Moriarty Are Functionally Important

The higher purity of the claimed product resulted in FDA approving a new assay purity for the treprostinil drug as noted in the January 2009 letter submitted to FDA by UTC. Ex. 2006 at 4-6; Ex. 2022 at ¶¶66-68; Ex. 2020 at ¶91. Furthermore, this change constitutes a "major" change according to the classification system for manufacturing changes used by FDA. Ex. 2022 at ¶¶70-72. FDA requires continuous testing of pharmaceutical batches to ensure that they fall within the established purity specification. Ex. 2022 at ¶¶32-40. If a given batch falls outside the established purity specification, then it will be rejected by FDA and cannot be sold for patient use. *Id.* at ¶32. FDA is so concerned about purity of pharmaceuticals that it requires companies to test for very tiny amounts of individual known impurities carried over into the final product based on the manufacturing process. *Id.* at ¶¶32-40. Thus, the change in the '393 product is commercially important and has real-world value.

IV. CLAIM CONSTRUCTION

In the Decision on Institution (Paper 28), the preliminary claim construction construes "[a] product comprising a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof" and "product" in an unreasonably broad manner. The Board is not bound by that preliminary construction based on an incomplete record. *See e.g., The Scotts Co., LLC v. Encap, LLC*, IPR2013-00110, Paper 79 (PTAB June 24, 2014) (overturning preliminary claim construction in final written opinion) (Ex. 2024). On the fuller record now available to it, the Board should adopt UTC's construction of the disputed terms.

A. Intrinsic Evidence Can Override The Presumption That "Comprising" Creates An "Open" Claim Construction

The claims at issue in an IPR must be given their broadest reasonable interpretation (BRI) in light of the specification, but the Board must still interpret claim terms according to established principles. The transition phrase "comprising" is only *presumed* to be an "open" phrase. *Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001) ("In the parlance of patent law, the transition 'comprising' creates a presumption that the recited elements are only a part of the device, that the claim does not exclude additional, unrecited elements."). "While it is true that, as a general rule, the words of a patent claim are to be given their plain, ordinary and accustomed

meaning to one of ordinary skill in the relevant art, *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999), a court must nevertheless examine the remaining intrinsic evidence to determine whether the patentee has set forth an explicit definition of a term contrary to its ordinary meaning, has disclaimed subject matter, or has otherwise limited the scope of the claims." *Day Intern., Inc. v. Reeves Brothers, Inc.*, 260 F.3d 1343, 1349 (Fed. Cir. 2001).

The intrinsic record, both the specification and the prosecution history, must be reviewed to determine if there are limits to terms in the claims that would otherwise be given their presumptive plain meanings. Prosecution history "limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance." *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985). Similarly, the specification may contain repeated statements distinguishing the prior art that limit the claims. *SafeTCare Mfg., Inc. v.Tele-Made, Inc.*, 497 F.3d 1262, 1269-70 (Fed. Cir. 2007) (finding disclaimer where the specification repeatedly indicated that the invention operated by "pushing (as opposed to pulling) forces," and then characterized the "pushing forces" as "an important feature of the present invention").

Under the BRI standard, the Board should take into account both the specification and the prosecution history because the patent examiner and the

applicant have already worked together to determine the scope of the claimed invention. *See In re Buszard*, 504 F.3d 1364, 1366-67 (Fed. Cir. 2007) ("The patent examiner and the applicant, in the give and take of rejection and response, work toward defining the metes and bounds of the invention to be patented."); *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989) ("When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.").

The Board has followed these principles of claim construction in other IPR proceedings. *See, e.g.*, *The Scotts Co., LLC v. Encap, LLC*, IPR2013-00110, Ex. 2024 at 14-16. In *Scotts*, the Board changed its preliminary claim construction of "being in a solid state at time of coating" because the Board found that the patent owner had disavowed claim scope during prosecution in order to overcome a specific prior art reference. Ex. 2024 at 15. The Board relied on statements made in Examiner Interview Summaries which confirmed that claim amendments and arguments presented overcame the prior art. *Id.*; *see also* Prosecution History of U.S. Patent No. 6,209,259 (Ex. 2025). As another example, the Board recently construed a phrase to exclude trace amounts of a substance based on statements made during prosecution distinguishing prior art containing trace amounts of the substance. *Daicel Corp. v. Celanese Int'l Corp.*, IPR2015-00171, Paper 86 at 41

(PTAB June 23, 2016). Thus, the BRI cannot be divorced from the intrinsic evidence, including the prosecution history. Such a construction is not reasonable.

B. The Distinct Impurity Profile And Higher Purity Of the '393 Patent Product Were Clearly Considered Part of the Claimed Product During Prosecution

As explained during prosecution,"[e]ach of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 . . . is physically different from treprostinil prepared according to the process of 'Moriarty' due to differences in their impurity profiles." Ex. 1002 at 344. In fact, the Examiner required UTC to provide evidence in declaration form showing that the product of claims 1 and 10 was different than Moriarty's product. *Id.* at 328. In response, UTC filed the Walsh Declaration, which demonstrated that the claimed product had a different impurity profile and higher purity than Moriarty's product. *Id.* at 347-349. It was upon these statements and evidence that Moriarty was overcome, and shortly thereafter the Examiner issued a Notice of Allowance. *Id.* at 354-360.

In addition, the '393 specification repeatedly refers to the differences of the '393 product compared to Moriarty. The entirety of Example 6 in the '393 specification is a large scale, side-by-side comparison between Moriarty and the '393 product, which shows a purity of 99.0% for Moriarty and 99.9% for the '393 product. Ex. 1001, 17:step 53. At the end of this example, the '393 specification

further states that "impurities carried over from intermediate steps (i.e., alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and salt formation step" (Ex. 1001, 17:29-32), which are the same differences (higher purity and different impurity profile) that UTC relied upon in the Walsh Declaration during prosecution as noted above.

These statements by UTC demonstrate that the claimed "product" must have an impurity profile conferred by its process steps. *See Purdue Pharma L.P. v. Endo Pharms. Ins.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006); *see also Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 997 (Fed. Cir. 2006) (statements made during prosecution history that distinguished the claimed invention from the prior art constituted a prosecution disclaimer); *see also United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153, *54-56 (D.N.J. Aug 29, 2014) (finding compounds made by different processes resulted in different impurity profiles meaning they were structurally different).

D. The Plain Meaning Of "Product" In The Context Of The '393 Product-By-Process Claims Requires The Characteristics Conferred By The Process Steps Be Present

The term "product" in the context of the '393 patent should be construed as "a substance resulting from a chemical reaction." This is consistent with the '393 patent itself (Ex. 1001 at col. 3, lines 3, 4, 65, and 66; col. 5, line 45; col. 6, lines 65 and 66; and col. 7, line 17), as well as the understanding of a POSA and the

generally accepted definition in chemistry. Ex. 2020 at ¶¶60-62. Additionally, Dr. Williams and Dr. Winkler both use the term product to refer to the result of a chemical reaction in their own work. Id. at ¶¶63-65; *see also* Ex. 2031 at 155:2-11 ("the product of a chemical reaction would be essentially all of the substances that result from the treatment of a particular reactant with a particular set of reagents."). To construe the term "product" as "a chemical composition" is too broad and improperly disregards a significant portion of the intrinsic record. As described above, a product is the result of a chemical reaction and has its own impurity profile depending upon how it is made. "A chemical composition" could be anything and is in no way limiting to what the term "product" actually means. Ex. 2020 at ¶¶66-68.

V. GROUND 1: PHARES FAILS TO EXPLICITLY OR INHERENTLY DISCLOSE EACH AND EVERY LIMITATION OF CLAIMS 1-5, 7-9, 11-14 OR 16-20

The Board instituted Ground 1 based on the conclusion that Phares teaches the treprostinil diethanolamine salt product recited in claims 1 and 9, and that the recited process steps of the claims do not impart structural or functional differences over Phares' treprostinil diethanolamine salt. As discussed below, SteadyMed has failed to establish anticipation based on Phares.

A. SteadyMed Cannot Pick and Choose From Unrelated Portions of Phares to Establish Anticipation

In attempting to show anticipation, SteadyMed cites four different portions of Phares, Ex. 1005, as teaching the combined elements of claims 1 and 9. However, SteadyMed selectively ignores other portions in the Phares disclosure that suggest the four disparate portions of Phares should not be cobbled together to a single allegedly anticipatory embodiment. Petition at 22-24 and 33-34.

The portions of Phares cited by SteadyMed each relate to distinct subject matter, and Phares provides no description that would lead to the combination of these separate disclosures. Ex. 2020 at ¶¶79-84. Phares' only disclosure of steps (a) and (b) is directed to the enantiomer (-)-treprostinil, which are not the same as the synthesis for treprostinil. Ex. 2020 at ¶¶79-81. In fact, the intermediate products disclosed in the enantiomer synthesis as well as several reagents are different than the synthesis of treprostinil. *Id.* at ¶81. In contrast, Phares' separate alleged disclosure of step (c) is silent as to how the starting treprostinil acid was prepared. Ex. 1005 at 85. Thus, there is no reason set forth in Phares to combine the single teaching of steps (a) and (b) directed to one enantiomer with the other teachings of step (c), which are all directed to the other enantiomer. Ex. 2020 at ¶¶79-81.

Despite the alleged disclosure in Phares' that enantiomers of the disclosed compounds can be prepared using the proper chiral reagents, Phares itself teaches that treprostinil can be prepared in other ways that do not include steps (a) and (b), including the processes disclosed in US Patent Nos. 4,306,075 (Ex. 2032) and 5,153,222 (Ex. 2033). Ex. 1005 at 11; Ex. 2020 at ¶78. Thus, a POSA would reasonably conclude that the diethanolamine salts of Phares were prepared based on other disclosed methods that do not require steps (a) and (b). Ex. 2020 at ¶78. If the diethanolamine salts of Phares were prepared differently than the recited process steps, nothing in Phares establishes that the diethanolamine salts are necessarily the claimed product.

B. The Proper Construction of a "product comprising a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof" Precludes A Finding That Phares Anticipates the Present Claims

The Board's institution of Ground 1 was partly based on its preliminary finding that "comprising" does not exclude impurities that may possibly be produced by the process of Phares and that the impurity profile of Phares' diethanolamine salt is identical to that of the claimed product. *See* Paper 12 at 30. However, such a finding does not take into consideration the reasonable construction of "product comprising a compound [of/having] formula [I/IV] or a

pharmaceutically acceptable salt thereof," which is set forth in this Response and supported by the record now before the Board.

As discussed above in Section IV, both the specification and the prosecution history of the '393 patent distinguish the claimed product from prior art treprostinil products based on its higher purity and different impurity profile, which is achieved through the recited process steps. Thus, to prevail on Ground 1, SteadyMed must show that the Phares' diethanolamine salt necessarily possesses an impurity profile that is distinct from that of the Moriarty product and with higher purity.

Steadymed simply assumes that the diethanolamine salt discussed by Dr. Winkler is prepared from Moriarty treprostinil and does not acknowledge that the source of treprostinil would impact both the overall purity and impurity profile of the resulting salt. As exemplified in the '393 patent, the claimed process provides an improved treprostinil product due to its superior purity. As evidenced by the Williams Declaration and the batch record data, the claimed product has an average purity of 99.71% and a distinct impurity profile from Moriarty's product. Ex. 2020 at ¶¶94-99. Importantly, SteadyMed has failed to show that, at a minimum, the Phares' diethanolamine salt possesses an impurity profile that is distinct from that of the Moriarty product and contains fewer overall impurities than the Moriarty product. Nor has SteadyMed shown that the Phares'

diethanolamine salt has a higher purity than the Moriarty product. Indeed, SteadyMed's only argument regarding the purity of Phares' diethanolamine salt is based on the theory that the higher melting point of Phares' diethanolamine salt necessarily means that it must be at least equal in purity to that of the exemplified batches in the '393 patent. *See* Petition at 27-28. However, for the reasons noted below, that is an incorrect conclusion based on the evidence now in the record.

C. The Higher Melting Point of Phares' Diethanolamine Salt Does Not Necessarily Mean That it is of Higher Purity Than the Diethanolamine Salts of the '393 Patent

The Board relied on incorrect statements in the Winkler Declaration alleging that Phares' diethanolamine salt must be more or at least equally pure as the claimed product solely because the former has a higher melting point. Paper 12 at 28-29. However, melting point is just one factor in assessing a compound's purity and is not necessarily a reliable metric of purity. This is especially applicable to Phares because only one melting point value was obtained in a sample for a polymorph screen. A POSA would not rely upon a single melting point value, absent any other impurity information, to determine the purity of a substance made under unspecified conditions. Ex. 2020 ¶76. Indeed, the "higher" melting point of Phares' diethanolamine salt could be indicative of the inclusion of impurities or the result of the use of different solvent systems for the crystal forms. *Id.* Accordingly,

the purity of a compound cannot be assessed based solely on its melting point value.

Moreover, even if the melting point could be relied upon, the data cited by Dr. Winkler does not indicate a product of high purity. To the contrary, Fig. 21 of Phares "shows a broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance." Ex. 2020 ¶76; *see also*, Marti, E., *Purity determination by differential scanning calorimetry*, Thermochimica Acta, 5(1972) 173-220 at 214 ("The melting of diphenyl is extremely sharp because of the purity level; on the other hand, the melting region of phenacetin-benzamide is rather broad.") (Ex. 2031).

Additionally, Phares discloses several different conditions for preparing Polymorph A of the diethanolamine salt and that Polymorph A is required to make Polymorph B. Ex. 2020 at ¶73. The '393 patent does not indicate that making Polymorph A first is required. *Id.* Phares also indicates many conditions used to make Polymorph A and Polymorph B, but it is not clear what conditions were specifically used for the sample analyzed in Figure 21 that Dr. Winkler relies upon. *Id.* at ¶¶73-74. It is well known that the use of different solvent systems in forming different crystal forms can have a significant effect on the melting point of a substance, as well as other characteristics, including purity, and a higher melting point does not always mean a higher purity. *Id.* at ¶¶75-76; *see also* R. Adhiyaman,

et.al., *Crystal modification of dipyridamole using different solvents and crystallization conditions*, Int'l J. Pharm.321 (2006) 27-34 at 33 ("Adhiyaman") ("In conclusion, it can be said that the crystallization conditions and medium used have major effect on dipyridamole crystals habit modification under ambient conditions. The crystals showed significant changes in the shape, size, melting points, dissolution rate, XRD patterns and DSC curves.") (Ex. 2030).

Dr. Williams, therefore, has concluded that "[i]t is known in the art that sample size, rate of heating, the recrystallization solvent(s) used, and the conditions under which the crystalline sample was obtained can significantly affect the DSC data. Dr. Winkler's conclusion based on this single vague and incompletely described DSC data is not scientifically sound." *Id.* at ¶76.

Thus, nothing in Phares establishes that the disclosed diethanolamine salt is at least of equal purity to the diethanolamine salts of the '393 patent. With respect to claim 2 of the '393 patent specifically, nothing in Phares discloses a purity of at least 99.5%. Ex. 2020 at ¶82. For this additional reason, Phares cannot anticipate claim 2.

D. Phares Fails To Disclose the Claimed Process for Making Treprostinil or Any Purity or Impurity Profile for Treprostinil Diethanolamine

SteadyMed has failed to establish that Phares' diethanolamine salt (Form B) is the claimed product.

First, as Dr. Williams notes, the samples of treprostinil diethanolamine disclosed in Phares were "made for a polymorph screen, not large scale batches." Ex. 2020 ¶73. Accordingly, "the samples of polymorph B described in Phares are prepared in a completely different way under different conditions than those described in the '393 patent." Ex. 2020 ¶75. Specifically, Phares discloses first preparing polymorph A by any one of a variety of methods and then preparing polymorph B from some sample of polymorph A. In contrast, the '393 patent makes no mention of first forming polymorph A. Ex. 2020 ¶¶73-74. Additionally, Phares describes reaction conditions for making the polymorph samples that are not described anywhere in the '393 patent. *Id.* In particular, the reaction conditions disclosed for the sample of polymorph B characterized by Phares, heated slurries of form A in 1,4-dioxane and toluene, are not described anywhere in the '393 patent. *Id.* It is well-known that the use of different reaction conditions, including different solvents, can significantly affect the characteristics of a given crystal form. Ex. 2020 ¶75. As a result, the diethanolamine salt disclosed in Phares cannot be directly compared to the diethanolamine salt disclosed in the '393 patent.

Second, the Williams Declaration clearly establishes that the claimed product has an average purity of 99.7%, thus giving it a superior purity and distinct impurity profile over that of the prior art treprostinil products. Ex. 2020 ¶¶94-99. The purity of the claimed product provides a structural difference from the prior art

treprostinil, as evidenced by the differences in the average impurity profiles for the Moriarty product and the '393 product. *Id.*, Ex. 2036, Ex. 2037. Indeed, the higher purity of the claimed product resulted in FDA approving a new purity specification for the treprostinil drug as noted in the January 2009 letter submitted to FDA by UTC. Ex. 2006 at 4-6; Ex. 2022 at ¶¶70-72; Ex. 2020 at ¶91.

The impurity profile of the *starting* treprostinil acid used to prepare the Phares diethanolamine salt is crucial to assess whether the diethanolamine salt is the same as the claimed product, *i.e.*, whether the impurity profile of the diethanolamine salt in Phares is identical to that of the claimed product. Ex. 2020 ¶¶76-78. However, nowhere does Phares disclose the process of preparing the treprostinil acid used to prepare the diethanolamine salt. As acknowledged in both Phares and the '393 patent, several different processes can produce treprostinil acid. *See, e.g.*, Ex. 1005 at 11; *see also,* Ex. 2020 ¶78. Each known process can produce a treprostinil acid with a unique impurity profile. Ex. 2020 ¶78. Because Phares does not disclose the process of preparing the starting treprostinil acid for the diethanolamine salt, the impurity profile of the diethanolamine salt cannot be established. Without knowing the impurity profile and level of purity of Phares' diethanolamine salt, SteadyMed cannot show that it is necessarily identical to the claimed product or has equal purity to the claimed product.

Consequently, SteadyMed has not carried its burden on Ground 1.

VI. GROUND 2: MORIARTY AND PHARES FAIL TO RENDER OBVIOUS CLAIMS 1-5, 7-9, 11-14, OR 16-20

Moriarty does not teach salt formation and regeneration of the free acid. SteadyMed attempts to cure this deficiency in Moriarty by citing Phares for allegedly teaching step (c). However, Moriarty teaches three distinct methods of preparing the treprostinil free acid. Nothing in Moriarty directs a POSA to select one specific process over the three disclosed for purposes of further modification by adding a salt formation step. Furthermore, SteadyMed fails to recognize that the performance of step (c) after steps (a) and (b) unexpectedly results in a product with an improved average purity over that of the prior art. Indeed, the Williams Declaration demonstrates that, out of 122 samples, the claimed product has an average purity of greater than 99.7%. Ex. 2020 at ¶¶94-95 and Appendices A-B.

As discussed above, the claimed product is structurally different from Moriarty's product because the claimed product has a distinct impurity profile, including a marked reduction in several specific impurities, and a higher average purity relative to Moriarty's product. Ex. 2020 at ¶¶94-99 and Appendices A-B. This evidence shows that, in the recited combination, performing step (c) in conjunction with steps (a) and (b) of the present claims produces a treprostinil product that is significantly improved over that of the prior art. Ex. 2020 at ¶¶48-49, 70.

Moreover, Moriarty's product cannot render obvious the claimed product because during prosecution of the '393 patent, UTC overcame a rejection based upon Moriarty by providing evidence of representative sample impurity profiles, showing the physical difference between the product of the '393 patent and the Moriarty product. Ex. 1002 at p. 347. Phares does not cure this deficiency because, as noted above, nothing in Phares establishes that the diethanolamine salt either 1) has an impurity profile similar to the claimed product or 2) has an overall purity at least equal to the claimed product.

In particular, it would not have been obvious to use the salt formation step of Phares to decrease amounts of at least 1AU90 and 2AU90, which are stereoisomers of treprostinil, and accordingly, are acidic rather than neutral or basic. Ex. 2020 at ¶102. Thus, when subject to salt-forming conditions, a POSA would expect that any undesired stereoisomer of treprostinil would be included in the final salt product because the stereoisomer would also be converted to the corresponding salt under such salt-forming conditions. A POSA has no reasonable expectation of success in removing any undesired treprostinil stereoisomer impurities by salt formation and subsequent regeneration of the free acid. *Id.* Instead, a POSA would expect the salt formation and subsequent regeneration to produce a final product with the same initial amount of stereoisomer impurities before the salt formation step. *Id.* Yet these impurities are each detected in only a single optimization batch

of the '393 product, and in none of the commercial batches. Even taking these optimization batches into consideration, this represents a greater than 100-fold reduction as compared to the Moriarty product. *Id.* at ¶¶94-96.

Additionally, as described above, there is no basis for comparing the "purity" in Moriarty with the purity described in the Walsh Declaration. *Id.* at ¶88. Walsh's Declaration makes clear that purity in terms of the '393 patent is assessed by looking to the total related substances of a batch. *Id.* at ¶¶88-89. The Moriarty reference, while not specifying a reference standard, does refer to a comparison to an authentic sample. *Id.* As a result, it is not clear what method was used to determine the purity in Moriarty and therefore a direct comparison of the value reported in Moriarty cannot be made to the '393 patent.

Moreover, Dr. Winkler fundamentally misunderstands the error associated with various purity measurements used in the Walsh Declaration, the '393 patent, the prior art, and FDA. Dr. Winkler states in his declaration that:

> even a difference of 0.4% as discussed below, between the claimed processes of the '393 Patent and the prior art, such as Moriarty (Ex. 1004), would be attributable to experimental error, and thus the claimed degree of purity under the claimed processes of the '393 Patent presents no distinction from the prior art.

Ex. 1009 at ¶69.

He goes on to state that "HPLC's precision indicates that the 'RSD' or 'relative standard deviation' for a typical instrument is about 1%." *Id.* at ¶70.

This is wrong for several reasons. First, during his deposition, Dr. Winkler admitted he did not know what the actual error in the measurement was for the data submitted in the Walsh Declaration during prosecution of the '393 patent. Ex. 2051 at 62:16-25; 63:2-14.[2] While he did not know the error associated with the measurements made in the data submitted with the Walsh Declaration, he did admit that "the error in the measurement for the 2AU90 [treprostinil impurity] would be, should be less than .1 percent," and in general, "[t]he error should be less than the maximum number reported, that's correct, for the measurement of the materials described here." Ex. 2051 at 63:25-64:4; 64:7-16. By his own admission, the error associated with the measurement of impurities in treprostinil batch records such as those submitted in Walsh's Declaration are therefore far less than the alleged error of 1% or 0.4% he stated in his declaration.

[2] Indeed, Dr Winkler admitted he was not familiar with FDA guidelines regarding impurity profiles for a drug, did not know what is required in order to change a drug specification, and was not familiar with published guidances from FDA regarding changes to new drug applications or abbreviated new drug applications. Ex. 2051 at 19:3-24.

In contrast, FDA requires that impurity determinations must be measured at or below 0.05% for drugs such as treprostinil. *See*, Ex. 2022 at ¶47; Ex. 2020 at ¶92. As Dr. Ruffolo explains, impurities in drug substances such as treprostinil that are administered in dosages less than 2 grams per day require that impurities be reported if they are present at a level less than or equal to 0.05%. *See, e.g.*, Ex. 2022 at ¶¶44-47; *see also* ICH Impurities in New Drug Substances Q3A(R2) monograph at 5-11 (Ex. 2038). "As a result of these thresholds, by definition, the limit of detection for impurities (and therefore total related substances) must be at least as low as 0.05%." Ex. 2022 at ¶50.

Furthermore, the '393 patent is directed to an improved and more pure treprostinil product. *See, e.g.*, Ex. 1001, 17:27-40. Given that Moriarty discloses the use of column chromatography for purification, a POSA would not be motivated to create the salt form in Phares, as Phares does not disclose any benefit or increased purity as a result of using the diethanolamine salt. Ex. 2020 at ¶101. "In fact, Phares does not allege that the diethanolamine salt is superior in any way to the treprostinil product of Moriarty and instead identifies other earlier treprostinil disclosures as a means to create the treprostinil used to form the diethanolamine salt." *Id.* A POSA would not have a reasonable expectation of success by using salt formation as a purification step separate from or in addition to the column chromatography of Moriarty, as Phares does not disclose any alleged

benefit to forming the salt and a POSA would have no expectation that only certain acidic and neutral impurities would be reduced or completely eliminated while others remained. *Id.* at ¶102. Thus, the combination of Moriarty and Phares cannot render obvious claims 1-5, 7-9, 11-14, or 16-20.

Similarly, as described above, there is no basis to compare the purity disclosed in Moriarty to the measurements obtained in the '393 patent or those obtained by Dr. Walsh in his declaration, and therefore, claim 2 would also not be rendered obvious by the combination of Phares and Moriarty for this additional reason. *Id.* at ¶103.

Claims 8 and 16 also require the additional limitation that the formula (VI) compound of step (a) is not purified. In fact, the '393 patent specifically distinguishes this limitation over the prior art. Ex. 1001, Example 6. Moriarty expressly discloses that the compound of formula (VI) from step (a) is purified. Ex. 2020 at ¶104. Phares does not disclose any synthesis for treprostinil and, even in the abbreviated synthesis of the enantiomer, no details of purification are disclosed. *Id.* Thus, claims 8 and 16 are not rendered obvious by the combination of Phares and Moriarty for this additional reason. Process advantages should be considered as secondary considerations to rebut obviousness, even if the process steps or advantages are not considered in the initial determination of whether there is *prima*

facie obviousness (where the products are compared regardless of how they are made).

Consequently, SteadyMed has not carried its burden on Ground 2.

VII. GROUND 3: MORIARTY, PHARES, KAWAKAMI, AND EĞE FAIL TO RENDER OBVIOUS CLAIMS 6, 10, 15, 21, AND 22

A. The Product of Claims 6, 15, and 21 Are Different Than the Prior Art Treprostinil Products

The Board concluded that the process steps of claims 6, 15, and 21, including step (d), do not impart structural or functional differences over prior art treprostinil products. Paper 12 at 46-47.

Based on the evidentiary record now before the Board, and in view of the reasons set forth in Section III, above, the free acid substance formed by step (d) of claims 6, 10, 15, 21 and 22 is structurally different from the prior art treprostinil products in Phares and Moriarty. The evidentiary record shows that the free acid substance of claims 6, 10, 15, 21 and 22 contains a distinct impurity profile and a higher average purity over the treprostinil free acid of Moriarty, and thus is structurally different. Further, Phares' diethanolamine salt of treprostinil is structurally and functionally distinct from the free acid substance formed by step (d) of claims 6, 15 and 21.

1. The '393 Patent Product is Structurally and Functionally Distinct from Moriarty's Product

As explained in the Williams Declaration and discussed above, the free acid substances of claims 6, 10, 15, 21 and 22 are structurally distinct from Moriarty's product because the formation of the salt in step (c) leads to a product that has a distinct and improved impurity profile. *See* Sections III, VI, *supra*. Additionally, the average purity of the product of claim 21 is about 0.7% greater than that of Moriarty. Ex. 2020 ¶¶94-99 and Appendices A-B. Indeed, as evidenced by Dr. Ruffolo's Declaration, a 0.7% difference in average purity for a highly potent drug, such as treprostinil is a very significant difference. *See, e.g.*, Ex. 2022 at ¶70.

B. There Is No Motivation For A POSA To Combine Moriarty and Phares with Eğe and Kawakami

In the Institution Decision, the Board determined "on the record before us, and for purposes of institution, that the process steps recited in claims 6, 15, and 21 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps." Paper 12 at 47. However, the fuller record now indicates that the claimed treprostinil product is structurally and/or functionally different from Moriarty's treprostinil free acid and Phares' treprostinil diethanolamine salt. Thus, the recited process steps must now be considered.

Similarly, the board credited Dr. Winkler's opinion regarding the combination of Kawakami and Eğe with Moriarty and Phares. Paper at 42. Dr. Winkler, however, too easily dismisses the complexity and difficulty associated with further purifying a drug substance as complex as treprostinil. Dr. Winkler attempts to portray the chemistry involved in the '393 patent as "nothing more than basic organic chemistry techniques – in my view 'organic chemistry 101'" in an effort to minimize the significant invention of the '393 patent. Ex.1009 at ¶3. Yet, Dr. Winkler contradicts himself by defining a POSA as having "a master's degree or Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively a person of ordinary skill would include a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry." *Id.* at ¶14. Indeed, Dr. Winkler goes on to testify that to understand the science and chemistry of the patent, you would need that level of skill in the art. Ex. 2051 at 29:12-16. As a result, a POSA would not look to an undergraduate textbook like Eğe, for example, to figure out improved purification techniques for a complex drug substance such as treprostinil.

1. There Is No Motivation to Follow the Carboxylate Salt Formation With Regeneration of the Carboxylic Acid

The Board credited Dr. Winkler's opinion regarding the combination of Kawakami and Eğe with Moriarty and Phares. Paper 12 at 42. Dr. Winkler,

however, too easily dismisses the complexity and difficulty associated with further purifying a drug substance as complex as treprostinil. After first referencing "organic chemistry 101" to minimize the significance of the '393 patent (Ex. 1009 at ¶3), Dr. Winkler contradicts himself by defining a POSA as having "a master's degree or Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively a person of ordinary skill would include a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry." *Id.* at ¶14. At his deposition, Dr. Winkler conceded that, to understand the science and chemistry of the '393 patent, you would need this higher level of skill in the art. Ex. 2051 at 29:12-16. As a result, a POSA would not look to an undergraduate textbook like Eğe, for example, to figure out improved purification techniques for a complex drug substance such as treprostinil.

As explained previously, the claimed free-acid compounds, including treprostinil, produced by the processes of claims 6, 10, 15, and 21 provide a new product that induced FDA to adopt a new purity standard for treprostinil free acid due to the excellent purity of the final product. Furthermore, UTC demonstrated that treprostinil free acid made by the claimed methods provides a compound that lacks or reduces the levels of the impurities found in the free acid treprostinil of the Moriarty process.

Neither Phares nor Eğe provide a reason that a POSA would include a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step. *See* Petition, p. 54. Phares merely discloses forming a salt from treprostinil free acid of undisclosed origin. *See* Section V.E., *supra*. There is no suggestion that this salt should then be converted *back* to the free acid (*e.g.*, there is no suggestion of using the salt formation as a purification method). "Given that the purification techniques disclosed in Moriarty include chromatography and recrystallization after many years of research to optimize the process of making treprostinil, a POSA would not have been motivated to use a salt purification technique disclosed in an undergraduate chemistry textbook. More importantly, a POSA would not have had a reasonable expectation of success in further purifying the treprostinil product of Moriarty by using such a technique. To the extent a POSA was motivated to further purify treprostinil, a POSA would have focused on the known impurities and investigated methods of removing those." Ex. 2020 at ¶106. Indeed, stereoisomers were known impurities in treprostinil. *Id.* Eğe, however, simply discloses that "carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds." *Id.* at ¶107.

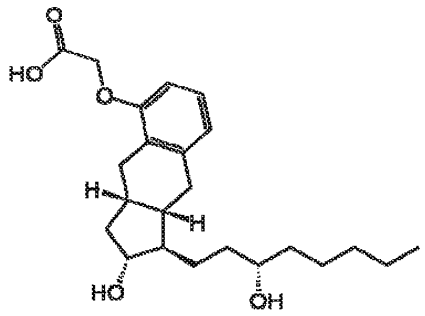
Indeed, the only example given in Eğe is of benzoic acid – a very simple aromatic acid that is quite different from the structure of treprostinil, as it has no chiral centers and therefore no stereoisomeric impurities. *Id.* at ¶108. Given that Eğe only predicts the removal of neutral and basic compounds by a salt purification step followed by acidification and only describes a simple non-chiral carboxylic acid, a POSA would have no motivation to look to Eğe for purification and no reasonable expectation of success given that many of the impurities in treprostinil are acidic stereoisomers. *Id.* at ¶¶108-109.

As discussed above, the average impurities found in samples of the Moriarty product include three different stereoisomers of treprostinil free acid. Eğe suggests that a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step would not remove these compounds from the product. Thus, a POSA would have understood Moriarty, Phares, and Eğe to suggest simply making the treprostinil free acid product of Moriarty, and not undergoing the additional time and expense of a "carboxylate salt formation and regeneration of the neutral carboxylic acid" step because Eğe actually teaches away from the usefulness of this step when impurities include acidic stereoisomers are present because a POSA would have to ignore Eğe's teaching that these types of impurities could not be removed by carboxylate salt formation. *See* Ex. 2020 ¶¶107-109; *see also United States v. Adams*, 383 U.S. 39, 42-43 (1966).

The Institution Decision cites *KSR* for the proposition that "a technique has been used to improve one device, and a POSA would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Paper 12 at 45. However, the simple application of this proposition regarding devices (a predictable art) should not be applied to an unpredictable field, such as the chemical arts, without truly examining whether the technique would improve *similar compounds* in the *same way*. *See, e.g., In re Fisher*, 427 F.2d 833, 839 (C.C.P.A., 1970)(contrasting "predictable factors, such as mechanical or electrical elements" from "unpredictable factors, such as most chemical reactions"); *see also, Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

For example, Kawakami teaches purification of a methanoprostacyclin derivative by forming the dicyclohexyl amine salt and then regenerating the free acid to achieve a "fairly high" purity. Analogizing to the language cited from *KSR*, a POSA must have recognized that the "technique" of salt formation followed by regeneration of the free acid would improve *similar compounds* in the *same way*.

However, as can be seen by the below comparison, the structures of treprostinil and the methanoprostacyclin derivative of Kawakami are structurally very different – they are not *similar compounds/devices*.



Treprostinil

methanoprostacyclin compound in Kawakami

First, the methanoprostocyclin compound in Kawakami is a-two fused-ring structure, while treprostinil is a three-fused-ring structure. Ex. 2020 at ¶112. Second, Kawakami does not actually disclose a purification method for separating diastereomers, but instead one for separating E and Z isomers. Ex. 2020 ¶¶112-113.

Indeed, Kawakami teaches that the starting material does not vary at each chiral center other than the alkene double bond. *Id.* In other words, Kawakami discloses a mixture of two compounds: (1) the E-isomer of a stereoisomerically pure compound and (2) the Z-isomer of a stereoisomerically pure compound. *Id.* at ¶113. Treprostinil contains no mixture of E and Z isomers because it does not contain a carbon-carbon double bond that is capable of forming E and Z isomers. Indeed, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of a much more complex compound with

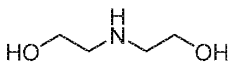
multiple chiral centers such as treprostinil could be isolated from entirely different impurities and then converted back to the free acid form. *Id.*

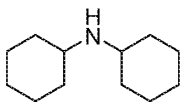
Thus, the purification of treprostinil from its stereoisomers and related impurities is quite different from the purification of the methanoprostacyclin derivative from its structural isomer – the compositions are not improved in the *same way*.

As a result of these differences, "a POSA would not have looked to Kawakami (or Eğe) if they were looking for additional purification techniques for treprostinil because neither reference discloses how to remove stereoisomeric impurities." *Id* at ¶112.

2. Kawakami Would Have Motivated One of Ordinary Skill In The Art To Select A Dicyclohexyl Amine Salt, Teaching Away From The Diethanolamine Salt of Claims 14 and 18

Not only are there structural differences between treprostinil and the "methanoprostacyclin compound" in Kawakami, but the counter-ion used to prepare the salt is structurally different. *Id.* at ¶114. Specifically, Kawakami teaches preparing the dicyclohexyl amine salt, whereas particular claims of the '393 patent require use of the diethanolamine salt.





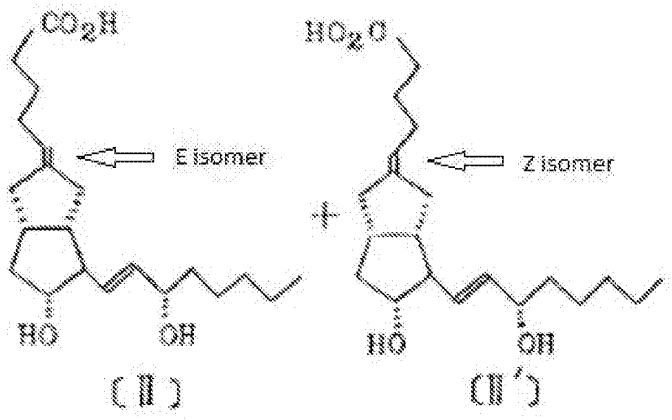
Diethanolamine **dicyclohexyl amine**

Because Kawakami uses a different salt to remove a different sort of impurity from a different structure, a POSA would have no reason to combine the teachings of Kawakami with Moriarty and Phares in the particular manner of the asserted grounds in the Petition, or a reasonable expectation of success of achieving a more pure treprostinil product by such a combination. Ex. 2020 ¶114. For this reason, claims 14 and 18 are separately patentable.

3. Kawakami Does Not Provide A Reasonable Expectation Of Success That Treprostinil Products Could Be Further Purified Because Different Impurities Are Targeted

The purification of treprostinil from its stereoisomers and related impurities is quite different from the purification of the methanoprostacyclin derivative from its structural isomer, and thus, Kawakami provides no reasonable expectation of success. Ex. 2020 ¶¶112-114

To illustrate this point further, Kawakami is directed to purifying E- and Z-isomers of methanoprostacyclin compound from one another. In order for the E- and Z-isomers to exist, the "prostacyclin compound" must have an alkene. For example, Kawakami discusses separating a mixture of the following compounds:



Treprostinil, on the other hand, contains no mixture of E/Z isomers. In fact, it cannot because it does not contain an alkene capable of E/Z isomerization. SteadyMed has failed to provide a factual basis as to how or why the separation of E/Z isomers of an alkene would provide a motivation to combine or reasonable expectation of success in a compound not containing an alkene capable of E/Z isomerization, such as treprostinil. As explained in the Williams Declaration, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of an entirely different compound, such as treprostinil, could be isolated from entirely different impurities, such as stereoisomers and related impurities. Ex. 2020 ¶¶112-114.

Furthermore, the Kawakami reference would have provided no motivation or rationale to attempt to remove the trace impurities of the Moriarty treprostinil free acid through the process of salt formation followed by conversion back to the

free acid. Indeed, Kawakami was concerned with isolating a particular isomer from a 7:2 E/Z isomeric mixture. Ex. 1007 at 4. In other words, the composition in Kawakami contained, at most, a purity of 77.8% prior to the salt formation step. Kawakami provides a crude purification of the desired E-isomer through a particular salt formation, and suggests that not all impurities were removed by formation of a salt and conversion back to the free acid. *Id.* at 5 ("purity can be further improved by recrystallization"). Nothing in the reference suggests that a substance as pure as the Moriarty treprostinil free acid (a substance with about 99.4% assay purity) – a substance that had already been "further improved" by recrystallization (*see* Ex. 1004 at 13, right column) – would be improved by formation of a salt and conversion back to the free acid. Ex. 2020 ¶¶113-114.

Thus, even if formation of a salt and conversion back to the free acid was known in the art, it would not have rendered the present claims obvious without some motivation and expectation of success in its use on the Moriarty treprostinil free acid. To put it another way, there would have been no reason to incur additional time and expense to form a salt of the valuable, relatively pure Moriarty treprostinil free acid only to then convert it back to the free acid, even though the addition would have been technologically possible. *In re Omeprazole Patent Litigation,* 536 F.3d 1361 (Fed. Cir. 2008).

4. Any "Close" Structural Similarity of the Moriarty Free Acid Does Not Render the Claims Obvious

As explained above, the claimed substance is structurally different from Moriarty's treprostinil free acid because the claimed substance has an improved and different impurity profile. Even if the Board views an improvement in impurity profile of, e.g., 0.7%, as a close relationship between the substances of the present claims and of Moriarty, there is no obviousness because there was not a known or obvious process for making the claimed free acid substance. *See In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968)("the absence of a known or obvious process for making the claimed compounds overcomes any presumption that the compounds are obvious based on close relationships between their structures and those of prior art compounds"). For the reasons set forth in the previous sections, conducting a salt-formation purification step on the known treprostinil free acid of Moriarty would not have been obvious, so the mere existence of a "close relationship" in the products cannot be used to deny patentability.

5. Additional Claim Limitations Are Not Disclosed by the Cited Prior Art

In addition to the reasons above, certain dependent claims would also not have been obvious in light of the combination of Phares, Moriarty, Eğe, and Kawakami. Claim 6 requires the acid in step (d) to be either HCl or H_2SO_4 and

claim 15 requires the acid to be HCl. Similarly, claim 21 requires step (d) is performed. Phares, Moriarty, and Kawakami all do not disclose the use of either HCl or H_2SO_4 and do not disclose converting a carboxylic acid salt back to its salt form using an acid. Ex. 2020 at ¶115. "Eğe cites HCl as an example in the conversion of benzoic acid, but as described above, a POSA would not have looked to Eğe to further purify a complex carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure." *Id.* In addition to the reasons above, claims 6, 15, and 21 would not be obvious in light of any combination of the cited prior art.

Like claim 2, claim 10 requires that the product be 99.5% pure and that step (d) be performed. The only purity limitation disclosed in any cited prior art reference is in Moriarty and, as explained above, that purity cannot be directly compared to the purity recited by the claims. Similarly, Moriarty does not perform steps (c) or (d). *Id.* at ¶116. A POSA would have no motivation to look to Phares, Kawakami or Eğe to improve the purity to at least 99.5% and, given that none of these references disclose a purity amount, would have no reasonable expectation of success in achieving that purity. *Id.* Finally, claim 22 requires an extra step of forming a pharmaceutically acceptable salt from the product of step (d). SteadyMed and Dr. Winkler cite no evidence whatsoever for this additional step.

"In fact, none of the references cited even suggest converting a carboxylic acid to a salt form, then regenerating the carboxylic acid, then forming a pharmaceutically acceptable salt from that." *Id.* at ¶117. For this additional reason, claim 22 is not obvious in light of the combination of Phares, Moriarty, Kawakami, or Eğe.

Consequently, SteadyMed has not carried its burden on Ground 3.

VIII. SECONDARY CONSIDERATIONS REBUT ANY POSSIBLE CASE OF OBVIOUSNESS

SteadyMed has not established a *prima facie* case of obviousness. Thus, UTC is not obligated to provide evidence of objective indicia of non-obviousness. Nonetheless, objective indicia of non-obviousness confirm that the claims of the '393 patent would not have been obvious and, in fact, represent a surprising solution to the problem of minimizing impurities and providing a safer and purer treprostinil product.

A. Long-Felt Unmet Need

At the time of the invention, there was a long-felt need to have a more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner. *See generally*, Ex. 2022 at ¶¶31, 65. Treprostinil has five chiral centers resulting in 32 possible diastereomers, so the potential for diastereomeric impurities is high; only the treprostinil stereoisomer has the desired pharmaceutical effect. Ex. 2013, at pp. 11, ll. 18-25, pp. 15, ll. 1-pp. 16, ll. 8, pp. 19, ll. 14-25.

Treprostinil is also a very potent drug so any diastereomeric impurities would also potentially be potent. *Id.*; Ex. 2022 at ¶54. Specifically, the FDA as a matter of course seeks to minimize all impurities in drug substances and particularly in highly potent drug substances such as treprostinil. Ex. 2022 at ¶¶ 31, 54. The reduction and removal of several types of impurities met the long-felt need expressed by the FDA to minimize impurities as much as possible. *Id.* at ¶¶ 31, 75. Additionally, because the '393 patent product was so successful, it resulted in a change in the drug specification submitted to FDA. *Id.* at ¶¶66-67. The change indicated that the assay purity of the new drug substance made by the '393 patent process increased in purity from an assay range of 97.0 – 101.0 % to 98.0 – 102.0% - a full 1% increase in assay purity. *Id.* at ¶ 70. The range of assay values of 4% as well as the amount above 100% does not indicate an error associated with the measurement, but just the acceptable value of this measurement approved by the FDA. *Id.* at ¶¶ 69-70. The fact that UTC submitted a 1% increase in assay purity to FDA is considered a "major" change by FDA. *Id.* at ¶ 72. *See Knoll Pharm. Co., Inc. v. Teva. Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir. 2004) (while FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness). In fact, even a change as small as 0.1% of impurities can have an impact on a drug substance. *See, e.g., id.* at ¶¶ 32, 45. Given that FDA consistently wants drug substances to have fewer

impurities and in less amounts, the '393 patent invention met that need by further reducing and removing certain specific impurities and by increasing the overall assay purity of the drug substance.

B. Unexpected Results

The results of the claimed inventions in the '393 were unexpected. The use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was an unexpected result. Moreover, it was unexpected that the salt purification step reduced not only diastereomeric impurities, but also certain non-acidic impurities as well. *See, supra*, Section XI.B.1; Ex. 2020 ¶¶94-97, 102, 108-109. Indeed, Eğe itself predicted that a salt formation followed by regeneration using an acid would remove only basic and neutral impurities. *Id.* at ¶107. The unpredictability of this result is supported by the fact that the salt purification step did not reduce all non-acidic impurities; in fact, the '393 product has slightly increased levels of one such impurity, treprostinil ethyl ester. Ex. 2020 ¶96. Thus, a person of skill in the art would not have expected the results of the '393 patent to be so successful at reducing the levels of so many impurities.

IX. Conclusion

For the foregoing reasons, the Board should hold that SteadyMed has failed to carry its burden attacking the patentability of the instituted claims because none

of the prior art cited by SteadyMed anticipates or renders obvious any claim of the '393 patent.

Respectfully submitted,

Date: July 6, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Reg. No. 35,264

CERTIFICATE OF COMPLIANCE

This Paper contains 11,230 words according to the word processing program in which it was created, excluding the portions exempted by 37 C.F.R. ¶42.24(a)(1). Accordingly, this Paper complies with the requirements of 37 C.F.R. § 42.24(b)(1).

Date: July 6, 2016

Signature: /Stephen B. Maebius/
Stephen B. Maebius

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner Response and accompanying exhibits was served on counsel of record for Petitioner on July 6, 2016 by filing through the Board's PRPS system and by delivering a copy via email to Stuart Pollack and Lisa Haile (the counsel of record for the Petitioner) at the following address:

Steadymed-IPR@dlapiper.com

Date: July 6, 2016 Signature: /Stephen B. Maebius/
Stephen B. Maebius

4814-0612-4340.3

[redacted]

United Therapeutics

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

United Therapeutics

[redacted]

[redacted]

[redacted] The chemical manufacturing steps have not changed during the transfer to [redacted] and [redacted] from the process used by UT in Chicago to prepare benzindene triol. [redacted] There is a release specification for benzindene triol that must be achieved for each lot of benzindene triol before it is released for use by UT to prepare treprostinil. This is the same specification that was used by United Therapeutics in our Chicago facility.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] In all lots, the total unidentified impurity level (%AUC) decreased from triol to UT-15C intermediate. [redacted]

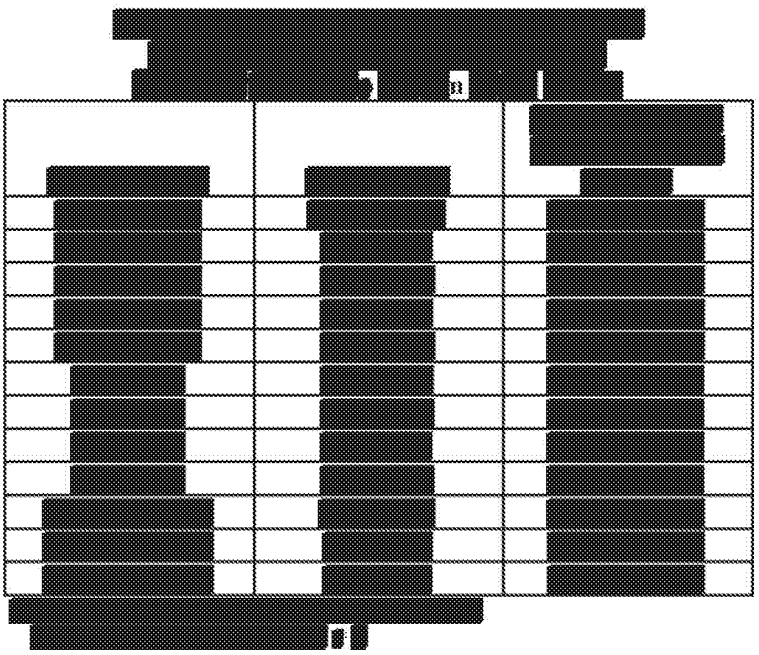
[redacted]

[redacted]

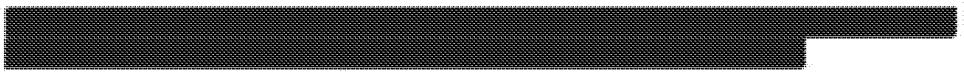
[redacted]

[redacted]

[redacted]



[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-00006
Patent 8,497,393

DECLARATION OF ROBERT M. WILLIAMS, Ph.D., IN SUPPORT OF PATENT OWNER RESPONSE TO PETITION

TABLE OF CONTENTS

I have been retained by the law firm of Wilson Sonsini Goodrich & Rosati ("WSGR") as an expert consultant to United Therapeutics Corporation ("UTC") in connection with the above-identified matter to provide expert testimony concerning U.S. Patent No. 8,497,393 ("the '393 Patent", Ex. 1001) by Batra *et al.*, entitled "Process to prepare Treprostinil, the active ingredient in Remodulin," issued on July 30, 2013. At the request of Counsel for UTC, I hereby submit this expert declaration.

I. Qualifications and Background

A. Education and Experience

1. I am a tenured University Distinguished Professor of Chemistry at Colorado State University (CSU). I currently serve as the Director for the Colorado Center for Drug Discovery. I also served as co-Director (Experimental Therapeutics) for the Infectious Diseases Supercluster Initiative and also served as co-Director for the Cancer Supercluster Initiative at CSU. My *curriculum vitae* is attached hereto as Exhibit A (Ex. 2021).

2. I received a B.A. in Chemistry from Syracuse University in 1975, and did laboratory research in the field of synthetic organic chemistry under the guidance of the recent Nobel Laureate Professor Ei-ichi Negishi. In 1979, I received both a Master's degree and Ph.D. degree in Organic Chemistry from the Massachusetts Institute of Technology (MIT) under the direction of Professor William H. Rastetter. Upon graduating from MIT, I spent one year (1979-80) as a postdoctoral fellow at Harvard University in the laboratories of the Nobel Laureate, the late Professor Robert B. Woodward, whose laboratory was subsequently managed by Professor Yoshito Kishi.

3. Subsequent to my fellowship at Harvard, I served as an Assistant Professor at Colorado State University from 1980–84. I was tenured and promoted early, to the rank of

Associate Professor in 1985, and in 1988, I was promoted to the rank of Full Professor. In 2002, I was named a University Distinguished Professor, which is my current position. University Distinguished Professor is the highest academic rank at Colorado State University, and there are a maximum of twelve University Distinguished Professors at any given time out of a faculty of 1,200. This is a lifetime appointment until retirement, whereupon Emeritus status is granted. In addition to my positions at Colorado State University, I was a Visiting Professor of Chemistry at Harvard University from 1994–95, at which time I was sponsored by Professor Stuart L. Schreiber and taught a sophomore organic chemistry course for pre-medical students, Chem 17. I was also a Visiting Professor of Chemistry at the University of California at Berkeley in 1990 and worked in the laboratory of Professor Peter G. Schultz.

4. I have extensive experience in the field of synthetic organic chemistry and medicinal chemistry with an emphasis on biologically active compounds including anti-tumor agents, heterocycles, antibiotics, anti-fungal agents, anti-viral agents, immunomodulators, amino acids, peptides and alkaloids, among many other classes of biologically active organic substances. My organic chemistry research interests include the total synthesis of novel natural and synthetic products, heterocyclic chemistry, asymmetric synthesis, synthetic methodology, process chemistry, and reaction mechanisms. I have extensive experience in the synthesis, chemistry, conformational analysis, biochemical activity, and biological activity of a range of organic compounds.

5. My research laboratory at Colorado State University has worked extensively on the chemistry and biology of numerous drugs over my career, including Quinocarcin (Quinocarmycin citrate), Tetrazomine, Bioxalomycin, Ecteinascidin 743 (Yondelis® or trabectidin), Renieramycin, Cribrostatin-4, Jorumycin, the Mitomycins, FR900482, FK973,

FK317, FK228 (Romidepsin), Largazole, Stephacidins A and B, Avrainvillamide, Spirotryprostatins, TMC-95A/B, Rottlerin, and Antimycin, amongst many others.

6. I have been the Principal Investigator on numerous research grants from Federal agencies, such as the National Institutes of Health (NIH) and the National Science Foundation (NSF) as well as from various Foundations, and corporations to synthesize biologically active compounds on both small laboratory scale as well as larger industrial scales.

7. I held a funded research collaboration with the Infectious Diseases Research Institute (IDRI), in Seattle, Washington, to develop several novel adjuvants for the treatment and prevention of autoimmune diseases, infectious diseases and cancer (2010).

8. From 1991-1993, I held a research grant from Symphony Pharmaceuticals, located in Philadelphia, Pennsylvania, to prepare anti-HIV drugs based on inhibition of the HIV protease. I supervised a graduate student who prepared several very potent peptide isosteres that exhibited in vitro activity against HIV.

9. I have taught undergraduate and graduate courses in organic chemistry, organic synthesis, biosynthesis, biological chemistry, drug design, and the synthesis of natural products. I have also lectured at numerous professional conferences, universities, and in corporate R&D laboratories in those areas.

10. I am a Scientific Founder, Acting President, and Chair of the Scientific Advisory Board of Cetya Therapeutics, a company that is developing several drugs, including drugs for the treatment of various cancers, multiple myeloma, autoimmune diseases, and hemoglobinopathies. I also direct all of the process scale synthesis optimization and drug formulation studies being conducted on Cetya's HDAC inhibitors. This includes injectable formulations as well as oral formulations. Specifically, I directed and supervised post-doctoral researchers in my laboratory

(on behalf of Cetya Therapeutics) to formulate the poorly water-soluble drug Largazole, including a myriad of synthetic analogs of Largazole prepared in my laboratory, as a polysorbate-80/ethanol co-solvent excipient system. This formulation has been used in animal studies for obtaining critical dose-escalation and pharmacokinetic data. I have also specifically directed and supervised the formulation of Largazole and related analogs in various PEG-based (polyethylene glycol) excipient systems. This work is currently being conducted in collaboration with oncologist Dr. Douglas Thamm of the Colorado State University Animal Cancer Center, pharmacologist Dr. Dan Gustafson of the Colorado State University Animal Cancer Center, Dr. Kimberly Stegmaier of the Dana-Farber Cancer Institute/Harvard Medical School and Dr. James E. Bradner of the Dana-Farber Cancer Institute/Harvard Medical School. The animal studies commenced in 2010, and the drug formulation studies are being conducted in my laboratory at Colorado State University under my direction.

11. I was a Scientific Founder, Member of the Scientific Advisory Board, and Member of the Corporate Board of Directors for Xcyte Therapies, a company devoted to developing *ex vivo* T-cell therapies for treating cancer, autoimmune, and infectious diseases, including HIV. As a Scientific Founder and Member of the Board of Directors of Xcyte Therapies, I was deeply involved in writing the patents and developing formulation strategies for both topical and injectable drugs based on FK228 (Romidepsin).

12. As a Scientific Founder and Acting Vice-President of Discovery Chemistry of HemaQuest Pharmaceuticals (Seattle, Washington), I have directed the pre-clinical and clinical synthesis, scale-up and formulation studies of several of the companies' drugs. These include both water-soluble drugs and hydrophobic, poorly water-soluble drugs for therapeutic applications in both cancer and hemoglobinopathies. I directed both the medicinal chemistry

efforts as well as the pre-process optimization work for potential industrial-scale syntheses of our lead drug candidates.

13. In addition, I am a Scientific Founder and member of the Scientific Advisory Board of Sapientia Therapeutics, located in Philadelphia, Pennsylvania. I am the acting Director of the Medicinal Chemistry, Process Chemistry and Drug Formulation efforts of this company to develop novel small-molecule inhibitors of protein kinase C-delta for autoimmune diseases, cancer and scleroderma. My laboratory has synthesized the first lead compounds, which are protein kinase C-delta (PKC-Δ) inhibitors and are water-insoluble substances. Under my direction we have engaged in early scale-up and route optimization for our leading drug candidates.

14. As a chemist with expertise in structure-activity studies and synthesis of biologically active agents, I have been retained to consult for a number of pharmaceutical and biopharmaceutical companies for both drug discovery and process research applications over the past thirty years. I consulted for Ajinomoto Co., Japan from 2002-2014 in the general area of process chemistry in the manufacture of amino acids, their derivatives, pharmaceutical intermediates and peptide synthesis. I served as a consultant for Cubist Pharmaceutical Company (2000–03) in the general field of antibacterial agents. I consulted for NewBiotics, Inc. (2001–02) in the general fields of anti-infective agents and anti-cancer agents. I consulted for Hoffman-La Roche, Inc. (1989–92) in the field of cephalosporin-fluoroquinolone dual-action antibacterial agents, as well as on a project concerned with inhibitors of diaminopimelic acid (DAP) biosynthesis as potential antibacterial agents. I consulted for W.R. Grace (1985–90) in the area of specialty chemicals and pharmaceutical intermediates process manufacturing and process development. I was a Scientific Founder, Member of the Scientific Advisory Board,

Consultant and sub-contractor for Microcide Pharmaceutical Co. (Microcide) in their drug discovery and early process research efforts. Microcide was a biopharmaceutical company devoted to developing antibacterial agents against a range of drug-resistant bacterial and fungal infectious diseases. In addition, I have consulted for EPIX Medical, G. D. Searle, Nutrasweet, and Boehringer-Ingelheim, among others. The consulting work I performed for Nutrasweet (1990-1991), was concerned with large-scale manufacturing process chemistry for Aspartame.

15. I was a co-organizer of a special Symposium on process chemistry at The International Chemical Congress of Pacific Basin Societies, PacifiChem 2015 (December 15-18. Honolulu, Hawaii) entitled: *"New Horizon of Process Chemistry by Scalable Reactions and Technology."*

16. I have directed the research activities of more than sixty PhD students and eighty post-doctoral fellows; most of my former co-workers have gone on to successful careers in the pharmaceutical industry in both process research and medicinal chemistry.

17. I have delivered numerous named and plenary lectures at Universities, corporations, and scientific societies on the synthesis, chemistry, biology, and mechanism of action of numerous classes of therapeutic agents, as detailed in my *curriculum vitae* attached hereto as Exhibit A.

18. I have published more than 315 scientific research articles, authored numerous chapters in books, and have written a well-known textbook on the synthesis of optically active amino acids. I have particular expertise in the large-scale industrial synthesis of amino acids and their derivatives. I am also a named inventor on seventeen issued U.S. patents and published patent applications. My publications and patents are listed on my CV, provided in Exhibit 2021.

19. I currently serve on the Editorial board for *Chemistry & Biology*. I have served as Editor for the *Organic Chemistry Series* published by Pergamon Press and Elsevier (1997-2012), and *Mini Reviews in Organic Chemistry* (Bentham Science). I have also served as an editor for several other journals in the past, including *Tetrahedron: Asymmetry*, *Tetrahedron Publications*, *Amino Acids*, and the *Journal of the American Chemical Society*.

20. I am a member of the American Chemical Society, the Japan Antibiotics Research Association, the International Society of Heterocyclic Chemistry, and the American Association for the Advancement of Science. I am a Member of the University of Colorado Cancer Center, located in Aurora, Colorado. I have served as organizer or co-organizer of numerous scientific meetings and symposia, and served as the Vice President of the International Society of Heterocyclic Chemistry, Chairing the 2003 International Congress of Heterocyclic Chemistry.

21. I serve on the Scientific Advisory Board of Arch Therapeutics, located in Boston, Massachusetts, that is developing self-assembling peptides for wound healing and surgical closure.

22. I have also served on the Scientific Advisory Boards for a number of other companies. I currently serve on the External Advisory Committee for the Puerto Rico Alliance for the Advancement of Biomedical Research Excellence. I was a Scientific Founder, Director of Chemistry, and member of the Scientific Advisory Board for HemaQuest Pharmaceuticals. I was a Founding Scientist and Member of the Scientific Advisory Board of Microcide Pharmaceuticals from 1993 to 1998.

23. I have expertise in drug formulation for injectable, topical and oral medications. I have directed research programs, both through my academic laboratory at Colorado State University as well as through my various consulting engagements and as a research director

and/or consultant for companies developing medicines for numerous therapeutic indications. I have consulted on many aspects of pharmaceutical drug discovery, development, formulation, and manufacturing. This includes basic discovery and optimization, early process research, large-scale manufacturing, and drug formulation.

24. I have served as a consultant for a number of companies for both drug discovery and process research applications, including, for example, W.R. Grace Company (1985-1990, fine chemicals synthesis); Symphony Pharmaceuticals (1991-1993, anti-HIV drugs); G.D. Searle Co. (1988-1990, memory and learning enhancement agents based on NMDA receptor antagonists); Nutrasweet Co. (1990-1991, artificial sweeteners); EPIX Medical (1993-1997, MRI imaging and contrast agents); Hoffman-La Roche, Inc. (1989-1992, cephalosporin-fluoroquinolone dual-action antibacterial agents); Boehringer-Ingelheim Pharmaceuticals (1992-1993, antiviral agents); Cubist Pharmaceutical Company (2000-2003, macrocyclic peptide antibacterial agents); NewBiotics, Inc. (2001-2002, anti-infective agents and anti-cancer agents); Microcide Pharmaceutical Co. (1993-1998, analogs of macrocyclic anti-fungal agents related to echinocandin, cephalosporins, and quinolones); Xcyte Therapies (1996-2006, T-cell activation); Ajinomoto Co, Japan (2002-2014, amino acids, peptides, and other specialty chemicals); HemaQuest Pharmaceuticals (2006-2014, short chain fatty acids for treating hemoglobinopathies); Sapientia Therapeutics (2012-present, small-molecule inhibitors of protein kinase C-delta); Arch Therapeutics (2010-present, self-assembling peptides for wound healing); and most recently, Cetya Therapeutics (2012-present, histone deacetylase inhibitors as therapeutic agents for treating cancers, multiple myeloma, autoimmune diseases, and hemoglobinopathies).

25. Under my direction, my laboratory developed the technology for the asymmetric synthesis of amino acids in 1985 that was commercialized by Aldrich Chemical Co. in 1988. My laboratory devised several large-scale (multi-kilogram) process routes for the manufacture of the so-called "Williams Lactone" that has been sold by Sigma-Aldrich Chemical Company since 1988. Early manufacturing was conducted in China by several of my former co-workers at the Chengdu Institute of Organic Chemistry.

26. I have been awarded numerous prizes and awards including the NIH Research Career Development Award (1984-89), the Eli Lilly Young Investigator Award (1986), the Merck, Sharp & Dohme Academic Development Award (1991), an award from the Japanese Society for the Promotion of Science Fellowship (1999), the Arthur C. Cope Scholar Award sponsored by The American Chemical Society (2002), the Multiple Myeloma Research Foundation Senior Award (2010), the ACS Ernest Guenther Award in the Chemistry of Natural Products sponsored by Givoudan and The American Chemical Society (2011), an award from the Japanese Society for the Promotion of Science Long-term Fellowship (2012-2013), and the Organic Synthesis Award from the local Rocky Mountain section of the American Chemical Society (2012).

27. I have testified numerous times as an expert witness in process chemistry patent litigation in the following matters: Great Lakes Chemical *versus* Archimica SPA. Civil Action No. 99–728-JJF; Ranbaxy Laboratories *versus* Abbott Laboratories. Case No. 04 C 8078; Lundbeck *versus* Infosint. 06 Civ. 2869 (LAK); United Therapeutics Corp. *versus* Sandoz, Inc. C.A. Nos.: 12-1617 (PGS)(LHG) and 13-316 (PGS) (LHG); Gilead Sciences, Inc. and Emory University *versus* Cipla, Limited. Civil Action No.: 1:12-cv-06350-RJS; United Therapeutics

Corp. *versus* Teva Pharmaceuticals, USA, Inc. C.A. No.: 3:14-cv-05498 (PGS)(LHG); United Therapeutics Corp. *versus* Sandoz, Inc. C.A. No.: 3:14-cv-05499 (PGS)(LHG).

B. Materials Considered

28. In forming my opinions in this report, I have relied upon my professional experience and personal knowledge. I have also reviewed a number of documents in this case including all documents cited by the SteadyMed and UTC as well as the materials I have cited in this declaration. In this report, I have provided representative citations to exemplary documents that I have relied upon in reaching my opinions. If I am provided additional information or documents in this proceeding, I may offer further opinions regarding the additional information.

II. Legal Standards Provided By Counsel

29. I have been informed by Counsel that, during an *inter partes* review (IPR), a petitioner must prove invalidity by a preponderance of the evidence. Accordingly, I understand that the burden is on a petitioner to prove invalidity, rather than a patent owner to prove validity. I have been informed by Counsel that because each claim defines a separate invention, the validity of each claim in a patent is addressed independently of the validity of the other claims in that patent.

30. I have also been informed by Counsel that the claims of the '393 patent are "product-by-process" claims. I have also been informed by Counsel that when evaluating the validity of a patent claim, the "product" of product-by-process claims must include structural and/or functional differences over the prior art, even if they are not explicitly claimed.

A. The Person of Ordinary Skill in the Art

31. I have been informed by Counsel that a patent is to be interpreted from the perspective of a hypothetical person referred to as the person of ordinary skill in the art ("POSA")

to which the patent pertains. I am further informed that a determination of the level of ordinary skill is based on, among other things, the type of problems encountered in the art, prior art solutions to those problems, rapidity with which innovations are made, sophistication of the art, and the educational level of active workers in the field. I have been informed that in any particular case, every factor may not be present, and one or more factors may predominate. I understand the person of ordinary skill in the art is presumed to know all prior art that is reasonably relevant to the subject matter of the claimed invention.

32. I understand from Counsel that the validity of a patent claim must be assessed from the perspective of a POSA at the time of the invention.

33. Given the complexity of the chemistry involved in the '393 patent, it is my opinion that a POSA with respect to the patent-in-suit would have had, at the time of the claimed invention, a doctorate degree in chemistry, pharmaceutics, pharmaceutical sciences, medicine, or a related discipline. Alternatively, the POSA may have had a lesser degree in one of those fields, with correspondingly more experience. To the extent necessary, a POSA may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds. It is my understanding that a patent is to be interpreted from the perspective of a person of ordinary skill in the art at the time of the patent's priority date.

34. I understand that SteadyMed's expert Dr. Winkler has opined that a POSA would have "a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively, a person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry." Ex. 1009 at ¶14.

35. All of my opinions regarding validity contained in this report are expressed from the view of a POSA at the time of the priority date of the '393 patent. These opinions apply equally whether my definition of a POSA or Dr. Winkler's is applied.

B. Anticipation

36. I understand from Counsel that anticipation requires that each and every element of a claim is set forth in a single prior art reference, and that these elements are arranged or combined in that reference in the same way as recited by the claim. I further understand from Counsel that if there is any difference between the prior art reference and the claimed invention, there is no anticipation by that reference. Further, I understand that there is no anticipation if the elements disclosed in a prior art reference must be combined with the knowledge of one skilled in the art to achieve the subject matter of the claim. I understand that for a prior art reference to be anticipatory, it must enable a POSA to make or practice the invention without undue experimentation.

37. I also understand from Counsel that if the single prior art reference is missing a claimed feature, the reference may inherently anticipate if that missing feature is necessarily present in the single prior art reference.

38. I also understand from Counsel that if there are structural or functional differences in the product of the product by process claims of the invention from the product of the prior art that arise from the process in which it was made, those differences may be evidence of no anticipation even if those differences are not explicitly claimed.

C. Obviousness

39. I understand from Counsel that obviousness requires that a POSA would have been able to arrive at the claimed invention by modifying a single prior art reference or by

combining two or more prior art references. I also understand from Counsel that obviousness analysis must be conducted from the point of view of a POSA at the time of the invention, and that it is improper to employ hindsight or consider the inventors' own path to the invention as proof of obviousness.

40. Counsel has also informed me that obviousness requires that a POSA would have had a reasonable expectation of success in achieving the claimed invention.

41. I understand from Counsel that four factual issues are relevant to obviousness analysis: the scope and content of the prior art; the level of ordinary skill in the field of the art at the time of the invention; the differences between the claimed invention and the prior art; and various objective indicia of non-obviousness.

42. I understand from Counsel that, in addition to considering the prior art, certain objective indicia may also provide evidence that a claimed invention is not obvious. I am informed by Counsel that these objective indicia, which are also referred to as secondary considerations, may include factors such as commercial success, unexpected results, the resolution of long-felt but previously unmet needs, skepticism by others prior to achieving the invention, failure of others to achieve the invention, praise from others for the invention, and copying by others.

43. I understand from Counsel that, like anticipation, if there are structural or functional differences in the product of the product by process claims of the invention from the product of the prior art that arise from the process in which it was made, those differences may be evidence of non-obviousness even if those differences are not explicitly claimed.

III. Summary of Opinions

44. It is my opinion that the term "product" as it is used in the claims of the '393 patent should be construed using UTC's construction: "a substance resulting from a chemical reaction."

45. It is my opinion that the term "[a] product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof" as it is used in the claims of the '393 patent should be construed using UTC's construction: "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof."

46. It is also my opinion that none of the claims of the '393 patent are anticipated by or rendered obvious by the prior art.

47. My opinions and the bases for them are based on information that I know, that I have reviewed, and that I am currently aware exists. I reserve the right to supplement or amend my opinions in light of any additional evidence, testimony, or other information that may be provided to me after the date of this declaration. Additionally, I may use the cited materials to assist me in preparing demonstratives such as graphics and animations if I am asked to testify.

IV. The '393 Patent

48. The '393 patent is directed to an improved treprostinil product and improved process for making the product. I understand from Counsel that the priority date for the '393 patent is December 17, 2007.

49. The synthesis of treprostinil is complex as several improvements resulting in improved products are disclosed in the '393 patent itself. The structure of treprostinil has five chiral centers (stereogenic centers) resulting in 32 possible stereoisomers of treprostinil.

50. The '393 patent has two independent claims: Claims 1 and 9. Claim 1 requires "a product comprising a compound of formula I…or a pharmaceutically acceptable salt thereof," in which formula I can be several structures including treprostinil. Claim 9 requires "[a] product comprising a compound having formula IV…or a pharmaceutically acceptable salt thereof," in which is the structure of treprostinil. Both Claims 1 and 9 then specify that the product is prepared by a process comprising (a) alkylating a compound of Formula II or V [a benzindene triol structure] with an alkylating agent to produce a compound of Formula III or VI [a benzindene nitrile intermediate], (b) hydrolyzing the product of formula III or VI of step (a) with a base, (c) contacting the product of step (b) with a base B to form a salt of Formula Is or IVs [indicating a salt form of treprostinil with an HB+ counterion], and (d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I or IV. Dependent Claim 7 further identifies the specific structure of Formula I of the product of Claim 1 as treprostinil. Because the other possible structures of Claim 1 are not at issue here, I will consider these Claims 1, 7, and 9 together in my analysis. Likewise, I will consider the following dependent claims together that have similar claim limitations.

51. Dependent Claims 2 and 10 provide a further purity limitation. Claim 2 further requires "[t]he product of claim 1 wherein the purity of compound of formula I in said product is at least 99.5%." Similarly, Claim 10 requires "[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%." Thus, step (d) must be performed in claim 10, but both of these claims require a purity of at least 99.5%.

52. Dependent Claims 3 and 11 provide a further limitation on what alkylating agent may be used. Claim 3 requires the alkylating agent be $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$. Claim 11 requires the alkylating agent be $Cl(CH_2)_wCN$.

53. Dependent Claims 4 and 12 specify what base may be used in step (b). Claim 4 requires the base in step (b) to be KOH or NaOH and Claim 12 requires the base to be KOH.

54. Dependent Claims 5, 13, 14, 17 and 18 specify what the base B in step (c) may be selected from certain specific bases. Claims 5, 13, and 17 limit base B to the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine. Claims 14 and 18 specify that the base B is diethanolamine.

55. Dependent Claims 6 and 15 specify what acid is used in step (d). Claim 6 specifies the acid is HCl or H_2SO_4. Claim 15 specifies the acid is HCl.

56. Dependent Claims 8 and 16 specify that the process does not include purifying the compound of formula III or VI produced in step (a).

57. Dependent Claims 19 and 20 depend on Claims 1 and 9, respectively. Each dependent claim further specifies the base in step (b) is KOH or NaOH and the base in step (c) is selected from the same group specified in Claims 5, 13, and 17.

58. Claim 21 depends on Claim 1 and requires that step (d) is performed. Claim 22 depends on Claim 21 and further requires that the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

V. Claim Construction

59. I understand from Counsel that different claim constructions for certain terms used in the claims of the '393 patent have been proposed by SteadyMed and UTC, and that the U.S. Patent and Trademark Office ("PTO") has entered a preliminary claim construction for certain terms.

60. I agree with UTC's construction of the term "product" as "a substance resulting from a chemical reaction" which is consistent with the plain and ordinary meaning of the term.

61. In the chemical context, "product" generally refers to the real world outcome or result of a reaction:

Generalized Chemical Reaction

Reactants → Products

I agree with UTC that the '393 patent itself distinguishes "product" to identify it as what comes at the end of a chemical process or chemical reaction. Prelim. Resp. at pp.17-18.

62. I also agree with the consistent definitions given by the several textbooks cited by UTC all referring to "product" as the result of a chemical reaction. *Id.* at 19.

63. In fact, I have used the term "product" consistently in my own publications to refer to the real world result of a chemical reaction. *See, e.g.*, Williams, et.al., *Asymmetric, Stereocontrolled Total Synthesis of Paraherquamide A*, J. Am. Chem. Soc. 2003, 125, 12172-178. ("However, the reaction was very slow and gave the desired cyclization product 64 in only 25% yield, accompanied by products from competing pathways.") (Ex. 2026); Williams, et.al., *Stereocontrolled Total Synthesis of (+)-Paraherquamide B*, J. Am. Chem. Soc. 1996, 118, 557-579 ("Compound 66 was refluxed in benzene with 20 equiv of sodium hydride, resulting in a very clean and high yielding cyclization reaction furnishing the desired product 68 in 93% yield.") (Ex. 2027); Williams, et.al., *Synthetic Studies on Et-743. Assembly of the Pentacyclic Core and a Formal Total Synthesis*, J. Org. Chem. 73.24 (2008): 9594-9600. ("The scarcity of the natural product from marine sources renders Et-743 an important target for synthesis.") (Ex. 2028).

64. Dr. Winkler also uses the term "product" as the result of a chemical reaction in his own publications and confirmed that understanding during his deposition. *See, e.g.*, Winkler, J., et.al., *A Pauson-Khand Approach to the Synthesis of Ingenol*, Org. Lett., 2005, 8, 1489-1491 at Abstact ("Pauson-Khand cyclization of dioxanone photoadduct 21 leads to the formation of a single product in good yield.") (Ex. 2029); *see also* Ex. 2051 at 155:12-157:3.

65. Specifically, Dr. Winkler confirmed that "the product of a chemical reaction would be essentially all of the substances that result from the treatment of a particular reactant with a particular set of reagents." Ex. 2051 at 155:2-11. This is consistent with UTC's definition as well as how Dr. Walsh interpreted the product in his Declaration submitted during prosecution of the '393 Patent. Ex. 1002 at 346-347 (showing the products containing certain other substances as impurities).

66. I disagree with the PTO's preliminary construction and SteadyMed's construction of "product" as "a chemical composition." I believe that this proposed definition is too broad and does not accurately describe the term as it is customarily used in the art and in the context of how it is defined in the '393 patent. In the chemical context, there can be no "product" if there is no corresponding reaction, process, or synthesis that it refers to. A "chemical composition" could be used to describe the starting materials, solvents, reagents, catalysts, and even the glassware used during a chemical reaction as there is no limitation on SteadyMed's construction of the term "product" on how it relates to the chemical reaction at issue.

67. In the '393 patent and each of the references I describe above, the word "product" is exclusively used to describe a substance resulting from a chemical reaction, and it is not used to describe any and all "chemical compositions."

68. SteadyMed's construction is therefore inconsistent with the understanding of a POSA and inconsistent with the '393 patent specification regarding the term "product" because "a chemical composition" is not an accurate and specific definition of the term.

69. For the reasons I previously described regarding the term "product", a POSA would understand the plain and ordinary meaning of the claim term "A product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof," as UTC's construction: "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof." This definition is consistent with how a POSA would understand the term and is consistent with its plain and ordinary meaning.

70. I disagree with the PTO's preliminary construction and SteadyMed's construction of "[a] product comprising a compound of formula I/IV or a pharmaceutically acceptable salt thereof" as "a chemical composition that includes, but is not limited to, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and that may also include other non-mentioned substances (including impurities), additives, or carriers, without limitation as to the types of or relative amounts thereof." I believe that this proposed definition is too broad and does not accurately describe the term. The entirety of the '393 patent is directed to an improved product with lower amounts of impurities and therefore the product includes its own impurity profile which provides a high level of purity and does not indiscriminately include other substances and impurities "without limitation as to the types of or relative amounts thereof."

VI. Phares Does Not Anticipate Claims 1-5, 7-9, 11-14, or 16-20 of the '393 Patent

71. I have reviewed Dr. Winkler's opinions alleging that Phares (Ex. 1005) inherently anticipates Claims, 1-5, 7-9, 11-14, and 16-20. I have also reviewed the Institution Decision in which the Board credited Dr. Winkler's opinion regarding this lack of physical differences

between the treprostinil products of the '393 patent and Phares. Paper 12 at 23-31. I disagree. Additionally, the Board credited Dr. Winkler's opinion that Phares discloses the same process for synthesizing treprostinil as the '393 patent. Paper 12 at 29-30. This is not true. Because no synthesis of treprostinil is disclosed in Phares, the diethanolamine salt described would have an unknown impurity profile and therefore cannot anticipate any claim of the '393 patent.

A. The Product Disclosed in Phares is Physically Different Than the Products Disclosed in the '393 Patent Claims

72. In order for Phares to anticipate any claim of the '393 patent, Phares must disclose every claim limitation of the product. Phares does not disclose the same product as claimed in the '393 patent.

73. Contrary to Dr. Winkler's opinion, the polymorph form and purity of the treprostinil diethanolamine salt is not the same as that claimed in the '393 patent. Specifically, Phares discloses samples made for a polymorph screen, not large scale batches. *See, e.g.*, Ex. 1005 at 85-86. In fact Phares notes several different conditions to form polymorph A including preparation using fast evaporation, slow evaporation, freeze drying, heating, and slow cooling in a variety of solvent systems including water and ethanol; water, toluene, and tetrahydrofuran. *Id.* Once polymorph A is prepared, Phares then further states that polymorph form B must be made from polymorph A, listing several conditions under which polymorph B is prepared. *Id.* Phares further notes that the polymorph B sample that was used for characterization was made from heated slurries of form A in 1,4-dioxane and toluene. *Id.* at 87. In fact, it is not clear which sample of polymorph form A was further used to create the characterized sample of polymorph B that Dr. Winkler discusses. Ex. 1009 at ¶¶58-61.

74. The '393 patent does not discuss that polymorph A must be formed first. *See, e.g.*, Ex. 1001 at col. 12-13 and 15. The '393 patent also does not describe the use of 1,4 dioxane or toluene and only describes forming the diethanolamine salt followed by cooling and filtering the salt with ethyl acetate and ethanol, and then drying. *Id.* Thus, the treprostinil diethanolamine salt formed in Phares required an extra step to first form polymorph A, under different reaction conditions with different solvents.

75. It is well-known that the use of different solvent systems in forming different crystal forms can have a significant effect on the melting point of a substance as well as other characteristics including purity. *See, e.g.*, R. Adhiyaman, et.al., *Crystal modification of dipyridamole using different solvents and crystallization conditions*, Int'l J. Pharm.321, 2006, 27-34 at 33 ("Adhiyaman") ("In conclusion, it can be said that the crystallization conditions and medium used have major effect on dipyridamole crystals habit modification under ambient conditions. The crystals showed significant changes in the shape, size, melting points, dissolution rate, XRD patterns and DSC curves.") (Ex. 2030). Given that the samples of polymorph B described in Phares are prepared in a completely different way under different conditions than those described in the '393 patent, their melting points and other analytical data cannot be directly compared.

76. Furthermore, the only data that Dr. Winkler relies upon to conclude that the polymorph B sample of treprostinil diethanolamine salt in Phares has a "higher purity than the '393 product" is that the recorded melting point was higher in one sample than the melting point of the diethanolamine salt sample of the '393 patent. Ex. 1009 at ¶¶ 59-60. This is incorrect for several reasons. First, as mentioned above, the different solvents and conditions used to form the salt can greatly affect the melting point – which is the only purported evidence

that Dr. Winkler cites for purity. Second, there is absolutely no actual purity data disclosed in Phares for the diethanolamine salt or treprostinil free acid and a POSA would not have concluded based on a single melting point example of polymorph B prepared under unknown conditions (e.g., recrystallization solvent and recrystallization conditions are not identified) would be of a higher purity than the known purity of the '393 patent. Third, even if the diethanolamine salt samples were prepared under the same work-up and purification conditions, a higher melting point does not mean that the substance must be of a higher purity. *See*, Ex. 2030 at Fig. 5 showing modified crystals in several different solvents had a higher melting point than the pure dipyridamole). Fourth, the DSC curve cited by Dr. Winkler in Fig. 21 of Phares (Ex. 1009 at ¶59) shows a broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance. *See*, Marti, E., *Purity determination by differential scanning calorimetry*, Thermochimica Acta, 5(1972) 173-220 at 214 ("The melting of diphenyl is extremely sharp because of the purity level; on the other hand, the melting region of phenacetin-benzamide is rather broad.") (Ex. 2031). Additionally, the DSC data provided does not describe the sample size, the rate of temperature increase as a function of time and does not compare this with an authentic standard of known purity melted under identical conditions. It is known in the art that sample size, rate of heating, the recrystallization solvent(s) used, and the conditions under which the crystalline sample was obtained can significantly affect the DSC data. Dr. Winkler's conclusion based on this single vague and incompletely described DSC data is not scientifically sound.

77. Dr. Winkler also points to the brief description of the formation of the treprostinil diethanolamine salt (Ex. 1009 at ¶¶50-54), but that description does not indicate what treprostinil free acid was used to make it. While the Board agreed with Dr. Winkler regarding the similarity

of the products of Phares and the '393 patent, the source of the treprostinil used to make treprostinil diethanolamine is very important and would greatly affect the impurity profile and other analytical characteristics, including DSC, of the sample.

78. In fact, Phares itself describes several references that could be used to make treprostinil, but does not identify which one, if any, was used to make the sample for the treprostinil diethanolamine salt. *See, e.g.*, Ex. 1005 at 9 ("Compounds of the present invention can also be provided by modifying the compounds found in U.S. Patent Nos. 4,306,075 ("the '075 patent", Ex. 2032) and 5,153,222 ("the '222 patent", Ex. 2033) in like manner."). The '075 patent, for example, discloses a very different and less pure treprostinil product than that of Moriarty (Ex. 1004). *See, e.g.*, Ex. 1004 at 1892-93. Thus, without knowing the source of the treprostinil used in Phares to make the treprostinil diethanolamine salt, the resulting product could have a very different purity and impurity profile and would necessarily have a distinct impurity profile if it were made by a different process than that disclosed in the '393 patent.

B. Phares Does Not Disclose Several Other Claim Limitations

79. Dr. Winkler alleges that Phares discloses the same synthesis to make treprostinil diethanolamine as the synthesis described in the '393 patent and the Board credited his opinion on this point. *See*, Ex. 1009 at ¶¶51-57; Paper 12 at 29-30. I disagree. First, there is no description whatsoever in Phares of how to make treprostinil free acid. Instead, Dr. Winkler points to the synthesis of the enantiomer of treprostinil ((-) treprostinil) which is a completely different synthesis for a different stereoisomer. Ex. 1009 at ¶57. Winkler alleges that because certain steps are used in forming the enantiomer, those steps are inherently disclosed for use with treprostinil. Ex. 1009 at ¶¶56-57.

80. I understand the Board decision did not address the additional limitations of independent Claims 1 and 9 nor the dependent claim limitations in its anticipation analysis because "the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product." Paper 12 at 31. I disagree with this assertion. Even if Phares used the synthesis of Moriarty to make treprostinil, there are significant differences between the product of Moriarty and the product of the '393 patent. *See*, Section VII(A) below. Because the products are different, the process differences are relevant to the anticipation analysis.

81. The synthesis for the enantiomer of treprostinil disclosed in Phares, however, is different than the synthesis of treprostinil disclosed in the '393 patent. First, contrary to Dr. Winkler's claims, the earlier part of the synthesis used in Phares to make the enantiomer is not the same synthesis disclosed in Moriarty. Specifically, the Moriarty reference obviously does not describe the synthesis of the enantiomer of treprostinil, but also does not include the Mitsunobu inversion step described by Phares wherein the stereochemistry of the secondary alcohol moiety has to be chemically reversed. Ex. 1005 at 40. In fact, because (S)-2-methyl-CBS-oxazaborolidine is used on structure 5, the resulting structures 6-11 are diastereoisomers of the intermediates used in the synthesis of the '393 patent. As a result, intermediate products of formulas (II) and (III) of Claim 1 and intermediate products of formulas (V) and (VI) of Claim 9 of the '393 patent are not disclosed in Phares. Thus, because steps (a) – (c) of *every claim* of the patent requires these products, Phares cannot anticipate any claim of the '393 patent.

82. Second, Claim 2 requires a specific purity of 99.5%. As I discussed above, there are no specific purity measurements disclosed in Phares and a single broad melting point determination with a large melting point range does not provide evidence that the purity of the

treprostinil diethanolamine sample is at least 99.5%. *See*, Section VI(A) above. For this additional reason, Phares does not anticipate Claim 2. The purity of that sample was not calculated from the DSC data as no control to an authentic standard of known purity was performed or reported.

83. SteadyMed claims that because the synthesis of the enantiomer of treprostinil in Phares does not describe a purification step, that the claim limitation of Claims 8 and 16 that the process does not include purifying the compound of Formula III (or VI) produced in step (a) is satisfied. That is not correct. In fact, Phares does not disclose any specific details of those steps whatsoever. Indeed, if the same synthesis from Moriarty was used as Dr. Winkler suggests, purification at step (a) is specifically described in that reference. Ex. 1004 at 1901-1902. Regardless of what synthesis was used, however, the fact remains that compounds of Formula III and VI do not appear in Phares as described above.

84. Under my interpretation of the highly pure product described in each of the claims of the '393 patent, Phares does not anticipate Claims 1-5, 7-9, 11-14, or 16-20 because it does not disclose the highly-pure product of the '393 patent, the synthesis of treprostinil, nor compounds of structures (II) and (III) from independent Claim 1 or structures (V) and (VI) from independent Claim 9, which are required by all of the claims.

VII. None of the Claims of the '393 patent Are Rendered Obvious by the Prior Art

85. I understand that the Board cited additional grounds for unpatentability including obviousness based on the combination of Moriarty and Phares and obviousness based on the combination of Moriarty, Phares, Kawakami (Ex. 1007), and Eğe (Ex. 1008). I disagree that any claim of the '393 patent is rendered obvious by any combination of these references.

A. The Product of the '393 Patent Is Structurally Different Than the Product of the Prior Art

86. In his declaration, Dr. Winkler expresses his opinion that "the '393 patent processes do not result in a physically different or unique product than that disclosed in the prior art." Ex. 1009 at ¶71. I am aware that, in the Institution Decision, the Board credited Dr. Winkler's opinion regarding this lack of physical differences between the treprostinil products of the '393 patent and the prior art. Paper 12 at 16-17. I disagree with Dr. Winkler's opinion for at least the following reasons.

87. Dr. Winkler appears to base his opinion on a comparison between the '393 patent process batches identified in the declaration submitted by Dr. David Walsh, one of the inventors of the '393 patent, during prosecution (Walsh Declaration), and a single prior art process batch identified in a particular prior art publication by Moriarty . Ex. 1009 at ¶¶63-71. However, Dr. Winkler's comparison suffers from several critical flaws.

88. First, and most fundamentally, there is no basis for comparing the "purity" reported in Moriarty with the purity discussed in the Walsh Declaration. When purity is determined by comparison of a sample to a reference standard such as assay purity (*see, e.g.*, ICH Guidance For Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (2001) ("Q7A") at 28-29 (Ex. 2034); see also Reviewer Guidance: Validation of Chromatographic Methods (1994) ("Reviewer Guidance") at 5-8) (Ex. 2035), one cannot directly compare the purity values of two samples in any meaningful way unless each value was achieved by comparison to the same reference standard. Neither the Walsh Declaration nor Moriarty identifies a specific reference standard. While Moriarty notes that the

treprostinil product obtained was compared to an authentic sample of UT-15, there is no mention of any such comparison in the Walsh Declaration.

89. Instead, with respect to the Walsh Declaration, purity must be understood not with respect to any reference standard, but with respect to the amount of total impurities reported as detected in each of the sample batches. The term "purity" must also be understood with respect to the amount of total impurities detected in the context of the '393 patent itself; wherever assay purity is referred to, the '393 patent specifies that the number indicated refers to "HPLC (Assay)." For each of the representative batches discussed in the Walsh Declaration, impurity data is presented in the same way, and thus the purity of these samples can properly be compared to each other; the same cannot necessarily be said of the sample data reported in Moriarty.

90. Second, Dr. Winkler concludes from Example 4 of the '393 patent that the instrumentation used to measure purity "can have variations of at least 0.4%," and thus any detected difference less than that can be attributed to experimental error. Ex. 1009 at ¶¶69-70. Dr. Winkler bases his estimate of experimental error on the statement "that Example 4's Batch 1 had an HPLC Assay of 100.4%, which is obviously greater than the 100% value theoretically achievable." Ex. 1009 at ¶70. This is unsupported and appears to arise from Dr. Winkler's fundamental misunderstanding of how assay purity values are calculated. HPLC assay values are calculated with respect to a reference standard; thus, any time that the sample you are measuring has a greater purity than the reference standard, the assay value will exceed 100%. As such, it is incorrect to conclude that an assay value of 100.4% must indicate an error of at least 0.4%. Dr. Winkler's conclusion on this point is therefore fundamentally flawed.

91. This explains why the assay value for drug specification submitted to the FDA changed from a range of 97-101% to 98-102%. *See*, Ex. 2003 at 6. This change was not due to

an increase in impurities, but because the purity of the product using the '393 patent process improved (as compared to the already-established reference standard) thus moving the acceptability range to a higher purity specification. *Id.* The letter notes that the scope of the range remained unchanged which simply indicates the acceptability criteria was increased, and does not index an error rate or limit of detection. Indeed, the change to the specification is further evidence that the product of the '393 patent is physically different than the product of Moriarty.

92. Indeed, Dr. Winkler's conclusion is contradicted by the impurity data actually measured for the treprostinil product made by both the '393 patent process and the prior art process according to Moriarty. For both processes, impurities are reported with specific numbers unless the amount detected fell below 0.05%; in cases where some amount of an impurity less than 0.05% was detected, it was reported as simply "less than 0.05%" or "< 0.05%." This means that the level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%, not something in excess of 0.4% as Dr. Winkler erroneously concludes.

93. Third, as Dr. Winkler himself points out, there is the possibility for "significant batch-to-batch variations in the impurity profile of each batch of treprostinil." Dr. Walsh stated that the data presented in his declaration came from representative samples of each synthetic process. Ex. 1002 at 346-347. However, there is no such indication that the purity data reported in Moriarty comes from a representative sample of the prior art process. Due to the possibility of batch-to-batch variations, if a small number of batches are to be used as the basis for comparison, it is critical that those batches be representative of their respective products and processes. Thus while one could reasonably rely on a comparison between the representative batches presented in

the Walsh Declaration, one could not reasonably add the batch discussed in Moriarty to that comparison. It is exactly this scientifically unsound comparison to Moriarty upon which Dr. Winkler bases his opinion.

94. Ideally, to avoid the risk of batch-to-batch variations unintentionally biasing the data, a comparison should be made between the average impurities detected in treprostinil products made by the '393 patent process and treprostinil products made by the prior art process. To this end, I have prepared a chart containing impurity data for 56 samples of treprostinil product as produced by the prior art process according to Moriarty through 2004 (the date of the publication), attached as Appendix A to this declaration[1], and another chart containing impurity data for 122 samples of treprostinil product as produced by the '393 patent processes, attached as Appendix B to this declaration. I have prepared these charts using impurity data from release testing of samples of the respective treprostinil products that were produced by or for UTC for the purposes of obtaining regulatory approval and/or commercial sale. *See* Appendix A, Appendix B; Ex. 2005; Ex. 2036; Ex. 2037; Ex. 2052; Ex. 2053. As the purpose of these charts is to calculate the average impurities – both specific and total – found in the treprostinil products of each process, I have necessarily assigned a value of zero where the level of impurities was

[1] I am aware that UTC's Process Optimization Report for treprostinil prepared according to the '393 process included Table 2, which provided average impurity data for 96 batches of treprostinil made according to the prior art process. UT Ex. 2005, at 7. However, Table 2 does not provide exact values for four of the eight impurities under consideration, (1AU90, 2AU90, 97W86, and methyl ester) and does not identify the underlying batch data. *Id.* As such, I have prepared my own chart using data on 56 treprostinil samples made by the prior art method and have based my analysis, including my calculations of average for total and individual impurities, upon this chart. While I believe my chart allows for a more precise comparison between Moriarty treprostinil products and '393 treprostinil products, the averages presented in the Process Optimization Report still show significant differences between '393 treprostinil products and the Moriarty treprostinil products. Specifically, Table 2 of the Process Optimization Report shows that on average 97W86 was detectable in these 96 batches, and that these 96 batches contained higher average levels of 3AU90, 750W93, 751W93, and total impurities as compared to the averages for the '393 treprostinil product. Ex. 2005 at 7; Appendix B.

reported as "ND" (Not Detected), and a value of 0.05 where the level of impurities was reported as being less than 0.05%. From these data, I have found the following average impurity levels:

Moriarty Process Impurities (Average Percent Detected)								
1AU90	**2AU90**	**3AU90**	**750W93**	**751W93**	**97W86**	**ethyl ester**	**methyl ester**	**Total Related Substance**
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	**0.9545**
'393 patent Process Impurities (Average Percent Detected)								
1AU90	**2AU90**	**3AU90**	**750W93**	**751W93**	**97W86**	**ethyl ester**	**methyl ester**	**Total Related Substance**
0.0004	0.0004	0.0455	0.0642	0.0488	0	0.1207	0.005	**0.2936**

95. These averages make clear that the '393 patent process does result in a treprostinil product that is physically different from the prior art treprostinil product. In terms of total volume of impurities, the Moriarty process resulted in 3.25 times the amount of impurities that is achieved with the '393 patent process.

96. The products from the two processes also differ significantly with respect to the individual impurities in each product's impurity profile. Notably, the '393 patent process produces a treprostinil product that does not contain any detectable amounts of 97W86. Additionally, the '393 patent process produces a treprostinil product that, on average, contains only 0.0004% each of 1AU90 and 2AU90 and only 0.005% of methyl ester; as compared to the Moriarty process, this represents greater than a 100-fold reduction in each of the 1AU90 and 2AU90 impurities and a 20-fold reduction in the methyl ester impurity. The '393 patent process also produces a treprostinil product that, on average, has significantly reduced amounts of several other identified impurities; as compared to the average of the Moriarty process, the '393 patent process produces a treprostinil product with less than one-half the amount of 751W93, approximately a third the amount of 750W93, and approximately one-sixth the amount of

3AU90. Conversely, the '393 patent process produces a treprostinil product which actually contains slightly more ethyl ester impurity than was detected in the treprostinil product of the Moriarty process.

97. Looking past the average data, it is also worth noting that, out of all the batches of treprostinil product made by the '393 patent process which I reviewed, 1AU90 was only detected in a single batch (01A07001) and 2AU90 was also only detected in a single batch (01A07003), and both impurities were only detected at a level of 0.05% or less. Furthermore, batches 01A07001 and 01A07003 were both identified as "optimization batches" (as distinguished from commercial batches) and thus are not properly representative of treprostinil products made by the '393 patent process.

98. From these data, it is clear that the treprostinil product produced by the '393 patent process has a markedly different impurity profile than the treprostinil product of the Moriarty prior art process, and as such is physically distinct from the prior art product. Moreover, it could not have been obvious that employing the process of the '393 patent would result in a reduction of impurities as compared to the Moriarty process. Indeed, the '393 patent process actually results in an increase in one detected impurity, ethyl ester. Furthermore, it is also clear that the treprostinil product produced by the '393 patent process has a higher average purity than the Moriarty product. The treprostinil product of the '393 patent has an average purity of 99.71% while the Moriarty product has an average purity of 99.05%. Thus, the treprostinil product of the '393 patent has an average purity that is 0.7% higher than that of Moriarty's.

99. Therefore, it is my opinion that the treprostinil product produced by the process used in the '393 patent Claims 1 and 9 is physically different than the treprostinil product produced by Moriarty.

B. Claims 1-5, 7-9, 11-14, and 16-20 Are Not Rendered Obvious by the Combination of Moriarty and Phares

100. As described above, the product of Moriarty is physically different than the product of the '393 patent process. Even if the Moriarty synthesis was used to make treprostinil, a POSA would not have been motivated to make the diethanolamine salt identified in Phares.

101. Specifically, the '393 patent notes that the salt formation step results in an improved and more pure treprostinil product. Given that Moriarty discloses the use of column chromatography for purification, a POSA would not have been motivated to create the salt form in Phares as Phares does not disclose any benefit or increased purity as a result of using the diethanolamine salt. In fact, Phares does not allege that the diethanolamine salt is superior in any way to the treprostinil product of Moriarty and instead identifies other earlier treprostinil disclosures as a means to create the treprostinil used to form the diethanolamine salt. *See*, Section VI(A) above.

102. Additionally, a POSA would not have had a reasonable expectation of success in making the higher purity treprostinil product claimed in the '393 patent by the use of a salt formation step. As identified above, the impurities of treprostinil include three stereoisomers (1AU90, 2AU90, and 3AU90), two dimers (750W93 and 751W93), the benzindene triol starting material (97W86), and the methyl and ethyl esters. As described above, the '393 patent process essentially eliminated the acidic impurities 1AU90, 2AU90, and neutral impurity 97W86, but did not eliminate another stereoisomer 3AU90 which likely has the same acidity as the other

stereoisomers. Similarly, the ethyl ester impurity increased while the methyl ester impurity decreased. A POSA would have expected that all of the stereoisomers would remain as salt impurities, but that is not the case. Instead, the impurity profile of the '393 patent process yields an unexpected result by removing two of three diastereomers while increasing one ester impurity and decreasing another. A POSA could not have predicted this outcome based on the salt formation described in Phares.

103. Regarding Claim 2, neither Moriarty nor Phares discloses treprostinil or treprostinil diethanolamine at a purity of 99.5%. As described above, Phares does not disclose any purity measurement (see Section VI above) and the purity measurement identified in Moriarty does not identify how the measurement was taken (see Section VII(A) above). Regardless of the purity identified in Moriarty, a further analysis of all batches made by the Moriarty process up to the time of the reference itself reveals an average purity of 99.05% while the average purity of the '393 patent batches is 99.74%. Given that the error rate must be below 0.05% for these measurements (see Section VII(A) above), the '393 patent process batches are significantly better in terms of overall purity. For this additional reason, Claim 2 is not rendered obvious by the combination of Moriarty and Phares.

104. Regarding Claims 8 and 16, Phares does not disclose any synthesis for treprostinil and therefore cannot disclose whether purification was needed for step (a). (*See*, Section VI(B) above). As previously described, Moriarty specifically discloses that purification is performed at step (a). See Section VII(B) above). In fact and most significantly, the '393 patent itself identifies that as a distinguishing feature over the prior art. *See, e.g.*, Ex. 1001 at Example 6. For this additional reason, Claims 8 and 16 are not rendered obvious by the combination of Moriarty and Phares.

C. Claims 6, 10, 15, 21, and 22 Are Not Rendered Obvious by the Combination of Moriarty, Phares, Kawakami, and Ege

105. Each of Claims 6, 10, 14, 21, and 22 require the additional step (d) of independent Claims 1 and 9 which is to react the salt formed in step (c) with an acid to form the compound of formula I or IV (treprostinil). Claim 22 further requires a pharmaceutically acceptable salt formed from the product of step (d). Step (d) is not disclosed in any way in Moriarty, Phares, Kawakami, or Eğe. Additionally, it is my opinion that it would not have been obvious to combine these references to arrive at the claimed inventions of Claims 6, 10, 15, 21, or 22.

106. First, there is no teaching or suggestion to perform step (d) in either Moriarty or Phares and similarly no reference to reverting back to treprostinil free acid from any treprostinil salt. Given that the purification techniques disclosed in Moriarty include chromatography and recrystallization after many years of research to optimize the process of making treprostinil, a POSA would not have been motivated to use a salt purification technique disclosed in an undergraduate chemistry textbook. More importantly, a POSA would not have had a reasonable expectation of success in further purifying the treprostinil product of Moriarty by using such a technique. To the extent a POSA was motivated to further purify treprostinil, a POSA would have focused on the known impurities and investigated methods of removing those. At the time of the invention, it was known that the formation of diastereomers occurred in the formation of treprostinil. *See*, Ex. 1004 at 1897-99. Thus, a POSA would have focused on how to remove those types of impurities.

107. Eğe simply discloses that "carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties

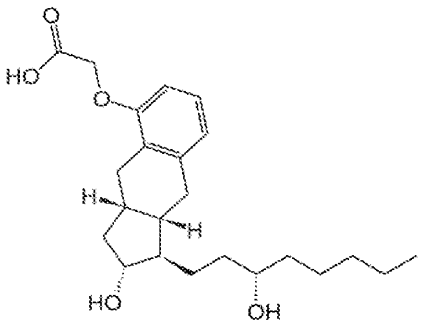
of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds." Ex. 1008 at 8. This disclosure, however, would not have provided a POSA with a motivation to make the treprostinil free acid disclosed in Moriarty, convert that to the salt form of Phares, then convert the salt form back to the free acid.

108. First, Eğe does not provide any detail regarding how this reaction could be applied to more complex carboxylic acids or if it even could be applied. Specifically, the only carboxylic acid referenced in Eğe as an example is benzoic acid, a very simple aromatic acid, which is structurally very different from treprostinil acid. Indeed, benzoic acid has no chiral centers and therefore no stereoisomers and there is no suggestion in Eğe that this step could be used in purifying more complex carboxylic acids such as treprostinil which have stereoisomeric impurities. Second, Eğe specifically notes that "these properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds," therefore Eğe would not apply to purifying carboxylic acids with stereoisomeric impurities because each stereoisomer would necessarily be an acidic impurity. As described above, the impurities that are removed from the '393 patent product include some, but not all acidic impurities and some but not all neutral impurities. *See*, Section VII(B) above. For these reasons a POSA would not have been motivated to combine Eğe with either Moriarty or Phares and would not have had a reasonable expectation of success in further purifying treprostinil using the acid reformation step described in Eğe.

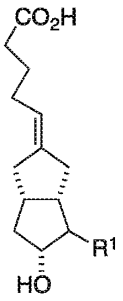
109. Indeed, given that Eğe predicts that only neutral and basic impurities would be removed, the actual average impurity profile for the '393 patent product is an unexpected result given that some but not all neutral impurities are removed as well as some but not all acidic impurities. *See*, Section VII(B) above.

110. Kawakami similarly does not provide any motivation for combining with either Phares or Moriarty and a POSA would not have had a reasonable expectation of success in preparing the products of Claims 6, 10, 15, 21, or 22 by combining these references.

111. Kawakami discloses the purification of a methanoprostacyclin derivative by forming the dicyclohexyl amine salt then regenerating the free acid to achieve a "fairly high" purity. Ex. 1007 at 6. Treprostinil and methanoprostacyclin, however, are very different structures:



Treprostinil



methanoprostacyclin compound in Kawakami

112. As shown here, the methanoprostacylin compound in Kawakami is a two-fused ring structure which is different than the three-fused ring structure of treprostinil that also includes an aromatic ring absent in the Kawakami methanoprostacyclin. These differences matter because a POSA would not have looked to Kawakami (or Eğe) if they were looking for additional purification techniques for treprostinil because neither reference discloses how to remove stereoisomeric impurities.

113. Instead, Kawakami provides a purification method for separating E and Z isomers of a starting material that is otherwise free of impurities, and not diastereomers that result from the various chiral centers that treprostinil was known to have as impurities. In fact, treprostinil

contains no mixture of E and Z isomers because it does not contain a carbon-carbon double bond that is capable of forming E and Z isomers. Indeed, the use of a specific salt to isolate a specific E/Z isomer does not reasonably suggest that salt formation of a much more complex compound with multiple chiral centers such as treprostinil could be isolated from entirely different impurities and then converted back to the free acid form. In fact, nothing in Kawakami suggests that this method could be used for a substance that was already fairly pure such as the treprostinil disclosed in Moriarty.

114. Similarly, Kawakami uses a dicyclohexylamine salt and does not use a diethanolamine salt, nor any salt counterion disclosed in the '393 patent. A POSA would have had no reason to combine the synthesis of Moriarty, use the salt only disclosed by Phares, and convert back to the free acid based on the teaching of Kawakami because Kawakami uses a different salt to separate a different structure from different types of impurities. Even if a POSA did combine these references in this way, a POSA would not have had a reasonable expectation of success in forming a more pure treprostinil product because Kawakami does not provide any information regarding the high level of purity required by the '393 patent and does not describe the separation of the types of stereoisomeric impurities known to be present in the treprostinil product. Dr. Winkler's obviousness analysis using these combinations is flawed and suffers from hindsight analysis.

115. Claim 6 requires the acid in step (d) be either HCl or H_2SO_4 and Claim 15 requires the acid to be HCl. Claim 21 requires that step (d) is performed. Phares, Moriarty, and Kawakami all do not disclose the use of either HCl or H_2SO_4 in converting a salt back to a carboxylic acid of any kind. Eğe cites HCl as an example in the conversion of benzoic acid, but as described above, a POSA would not have looked to Eğe to further purify a complex

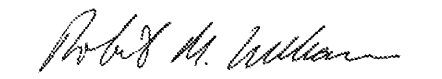
carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure. For this additional reason, Claims 6 and 15 would not have been rendered obvious by any combination of Phares, Moriarty, Kawakami or Eğe. Similarly, given the deficiencies described above regarding Eğe and Kawakami, Claim 21 would not have been rendered obvious by any combination of Phares, Moriarty, Eğe, or Kawakami.

116. Claim 10 requires that step (d) is performed and further requires the product to be at least 99.5% pure. The only purity limitation disclosed in any of the cited prior art references is to Moriarty in which neither step (c) or (d) is performed. There is absolutely no other disclosure of a purity of at least 99.5% in any other cited prior art reference. A POSA looking to improve the purity of treprostinil above that level would have had no reason to look to Phares, Kawakami, or Eğe and based on their disclosures, would have had no reasonable expectation of success in making a treprostinil product with that level of purity as it simply is not present in the prior art allegedly disclosing step (d).

117. Claim 22 depends on Claim 21 and further requires a pharmaceutically acceptable salt be formed from the product of step (d). Dr. Winkler cites no evidence for this additional step in the prior art. In fact, none of the references cited even suggest converting a carboxylic acid to a salt form, then regenerating the carboxylic acid, then forming a pharmaceutically acceptable salt from that. It is my opinion that there is no evidence in the prior art supporting the additional claim limitation of Claim 22 and therefore no combination of Moriarty, Phares, Kawakami, or Eğe would render this claim obvious.

I declare under penalty of perjury that the foregoing is true and correct.

Date: July 6, 2016



Robert M. Williams, Ph.D.

APPENDIX A

Sample of product of Moriarty process	Impurities (Percent Detected)									Data Source
	1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substances	
LRX-97J01	0.3	0.3	0.4	1.2	0.7	0.1	0	0.7	5.4	Ex. 2052, pp. 25-27
LRX-98A01	0.4	0.07	0.5	0.1	0.09	0.2	0	0.3	4.4	Ex. 2052, pp. 25-27
LRX-98B01	0.4	0.1	1	0.1	0.06	0.2	0	0.3	4.8	Ex. 2052, pp. 25-27
UT15-98H01	0.2	0.07	0.4	0.6	0.3	0	0	1.2	3.6	Ex. 2052, pp. 25-27
UT15-98I01	0.2	0.07	0.4	0.6	0.4	0.05	0	0.8	3.8	Ex. 2052, pp. 25-27
UT15-98I001	0.3	0.06	0.4	0.8	0.4	0	0	0.8	3.5	Ex. 2052, pp. 25-27
UT15RP-98K001	0.1	0.06	0.3	0.4	0.2	0	0	0.1	1.6	Ex. 2052, pp. 25-27
UT15-RP99D002	0.05	0.05	0	0.2	0.1	0.05	0.1	0.05	0.4	Ex. 2052, pp. 28-30
UT15-99E001	0.05	0.05	0.2	0.1	0.1	0	0	0.05	0.7	Ex. 2052, pp. 28-30
UT15MIX-99G001	0.05	0.05	1.1	0.3	0.2	0.6	0.6	0.05	2.8	Ex. 2052, pp. 28-30
UT15-99H001	0.05	0.05	0	0.5	0.3	0	0.1	0.06	1.0	Ex. 2052, pp. 28-30; Ex. 2036, pp. 2-3
UT15-000701	0	0.05	0.1	0.06	0.05	0	0	0.05	0.2	Ex. 2053, p. 19; Ex. 2036, pp. 88-89
UT15-000801	0	0.05	0.2	0.07	0.05	0	0	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 91-92
UT15-000802	0	0.05	0.1	0.1	0.07	0	0	0.05	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 94-95
UT15-000803	0	0.05	0.2	0.2	0.09	0	0	0.05	0.6	Ex. 2053, p. 19; Ex. 2036, pp. 100-101
UT15-000901	0	0.05	0.3	0.05	0.05	0	0.05	0.05	0.05	Ex. 2053, p. 19; Ex. 2036, pp. 33-34
UT15-000902	0	0.05	0.2	0.1	0.06	0	0.05	0.05	0.5	Ex. 2053, p. 19; Ex. 2036, pp. 97-98

UT15-001001	0.05	0.05	0.2	0.09	0.06	0	0.05	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 35-36
UT15-010201	0	0.05	0.2	0.09	0.05	0.05	0	0	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 37-38
UT15-010202	0	0.05	0.2	0.09	0.05	0.05	0	0.05	0.4	Ex. 2053, p. 19; Ex. 2036, pp. 39-40
UT15-010203	0.2	0.05	0.3	0.4	0.2	0.08	0.05	0.05	1.5	Ex. 2053, p. 19; Ex. 2036, pp. 41-42
UT15-010301	0	0.05	0.3	0.09	0.05	0.05	0.05	0	0.5	Ex. 2053, p. 19; Ex. 2036, pp. 43-44
UT15-010302	0.05	0	0.2	0.05	0.05	0.05	0.08	0	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 45-46
UT15-010303	0	0	0.2	0.1	0.05	0.05	0	0	0.3	Ex. 2053, p. 19; Ex. 2036, pp. 47-48
UT15-010801-RP	0	0.05	0.1	0.2	0.1	0.05	0.2	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 60-61
UT15-010802	0.05	0.05	0.2	0.05	0.05	0	0.05	0.05	0.2	Ex. 2053, p. 20; Ex. 2036, pp. 50-52
UT15-010803	0.05	0.05	0.2	0.1	0.06	0	0.07	0.05	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 52-53
UT15-010901	0	0.05	0.2	0.1	0.08	0.07	0.09	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 54-55
UT15-010902	0	0.05	0.2	0.05	0.05	0	0.1	0	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 56-57
UT15-011001	0	0.05	0.3	0.08	0.05	0.05	0.1	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 58-59
UT15-020101	0	0.05	0.2	0.05	0.05	0	0.05	0	0.4	Ex. 2053, p. 20
UT15-020201	0	0.05	0.2	0.1	0.1	0	0.1	0	0.4	Ex. 2053, p. 20
UT15-020202	0	0.05	0.1	0.1	0.1	0.05	0.2	0	0.6	Ex. 2053, p. 20; Ex. 2036, pp. 62-63
UT15-020203	0	0	0.05	0.05	0.05	0	0.1	0.05	0.2	Ex. 2053, p. 20; Ex. 2036, pp. 64-65

UT15-020301	0	0.05	0.2	0.05	0.05	0	0.1	0	0.3	Ex. 2053, p. 20; Ex. 2036, pp. 66-67
UT15-020302	0	0.05	0.2	0.06	0.05	0	0.1	0	0.4	Ex. 2053, p. 20; Ex. 2036, pp. 68-69
UT15-020303	0	0.05	0.2	0.05	0.05	0	0.1	0	0.3	Ex. 2053, p. 20; Ex. 2036, pp. 70-71
UT15-021001	0	0	0.4	0.1	0.08	0.05	0.1	0.05	0.8	Ex. 2053, p. 21; Ex. 2036, pp. 72-73
UT15-021002	0	0.05	0.3	0.06	0.05	0.05	0.2	0.05	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 74-76
UT15-021003	0	0	0.4	0.05	0.05	0	0.1	0.05	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 78-79
UT15-021101	0	0	0.2	0.09	0.06	0	0.1	0	0.5	Ex. 2053, p. 21; Ex. 2036, pp. 80-82
UT15-021102	0	0	0.1	0.2	0.1	0.07	0.1	0	0.6	Ex. 2053, p. 21; Ex. 2036, pp. 83-85
UT15-030401	0	0	0.3	0.06	0.05	0	0.2	0.05	0.5	Ex. 2053, p. 21; Ex. 2036, pp. 31-32
UT15-030501	0	0	0.3	0.1	0.07	0	0.1	0.05	0.6	Ex. 2036, pp. 29-30
UT15-030502	0	0	0.3	0.1	0.06	0	0.1	0.05	0.6	Ex. 2036, pp. 27-28
UT15-030503	0	0	0.3	0.2	0.1	0.05	0.2	0.05	0.9	Ex. 2036, pp. 25-26
UT15-030504	0.05	0.05	0.2	0.06	0.05	0.05	0.1	0.05	0.4	Ex. 2036, pp. 23-24
UT15-030601	0.05	0.05	0.2	0.05	0.05	0.05	0.09	0.05	0.3	Ex. 2036, pp. 21-22
UT15-030602	0.05	0.05	0.2	0.06	0.05	0.05	0.1	0.05	0.4	Ex. 2036, pp. 19-20
UT15-031001	0	0	0.2	0.2	0.08	0.05	0.1	0.05	0.6	Ex. 2036, pp. 17-18
UT15-031002	0	0	0.2	0.05	0.05	0	0.1	0	0.4	Ex. 2036, pp. 15-16
UT15-031003	0	0	0.2	0.1	0.06	0.05	0.2	0.05	0.6	Ex. 2036, pp. 13-14
UT15-031101	0	0	0.2	0.05	0.05	0	0.2	0	0.5	Ex. 2036, pp. 11-12
UT15-031102	0	0	0.1	0.1	0.06	0.05	0.1	0.05	0.4	Ex. 2036, pp. 8-10
UT15-031201	0	0	0.2	0.09	0.05	0	0.1	0.05	0.4	Ex. 2036, pp. 6-7

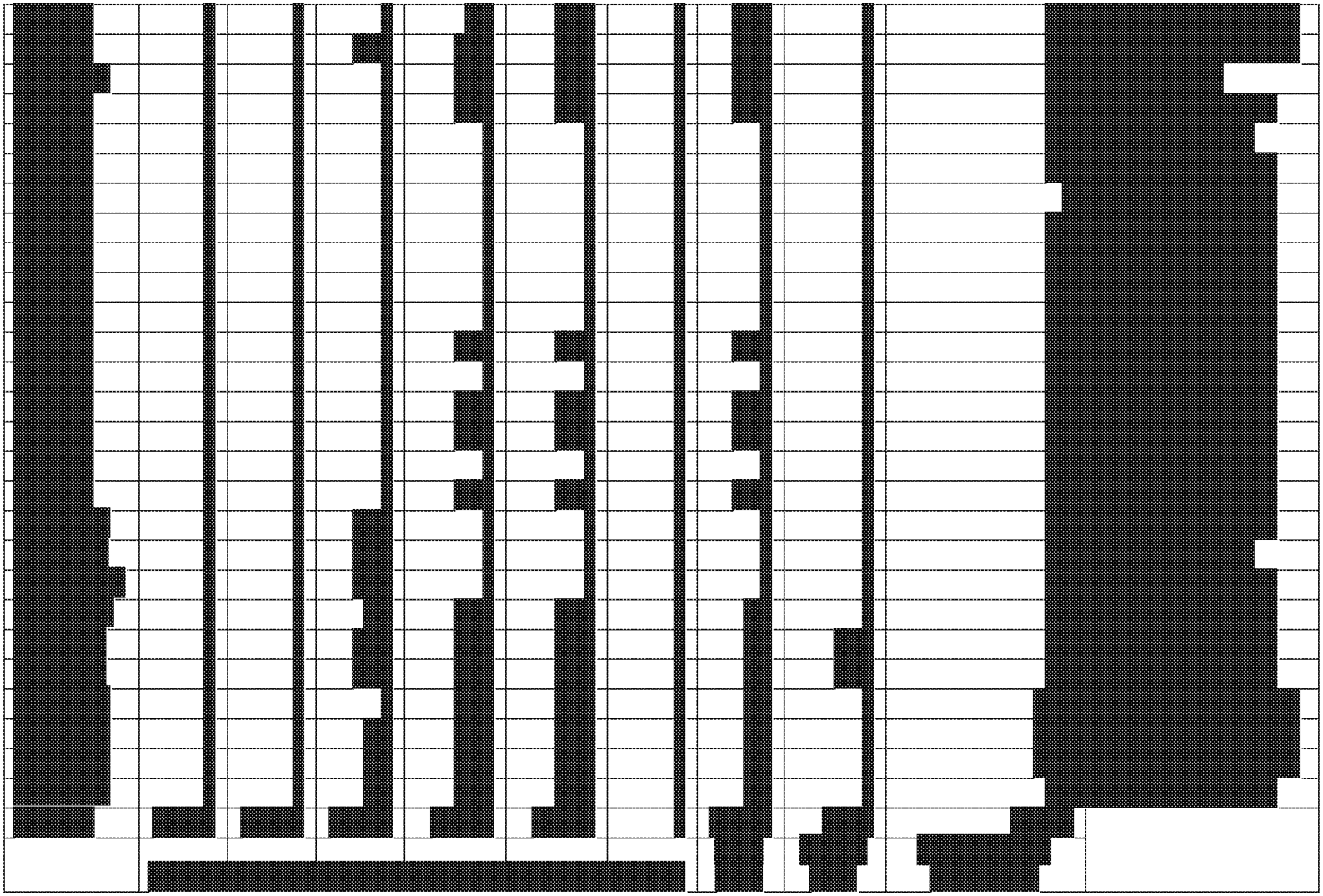
UT15-031202	0	0	0.2	0.07	0.05	0	0.2	0.05	0.5	Ex. 2036, pp. 4-5
Average	**0.0473**	**0.0407**	**0.2545**	**0.1646**	**0.1025**	**0.0405**	**0.0889**	**0.1028**	**0.9545**	
	1AU90	**2AU90**	**3AU90**	**750W93**	**751W93**	**97W86**	**ethyl ester**	**methyl ester**	**Total Related Substances**	

Note: For impurities reported as not detected ("ND") a value of 0 has been assigned; for impurities reported as <0.05, a value of 0.05 has been assigned.

APPENDIX B

P. 48

02M11044
1100007
0
0
0.05
0
0
0
0
0.06
0
0
0.05
0
0
0
0.13
0
0
0.1
Ex. 2037, p. 44
0.2
Ex. 2037, pp. 195-196
4851-2371-9220.1
P. 50



Note: For impurities reported as not detected ("ND") a value of 0 has been assigned; for impurities reported as <0.05, a value of 0.05 has been assigned.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner.

Case IPR2016-00006 (Patent 8,497,393)

VIDEO DEPOSITION OF

ROBERT R. RUFFOLO, JR., PHD

Wilson Sonsini Goodrich & Rosati

1700 K Street NW, Suite 500

Washington, DC 20006

Friday, August 19, 2016

9:29 a.m.

Reported by:

Denise D. Vickery, CRR/RMR JOB NO. 178626

A P P E A R A N C E S

For Petitioner:

DLA PIPER LLP (US)

1251 Avenue of the Americas

New York, NY 10020-1104

BY: STUART E. POLLACK, ESQ.

-and-

33 Arch Street, 26th Floor

Boston, MA 02110-1447

BY: MAYA PRAKASH CHOKSI, ESQ.

For Patent Owner and the Witness:

WILSON SONSINI GOODRICH & ROSATI

900 South Capital of Texas Highway

Las Cimas IV, Fifth Floor

Austin, TX 78746-5546

BY: ROBERT DELAFIELD, ESQ.

A P P E A R A N C E S (Continued)

For Patent Owner:

FOLEY & LARDNER LLP

Washington Harbour

3000 K Street, NW, Suite 600

Washington, DC 20007-5109

BY: STEPHEN B. MAEBIUS, ESQ.

Also Present:

Solomon Francis, Videographer

I N D E X

E X H I B I T S

E X H I B I T S

(Exhibits attached to transcript.)

P R O C E E D I N G S

- - -

THE VIDEOGRAPHER: Good morning. This begins Media Unit No. 1 of the audiovisual deposition of Dr. Robert Ruffolo taken in the matter of SteadyMed Limited, Petitioner versus United Therapeutics Corporation, Patent Owner, before the Patent Trial and Appeal Board, IPR No. 2016-00006.

This deposition is being held at the law offices of Wilson Sonsini Goodrich & Rosati located at 1700 K Street, Northwest, Washington, DC on August 19, 2016 at approximately 9:29 a.m.

My name is Solomon Francis and our court reporter, Denise Vickery, for Elisa Dreier Reporting Corp. located at 950 Third Avenue, New York, New York.

For the record, would counsel introduce themselves and whom they represent.

MR. POLLACK: Stuart E. Pollack, DLA Piper LLP(US) on behalf of the petitioner, SteadyMed Limited.

MS. CHOKSI: Maya Choksi, DLA

Piper, on behalf of the petitioner.

MR. DELAFIELD: Bobby Delafield, Wilson Sonsini Goodrich & Rosati, on behalf of United Therapeutics and the witness.

MR. MAEBIUS: And Steven Maebius from Foley & Lardner LLP on behalf of patent owner.

THE VIDEOGRAPHER: At this time, will the court reporter please swear in or affirm the witness.

- - -

ROBERT R. RUFFOLO, JR., PHD

called for examination, and, after having been duly sworn, was examined and testified as follows:

EXAMINATION

THE VIDEOGRAPHER: Please proceed, counsel.

BY MR. POLLACK:

Q. Good morning, Dr. Ruffolo.

A. Good morning.

Q. To get started, if you could just state your name and your current position for the record.

A. Okay. My name is Robert Richard

Ruffolo, and I am the retired president of research and development at Wyeth and the retired senior corporate VP of Wyeth and I -- and self-employed as a pharmaceutical consultant.

Q. Do you have like a consulting company or agency?

A. Yes, I do. It's -- it's Ruffolo Consulting, LLC.

Q. And that's a company that you are the only member of?

A. Yes, I am.

Q. Have you been deposed before?

A. Yes, I have.

Q. How many times have you been deposed before?

A. Well, maybe 10.

Q. Just briefly, can you tell me what kinds of cases those 10 cases were?

A. Yes. In -- four of those were in two cases of product liability for companies that I worked for where I was a company witness as well as an expert witness in both of those cases, and then the remaining depositions were in cases like this.

Q. Those were patent litigation cases?
A. Yes, they were.
Q. Okay. And about six depositions?
A. About -- yeah, about six.
MR. POLLACK: Just to get some formalities out of the way, I'm going to mark as Ruffolo Deposition Exhibit 1 the Petitioner's Notice of Deposition of Robert R. Ruffolo, Ph.D.
(Document marked for identification purposes as Ruffolo Exhibit 1.)
THE WITNESS: Thank you.
BY MR. POLLACK:
Q. And are you in attendance here today for this deposition in response to petitioner's notice of deposition?
A. Yes, I am.
Q. Have you testified in any other -- you understand this is a proceeding called an inter partes review?
A. Yes, I do. Yes.
Q. Okay. Have you testified in any other inter partes review?
A. No, I don't believe so.

Q. In the six patent litigations that you testified in, what did those concern?

A. Do you want the specific company, law firms?

Q. Yeah. Yes.

A. Okay. I'll do the best I can.

Q. Okay.

A. One was Gardiner Roberts and the drug was an ACE inhibitor and Tandrolapril. Tandolapril, I think. Trandolapril, I think.

Q. Trandolapril?

A. I think so. I can't be certain. I just simply don't remember.

Q. Okay.

A. Then --

Q. Was that for the brand name company or for the generic company that you were testifying?

A. That one was for the generic and --

Q. Do you remember which company?

A. Yes. It was Novartis. Sandoz, their generic division.

Q. Okay.

A. Then there --

Q. Let me ask you. Was that

Sanofi-Aventis on the other side or --

A. It was Boehringer Ingelheim.

Q. Boehringer Ingelheim.

A. So that's why I'm not sure of the drug match. I don't remember. That was the first one I did quite a while ago.

Q. Okay. What did you testify about in that case?

A. It was mostly about the R&D process in that case. I was an expert on -- on R&D process, regulatory requirements, and the FDA.

Then there was another case. The law firm was Goodwin Procter. The drug was Azilect, and I represented the patent holder in that case, and that the patent holder was Teva, a generic company, but they do have --

Q. Right.

A. -- some, as you know I'm sure, they have a few branded drugs that they developed. And then there was --

Q. Let me ask you. What was your testimony about in that case?

A. Oh, it was everything basically. So I was originally hired -- there were 21 parts to that case. So I was originally hired

just to do the R&D part, but then I did -- ended up doing 17 of the 21 parts. So I did virtually everything on that.

Q. Infringement, invalidity?

A. Yes, and all of the science related to stereochemistry and the R&D process and so on. It was a very long case, and that one did go to trial.

Q. Who won?

A. We did.

Q. Okay. What about in the ACE inhibitor case? Who won?

A. That one was settled and I never asked the settlement terms, but I was told that the client was -- was pleased with the settlement.

Q. Okay.

A. So that's all I know.

Then I did one with -- and still in the process -- Perkins Coie on esomeprazole, and I did, I think, two depositions on that one and I think I did two on the one with Goodwin Procter. And --

Q. You were on the generic side then not the AstraZeneca side?

A. I was on the generic side on that one, yes.

Q. You said you did two depositions. Were there two different cases?

A. No, there was one case. I did two and sometimes I do two, and I never know exactly why.

Q. Okay. What was that? What was your testimony about?

A. That one was on crystal structure, physical properties of molecules. The, again, always the R&D process, FDA regulation as -- and pharmaceutics in that case as well.

Q. Let me ask you. Are you an expert on crystal structure? Is that one of your areas?

A. It depends how you describe expert. Being president of research and development, I supervised every single group.

Q. Sure.

A. And these are groups of thousands of people each. So in the pharmaceutics group, it would be thousand -- a thousand people and I -- and I've obviously had to review and evaluate and assess all that work. But I also

had extensive training in physical properties of molecules, physical chemistry, organic chemistry, extensive medicinal chemistry. So that's -- so I wouldn't -- I'm a pharmacologist by training, so...

Q. Right. What does that mean, to be a pharmacologist? Does that mean you're basically an animal guy?

A. Well, yeah, to put it crudely. I study and discover drugs based on animal models of disease, and pharmacology is basically the study of drugs in living systems. And it's -- it's not necessarily animals, but I've studied drugs personally from the gene all the way up to the animal. And then, of course, I am involved and have always been involved in clinical trial design. So in a sense, I do it from the gene to the human but --

Q. The work that you personally did in the lab, was it more animal focused or more gene focused or where would you say your work was?

A. It was all of them. I would say it's fairly balanced, and also a good part of my career was based on stereochemistry and

structure activity relationships, which involves a great deal of organic chemistry. So I have very broad training.

And so to get back to your question, I don't necessarily pass myself off as an expert in all those areas, but I have extensive experience because I've managed, well, tens of thousands of scientists and been responsible for large R&D groups. At Wyeth, it was 7,000 people in every single discipline from the gene through the human.

So -- so that's my -- my experience.

Q. You said -- which areas do you pass yourself off as an expert?

A. I --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The -- certainly I am a pharmacologist and I feel competent to deal with all areas of pharmacology in all therapeutic areas, and I am -- I am, indeed, recognized worldwide as an expert in stereochemistry and in structure activity relationships, which is a complex intermix

between chemistry and pharmacology. And I've directed my own personal chemistry laboratories.

BY MR. POLLACK:

Q. How many people working in those chemistry laboratories that you directed?

A. In the -- because those laboratories were involved in making compounds primarily for me in my laboratories because I kept my laboratory throughout my entire career in the industry, both in the structure activity field and in the stereochemistry field.

So those laboratories would have three or four people, usually a Ph.D. or a master's level of person and several technical staff, but I also was responsible for all of medicinal chemistry at Wyeth, which would have about 500 chemists, and all of the analytical chemistry laboratories, which would have, oh, maybe 3-, 400 chemists. And as you can imagine, I had to resolve issues related to those areas which often cause us problems in drug development.

Q. Okay. In other words, you didn't know the details of everything those 8- to 900

people were doing, I assume, day to day?

A. No, I didn't know all the details of everything that they were doing day to day, but ultimately I was responsible for making the decisions with respect to drug discovery and even development that came from all those groups. Those had to be my personal decisions. I was responsible for that.

Q. Right. You were the decider?

A. Yes. So I needed to be deeply enough involved in the science to make those kinds of decisions.

Q. Okay. I assume, though, you relied on the advice of the medicinal chemists and analytical chemists in making those decisions?

A. Yes. I, as an executive, would rely on the best people around me, but ultimately I had to make those decisions and sometimes, actually not uncommonly, experts disagree, and I would still have to make that decision.

Q. All right. We were talking about your patent cases.

A. Oh, I'm sorry. Could you remind me where?

Q. Yes. We were last on esomeprazole, which you were doing with Perkins Coie.

A. Perkins Coie. And --

Q. Let me ask you. You said you talked about crystal structure in that case.

What did you talk about in regard to crystal structure in that case?

A. Oh, polymorphs, amorphic, amorphous forms. Mixtures between polymorphs and amorphous, X-ray crystal, X-ray crystallography, XRPD, Raman spectra. All of the technologies involved in determining crystal structure and the pharmaceutics involved in formulating crystal structures, and there were other. Also, of course, as I said, the R&D process and regulatory process and FDA.

Q. Okay. All right. What's the next case on your list?

A. Oh. There is a case that just happened to be on a drug that I discovered and I held the patent on where I testified both as an expert witness for a former employer as well as an expert scientifically on the drug. The drug is called carvedilol and the law firm was Fish, et al. I don't remember the other names.

In fact, that's still ongoing and --

Q. Fish & Richardson?

A. Yes, that's right.

And -- and I testified on behalf of the patent holder, obviously. And that involved every single aspect of that drug from the first day that I touched it until even now and that included, well, basically everything.

Q. Were you the inventor on the patent in that case?

A. Yes.

Q. So are you an expert in that case or you're testifying as the fact witness --

A. Both.

Q. -- in that case?

A. Both. Because I was a company employee and obviously I'm the world's expert on that drug and so -- and that turned out to be a very, very important, highly visible drug. I mean, that drug changed how heart failure is treated. It's now the standard of care for this disease. So -- so I was hired to do both roles.

Q. What's the patent about? What is it that was invented?

A. The patent is about congestive heart failure.

Q. What about congestive heart failure?

A. Well, the contention in that case is that the drug, which is a beta blocker, among many other activities that it has, all of which are relevant to heart failure, were discovered in my laboratory -- my laboratories at the time -- was obvious and, of course, beta blockers at the time and still are contraindicated by the FDA and that's the FDA's most significant warning against the use of such drugs.

And so the company challenging that -- and I don't remember, I should, I gave my deposition a few months ago, but I don't remember -- is arguing that it's obvious. And, of course, how could it be obvious if it's contraindicated? And, of course, I also had internal notes of all of the opposition within at that time GlaxoSmithKline, who was my employer at that time, against developing that drug because they thought it would kill people.

And so as the person who had to

live all that and waking up every morning thinking everybody says I'm going to kill people with this drug in these clinical trials and now it's a standard of care, it clearly wasn't obvious.

Q. That's it?

A. So that's basically what my role was.

Q. Is the patent on the chemical?

A. The patent is on the use in heart failure --

Q. Use in heart failure. Okay.

A. -- which is mainly what the drug is sold for. It wasn't invented for that reason.

Q. Someone else invented the chemical; right?

A. Another person synthesized -- first synthesized that and -- and the use was in dispute for a number of years. And when my laboratories -- and I was the senior vice president in the company at that time, but my laboratories were pointing us into the direction of heart failure, and that wasn't a very popular decision given, again, the FDA's contraindication for drugs like that in heart

failure.

So it was quite literally a very difficult situation for 17 years, although I loved every minute of it, but that drug did not have a lot of friends until the FDA approved it as, and the Wall Street Journal indicated it was one of the top three developments of all time in medicine.

Q. Your role in that was in supervising the clinical trials or what was your role?

A. It was everything. My role was everything. I ran all of the preclinical discovery work. I was on the team. In fact, I wrote the entire development plan for that drug early on, and I was on the team that monitored every step of that process, including the clinical trials. I had input into everything.

Q. Okay. And are there any other cases?

A. There may be, but I'm not -- they're not coming to mind.

Q. Okay.

A. Sorry. That's -- that's all I'm coming up with right now.

Q. Okay. Anything else you're working on right now?

A. Yes. Obviously this and there are two others that are just beginning right now, and in one of them I don't even know yet all of the issues. I know that they fall in my area of expertise and -- and so there are two of those.

Q. Other than this particular proceeding that we're doing right now, have you done any other work for United Therapeutics?

A. No, I have not done anything with United Therapeutics before.

Q. Okay. So this is including any litigations or anything else on this same drug?

A. No, nothing on any. I don't think I've ever had any contact with United Therapeutics before.

Q. And what about with either of the law firms that are present here on behalf of United Therapeutics, either Foley & Lardner or Wilson Sonsini? Had you worked with them before?

A. No, I had not.

Q. When did you first get hired to

work on these IPRs?

A. I believe it was April of last year.

Q. April 2015?

A. Yes, I believe so. Around that -- that period.

Q. And how did you get hired?

A. I was contacted by Mr. Delafield, and that's how I got contacted.

Q. What's your -- what's your hourly rate?

A. $500 an hour.

Q. And that's what you're being paid in this case?

A. Yes, it is.

Q. And is that what you were paid in -- approximately in your other cases as well?

A. Of the recent ones, yes, and the first one or two was a little bit less than that.

Q. About how much less?

A. 400 I think.

Q. Do you have an idea how much time you've spent working on this IPR?

A. I would guess between 30 and 40 hours maybe.

Q. That's it, the 30 to 40?

A. I'm guessing. I -- that's something in that range, plus or minus.

Q. Okay. Have you sent either Wilson Sonsini or United or Foley & Lardner an invoice?

A. I sent Wilson et al. two or three invoices, I think. Could be four.

Q. Okay. Do you have an estimate of how much the invoices totaled?

MR. DELAFIELD: Objection. Relevance.

THE WITNESS: I guess they may have totaled between 30 and 40 thousand dollars maybe.

BY MR. POLLACK:

Q. Okay. So that sounds more like maybe 60 hours?

A. Well, there were expenses included in that and -- and so it could have been more than 30 or 40 hours. I just don't remember.

Q. Okay. Somewhere between 30 and 60; does that sound fair?

A. I'm not sure it would be as high as 60.

Q. Okay. 30 and 50?

A. Maybe.

Q. Okay.

A. I'm sorry. I meant to say something at the beginning and I forgot.

I have one change in my expert report that -- that I'd like to make.

Q. Okay.

A. It was --

Q. Tell you what. Let's --

A. Wait till then?

Q. Yeah.

A. Okay.

Q. I'll bring out the expert report and I'll ask you about that.

A. Okay.

MR. POLLACK: I'm going to mark as Ruffolo Deposition Exhibit 2 UT Exhibit 2023, the curriculum vitae of Robert Ruffolo.

(Document marked for identification purposes as Ruffolo Exhibit 2.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. Can you confirm for me that that is your CV?

A. Yes, this is my CV.

Q. Okay. Are there any corrections you want to make to the CV?

A. Not -- not that I know of.

Q. And if you can turn to page 13 in the exhibit.

A. Okay.

Q. I just wanted to look at the section that says "Expert Witness in Lawsuits."

A. Uh-huh.

Q. So the first two cases, one is a SmithKline Beecham litigation?

A. Yes.

Q. Okay. And the second is a Wyeth Pharmaceuticals litigation?

A. Yes.

Q. Were those both product liability kinds of cases?

A. Yes, they were. They were the two that I --

Q. That you mentioned?

A. -- mentioned earlier, yes.

Q. What was the SmithKline Beecham one about?

A. Well, that was the diet drug litigation. The so-called Fen-Phen.

Q. Fen-Phen?

A. Yes.

Q. What was your testimony about in that case? Were you an expert or a fact witness?

A. I was both a fact witness and an expert witness because it fell within my field of autonomic pharmacology and so I served both roles.

Q. Okay. Were you involved at all in the development of Fen-Phen?

A. Oh, no, no. SmithKline Beecham made phentermine, and I think that drug maybe hit the market before I was born.

Q. Uh-huh. Yeah, right.

Okay. So why did they involve you in -- in that case?

A. I was the highest ranking scientist in the organization, and the phentermine is an indirectly acting sympathomimetic amine, and

that happens to be one of my fields of expertise and so I was both a fact witness and an expert witness.

Q. And what did you do in the Wyeth case?

A. It was basically the same type role. I was the president of research and development and, as I said, senior corporate VP and -- and so I was obviously the senior scientist in the company, but it's also an area that I knew a great deal about. It was pharmacological as well as clinical.

Q. And then we have two patent litigations. Those are the first two that you and I discussed today?

A. Yes, those first two.

Q. Okay. And the first one is the Gardiner Roberts one --

A. Right.

Q. -- correct?

And the second is the Goodwin Procter one?

A. That's correct.

Q. Okay. I see the other ones aren't -- aren't listed.

A. Yeah, I don't know what -- what -- when I made this one, and those others are very recent and so I probably haven't added -- I just didn't add it yet.

Q. Okay. Do you know when this CV was made? When it was last updated?

A. Oh, let's see what publication number there is.

Oh, maybe a year or two ago. Being retired, I'm not publishing so much anymore and so this CV doesn't get updated as frequently. So I don't -- I don't know when it was, but it's relatively current, but I haven't updated it in a little while.

Q. Okay. You didn't have a chance to update it with the additional litigations?

A. No, and also I didn't -- don't know -- on almost all of them, I had to sign some order issued by a judge saying you can't disclose anything about it and so it's -- I'm not sure I was allowed to list it. These were cases that were finished and the others are, I think, all still ongoing, and I didn't know if I'm allowed to do that.

Q. Okay. Do you still update your CV

-- do you -- do you update your CV yourself or do you have someone do it for you?

A. Now I do it myself.

Q. Back when you were in at Wyeth, you had someone do it for you?

A. Well, I had an army of -- of assistants and so I didn't have to do that myself.

Q. Okay. Let's mark a third exhibit, which will be your declaration.

A. Okay.

(Document marked for identification purposes as Ruffolo Exhibit 3.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. All right. Ruffolo 3 is titled declaration of Robert -- Ruffolo 3 is entitled "Declaration of Robert R. Ruffolo, Jr., Ph.D. in Support of Patent Owner Response to Petition."

Can you just verify for me that this is the declaration that you submitted?

A. Yes, this is -- this is my declaration.

Q. Are there any corrections that you would like to make to your --

A. Yeah. Yes.

Q. -- declaration?

A. There's one on page 26, and I apologize. I caught this in the penultimate draft and I forgot to add it.

On page 26, five lines up from the bottom.

Q. Uh-huh. This is in paragraph 56?

A. Yes, and on that line it says "toxic to humans, and yet may not be identified." It should read "and yet still would be identified."

And I found that and I just failed to carry that through in the final draft.

So it should read "and yet still would be identified or qualified."

Q. Okay. Can you do me a favor? Can you read the whole sentence with the corrected language for the record?

A. Yes. Where does it start? Okay.

"Based on the present FDA and ICH guidelines, a potentially toxic impurity that is not demonstrated to be a risk in animals,

could still present -- could still be present in a drug substance at a level resulting in exposures of up to 1 milligram per day that could, in fact, be toxic to humans, and yet still identified and qualified -- still be identified and qualified."

Can I write that correction on this draft?

Q. Sure.

A. Just in case we --

Q. Yeah.

A. (Marking). Okay.

Q. So it's actually two corrections; right? "Still" after the word "could"? "Could present -- could still be present"?

A. "And yet may still be identified and qualified."

Q. Yes. You also added the word "still" after about two lines up from that?

A. Oh, no, I'm sorry. If I -- if I said that --

Q. You didn't?

A. -- I was -- I was correct. There was only that one correction on that one line. So not -- "not need to" should be "still."

Q. Okay. Could you do me a favor then? Can you read the sentence as you would like it --

A. Okay.

Q. -- to be --

A. Sure.

Q. -- into the record?

A. Okay.

"Based on the present FDA and ICH guidelines, a potentially toxic impurity that is not demonstrated to be a risk in animals, could be present in a drug substance at a level resulting in exposures of up to 1 milligram per day that could, in fact, be toxic to humans, and yet may still be qualified -- identified and qualified."

Q. And who discovered that error?

A. I did when I was reviewing my declaration.

Q. Okay. How was this declaration drafted?

A. About a year ago, I put together a draft of this declaration by myself and sent it to Mr. Delafield.

Q. Okay. So that's before you saw any

-- a year ago would mean that would be before you saw any dec -- at that time had you seen the declaration of Professor Winkler?

A. I may have. I may have.

Q. Okay.

A. It would have been around that time when I would have first reviewed that and I -- I may or may not have. I don't know.

Q. Okay. But at that time you hadn't seen the decision of the Patent Trial and Appeal Board regarding institution of this review?

A. Again, I don't recall if I did or didn't at the time I prepared the first draft. I just don't remember.

Q. Did you -- did you revise the draft after that?

A. Oh, probably 20 or 30 times.

Q. Did Mr. Delafield suggest revisions to your draft?

MR. DELAFIELD: Objection. Just -- just caution the witness not to disclose any privileged communications between us, so...

THE WITNESS: Not much. This is

my draft and his suggestions were few, if any. There might be a couple of legal sentences, but that's something that I certainly wouldn't understand on my own.

BY MR. POLLACK:

Q. Right. For example, if you turn to page 10 paragraph 18 and going through --

A. Uh-huh.

Q. -- page 12, did you draft those paragraphs?

A. Yeah, that's what I was referring to. That's where -- where he would have helped me or made suggestions because I am not an attorney and would not have been able to do that on my own.

Having said that, I in every draft after that was added, which was early on, I revised over and over. That's how I operate. I do draft after draft after draft until every word is exactly the way I want it, despite the fact that I missed the correction, and so -- but I -- so -- so, yes, that I was helped with that.

Q. Other than the correction you pointed us to in paragraph 56, are there any

other corrections that you'd like to point out?

A. Not that I'm aware of.

Q. Are there any other opinions regarding this case that you'd like to express as you sit here today that are not in your declaration?

A. I -- I've read so many things. I don't recall that there are other opinions. I was asked to deal with long-felt need and that was pretty much what my -- my task was and so that's what I focused on, but I am familiar with other aspects that I've -- you know, based on my reading.

Q. Okay. But as you sit here today, there are no other opinions that you intend to provide in this case other than what's in your declaration?

A. This is what I was asked to -- to testify about.

Q. Okay. And by "this" we're referring to --

A. This document. The contents of my --

Q. -- Ruffolo Exhibit 3?

A. Correct.

Q. As you said, this is a report on long-felt need?

A. Yes. Yes, it is.

Q. What's your understanding of long-felt need? What is that?

A. Well, again, not being an attorney, my understanding of long-felt need is something that results in an improvement in a product that has a significance and something that other people hadn't done. That's my simple layman's understanding.

Q. You said it had a significance. A significance to whom?

A. Well, I'm assuming to anybody. I don't know that it applies to any individual case in terms of your general question.

Q. Well, do you know, does -- does a long-felt need to be something that was recognized or understood in the art?

A. I don't understand.

Q. Maybe I used too many patent terms.

Does a long-felt need need to be something that other people felt a need for?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Could -- could you define "other people" for me? I'm sorry. I just --

BY MR. POLLACK:

Q. Well, besides yourself, for example.

MR. DELAFIELD: Same objection.

THE WITNESS: I would assume somebody would have to think it was an improvement or -- or a significant change.

BY MR. POLLACK:

Q. I'm not asking about an improvement.

Long-felt need. That's like a yearning for something. Would that be a fair way to describe it?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I suppose that would perhaps be -- be something that would -- would represent a long-felt need.

BY MR. POLLACK:

Q. Okay. Do you know when the '393 patent was filed, was there -- have you identified anyone who expressed a desire or a

need that was addressed by the '393 patent?

A. Well, based on almost 40 years of experience in the industry dealing with the FDA, the FDA is always looking for the highest level of purity that's possible and practical and -- and obviously so did physicians and patients, and so that to me would represent a long-felt need.

Q. Okay. But did you identify anyone, say anyone in the FDA or elsewhere, who stated or expressed a need or desire for a purer treprostinil?

MR. DELAFIELD: Objection. Compound and vague.

THE WITNESS: The FDA in general is always looking for the highest level of purity, but specifically they do so for drugs like this that are exquisitely potent and used on a chronic basis where exposure to -- to impurities, especially those that are structurally related to the drug, have the same pharmacophore, we call it, and that are going to be given for the life of the patient and, therefore, exposure would be over a long period.

For those types of drugs, they are especially interested in higher levels of purity and lower levels of impurity.

BY MR. POLLACK:

Q. Now, you understand when this patent was filed, treprostinil was an approved drug being used by patients; correct?

A. Yes.

MR. DELAFIELD: Objection. Vague.

BY MR. POLLACK:

Q. Okay. Now, my question, which you really didn't answer, was: Did you identify anyone at the FDA or elsewhere who expressed at the time this patent was filed a need or a desire for a purer treprostinil?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: The FDA has that desire for every drug to have an increase in purity, even if it's already in the market, and I've had to deal with that before as well.

And -- and they're especially receptive to that with drugs that are

exquisitely potent and drugs that are given on a chronic basis, and so that's -- and the fact that they allowed the specification to change indicates to me that they believed that this was a significant change.

BY MR. POLLACK:

Q. Okay. But you don't know of any document, either from the FDA or from in the literature or from any physicians, asking for a change in purity for treprostinil at the time this patent was filed or before?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: The -- I don't know if whether or not anyone from the FDA asked for that, but it doesn't need to be the FDA. A company can have a desire to increase purity and, again, because the FDA permitted it and they don't actually really like making changes unless they're significant, they did so and changed the specification.

BY MR. POLLACK:

Q. So the FDA changed the specification?

A. Ultimately you can't change a specification without FDA approval.

Q. Sure, but --

A. So they ultimately changed the specification at the request of UTC.

Q. They allowed UTC to change the specification?

A. They approved the change that UTC had suggested after a detailed analysis. That's one of the things they have to do. These are considered significant changes by the FDA.

Q. Can you turn to your paragraph 69 and in particular I'm looking on page 34 of your declaration, Exhibit 3.

A. Okay. 69 I think starts on 30 -- 33 it starts.

Q. Right.

A. Which page would you like me?

Q. I'd like you to focus on 34 but, you know, feel free to read whatever you need to read.

A. Okay.

Q. I'm going to ask you about the first full sentence on 34, which reads:

I have repeatably -- excuse me.

"I have repeatedly observed during the course of my career that the FDA balances their strong desire for the highest levels of purity against the practical need for a company to be able to manufacture the drug product reliability" -- I'm sorry.

A. Reliably.

Q. Reliably. Let me read the whole sentence again.

A. Okay.

Q. "I have repeatedly observed during the course of my career that the FDA balances their strong desire for the highest levels of purity against the practical need for a company to be able to manufacture the drug product reliably."

Did I read that correctly this time?

A. Yes, you did.

Q. Okay. Finally.

You still agree with that sentence?

A. Oh, yes.

Q. Okay.

A. Yes.

Q. Doesn't that sentence mean that the FDA is not going to insist on the highest purity possible because there are practical concerns with making a drug purer and purer and purer; isn't that the case?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: That's only partially correct.

BY MR. POLLACK:

Q. What's incorrect about it?

A. Your -- your description left out the fact that the FDA can, in fact, insist that you increase purity.

Q. Did the FDA do that in the case of treprostinil? Did they insist that UT increase purity?

A. I don't know.

MR. DELAFIELD: Objection. Compound.

THE WITNESS: Yeah, I don't know whether they did or did not.

BY MR. POLLACK:

Q. Do you know if anyone else insisted that United Therapeutics increase purity?

A. I don't know if United Therapeutics insisted on it themselves. They obviously wanted to do that because they took the issue to the FDA, and after a long review period and significant rebuttal by the FDA, as is normal as with any submission to the FDA, the FDA agreed and approved that change.

Q. Let me ask you.

I can always purify a drug further just by purifying it again and again and again; isn't that so?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Not necessarily, no.

BY MR. POLLACK:

Q. But in many cases I can; right?

A. Yeah, in some cases you can.

Q. Right. Now, one reason for not doing that is when I do that, one, it's expensive and, two, it decreases yield; correct?

MR. DELAFIELD: Objection. Lack of foundation.

THE WITNESS: Not necessarily.

BY MR. POLLACK:

Q. But in many cases?

MR. DELAFIELD: Same objection.

THE WITNESS: It can happen, yes. That can happen.

BY MR. POLLACK:

Q. And that's one reason that scientists need to balance purity against other manufacturing considerations; correct?

MR. DELAFIELD: Same objection.

THE WITNESS: I was not talking about scientists. I was talking about FDA.

BY MR. POLLACK:

Q. Okay. Well, what about scientists then? What's your opinion about scientists?

A. A vast majority of scientists in the pharmaceutical industry wouldn't be involved in any of this at all.

Q. Okay. What kind of people would be involved in this at all?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Could you be more specific in -- in what you're asking in "this"?

BY MR. POLLACK:

Q. Well, you just made the statement that a vast majority of scientists --

A. Would not.

Q. -- would not be involved in this at all. So I'm asking -- I'm just following up on the language you used.

What are you referring to? Who would be involved?

MR. DELAFIELD: Same objection.

THE WITNESS: There could be scientists in the -- in the laboratory at the laboratory level. Scientists in the kilo plant. Scientists in the scale-up facilities. And scientists inside the company in the manufacturing group who could want to produce a product that is, you know, has higher level of purity.

BY MR. POLLACK:

Q. Okay. Looking at only those scientists you've just identified, would it be the case that those scientists would balance manufacturing and other concerns against higher purity?

MR. DELAFIELD: Objection.

Vague and lacks foundation.

THE WITNESS: Most of those scientists that I mentioned wouldn't have any idea of the impact that additional purity would have on the practicality and expense because they don't work -- the majority of what I listed -- in the -- the large-scale manufacturing facilities.

BY MR. POLLACK:

Q. Okay. Well, which scientists would know about that impact?

A. Inside manufacturing facilities are process research chemists, and they make estimates of the cost of adding a purification step and, of course, some purification steps decrease cost. They don't all increase. Many do, but they don't all.

Q. Are you a process research chemist?

A. Process research chemists -- chemistry reported to me as did the kilo plant chemists and the process transfer chemists that transfer the process to the manufacturing facilities. They all reported to me.

Q. Well, you were president of the company so everyone reported to you; right?

A. I was president of research and development.

Q. Yeah. So everyone?

A. Not --

Q. All the scientists?

A. Not the company.

Q. Sure. But all the scientists reported to you?

A. There are some scientists in the manufacturing facility that did not report to me.

Q. Okay. But my question was: Are you a process research chemist?

A. I have extensive training in chemistry, but I am not a process research chemist per se, no.

Q. Okay. Let me ask you.

A. However, those decisions, as I said earlier when we were talking about another area, ultimately were mine, and -- and I was responsible for reaching those decisions and making them.

Q. So when you made those decisions, didn't -- didn't you balance purity against other manufacturing concerns?

A. Yes, I did.

Q. If you could turn to page 12 in your declaration, Exhibit 3, paragraph 24.

A. 24, yes.

Q. And you say there:

"I understand that SteadyMed's expert, Dr. Winkler, in his declaration has opined that a POSA" -- do you understand that to be a person of ordinary skill in the art?

A. Yes, I do.

Q. Let me start it again then.

"I understand that SteadyMed's expert, Dr. Winkler, in his declaration has opined that a person of ordinary skill in the art would have 'a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively, a person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry.'"

Do you disagree with that statement?

A. Yes, I do disagree with that statement.

Q. Why?

A. Based on my experience in the pharmaceutical industry, a person involved in the type of chemistry that we're talking about in the patent is a very high level. I consider it to be complex chemistry, and I would have changed that to be a Ph.D. in -- I would have taken out master's degree. I have not seen master's degree chemists make these kinds of decisions or -- or judge this type of chemistry. I would have had the level set higher.

Q. Okay. Because Dr. Winkler's level is too low?

A. I believe it's too low based on my experience working in the industry and that I would have set that higher.

Q. Okay. Let me ask you then.

If he had written that a person of ordinary skill in the art would have a Ph.D. in medicinal or organic chemistry, or a closely related field, would you agree with that?

A. I would agree with that based on my experience on the types of people that actually do this work because I've managed those people

for many, many years.

Q. Then let me ask you.

Under that -- oh, what about the next, his alternative? Do you disagree that an individual with a bachelor's and five years of experience would be skilled enough?

A. I have --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I have not observed in my experience someone with a bachelor's degree and five years of experience to be capable of judging and making decisions based on that kind of chemistry.

And if I could add, while I agree with the -- with what we just discussed that a Ph.D. in medicinal chemistry or organic chemistry, I don't believe that's sufficient either.

I would add several years of experience in the pharmaceutical industry on top of that. A graduating Ph.D. in chemistry or medicinal chemistry couldn't judge this type of chemistry in real life in

the pharmaceutical industry.

BY MR. POLLACK:

Q. Okay. Now, it says "a Ph.D. in medicinal or organic chemistry, or a closely related field."

In your view, what would be appropriate closely related fields?

A. Pharmaceutical chemistry, analytical chemistry, stereochemistry, physical chemistry. Another specialized field is physical pharmaceutics.

Q. Anything else?

A. That's all that's coming to mind. There may be others.

Q. Okay. Am I correct then that you, yourself, you don't have a Ph.D. in medicinal chemistry or organic chemistry or physical chemistry or analytical chemistry or physical pharmaceutics or -- or even pharmaceutics; is that correct?

A. No, I have extensive training in all those areas, but I do not have a Ph.D. in that area. I have a Ph.D. in pharmacology.

Q. Right. Okay. So you wouldn't meet this person of ordinary skill in the art that

we were just discussing, this standard?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: As you recall, I also indicated experience in the pharmaceutical industry as being required, and in that regard, I believe I would be a POSA.

BY MR. POLLACK:

Q. Okay. But you don't have the Ph.D. that you required?

A. Not -- not the P -- well, it says "or related field." My Ph.D. is in pharmacology dealing with stereochemistry and structure activity relationships, and I consider those to be highly chemistry-dominated disciplines and that would fit in a closely related field.

Q. Okay. But when I asked you which fields you would include, you didn't include pharmacology.

MR. DELAFIELD: Objection. Asked and answered.

BY MR. POLLACK:

Q. Is that fair?

A. I -- well, if you're asking would I include pharmacology with those qualifications that I just listed, I would agree to that. That that would be -- that would fit a POSA.

Q. So --

A. Just -- just pharmacology without those qualifications that I just listed for you, I would not list a Ph.D. only in pharmacology without the qualifications, which I do have.

Q. Okay. Yeah, let me make sure I understand then the qualifications.

So it's a Ph.D. in pharmacology plus what? What else would you need?

A. Plus experience in structure activity relationships and stereochemistry, which in my case would -- would, in fact, fit that description, and I suppose there are others. There are pharmacologists that have experience in analytical chemistry and so on.

Q. Do you have experience in analytical chemistry?

A. Yes, I do.

Q. What's your experience in analytical chemistry?

A. In addition to having managed hundreds of medicinal -- of analytical chemists, I have taken as part of my training, both as an undergraduate in pharmacy school and as a graduate student, physical chemistry, analytical chemistry, pharmaceutical analytical chemistry, quantitative analytical chemistry, and obviously a great deal of medicinal chemistry and organic chemistry.

Q. Okay. I didn't ask you earlier.

Have you worked on any other -- maybe I did ask you.

Have you worked on any other inter partes reviews, or is this your first one?

A. I believe this is my first one.

Q. Okay. Let's go to paragraph 28 of your report.

And there you say that in forming your opinions, you've reviewed several documents.

Who provided you with those documents?

A. The compilation of the documents was sent to me by Mr. Delafield, but most of those documents were documents that I

identified early in the preparation of my first draft of this report.

Q. Do you recall which documents you identified and which ones Mr. Delafield provided?

MR. DELAFIELD: Objection. To the extent it discloses communications, I instruct you not to answer.

THE WITNESS: So I should not answer?

MR. DELAFIELD: Well, you're asking him who provided what, which I think --

MR. POLLACK: He is an expert. He's not a fact witness.

MR. DELAFIELD: I know but --

MR. POLLACK: So I'm asking the basis of his, you know, reliance. If he relied on your stuff, that stuff is not privileged.

MR. DELAFIELD: Okay. But he can answer in terms of what he provided.

THE WITNESS: I provided documents from the FDA, from the ICH, some references related to the FDA, documents

related to purity issues and -- and effects of trace impurities. The effect that trace impurities can have on a patient.

BY MR. POLLACK:

Q. Which documents had to do with the effects of trace impurities on patients?

A. There --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: There is a document on penicillin contamination, cephalosporin contamination, bacterial contamination -- not bacterial -- bacterial component contamination.

BY MR. POLLACK:

Q. E. coli component?

A. E. coli.

Q. And that was in insulin?

A. That's correct.

Q. And the penicillin contamination, that was in other antibiotics?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I'm sorry. Could you --

BY MR. POLLACK:

Q. The penicillin contamination, that was concern for other antibiotics?

A. No.

Q. Oh, that was concern for which drugs?

A. For any --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: It was concern for any drug manufactured by a company that makes -- that also makes a penicillin analog.

BY MR. POLLACK:

Q. Okay. As far as you know, United Therapeutics doesn't make any antibiotics; correct?

A. I don't know.

Q. You don't know?

A. No.

Q. Are you aware at all of what drugs --

A. I'm sorry?

Q. Are you aware at all of what drugs United Therapeutics makes?

A. I'm only aware of this, of this product.

Q. Okay. So you're not aware that treprostinil is the only drug substance that is sold by United Therapeutics?

A. I --

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: I don't know very much about United Therapeutics beyond this product and -- and this litigation.

BY MR. POLLACK:

Q. And you didn't look into whether or not United Therapeutics made any -- any antibiotics?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: No, I did not.

BY MR. POLLACK:

Q. Okay. And you didn't look into whether or not United Therapeutics works with E. coli or any other kinds of bacteria?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: No, I did not.

MR. POLLACK: I'm going to mark as Ruffolo Exhibit 4 a document also called Exhibit 1001 in the case. It's US patent number 8,497,393.

(Document marked for identification purposes as Ruffolo Exhibit 4.)

THE WITNESS: Thank you.

MR. DELAFIELD: Thank you.

BY MR. POLLACK:

Q. I assume you reviewed this patent thoroughly in forming your opinion?

A. Yes, I did.

Q. Okay. And this is the patent at issue in this IPR proceeding; correct?

A. Yes, that's my understanding.

Q. Okay. If you could turn to the claims of the patent, they begin at column 17.

Now, do you see claim 1 there?

A. Yes, I do.

Q. Tell me, how many compounds would you say are claimed in claim 1? Do you have an estimate?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: There are many compounds. I have no idea how many. I couldn't estimate, but there potentially are many.

BY MR. POLLACK:

Q. Millions?

A. I don't know.

Q. You didn't look into that?

A. I didn't look into the number of compounds. No, I did not count them.

Q. Okay. But it's at least thousands; right? Is that fair?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: It's a good many compounds. I don't know the quantitation.

BY MR. POLLACK:

Q. Okay. Well, you're an expert in chemistry, I understand.

So based on that, can you give me some estimate looking at the --

A. That misstates --

Q. -- number of groups there?

A. That misstates --

MR. DELAFIELD: Objection.

Form.

THE WITNESS: -- my prior testimony.

BY MR. POLLACK:

Q. Okay. Would you correct it for me?

A. Yes. I did not claim I was an expert in chemistry. I claimed I had extensive training in chemistry.

Q. Okay. Thank you.

What can you tell me then about the purity of some of the other compounds that are in claim 1?

MR. DELAFIELD: Objection. Outside the scope of his declaration. Lacks foundation.

THE WITNESS: Again, I am -- was told to prepare for long-felt need. This is not something I've been asked to do, and I don't know what purity of other compounds would be.

BY MR. POLLACK:

Q. Well, you said you were asked to prepare a long-felt need.

Are you talking about the long-felt need for the compounds in claim 1 or is that

not part of your opinion?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: I prepared to talk about treprostinil and not other compounds.

BY MR. POLLACK:

Q. Okay. So as you sit here today, there's nothing you can tell me about the long-felt need for all those other compounds in claim 1?

A. No, there's nothing I can tell you about the long-felt need for those other compounds.

Q. What about claim 2? Is there anything you can tell me about the long-felt need for the compounds of claim 2 which -- which relates to claim 1?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: I'm sorry. Could you repeat the question?

BY MR. POLLACK:

Q. Sure. Is there anything or do you have any opinion regarding the long-felt need of the compounds in claim 2, which is a

dependent claim, from claim 1?

Let me step back a second.

Do you understand what a dependent claim is? I don't want to --

A. Yes, I think I do.

Q. What -- what's your understanding?

A. The dependent claims follow on from the independent claims. It's about all I understand.

Q. Okay. So you need everything in the independent claim plus something else in the dependent claim; is that how it works?

MR. DELAFIELD: Objection. Calls for legal conclusion.

THE WITNESS: Can you say that again, please?

BY MR. POLLACK:

Q. Yeah. In your understanding, you need everything that's in the independent claim plus what's in the dependent claim and that's how the claim is read?

MR. DELAFIELD: Same objection.

THE WITNESS: Again, I'm not an attorney and I -- my understanding is basic as what I just described.

BY MR. POLLACK:

Q. Can you describe it again?

A. That it follows a dependent claim, but I don't know everything that's included or not included.

Q. Oh, okay. What did you mean by "follows" then?

MR. DELAFIELD: Same objection.

THE WITNESS: To put it crudely, the -- not crudely, but probably in an unsophisticated manner, not being an attorney.

The dependent claim is related to the independent claim, but I don't understand the legal significance between those, and it's not something I think about or was asked to comment on and not something I've been trained to do.

BY MR. POLLACK:

Q. You said, though, it was related, but what's your understanding of the relationship?

MR. DELAFIELD: Objection. Asked and answered. Outside the scope of his declaration.

THE WITNESS: I can't be more specific than I -- than I have been. I'm sorry. I just don't have the legal training to do that.

BY MR. POLLACK:

Q. Okay. You're not sure how it's related?

MR. DELAFIELD: Objection. Mischaracterizes testimony.

THE WITNESS: Just as I said, it is related. In terms of specifically how, I don't know.

BY MR. POLLACK:

Q. So let me get back then. Let me ask again then.

Are you here to give an opinion about the long-felt need for the compounds in claim 2?

A. I'm here to give testimony on the long-felt need of treprostinil.

Q. And treprostinil only?

A. And the diethanolamine salt.

Q. And the diethanolamine salt as well?

A. Yeah.

Q. Okay.

A. I consider them the same. They're both -- one is a salt and one is a free acid. That's similar compounds.

Q. Well, let me ask you.

Claim 9. Do you know which one is claim 9?

A. Yes.

Q. Okay.

A. I'm just reading it.

Q. Am I correct that claim 9 includes both treprostinil and the diethanolamine salt and other salts?

A. I agree that claim 9 includes treprostinil and it would include the diethanolamine salt and other pharmaceutically acceptable salts.

Q. Fair enough. Let's start with other pharmaceutically acceptable salts.

What can you tell me about the long-felt need and the purity of those other pharmaceutically acceptable salts?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Those other salts,

to my knowledge, aside from the diethanolamine salts, are not on the market; and as I described before, the long-felt need is by the FDA and those other salts not being marketed products or being developed for the market, as far as I know, would have -- would be of no interest to the FDA.

So I don't believe there would be -- I'm not here to talk about the long-felt need of something that is not a product.

BY MR. POLLACK:

Q. You're saying there is no long-felt need for something that is not a product?

MR. DELAFIELD: Objection. Mischaracterizes testimony.

THE WITNESS: There may be, but I'm not prepared to talk about that, and I don't believe the FDA would have an interest.

BY MR. POLLACK:

Q. Okay. What about -- you understand when claim 9 is completed, step (d) is only optional; right?

A. No, I don't agree with that.

Q. You see where it says "optionally reacting the salt"?

A. Yes.

Q. Okay. In your view, that's not optional?

A. Because in the chemical structure directly above -- above that, we see the free acid, the -- the reaction involving step (d) would have to take place to generate that salt -- to generate that free acid.

Q. You see, though, that it doesn't just show the free acid.

A. I'm -- yeah.

Q. It shows "or a pharmaceutically acceptable salt thereof"?

A. Yeah.

Q. You see that?

A. Correct. I'm sorry. Can I rephrase my answer?

Q. Please.

A. The structure -- chemical formula 4, Roman numeral 4 in claim 9, is the result of step (d) and -- and so because that compound is part of this patent, step (d) is not optional when it comes to making that compound.

Q. Okay. But you can also make, instead of making that compound, you can make a pharmaceutically acceptable salt; correct?

A. That's correct. You can make a pharmaceutically --

Q. Right.

A. -- acceptable salt.

Q. For example, treprostinil diethanolamine salt is a pharmaceutically acceptable salt?

A. Yes, it is a pharmaceutically acceptable salt.

Q. And if I don't carry out -- I can make treprostinil diethanolamine salt without carrying out step (d); is that correct?

A. That's correct, and so my reference to that being not optional was specifically when I referred to the free acid of treprostinil.

Q. Okay. But you'd agree with me the claim doesn't just include the free acid. It also includes the salts?

A. It includes the salts.

Q. Okay.

A. The pharmaceutically acceptable

salts.

Q. Okay. And so when step (d) is not carried out and the pharmaceutically acceptable salts are made, what can you tell me about the purity of the treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The purity of the diethanolamine salt, based upon the material I've reviewed, is -- is quite high and higher than previous methods for preparation.

BY MR. POLLACK:

Q. Okay. Was there -- because I didn't see this in your report -- in your declaration. So that's why I'm asking.

Are you giving an opinion regarding the long-felt need for a treprostinil diethanolamine salt made according to the patent?

A. Yes, I'm giving an opinion on the marketed products.

Q. Okay. What evidence do you have that there was a long-felt need for a purer treprostinil diethanolamine salt?

A. As I explained earlier, for marketed products, the FDA is always looking for higher levels -- the highest levels of purity that are possible and practical, and especially so for drugs that have exquisitely potent pharmacophores and drugs that are given chronically, and that applies to both the free acid and the diethanolamine salt.

Q. Okay. Other than that general concept, do you have any statements from the FDA or anyone else specifically addressing the purity or commenting on the purity of the treprostinil diethanolamine salt?

A. Yes.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Yes. The FDA, one, in -- in granting the change clearly supported the increase in purity, and in the January 2009 letter submitted to the FDA answering questions from the FDA, of the three questions that the FDA had, two of them were related to purity of treprostinil and the diethanolamine salt.

So, yes, the FDA did have

concerns about purity when evaluating the new manufacturing process.

BY MR. POLLACK:

Q. Okay. You know what? Let's take a look at that. Can we mark as Ruffolo Deposition Exhibit 6 -- is it 6 or 5? -- 5. Can we mark as Ruffolo Deposition Exhibit 5 what's also been marked as UT Exhibit 2006, a letter from United Therapeutics to Norman Stockbridge at the FDA.

A. I'm sorry. Did I say 2009 before?

Q. It's a 2009 letter. You're correct.

A. Oh, okay. Okay. I'm sorry.

Q. Its exhibit number is 2006.

A. Oh, okay. My misunderstanding.

Q. Former exhibit number.

(Document marked for identification purposes as Ruffolo Exhibit 5.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. Okay. So is Ruffolo Exhibit 5 the letter to the FDA that you were just referring to?

A. Yes, it is.

Q. If you could turn to page 2 of the letter, do you see there's a heading with a bullet point regarding "Benzindene triol"?

A. Yes, I do.

Q. Okay. And do you see underneath that there's a paragraph that talks about their Chicago facility?

A. Yes, I do.

Q. Okay. In fact, this letter concerns a change in manufacturing which -- in which United Therapeutics wished to move their plant from Chicago to Maryland; correct?

A. That's my --

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: That -- that's part of my understanding, but also to approve a new manufacturing process.

BY MR. POLLACK:

Q. And one of the changes in that new manufacturing process is they're going to [redacted] instead of [redacted]; isn't that correct?

A. That's correct.

Q. Okay. And, in fact, changing how the [redacted] is [redacted] and [redacted] that can affect purity as well; isn't that correct?

MR. DELAFIELD: Objection. Lacks foundation. Vague.

THE WITNESS: Can you repeat the question?

BY MR. POLLACK:

Q. Sure. Changing how -- what [redacted] is used can change the purity as well; isn't that correct?

MR. DELAFIELD: Same objections.

THE WITNESS: The -- a change in the [redacted] of the [redacted] can have effects, and the FDA was clearly worried about impurities because it mattered so much. That's why there's so much guidelines on purity. They're worried about impurities that carry over into the final product.

BY MR. POLLACK:

Q. Right. And that change in [redacted] has nothing to do with the change in process that concerns the '393 patent in this case?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Can you ask that again, please?

BY MR. POLLACK:

Q. Sure. That change in [redacted] that's not the type of change that's described in the '393 patent?

MR. DELAFIELD: Same objection.

THE WITNESS: The change in the [redacted]?

BY MR. POLLACK:

Q. Right.

A. Okay. So could you ask it one more time, please?

Q. Sure.

A. Because now I've got --

Q. Okay.

A. I'm just trying to figure out what you were asking. It wasn't quite clear to me. I'm sorry.

Q. The change in [redacted] --

A. Yes.

Q. -- in this process --

A. The change of [redacted].

Q. -- that's not something that's described anywhere in the '393 patent?

MR. DELAFIELD: Same objections.

THE WITNESS: The '393 patent, the [redacted] is not [redacted]. It's something else many steps earlier.

BY MR. POLLACK:

Q. Now, let's take a look at that first paragraph after the bullet point, and the first sentence says:

"Historically at our Chicago facility, UT-15C."

Do you know what UT-15C is?

A. Yes, I do.

Q. Okay. What is it?

A. It's treprostinil free acid.

Q. Okay. You're sure that's not treprostinil diethanolamine salt?

You see how it's referred to as "UT-15C intermediate"?

A. Intermediate. Yes. I'm sorry. Intermediate. Yes, I -- can I -- can I start from the beginning --

Q. Absolutely.

A. -- of this letter and review?

(Reviewing document).

Yes, I -- I change my answer. It is not the free acid. I believe it is the -- the diethanolamine salt. I believe it's the diethanolamine salt.

Q. Okay. That's my understanding as well.

A. Okay.

Q. I just wanted to make sure we get the record correct.

"Historically at our Chicago facility, UT-15C" -- that's the diethanolamine salt; correct?

A. Yes, I believe so.

Q. Okay.

-- "is not a compound that was used during the conversion of [redacted] to treprostinil."

Did I read that correctly?

A. Yes.

Q. Then they say:

"This new process was necessary for the production of UT-15C API for our investigational oral formulation (IND 71,537),

but it also affords an additional purification step and an improvement in the process to synthesize treprostinil API."

Did I read that correctly?

A. Yes, you did.

Q. Okay. And in that sentence, they're referring to purification of treprostinil free acid; is that fair?

A. I believe so.

Q. Well, I mean, you've --

A. That's how I would read that.

Q. Okay. I mean, in your declaration, you focused on this --

A. Yes.

Q. -- exhibit; correct?

A. Yes.

Q. Okay. And then the next sentence it says:

"The data in Table 5 from the validation report (VAL-00131) show several impurities detected at low levels below the ICH identification limit of [redacted] percent."

Do you see that?

A. Yes, I do.

Q. Okay. And reading that together

with the next sentence, which reads:

"These impurities are not carried through to the final API, treprostinil as described below."

Based on those two sentences, there are impurities in the treprostinil diethanolamine salt; is that fair?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: Well, I'd like to see Table 5.

BY MR. POLLACK:

Q. Do you have -- you're commenting on this document.

Did you review Table 5 in your analysis?

A. I don't recall.

Q. Okay. Will you agree with me, though, that there's a set of impurities that are described?

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document.

THE WITNESS: Can I read that paragraph again?

BY MR. POLLACK:

Q. Absolutely.

A. (Reviewing document). Okay.

So could you ask the question again, please?

Q. Sure. So according to this paragraph, there are certain impurities that were found in treprostinil diethanolamine salt, also known as UT-15C; correct?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: I don't know of any compound that doesn't have impurities. So, you know, that doesn't surprise me that there would be impurities.

BY MR. POLLACK:

Q. Okay. But, I mean, this paragraph is describing that there's some impurities?

MR. DELAFIELD: Same objections. Asked and answered.

THE WITNESS: And, again, it's identify- -- it's saying that their impurities. I haven't seen Table 5 that I recall, and if you have it, I'd like to look at it, but it's something that would be common to any chemical reaction that

produces a drug, even one that lowers impurities. There are still going to be impurities.

BY MR. POLLACK:

Q. Yeah. What I want to know is: What can you tell me about the impurities that they found in the UT-15C salt using this process?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Again, I'm here to talk about long-felt need, but if you show me Table 5, I can answer that question.

BY MR. POLLACK:

Q. Right. You've never looked at Table 5, though?

A. I --

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: I said I didn't recall if I did or not.

BY MR. POLLACK:

Q. As you sit here now, you don't recall anything about Table 5?

A. I have --

MR. DELAFIELD: Same objections.

THE WITNESS: I have reviewed thousands of tables, and I don't know if I reviewed Table 5 or not. So if I could look at it, I can answer your question, but I can't do it off the top of my head.

BY MR. POLLACK:

Q. Okay. So as you sit here now, you're not able to tell me what the impurities are that would be in that Table 5?

MR. DELAFIELD: Objection. Vague. Asked and answered. Lacks foundation.

THE WITNESS: Not -- not unless you show me Table 5 I can't. Couldn't possibly remember all that.

BY MR. POLLACK:

Q. Okay. Let me ask you this then.

Can you tell me how the impurities that were found in Table 5 in this process differ from the impurities in any other process used to make treprostinil diethanolamine salt?

MR. DELAFIELD: Same objections.

THE WITNESS: The -- if you're asking with respect to Table 5?

BY MR. POLLACK:

Q. Right.

A. I need to see Table 5.

Q. And just to be clear, Table 5 is a document owned by United Therapeutics?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I didn't know that, but whoever owns it, if you can show it to me, I can try and answer your question.

BY MR. POLLACK:

Q. But you are relying on this document and in forming your opinion you didn't say, hey, I need to see Table 5, as far as you recall?

A. I may have seen it. I don't recall because as I said, I reviewed quite literally thousands of tables, and I don't recall if I've seen this one. I may have. I don't recall.

Q. Do you recall seeing any tables regarding the impurities in treprostinil diethanolamine salt?

A. Yes, I do.

Q. What document was that?

A. I saw the Walsh declaration.

Q. All right. Anything else?

A. There may have been others, but that's the one that's coming to mind.

Q. And based on the Walsh declaration, are you able to opine on any differences between the impurities in treprostinil diethanolamine salt according to the patent and any other methods of making the diethanolamine salt?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: I can only comment on Dr. Walsh's conclusion where he indicates that to be the case but, you know, again, I'm here to talk about long-felt need. I'm happy to answer that question if you can show me the table so I can make the comparison.

BY MR. POLLACK:

Q. By the "table" you mean the VAL-00131?

A. Yes.

Q. Okay.

A. But I simply can't do it from

memory.

Q. Yeah. Okay. Do you see at the top of this document it says "Protective Order Material"?

A. Yes.

Q. Okay. And do you understand that this is a -- considered a confidential and secret document by United Therapeutics?

MR. DELAFIELD: Objection. Lacks foundation. Mischaracterizes the document.

THE WITNESS: I see "Protective Order Material." I don't know what that means, but I assumed everything I looked at is confidential material.

BY MR. POLLACK:

Q. Well, you think the patent is confidential material?

A. No. I mean, everything -- all of the documents that are not public in the public domain.

Q. So you understand this is not a public document?

MR. DELAFIELD: Objection. Lacks foundation. Asked and answered.

THE WITNESS: I believe this is not a public document.

BY MR. POLLACK:

Q. Right. In fact, you signed a protective order?

A. Yes, that's what I was referring to. That's why I -- I said I didn't, you know, couldn't disclose certain things and so I -- to me, this is a confidential document, yes.

Q. Right. And what that means is, other than the group of us in this room, a few people at United Therapeutics, and a very small group of people at the FDA who were specifically involved, no one in the public has seen the information in this document?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Is that fair?

MR. DELAFIELD: Objection. Lacks foundation.

BY MR. POLLACK:

Q. Is that your understanding?

MR. DELAFIELD: Objection. Lacks foundation. Mischaracterizes testimony.

THE WITNESS: I don't know. I assume that's true. I don't know.

BY MR. POLLACK:

Q. Okay. But as far as you know, no physician in the public has seen this document?

MR. DELAFIELD: Same objections.

THE WITNESS: Say it again. I'm sorry, please.

BY MR. POLLACK:

Q. No physician in the public has seen this document?

A. Outside of the FDA?

Q. Yeah.

A. I assume they haven't.

Q. And even at the FDA, only the -- most likely only the people who are involved with this application would have seen this document?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: The -- there would be a good number of people at the FDA who would have had access to this document. I don't know who would review it, but all the way up to the final signature, which would

include a division director would have had access to it. I don't know who would have seen it.

BY MR. POLLACK:

Q. Right. Well, you're familiar with the FDA process; right?

A. Of course.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Of course.

BY MR. POLLACK:

Q. So this kind of detailed chemistry review, about how many people do you think at the FDA would have looked at this?

A. Oh.

MR. DELAFIELD: Objection. Calls for speculation and vague.

THE WITNESS: I could only guess.

BY MR. POLLACK:

Q. Okay.

A. I don't know the exact number.

Q. Okay. But it would be a small number?

MR. DELAFIELD: Same objections.

THE WITNESS: What does "small" mean?

BY MR. POLLACK:

Q. Five people?

MR. DELAFIELD: Same objections.

THE WITNESS: My guess is it would be more than that.

BY MR. POLLACK:

Q. More than 10?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know, but it could be. We're talking about approval of a manufacturing process. That's considered a major change according to the ICH, and so major changes undergo extensive review.

BY MR. POLLACK:

Q. Right.

A. And extensive review would involve, you know, quite a few people at the FDA, which is one of the reasons that they don't like to make changes in specification or manufacturing processes. It is very concerning to them, and it consumes a great deal of resource and a great deal of analysis by quite a few people,

but I don't -- I can't give you the number.

Q. You're not aware of -- you've seen the label for the treprostinil products; right?

A. Yes, I have.

Q. Okay. Was there any label change made when the process for making treprostinil described in this letter was made?

MR. DELAFIELD: Objection. Vague. Relevance.

THE WITNESS: Label changes don't include process changes.

BY MR. POLLACK:

Q. Okay. Is there anything on the label of the product indicating or any other public information indicating that the purity of the product changed?

A. FDA labels don't contain purity information.

Q. Is there any other kind of public announcement that the purity of treprostinil changed after this letter?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The FDA, to my knowledge, does not put out public

announcements on changes in purity.

BY MR. POLLACK:

Q. This is all secret information; right?

A. This --

Q. The purity of this product?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: This document would be, yes.

BY MR. POLLACK:

Q. Well, do you know is there any other document that has purity information that you know of that is public?

A. There are many, but not having to do with the FDA and NDAs. So when you purchase a compound for a study from some chemical supply company, they have purity on there.

Q. Sure. Sure.

A. But so there are lots of purities you can find on the Internet and then when you purchase material. But in an NDA, no, that information is not subject to announcements, inclusion in labels. It's not -- not done.

Q. This is all secret, in fact, which

is why it's stamped "Protective Order Material"?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: Well, I don't know who stamped that, but I assume this document is confidential.

BY MR. POLLACK:

Q. Right. I'm not allowed to show this to SteadyMed or anyone else who's outside of this room who's not under the protective order; correct?

MR. DELAFIELD: Same objections. Asked and answered.

THE WITNESS: I would assume that's true.

BY MR. POLLACK:

Q. Yeah. And that would also be true of this validation report, VAL-00131?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. That would also be confidential?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: That's Table 5 and

I would assume that would be confidential as well.

BY MR. POLLACK:

Q. Right. Now, it says that the impurities are not carried through, and that's the impurities in treprostinil diethanolamine salt; is that right?

A. Well, I'm going to have to read it again. Where are you referring?

Q. Yes. The same paragraph.

A. Same paragraph.

Q. This is on page 2 of Ruffolo Exhibit 5.

A. (Reviewing document).

Q. And do you see -- this is the penultimate sentence and it says:

"These impurities are not carried through to the final API, treprostinil as described below."

Do you see that?

A. I see that.

Q. Okay.

A. I need to -- I need to read a little bit more, I think.

Q. Sure. Let me ask you a question

and that way you can read more and try to find the answer to my -- to my question.

That sentence, that's referring to performing the optional step (d) in claim 9?

MR. DELAFIELD: Objection. Calls for speculation. Mischaracterizes the document.

THE WITNESS: (Reviewing document). Okay. So could you repeat the question?

BY MR. POLLACK:

Q. Yes. So my question is: That sentence which reads "These impurities are not carried through to the final API, treprostinil as described below," that sentence refers to carrying out step (d) of claim 9, the optional step?

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, I believe they're talking about the free acid, in which case it would include step (d), which wouldn't be optional.

BY MR. POLLACK:

Q. Right. So if step (d) was not carried out, there's a number of impurities

that would still be left in the tri- -- in the treprostinil diethanolamine salt; is that fair?

MR. DELAFIELD: Objection. Calls for speculation. Lack of foundation.

THE WITNESS: There would be impurities in any product, you know, that's part of the product.

BY MR. POLLACK:

Q. Sure. But there are impurities that are removed by step (d) in making treprostinil that are present in triethanol -- in treprostinil triethanol --

A. Ethanolamine.

Q. Let me start again.

There are impurities that are removed by optional step (d) that are present in treprostinil diethanolamine salt that is a result of carrying the process through step (c)?

MR. DELAFIELD: Objection. Calls for speculation. Lacks of foundation. Asked and answered.

THE WITNESS: There are impurities in any compound and that would include this. As I recall, in the Walsh

document, the impurities were very low.

BY MR. POLLACK:

Q. Yes, but there are impurities in triethanolamine -- in treprostinil diethanolamine salt that are not -- that are removed by step (d) and, therefore, not in the treprostinil free acid?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation. Asked and answered.

THE WITNESS: I'd like to look at the -- at the Walsh document before I answer that because that -- that will help me.

BY MR. POLLACK:

Q. Okay. Without looking at the Walsh document, you're not able to answer?

A. I don't have it memorized. I'm sorry.

Q. Okay. But, I mean, reading the text here, you're not able to conclude that there are impurities that were removed by carrying out step (d) --

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. -- based on the sentence that's written here?

A. There is not enough information here for me -- for me to make that kind of a conclusion without looking at the -- at Table 5, for example, and -- and other sources.

Q. And if I gave you the Walsh declaration, would you be able to answer my question?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: If I had the -- the table in the Walsh declaration, I could tell you whether there are differences in -- in the impurity profile.

BY MR. POLLACK:

Q. Okay. Let me ask you.

Do you know whether step (d) removes impurities from treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Calls for speculation. Lack of foundation.

THE WITNESS: And, you know, again, I'm here to talk about long-felt need, but I can deal with that question with

the Walsh declaration where there is a comparison between the diethanolamine salt and the free acid made by the new process.

BY MR. POLLACK:

Q. Okay. As you sit here now, you don't know whether step (d) removes impurities from the treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Asked and answered.

THE WITNESS: I can guess, which would be speculation, but I can answer if I see the Walsh document.

BY MR. POLLACK:

Q. Okay. Well, you're an expert and so part of the things you do is give opinions.

What is your opinion --

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. -- on whether or not -- let me finish my question -- on whether or not step (d) removes impurities from the diethanolamine salt?

MR. DELAFIELD: Same objections. Outside the scope of his declaration.

THE WITNESS: I am an expert, but I don't have an eidetic memory, and I can look at the Walsh document, which I reviewed a number of times, and answer your question very simply if -- if you give me that document.

BY MR. POLLACK:

Q. Okay. Without that document, you don't have an opinion on whether or not step (d) removes impurities from treprostinil diethanolamine salt?

A. As I said, I don't --

MR. DELAFIELD: Objection. Asked and answered. Vague. Outside the scope of his declaration. Calls for speculation.

THE WITNESS: I don't remember. I'm sorry.

BY MR. POLLACK:

Q. Okay. I need -- I need -- I'm actually asking if you have an opinion, not whether you remember anything.

Do you have an opinion one way or the other?

MR. DELAFIELD: Same objection.

Asked and answered six times now.

THE WITNESS: The -- I would not like to rely on my opinion. I'd like to rely on data. That's what scientists do. I mean, you've asked me a scientific question and I can do it if you -- if I have access to --

BY MR. POLLACK:

Q. Right. Right. The reason I'm asking you is: Do you have an opinion regarding how the purity of treprostinil diethanolamine salt differs from the purity of any prior art treprostinil diethanolamine salt?

If you don't, that's fine. I was just wondering if that's something you're giving an opinion on.

A. That's --

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: And I'm sorry, could you ask it again?

BY MR. POLLACK:

Q. Sure. Do you have an opinion on whether the treprostinil diethanolamine salt made in accordance with claim 9 differs from

prior treprostinil diethanolamine salts?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: For the diethanolamine salt, I don't remember and I need to look at -- at the data for diethanolamine salt.

BY MR. POLLACK:

Q. Well, let me ask you. You have in front of you your declaration.

Do you express in your declaration an opinion -- and feel free to look through it -- regarding whether or not there was a long-felt need due to a difference in impurity between the claim 9's patented treprostinil diethanolamine salt and prior art treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague and compound.

THE WITNESS: The -- my comments on long-felt need are based on the FDA's desire to have purity improved, even in an already pure compound, as far as possible and practical. So that would apply to the marketed products free acid and

diethanolamine salt.

BY MR. POLLACK:

Q. Do you have any opinion then that's specific to anything unique to treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The -- Dr. Walsh has made a -- I recall, I'd like to see the report to be certain -- has made a judgment that the '393 process produced a more pure diethanolamine salt, but I'd like to see the document.

BY MR. POLLACK:

Q. Yeah. Okay. I'm just asking you, though: Did you express that opinion in your declaration?

A. Which opinion? I'm sorry.

Q. That the tri- -- the treprostinil diethanolamine salt is purer made by the patent as opposed to the prior art.

MR. DELAFIELD: Same objections. Asked and answered.

THE WITNESS: The diethanolamine salt is the penultimate compound to the free

acid. Most of my comments refer to the free acid. I don't recall what I've said about the diethanolamine salt. So I -- that's -- that's what I remember.

BY MR. POLLACK:

Q. Okay. And feel free to look at your declaration. Can you look through and see if you made any comments about the treprostinil diethanolamine salt?

A. (Reviewing document).

Q. Let me refine my question.

Can you see if you made any comments in your declaration about the -- either the nature of the impurities or the amount of impurities in the treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Okay. Can I? Can I?

BY MR. POLLACK:

Q. Yes, please.

A. I can read it? (Reviewing document).

Could I make a note on here?

Q. Yeah.

A. Am I allowed to make a note?

(Marking). (Reviewing document).

Q. We need to just --

A. I'm almost --

Q. -- change the tape.

A. Oh.

Q. We can stay on the record as far as our court reporter is concerned.

A. Okay.

Q. But I don't think we need video of just him reading.

A. Okay.

MR. POLLACK: Yes, change the tape.

THE VIDEOGRAPHER: The time is 11:36 a.m. This completes Media Unit No. 1. We are off the record. Okay. I'm sorry for the delay.

The time is 11:37 a.m. This begins Media Unit No. 2. We're on the record. Please proceed, counsel.

BY MR. POLLACK:

Q. Do you need the question read back?

A. Yeah, I'm sorry for the delay and

if you could indulge me --

Q. No, that's fine.

A. -- by reading the question back please.

Q. No problem.

Can you see if you made any comments in your declaration about the nature of the impurities or the amount of impurities in treprostinil diethanolamine salt?

A. There are several references to treprostinil that -- and the patent that don't specify the salt or the diethanolamine and -- and that would include, therefore, both.

Q. Can you show me where?

A. Yes.

Q. Where you're referring to?

A. On paragraph 38, the last sentence.

"This desirable goal is one of the objects of the invention of the '393 patent with respect to the new preparation of treprostinil with a higher level of purity."

Q. Uh-huh. I'm sorry. Here at 38 it just says "treprostinil."

Does it say anything about treprostinil diethanolamine salt?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: As I said, because I didn't specify free acid or diethanolamine salt and I'm referring to the patent where both are produced, it would refer to both.

BY MR. POLLACK:

Q. Well, let me ask you something then. Can you go back to the patent --

A. Sure.

Q. -- for a second?

A. Yeah.

Q. Keep your declaration in front of you.

Let's take a look at -- did you ever look at claim 13?

A. Yes, I have.

Q. Okay. And in that claim, it says:

"The product of claim 9, wherein the base B in step (c) is selected from a group consisting of" and then there's "ammonia, N-methyl-glucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine."

Do you see that?

A. Yes, I do.

Q. Okay. Are you saying when you say "treprostinil" in the patent, does that include treprostinil ammonia salt?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Those are not marketed products and, as I said, because I'm dealing with long-felt need, I would only be considering marketed products.

And, in fact, as I get further along in here with other examples, you'll see I even refer to "product" which would only be the free acid and the diethanolamine salt.

BY MR. POLLACK:

Q. Okay. So you're not -- in regard to, for example, claim 13, you're not commenting on any long-felt need for treprostinil ammonia salt, treprostinil N-methyl-glucamine salt, treprostinil procaine salt, etc.?

MR. DELAFIELD: Objection. Asked and answered and vague.

THE WITNESS: As I mentioned

earlier back in earlier questioning, I'm only commenting on the products because, in my opinion, a long-felt need wouldn't involve a salt that is not being developed or marketed or on the market.

So I'm referring to, with respect to long-felt need, to the marketed products, which is really what the FDA is concerned about.

MR. DELAFIELD: I just wanted to interrupt for a second. Lunch is here.

MR. POLLACK: Oh.

MR. DELAFIELD: Just whenever you guys are ready. So we can keep going or --

THE WITNESS: I can go all day.

BY MR. POLLACK:

Q. Okay.

A. Whatever you want. Whatever you like.

Q. No, that's fine with me.

A. It's up to you.

Q. Let me ask you, for example, about claim 12. You see there where it talks about the potassium hydroxide base?

A. Yes, I see that.

Q. Okay. Are you commenting at all about a long-felt need in regard to claim 12?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Step (b) is the hydrolysis of the cyano nitrile.

So could you repeat the question?

BY MR. POLLACK:

Q. Yeah. Are you -- are you opining on a long-felt need in regard to claim 12?

MR. DELAFIELD: Objection. Vague. Asked and answered.

THE WITNESS: I -- again, I don't believe that the process of -- the product of step (b) is what? What is the product of step -- of step (b) in claim 12?

BY MR. POLLACK:

Q. You are the -- you are the expert. So let me ask you that.

What is -- do you know what the product of step (b) is?

A. Well --

MR. DELAFIELD: Objection.

Mischaracterizes the document and vague.

THE WITNESS: -- I said I was here to talk about long-felt need, and I'd like to know what that product is. And can you point to the chemical structure of the product for me? I could, you know, I guess I could work back.

BY MR. POLLACK:

Q. Yeah, I'm not trying to get you to form an opinion now.

I was wondering if you had expressed an opinion regarding the long-felt need of claim 12. Is that something you intend to do?

A. Well, claim 12 --

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: -- is referring to a product from claim 9 that's been reactive with a base in step (b) of potassium hydroxide, and I'd just like to know which one of those and I suppose I could work it back.

BY MR. POLLACK:

Q. You've reviewed the patent; right?

A. Oh, of course, yes.

Q. Yeah. Okay. Okay. So if you look at column 10?

A. Okay. I'm sorry. I can -- I just worked it back.

Q. Okay.

A. And I will tell you what I believe the product is, and on the assumption that I have that right and only on that assumption, I'll then try to answer your question.

The claim 12 reads:

The product of claim 9, which is the cyano nitrile, wherein the base step is -- where the base in step (b) is potassium hydroxide.

So as I look at the chemical reaction or the chemical structures, that would result in a potassium salt of the free acid and that, to my knowledge, is not a product.

And so I think, as I recall your question -- it was a while ago since I had to work -- since I worked back -- you asked if that would be the subject of long-felt need, and I would answer no, because it's not a marketed product and the FDA wouldn't --

wouldn't have an opinion about it.

Q. Okay. So you're not offering an opinion about the long-felt need for -- for claim 12?

MR. DELAFIELD: Objection. Mischaracterizes his testimony. Asked and answered.

THE WITNESS: Actually, I thought I did offer an opinion that the FDA would not have a concern about a long-felt need for a salt form that was not an approved product, and potassium salt is not an approved product.

BY MR. POLLACK:

Q. Okay. So you have an opinion and your opinion is there isn't a long-felt need for claim 12?

MR. DELAFIELD: The same objections.

THE WITNESS: There is not a long-felt need for the potassium salt formed from claim 12 because it's not a product, if I got this structure correct, which I believe I do.

BY MR. POLLACK:

Q. Okay. And what about for claim 11? It has to do with the alkylating agent.

A. Okay.

Q. Do you have a need for long-felt claim 11, and if -- and if so, what is it?

A. Yes, I do have an opinion. That one --

MR. DELAFIELD: Same objections.

THE WITNESS: That one is easier for me in that I know what the product is, and the product is the cyano nitrile, and the FDA would not have any concern about the cyano nitrile in terms of long-felt need because it's not a marketed product.

BY MR. POLLACK:

Q. And just to make sure I'm understanding, is it then your opinion that there's no long-felt need for -- with respect to claim 11?

MR. DELAFIELD: Objection. Mischaracterizes the document and asked and answered.

THE WITNESS: The product of claim 11, which is not a marketed product and therefore not being given to patients,

the FDA would not have a long-felt need for that. They -- it wouldn't fall on their radar screen.

BY MR. POLLACK:

Q. So I'm trying to sort of get a yes or a no here. So I'm asking a yes or no question.

Am I correct that, in your view, there's no long-felt need for the product of claim 11?

MR. DELAFIELD: Objection. Mischaracterizes the document and testimony. Asked and answered.

THE WITNESS: Again, the product of claim 11 is the cyano nitrile, which is not a marketed product, and the FDA wouldn't have any long-felt need.

BY MR. POLLACK:

Q. Okay. Was that a yes or a no to my question?

MR. DELAFIELD: Same objections.

THE WITNESS: It was the answer to your question. Some questions you can't answer yes or no, and I'm saying that --

BY MR. POLLACK:

Q. Okay.

A. -- because it's not a marketed product, there wouldn't be on the FDA's concern a need for -- a long-felt need with respect to that product.

Q. Let me go down to claim 16. You see that one where it says:

"The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a)."

Do you see that?

A. Yes, I see that.

Q. Would there be a long-felt need with respect to claim 16?

A. I can write on this?

Q. Yeah.

A. (Reviewing document).

I don't believe that question has an answer. It's elimination of a step and -- and so elimination of a step I don't believe would have a long-felt need. Unless --

Q. Okay.

A. Unless you can tell me if I've misinterpreted that and that claim 16 refers to a specific compound, either the free acid or

the diethanolamine salt.

Q. Let me ask you then about claim 17, which talks about, again, the ammonia and then methyl-glucamine.

A. Yes.

Q. Are you opining regarding a long-felt need regarding claim 17?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: (Reviewing document). So it's my interpretation of claim 17, if I have this correct, that one of those bases, diethanolamine, would produce the diethanolamine salt and because that is a product, only that one product resulting from that one salt would have a long-felt need.

BY MR. POLLACK:

Q. Okay. And the other products, the ammonia, the glucamine, the procaine, those wouldn't have a long-felt need?

A. They're not marketed products and would not have a long-felt need by the FDA.

Q. And same question for claim 19. Are you opining on whether there's a long-felt

need for claim 19?

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Why don't we do 19 and, in fact, 19 and 20 are somewhat similar, so why don't we do those together.

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Unless you feel otherwise --

MR. DELAFIELD: Objection. Compound and vague.

BY MR. POLLACK:

Q. -- that they're different.

A. I'd prefer to do one at a time. It will keep my --

Q. Okay.

A. -- mind more clear on what I'm answering. (Reviewing document).

If I understand the claim correctly, that derives from claim 1, which as we discussed earlier, has many, many, many compounds and I couldn't quantitate it, but there are a good many compounds.

And I believe it would only apply to one of those high number of compounds that

was reacted only with the diethanolamine to produce diethanolamine salt, which is a marketed product, and, therefore, there would be a long-felt need.

Q. And what about with respect to claim 20? Are you opining that there is a long-felt need for claim 20?

A. (Reviewing document).

So if I understand that claim correctly, that results -- that refers to a specific compound which, when reacted with diethanolamine, would form the diethanolamine salt, a marketed product, and that would, of course, fall within the scope of what I defined as a long-felt need.

Q. Okay. But the claim would also include the ammonia, glucamine, procaine salts. Am I correct you're not giving an opinion that the other members of that list of salts have a long-felt need?

A. The only one that I would say there was a long-felt need would be the diethanolamine salt.

Q. Now, let me just go to claim 22, and in claim 22, there's an extra thing that

after step (d) is done, so we formed the treprostinil acid --

A. Yes.

Q. -- is that fair?

A. That's -- that's my understanding, yes.

Q. After that is done, the product is converted to an unidentified pharmaceutically acceptable salt; is that a fair characterization?

MR. DELAFIELD: Objection. Mischaracterizes the document. Calls for speculation.

THE WITNESS: (Reviewing document). I'm sorry. Could you repeat that question? I think it doesn't make sense --

BY MR. POLLACK:

Q. Sure.

A. -- to me.

Q. After step (d) is performed --

A. Yes.

Q. -- in claim 22 --

A. Right.

Q. -- the treprostinil acid is

converted into a pharmaceutically acceptable salt.

Is that a fair interpretation of claim 22?

MR. DELAFIELD: Same objections.

THE WITNESS: As I understand it, no.

BY MR. POLLACK:

Q. Okay. How do you understand it?

A. But as I recall, step (d) generates the free acid, which can't be a salt because it's a free acid.

Q. Right.

A. So that free acid -- what confused me is you said "salt" and there is --

Q. Do you see the word "salt" in claim 22?

A. Oh, I'm sorry. I'm sorry. I was looking at claim 1.

Q. Yeah.

A. Claim 21. I apologize.

Q. Oh, okay. Yes. No, no. 22. I skipped over one.

A. I'm sorry.

Q. I didn't mean to throw you off.

A. I thought we were working down.

MR. DELAFIELD: Same objections.

THE WITNESS: My mistake.

(Reviewing document).

Okay. So, again, as I read the claim and if I understand it correctly, we're taking the product of claim 1, which is the free acid, and reacting it with a pharmaceutically acceptable salt, and there are no specified salts there.

So for that particular step, without specifying any salt, and I don't know if they're including diethanolamine in that, I can't say whether it would or wouldn't have a long-felt need. I don't know. They don't specify the salt. So I don't know what they're making.

BY MR. POLLACK:

Q. Can you take a look at the front of the --

A. Sure.

Q. -- '393 patent, Ruffolo 4?

A. Yes.

Q. And do you see there's a number 60 on the left and it says "Provisional

Application"? Do you see that on the left-hand column?

A. Oh, 60. Yes, I do see that.

Q. Okay. And do you see there's a provisional application filed on December 12, 2007?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: Yes, I do see that.

BY MR. POLLACK:

Q. Okay. Did you review the provisional application?

A. The '232 patent?

Q. Yes. The application. Well, it's an application --

A. Application.

Q. -- number, yeah.

A. I'd have to look at my -- at -- at the documents to -- to tell. I mean, I don't -- I don't know if I did. I may, I may not have.

Q. Okay. It is your understanding, though, that this application was -- applications leading to this patent were first

filed at the end of 2007?

MR. DELAFIELD: Objection.

Lacks foundation.

THE WITNESS: I know there were prior applications. I don't recall the dates. I think 2007 is a date that I do remember but, you know, I don't remember if that's the reason.

BY MR. POLLACK:

Q. Okay. Well, let me ask you.

In -- as you see, there's a bunch of filing dates on here. 2007, 2008, and 2012. Do you see that?

There's one at line 22.

A. I see 2008.

Q. Uh-huh.

A. 2007. I see 2012 at 65. At line 65. I see those.

Q. Yes.

A. Yeah. Okay.

Q. 2012 at -- at line 22 you mean?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: Oh, I see. Line 22. I was looking at the November 8th date.

Okay.

BY MR. POLLACK:

Q. I'm just talking about the dates of --

A. Filings?

Q. -- when things are filed you see.

A. Okay. I see that.

Q. Can you identify for me, can you name three people who felt there was a long-felt need for either treprostinil or treprostinil diethanolamine salt that was purer in any of 2008 -- 7, 2008 or 2012?

MR. DELAFIELD: Objection.

THE WITNESS: Can I look at --

MR. DELAFIELD: Vague.

THE WITNESS: Can I look at those patents? Or those filings?

BY MR. POLLACK:

Q. Well, why do you need to look at the filings?

A. I'd like to see who was on them and -- and maybe I'm not understanding your question. I'm sorry. Could you repeat that, please?

Q. Yeah. Let me -- let me rephrase it

then.

Other than the inventors, can you identify three people anytime between 2007 -- well, we'll do it this way -- anytime before 2012. Let me start my question again.

Can you identify for me at least three people other than the inventors prior to 2012 who expressed a long-felt need for a purer treprostinil or treprostinil diethanolamine salt?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: The people who express the need -- the long-felt need for products with greater purity typically are the people at the FDA for a variety of products, and in particular those that are exquisitely potent and used chronically, and in that general sense it would be people at the FDA. And I can name three of those but...

BY MR. POLLACK:

Q. All right. Let's start with that.

Why don't you name for me the three people who prior to 2012 expressed a general

need for lower impurities that you know of.

MR. DELAFIELD: Same objection. Relevance.

THE WITNESS: Janet Woodcock, Norm Stockbridge, John -- Bob Temple.

BY MR. POLLACK:

Q. And how do you know that they expressed that general need prior to 2012?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Because they are senior FDA executives and managers. They are involved in NDA decisions, and as I mentioned earlier, the FDA typically has the desire to have the highest purity possible and practical.

And they would have that -- they would have that desire, as well as the author on the letter from the FDA to UTC. That person would also have the -- and there are many others at the FDA, but those are names that -- that I -- that come to mind.

BY MR. POLLACK:

Q. Okay. But I think they were what you expressed -- I know you said that in your

declaration as well -- is that they would seek a high purity that's practical; is that fair?

MR. DELAFIELD: Objection. Mischaracterizes his testimony.

THE WITNESS: It's not just practical, it's possible and practical. They have to weigh both of those.

BY MR. POLLACK:

Q. Okay. But practical is part of the consideration?

A. It is part --

MR. DELAFIELD: Same objection.

THE WITNESS: -- of the consideration.

BY MR. POLLACK:

Q. Now, let me ask you if you could identify three people other than the inventors prior to 2012 who expressed a particular desire for greater purity particular to the drugs treprostinil or treprostinil diethanolamine salt.

MR. DELAFIELD: Objection. Vague. Relevance.

THE WITNESS: I don't know any employees at UTC and so I can't name any.

BY MR. POLLACK:

Q. As far as you know, United Therapeutics has never announced to the public that there was a change in the purity of its Remodulin product?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: Not to my knowledge I don't. I don't know.

BY MR. POLLACK:

Q. You didn't ask to see anything like that, did you?

A. No, I did not.

Q. Okay. Why not?

A. I didn't believe that it was relevant to me. I was commenting on long-felt need and typically from the standpoint of regulators who always express that opinion.

Q. By the way, when you were at -- when you were director of R&D at Wyeth and SmithKline, was there another department at those -- those companies called the regulatory department?

A. Oh, yes, of course.

Q. Okay. And that department, was

that under your supervision or did it have a separate --

A. At --

Q. -- group?

A. At SmithKline, which is now GSK, it was under a separate division. At Wyeth, it reported to me.

Q. Would you agree, though, that the people in the regulatory group would know more about FDA regulatory requirements than the people in the R&D group?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: So if your question is, would people in regulatory affairs know more than the scientists in the laboratory about what the FDA wants?

BY MR. POLLACK:

Q. Yeah.

A. The answer would be yes, they would.

Q. Okay.

A. And that's referring to the people in the laboratory.

Q. Right.
A. The scientists.
Q. Right.
A. Okay.
Q. Well, what about yourself? Would the people in the regulatory affairs group know more about what the FDA wanted in regard to impurities than -- than you would?
MR. DELAFIELD: Same objections.
THE WITNESS: Maybe not. I spent a lot of time walking the halls of the FDA and -- and regulatory -- regulatory positions are something that I've been invited to lecture on quite frequently, including to the FDA, and I consult with respect to regulatory positions to most large pharmaceutical companies and many mid-size.
So I don't believe everyone in regulatory affairs would know more than me. I'm sure some do, but I wouldn't agree that all of them or even the majority of them do.
BY MR. POLLACK:
Q. Okay. In forming your opinion today, though, did you -- other than the

attorneys, did you speak with anyone else to gain knowledge or other assistance in creating your declaration?

A. No, I did not.

Q. Okay. Did you speak to Professor Williams? I know you read his declaration; correct?

A. I read his declaration.

Q. Did you speak with him --

A. No.

Q. -- in regard to your -- let me finish my question.

A. I'm sorry.

Q. Did you speak with Professor Williams in regard to forming the opinions in your declaration?

A. No, I did not.

Q. Did you have an opportunity to ask Professor Williams questions about his declaration?

A. I guess I would have had an opportunity if I asked, but I didn't ask.

Q. Any reason why not?

A. Well, with respect to regulatory affairs, there isn't anything that Dr. Williams

could have told me or taught me about regulatory affairs.

Q. Okay. You do, though, refer to Dr. Williams' declaration in your -- in your declaration?

A. Oh, yes, in other capacities. I thought you were referring still to regulatory affairs.

Q. No, just in general.

A. Oh, I'm sorry.

Yes, I did refer to his -- his document.

Q. Okay. On those issues where you referred to his document, did you get an opportunity to ask him any questions about those issues?

A. I didn't ask him any questions.

Q. Okay. Any reason why not?

A. I didn't believe I needed to.

Q. Okay. Did you check or review any of the data that Dr. Williams was relying upon?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I reviewed, I think, all of the data that he relied upon,

and I did some calculations based on his data, which appear in my report.

BY MR. POLLACK:

Q. Let's -- let's take a look at that. I think that's in paragraph 70; is that right?

A. I'll have to check. (Reviewing document).

Q. I'm sorry. It's in paragraph 67. Is that the calculation you're referring to at paragraph 67?

A. (Reviewing document). Yes, that's correct. This is what I was referring to.

Q. Are there any other calculations in your declaration?

A. I don't think so, but I don't --

Q. Yeah, I didn't see any.

A. -- recall with certainty.

Q. I was just checking.

A. Yeah, I don't think so.

Q. Okay. Explain to me. What was the calculation you did in paragraph 67?

A. I calculated the percentage reduction in total impurities based on the

analysis that Dr. Williams did on the treprostinil free acid by the former process and by the '393 process.

Q. Let me ask you.

Is what you did -- this number .9545, where did that come from? Did that just come from Dr. Williams?

A. Yes, that came from his table.

Q. Okay. Did you calculate that number independently yourself?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: No, I did not calculate that myself.

BY MR. POLLACK:

Q. Okay. Did you go through the individual, you know, purity numbers that -- from the raw data that he reviewed and check those?

A. I reviewed every Certificate of Analysis that was provided to me on the former process and the '393 process, and I reviewed every single one of them and took notes on almost every one of them.

Q. Did you calculate any of the

averages or standard deviations or anything like that?

A. No, I did not.

Q. Okay. So you're relying on Dr. Williams' --

A. Yes.

Q. -- calculation?

A. I'm relying on his calculation.

Q. Okay. And what about the number .2936? Did you just take that from Dr. Williams?

A. Yes, I took that from Dr. Williams' calculation.

Q. Okay. You didn't calculate any averages or standard deviations?

A. No, I did not.

Q. So am I correct, is the calculation that you did is you just subtract .2936 from .9545?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: No.

BY MR. POLLACK:

Q. Well, what did you do?

A. I divided .2936 by 9545 and

multiplied by 100 and then subtracted 1 to get the percentage reduction.

Q. Okay. That's the only calculation you did?

A. Yes.

Q. Okay.

A. I'm sorry. I didn't subtract that. Yes, I did subtract that from 1, yeah, to get the percentage reduction.

Q. And other than that, you didn't do any -- any other calculations?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: I didn't do -- I believe I did a calculation of the absolute percent. It's not in my document, and I forget what number I got. It was something close to [redacted] percent.

BY MR. POLLACK:

Q. What do you mean by the "absolute percent"?

A. That's dealing with the purity of the -- the free acid.

Q. Can you explain to me how that calculation is done?

A. Well, you decide -- divide the one by the other and multiply by 100, and I don't remember what I got, but it's something between a [redacted] percent and [redacted] percent.

Q. Okay. You said you divide one by the other.

What's the first one?

A. The first one --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: -- would be the higher purity by the lower purity and then multiply by 100.

BY MR. POLLACK:

Q. The higher purity of what?

A. Of the free acid.

Q. When you say the "higher purity," are you referring to the purity of treprostinil made according to the '393 process?

A. That's correct.

Q. Okay. And there you're using the percentage. When you say the "higher purity" --

A. Yes.

Q. -- do you mean 1 minus .2936?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Is that what you were referring to?

MR. DELAFIELD: Vague.

THE WITNESS: Yes.

BY MR. POLLACK:

Q. Okay. Okay. So you -- you took 1 minus .2936 and you divided that by 1 minus .9545?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The other way around.

BY MR. POLLACK:

Q. Okay. I'm sorry.

You took 1 minus .94 -- 9545 and divided by 1 minus .2936?

A. Yes.

MR. DELAFIELD: Same objection.

THE WITNESS: Yes. Well, let me see. I just did it on the back of an envelope, so I don't remember.

No. I -- 1 minus -- yes. 1 minus .2936 divided by 1 minus .9545 multiplied by 100 to get the percent higher

level of purity.

BY MR. POLLACK:

Q. All right. What number did you get?

A. I don't remember. It was -- it was close to [redacted] percent, between a [redacted] and [redacted] percent.

Q. Between a [redacted] and [redacted] percent?

A. Between [redacted] -- yeah, [redacted] and [redacted] percent, something in that range.

Q. Okay. And why didn't you include that calculation in your report?

A. Oh, I just it did for my own interest. This was the number I wanted, the reduction in purity. Because the point I'm making here is that the FDA would certainly take a [redacted] percent reduction in purity -- in impurity level as being very significant, something they would like to see.

Q. Okay. Now, you're aware that the -- I think you are -- that there's a patent called the Moriarty -- not a patent, there's a paper in the Journal of Organic Chemistry that we've called the Moriarty paper.

You're aware of that; right?

A. Yes, I am aware of that.

MR. DELAFIELD: Objection.

Vague.

BY MR. POLLACK:

Q. And you're aware that in that paper they reported a purity of 99.7 percent?

A. I --

MR. DELAFIELD: Same objection.

Lacks foundation.

THE WITNESS: I believe that's what they reported at the -- in the very last sentence.

BY MR. POLLACK:

Q. Yeah, and that's -- that's the prior art Moriarty process in this case?

A. Yes, that's my understanding.

MR. DELAFIELD: Same objection.

Lacks foundation.

BY MR. POLLACK:

Q. Let me ask you.

If Dr. Williams made a mistake in his calculations and the set of data that he was relying on showed a purity of 99.7 percent for the Moriarty process, how would that change your opinion?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: It wouldn't change my opinion.

BY MR. POLLACK:

Q. So even if the prior art was 99.7?

A. It wouldn't change --

MR. DELAFIELD: Same objections.

THE WITNESS: -- my opinion.

BY MR. POLLACK:

Q. So you're saying even -- even if there was a 99.7 percent purity level in the -- in the prior art, there would still be a long-felt need?

A. That 99.7 from Moriarty?

Q. Right, from Moriarty.

A. Yeah, that wouldn't change my -- my opinion.

Q. Okay. So even if all of the -- prior to the patent all of the treprostinil that United Therapeutics was selling had a purity of 99.7 percent, you still feel there would be a long-felt need for --

A. No, that's not what I was saying.

Q. Okay. Explain it to me.

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: I know how Dr. Williams did his analysis. He was pretty clear. And the purities that he got were based on total -- total --

BY MR. POLLACK:

Q. Related impurities?

A. -- total related -- total related impurities, and I know how that's done.

Q. Uh-huh.

A. Nowhere could I find in the Moriarty paper, which I looked very hard for, how his purity was measured, whether it was against a reference standard or whether it was against a -- or whether it was done by total related impurities.

And so you can't compare unless they're apples and apples and there that number 99.7 percent didn't mean anything to me because I couldn't tell how he did the analysis. You will get different results with a reference standard versus total related impurities.

Q. No, the FDA, though, requires that

United Therapeutics, and everyone else, reports total purity by HPLC analysis; is that correct?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: There are options to use. They do happen to like the HPLC, but there are other analyses that are permissible.

And, of course, you have to run them by the FDA as part of your discussions, convince them of the reliability of that assay, show them the standard deviation, the relative standard deviation of the assay, the limit of quantitation, the limit of detection, and if they are convinced, you can use other assays.

BY MR. POLLACK:

Q. Okay. But in the case of treprostinil, United Therapeutics is submitting the HPLC assay analysis?

A. Yes, they are --

Q. Okay.

A. -- in the case of treprostinil.

Q. And that's not done by taking total related impurities?

MR. DELAFIELD: Objection. Mischaracterizes the documents and his testimony.

BY MR. POLLACK:

Q. Correct?

A. That's correct.

Q. Yeah. Okay.

A. They -- they do both, but the purity level by HPLC is what is required.

Q. Right. Actually --

A. Yes.

Q. -- you said they did both, but, in fact, they never total up the total related purities and subtract that from 100, do they?

MR. DELAFIELD: Objection. Lack of foundation. Calls for speculation.

THE WITNESS: No, because that's not a preferred analysis by the FDA. They want a reference standard and that's the HPLC.

BY MR. POLLACK:

Q. Right. And do you -- do you recall that the Moriarty reference he describes using an HPLC and a UV detector?

A. Yes.

MR. DELAFIELD: Objection.
Lacks foundation.
BY MR. POLLACK:
Q. Okay. Okay. Why are you then saying you don't -- you're not sure whether or not he used HPLC in a reference standard?
A. Well, H --
MR. DELAFIELD: Objection.
Lacks foundation.
THE WITNESS: -- HPLC is used for total related substances, too, but he didn't indicate whether he compared peak heights, which would be total related substances, or a reference standard, which would be the quantitation preferred by the FDA in their certificates of analysis, the release specs.
So I couldn't tell what Moriarty used, and I looked for it to see whether that was a number, a comparable number that I could use to compare apples to apples to -- to Dr. Williams.
BY MR. POLLACK:
Q. Let me ask you this.
Moriarty doesn't report anywhere

what the total related impurities are; right?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q. I mean, in the -- in the Journal of Organic Chemistry paper, he doesn't report it?

A. I don't know. He doesn't say what he did.

Q. Yeah. I'm saying, in the paper, he doesn't report the total related impurities?

MR. DELAFIELD: Objection. Lacks foundation. Mischaracterizes the document.

THE WITNESS: If he did his analysis by peak height comparison, he reported the total related impurities, and if he did it by HPLC, it was the HPLC quantitative assay. I don't know what he did.

BY MR. POLLACK:

Q. Yes, that's what I want to ask you. I'm asking if he reports what the related impurities are.

A. I don't know.

MR. DELAFIELD: Same objections.

THE WITNESS: He may and he may not. Depends how he did the assay, and he doesn't say.

BY MR. POLLACK:

Q. Yes. I'm asking if in the paper he reports what the related impurities are, in other words, identifying them, saying anything about them.

MR. DELAFIELD: Same objections. Asked and answered. Asked and answered.

THE WITNESS: He doesn't report what it is he's measuring, whether it's total related impurities or a quantitative HPLC assay, and the results are different.

BY MR. POLLACK:

Q. Yeah. Maybe we're misunderstanding each other.

In the Journal of Organic Chemistry paper, does Moriarty say, here's some of the impurities that are present in treprostinil?

MR. DELAFIELD: Objection. Same objections. Asked and answered.

THE WITNESS: I don't recall. I'd have to go review the paper.

BY MR. POLLACK:

Q. You're aware that Moriarty is associated with United Therapeutics that that's their patent?

A. Yes, of course.

Q. Did you ask United Therapeutics, hey, can you tell me how Moriarty did this analysis?

A. No, I did not ask.

Q. Take a look at the '393 patent. Can you show me in the '393 patent where they report what the impurities are in treprostinil or any other compound?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: So they report purities in -- I don't see a table number -- in column 14 at the bottom, and those are HPLC area under the curve. So those are reference standards.

In table -- on column 16, they report a purity and -- and because that is the process that they submitted to the FDA for approval, that has to be an HPLC quantitative assay with a reference

standard.

BY MR. POLLACK:

Q. Uh-huh.

A. And in claim 2 -- I'm sorry -- claim 2 and claim 10, that is total related substances.

Q. Why do you say that if every other place in the patent it reports HPLC assay analysis?

A. Because it's my understanding that the document that was submitted by Dr. Walsh to the Patent Office was the last document before approval and that convinced the agency to approve this patent and the claims, and he did total related substances.

Q. So you're saying we should look at what Dr. Walsh says, not what's written in the patent?

MR. DELAFIELD: Objection. Calls for speculation.

BY MR. POLLACK:

Q. That is your opinion?

A. No, that's not my opinion.

Q. Well, then, why aren't we looking at the HPLC analysis in the patent?

A. That's not in the claim. I think, actually, you should look at all of them, but what's in the claim was done by a different method, total related substances.

Q. So you see the words "total related substances" in the claim?

A. No, I don't. As I said, I reviewed Dr. Walsh's analysis and that was submitted just before approval, as I understand, and there were no further actions taken before the decision. And so it makes sense to me that because he reported total related substances that the claims, which is what was in dispute -- dispute, referred to total related substances.

Q. Okay. You'd agree with me that within the patent itself, those are all HPLC analyses that are reported?

MR. DELAFIELD: Objection. Lacks foundation. Calls for speculation.

THE WITNESS: It's my judgment based on the description of area under the curve and the HPLC assay, as well as the fact that example 6 refers to the process that was approved by the agency, which is an

HPLC quantitative assay involving a reference standard, that that is what was used.

BY MR. POLLACK:

Q. And by "that" you mean HPLC analysis?

A. Yes.

MR. DELAFIELD: Same objections.

THE WITNESS: When you get to a point, I'd like to use the restroom. I don't need lunch if you don't want, but I do -- would like to use the restroom.

BY MR. POLLACK:

Q. Do you want to break? It's up to you. Do you want to break for lunch now?

A. It doesn't matter to me. Whatever you want to do.

MR. DELAFIELD: Yeah, it's already 12:30.

MR. POLLACK: You guys want to break for lunch? That's fine.

MR. DELAFIELD: Sure.

THE VIDEOGRAPHER: The time is 12:34 p.m. This completes Media Unit No. 2. We're off the record.

(Whereupon, at 12:34 p.m., a luncheon recess was taken.)

AFTERNOON SESSION

(1:23 p.m.)

ROBERT R. RUFFOLO, JR., PHD

called for continued examination and, having been previously duly sworn, was examined and testified further as follows:

EXAMINATION (CONTINUED)

THE VIDEOGRAPHER: The time is 1:23 p.m. This begins Media Unit No. 3. We're on the record. Please proceed, counsel.

BY MR. POLLACK:

Q. Welcome back, Dr. Ruffolo.

A. Thank you.

Q. Was lunch good?

A. Yes.

Q. Okay. You didn't discuss your testimony with counsel during lunch, did you?

A. No, we didn't.

Q. I'd like to turn to paragraph 32 of your declaration that is Exhibit 3.

A. Okay.

Q. And you can read -- you can read all paragraph 32, but I want to focus on page 15 at the top of the page. You have a

statement there that reads:

"For example, if the actual purity of an API is 99.4 percent and the lowest limit of purity in the Drug Specification of the Certificate of Analysis is 99.5 percent, the entire batch of API must be rejected."

Do you see that?

A. Yes, I do.

Q. Okay. So let me see if I -- if I understand this.

By the way, do you agree with that statement still?

A. Yes. As an example, yes.

Q. Okay. So, for example, let's say I have a Certificate of Analysis and it says the HPLC analysis is 99.6.

A. Okay.

Q. Okay. Would that drug be sold to the public?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: That depends on what the specification was.

BY MR. POLLACK:

Q. Oh, I'm sorry. I was using --

A. Oh, in my example.

Q. -- your example. In your example.

A. I'm sorry. Yeah, could you repeat that, please? I'm sorry.

Q. Yeah. So using your example.

A. Okay. Yeah.

Q. Let's say I had a drug which its HPLC analysis shows --

A. Yes.

Q. -- it had a Certificate of Analysis by HPLC of 99.6 percent.

Would the FDA allow the company to sell that batch to the public?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: So if it was 99.6 and the specification was 99.5, yes, that would be allowed to be approved. I don't know if it could be sold to the public. That depends on many other steps because that API would go into that a drug product, and that has its own specs. So that would determine.

BY MR. POLLACK:

Q. Sure.

A. But it could move on in the manufacturing --

Q. It could move on in process?

A. -- in the manufacturing process.

Q. What if I had an API -- what does API stand for?

A. Active pharmaceutical ingredient.

Q. If I had an active pharmaceutical ingredient which had, just like your example, Certificate of Analysis, the specification is 99.5 percent. So let's say I had a batch and it had an HPLC assay analysis of 99.5 percent.

Could that move on in the process?

MR. DELAFIELD: Objection. Vague. Relevance. Calls for speculation.

THE WITNESS: Yes, that could move on if that 99.5 was the specification. Yes.

BY MR. POLLACK:

Q. Okay. Now, you're aware the limit for treprostinil that we're dealing with in this case is 98 percent; is that right?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation. Vague.

THE WITNESS: That is the current lower limit.

BY MR. POLLACK:

Q. Okay. So if I have a batch, let's say I have a -- I make a batch of treprostinil and it -- I measure its HPLC assay and it's 99 percent.

Do you have my assumptions?

A. Uh-huh.

Q. Can that batch of treprostinil move on in the process?

MR. DELAFIELD: Same objections.

THE WITNESS: Assuming all of the other specifications were met, yes, that could move on.

BY MR. POLLACK:

Q. Okay. And I make another batch of treprostinil API and I measure its HPLC analysis and it's [redacted] percent.

Could that batch move on in the process?

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, with that current level spec, that could move on.

BY MR. POLLACK:

Q. Okay. Based on your experience in the industry, if a company like United Therapeutics made a batch that was [redacted] percent on the HPLC analysis, it would be the normal expectation that the company would then move that batch into the rest of the process?

A. Yes.

MR. DELAFIELD: Objection. Relevance. Vague. Calls for speculation.

THE WITNESS: Yes, they could do that.

BY MR. POLLACK:

Q. Okay.

A. If they -- if they chose to.

Q. Now, Dr. Williams opined that certain batches that he looked at had an average HPLC analysis -- I'm sorry, I'm incorrect -- an average purity based on subtracting related impurities of 99 percent.

Is that -- is that what you recall?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Approximately 99 percent --

MR. DELAFIELD: Objection. Vague.

BY MR. POLLACK:

Q. -- for the Moriarty batches?

A. Oh, for the --

MR. DELAFIELD: Objection. Vague. Mischaracterizes document.

THE WITNESS: I would have to look again at those tables, but it was something close to that. I don't remember the number.

BY MR. POLLACK:

Q. Okay. Yeah. I'm not trying to --

A. Yeah.

Q. -- trying to trick you here. If you look at where we were --

A. No, I understand. I just don't remember --

Q. Yeah.

A. -- the number.

Q. Remember we were -- we were looking --

A. Yeah.

Q. -- at your paragraph 67?

A. Yeah. Yeah. Okay.

Okay.

Q. And maybe I misunderstood, but I

think here you refer to Dr. Williams' declaration and his Table 1?

A. Yes.

Q. Do you see that?

A. I did, yes.

Q. And I think what I'm supposed to conclude here is that the -- well, what am what am I supposed to conclude about the typical purity of the Moriarty process, if anything, from your -- your paragraph 67?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That the average relevant impurities are higher in the Moriarty process compared to the '393 process.

BY MR. POLLACK:

Q. Okay. Is there anything I'm supposed to conclude about what the average purity on the scale from zero to 100 percent is of API made by the Moriarty process?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: Oh, I can't answer that because there will be variability.

There will be some high, some low, and I haven't analyzed how many would fall below spec. So I don't know.

BY MR. POLLACK:

Q. Okay. Well, let me ask you this. This number .945. If I subtract that number from 1 and multiply by 100 --

A. Uh-huh.

Q. -- right, I get approximately 99 percent; is that fair?

A. About, yes.

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Okay.

MR. DELAFIELD: Mischaracterizes the document.

BY MR. POLLACK:

Q. Would you -- in your view is -- does that characterize the average purity of products made by the Moriarty process?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I believe that the analysis done by Dr. Williams gives a answer to the question that the Moriarty process

produces product that is less pure than the '393. And your question is?

BY MR. POLLACK:

Q. Okay. I was wondering if it gives an answer to the question of what the average purity was in the Moriarty process.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I think it gives a relative purity compared to the '393 process because, remember, it depends on how you do the analysis, whether it's against a reference standard or against total related product.

This I know was done against a reference standard, and so it gives an idea of average purity that one would expect with one process to another because you're comparing apples to apples in this case. And I think that's a fair comment what I said and --

BY MR. POLLACK:

Q. Okay. Let me just make sure you didn't --

A. Yeah.

Q. -- you didn't make an error here because you just said you know this was done by an HPLC analysis, but here it says total related substances in your paragraph 67.

A. Oh, I'm sorry. I'm sorry. I take that back.

The comparison is still valid because it's apples to apples total related substances. I apologize. But so it's apples to apples. The same relative purity is comparable. You can compare one to another, and it's higher with '393 than with Moriarty.

So I take it back. But you're right. It's total related substances.

Q. Okay. Based on this, are we able to say anything about how the HPLC analysis compares --

MR. DELAFIELD: Objection. Vague.

BY MR. POLLACK:

Q. -- for Moriarty versus '393 process?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: Okay. I have not seen that comparison done on -- on HPLC quantitative assay against reference standard. I did look at all of those certificate of release forms where that's done, but I didn't do an analysis.

BY MR. POLLACK:

Q. Okay.

A. But the analysis that Dr. Williams did, because it's apples to apples, gives a good comparison of one process to the other, but I can't relate that to an FDA release spec that's done by different analysis to a reference standard. That's -- that's what I'm trying to say.

Q. Okay. Okay. I understand.

Okay. So what you're saying here in effect is, look, the '393 patent does another purification step on top of Moriarty, so the purity is going to be higher?

A. I'm not --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I'm not -- I wouldn't agree with that statement.

BY MR. POLLACK:

Q. Why not?

A. Because it takes away a purity -- a purification process of the -- of the nitrile. The Moriarty process -- excuse me -- involves purification of the nitrile --

Q. Okay.

A. -- and that's not done with -- with '393.

Q. Let's talk -- let's -- you said it wasn't done in '393. If we could go back to the '393. You got it there?

A. The patent? Yes. Yes.

Q. Okay. Very good. And then that is in this proceeding, our deposition, Ruffolo Deposition Exhibit 4.

If you turn to claim 16, you'd see there's a --

A. Claim 16.

Q. That's in column 20.

A. Yes.

Q. You see there's a step that says "does not include purifying the compound in formula (VI)."

And formula (VI) is the nitrile;

correct?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: (Reviewing document). Yes, it says that the compounded formula (VI) does not include that purifying -- that purity step.

BY MR. POLLACK:

Q. Okay. So that's in claim 16?

A. That's in claim 16.

Q. Right. So then presumably the other claims you could include the purification of the nitrile.

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Is that your understanding?

MR. DELAFIELD: Objection. Vague. Lacks foundation. Calls for speculation.

THE WITNESS: That's not my understanding. The process that is the subject of this patent, which is, I think, referenced -- referenced in the claim 1 and claim 9, is referring to a process, which as I understand is the '393 process, which

doesn't have purification of the nitrile.

BY MR. POLLACK:

Q. Okay. I'm not -- I may be asking you something that's a little too legal, but do you have an understanding -- let me step back.

Do you have any patents?

A. I have a couple of patents, yes.

Q. Okay. Do you have any understanding of how patent claims work?

A. I have a -- compared to somebody like you -- a relatively low understanding of how patent claims work. I'm not totally ignorant on the subject, but I have some knowledge, but it's certainly nothing that I've devoted a great deal of time to.

Q. Are you familiar with the following concept? When a -- when a claim says "comprising" and it has a process comprising, that means the claim is met. If the steps of the claim are performed, plus in addition, because it says "comprising," it also includes processes which have additional steps that that's allowed, that's part of the claim as well.

MR. DELAFIELD: Objection.

Vague. Calls for a legal conclusion.

THE WITNESS: Yeah, that's getting a little bit beyond my -- my --

BY MR. POLLACK:

Q. Okay.

A. -- relative understanding.

Q. Yeah, I'm not asking you if that's right.

A. Yeah.

Q. I was just wondering if you knew about that.

A. Not -- not really.

Q. Oh, okay.

A. Not -- no. Again, I'm not a lawyer -- an attorney and -- and that is beyond my level of expertise.

Q. Okay.

A. So I'm sorry.

Q. Okay. Let me just ask you. Just going back to claim 16 where it said "wherein the process does not include purifying" the nitrile.

What was your understanding of how claim 16 was different from claim 9?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: Well, I -- because claim 9 says it's wherein the product is prepared by the process comprising, and that I understand is the '393 process, which doesn't have a purification step for the nitrile, I -- looks like claim 16 is reaffirming that. That's all I can say.

BY MR. POLLACK:

Q. Okay. So one of the -- one of the differences between the Moriarty process and what I call the '393 process -- that's what you call it in your declaration; right?

A. Yes, I think so.

Q. Is that in the '393 process, this purification step is -- of the nitrile has been removed?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That's my understanding, yes.

BY MR. POLLACK:

Q. Yeah. Okay. Are there other -- in addition, there's a further purification step at the end where they make the diethanolamine

salt in the treprostinil that -- that United Therapeutics makes by the '393 process; is that your understanding?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: It's my understanding that that crystallization was done, and it did result in an increase in the level of purity and a decrease in the level of impurities, which is what Dr. Williams analyzed.

BY MR. POLLACK:

Q. Other than that crystallization and the change in the purification of nitrile, did you identify any other differences between how United Therapeutics made treprostinil according to the Moriarty process and treprostinil according to what we're calling here the '393 process?

MR. DELAFIELD: Objection. Vague. Outside the scope of his declaration.

THE WITNESS: I would suggest that the formation of the diethanolamine salt as the step immediately before the

crystallization was part of the purification based on my -- on my review of -- of the documents.

BY MR. POLLACK:

Q. Now, you said that was a purification by crystallization; is that right?

MR. DELAFIELD: Objection. Vague. Mischaracterizes testimony.

THE WITNESS: That's the step (d), which is reacting the salt formed in step (c) with an acid to form the compound of formula IV, which is treprostinil free acid.

BY MR. POLLACK:

Q. That's called a crystallization?

A. That --

MR. DELAFIELD: Same objection.

THE WITNESS: -- to me would be a crystallization.

BY MR. POLLACK:

Q. Let me ask you.

Have -- have you seen crystallization used before to purify compounds?

A. Oh, yes. Yes, I have.

Q. How often?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: It's a process that's used not uncommonly to purify final product of the reaction.

BY MR. POLLACK:

Q. Wasn't this -- isn't crystallization unique to the '393 patent?

MR. DELAFIELD: Objection. Vague and ambiguous.

THE WITNESS: The crystallization, as I understand it, is not what's unique to the patent. It's the result of that crystallization that resulted in a different product with a higher purity and lower levels of impurity.

BY MR. POLLACK:

Q. How long has crystallization been around as a method of purification?

MR. DELAFIELD: Objection. Vague. Relevance. Outside the scope of his report.

THE WITNESS: I don't know how long it's been around.

BY MR. POLLACK:

Q. Before 2007?

A. Oh, yes.

MR. DELAFIELD: Same objections.

THE WITNESS: Yes.

BY MR. POLLACK:

Q. Did you learn about it when you were in college at the university?

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, I did.

BY MR. POLLACK:

Q. What course did you -- in what course did you learn about that?

MR. DELAFIELD: Same objections.

THE WITNESS: The inorganic chemistry, organic chemistry, physical chemistry, medicinal chemistry, pharmaceutical chemistry, analytical chemistry. Maybe some others.

BY MR. POLLACK:

Q. And when did you go to college?

A. In 1968 I started. In 1968.

Q. And when did you graduate?

A. I graduated with my BS in pharmacy in '73 and then my Ph.D. from the same

institution three or four years later.

Q. What school was that?

A. The Ohio State University, Football Capital of the World.

Q. Yeah. (Laugh).

And those courses you described taking where they talked about purification with crystallization, did you take those when you were an undergraduate or a graduate?

MR. DELAFIELD: Objection. Relevance.

BY MR. POLLACK:

Q. Or both?

A. Both.

Q. Okay. Okay. But you're an expert on or at least you have a lot of knowledge about stereochemistry; right?

A. Yes.

Q. Okay.

A. Yes.

Q. Okay. But I think it's the case -- is it the case that crystallization was not used to separate stereoisomers before 2007?

MR. DELAFIELD: Objection. Relevance. Vague. Calls for speculation.

THE WITNESS: Crystallization is often used to step -- separate stereoisomers. You have to conversion it to diastereomers by reacting with an optically active salt.

BY MR. POLLACK:

Q. Okay. But that wouldn't -- that technique of using crystallization to separate stereoisomers, that wouldn't apply to enantiomers, would it?

MR. DELAFIELD: Same objections. Outside the scope of his report.

THE WITNESS: To just the plain enantiomers?

BY MR. POLLACK:

Q. Yes.

MR. DELAFIELD: Same objections.

THE WITNESS: The same enantiomers -- crystallization of the same enantiomers wouldn't -- wouldn't separate them.

BY MR. POLLACK:

Q. I'm sorry. I didn't mean same enantiomers. I meant, you know, the two-direction, yeah.

A. The diastereomers -- excuse me.

MR. DELAFIELD: Same objections.

THE WITNESS: The enantiomers, dextro and levo --

BY MR. POLLACK:

Q. Right.

A. -- would not be separated alone by crystallization without first reaction with an optically active compound to produce diastereomers which then would be crystallized.

Q. Okay. All right. But how far back does doing that process you just described, how far back does that go?

MR. DELAFIELD: Objection. Relevance. Vague. Outside the scope of his report.

THE WITNESS: Decades.

BY MR. POLLACK:

Q. Before 2007?

A. Oh, yes.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Let me ask you some hypotheticals.

Suppose the -- just for this argument, for argument, suppose the Moriarty

process produced treprostinil and we had a batch of treprostinil made by the Moriarty product -- process and it had a 99 percent HPLC analysis purity.

Would United Therapeutics be allowed to send that Moriarty process treprostinil through the rest of the process and out to the public based on the current treprostinil specification?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: They would be permitted to move it down the manufacturing process, and if subsequent specifications were met, then it could go out to the public.

BY MR. POLLACK:

Q. By "subsequent specifications," you're referring to specifications for the drug product?

A. Correct.

MR. DELAFIELD: Same -- same objections.

BY MR. POLLACK:

Q. They wouldn't measure the purity of the API again later in the process?

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Once it's been formulated for a drug product?

MR. DELAFIELD: Same objections.

THE WITNESS: If the formulation had other components added to it, the API would not be tested again, but sometimes the API does just become the final product, so...

BY MR. POLLACK:

Q. Do you know in the case of treprostinil, does it just become the final product or does it need to be turned into a formulation?

MR. DELAFIELD: Objection. Relevance. Lacks foundation.

THE WITNESS: It needs to be turned into a formulation. I don't know what else is in the formulation, though.

BY MR. POLLACK:

Q. Let's suppose that the Moriarty process -- this is a hypothetical, this is my

assumption -- produces treprostinil on an HPLC analysis purity of [redacted] percent plus or minus [redacted] on the standard deviation. All right? So it might be [redacted]. It might be [redacted], but basically that's the range you're in.

In your opinion, would there be a reason for further purification?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: [redacted] -- what did you say?

BY MR. POLLACK:

Q. [redacted] plus or minus [redacted].

A. As a standard deviation, that doesn't mean -- standard deviation doesn't mean you add 2 and subtract 2.

Q. Sure. But it does mean that -- what is it? -- 67 percent of the samples will fall between those limits?

A. It means that --

MR. DELAFIELD: Objection. Lacks foundation. Vague. Calls for speculation.

THE WITNESS: It means that the

95 percent confidence limit would be approximately plus or minus [redacted].

BY MR. POLLACK:

Q. [redacted]?

A. Standard --

Q. [redacted] or [redacted]?

A. [redacted].

Q. [redacted]?

A. Standard deviation is not plus or minus the actual number. Standard deviation is a statistical assessment of the variability, and when you have a standard deviation of 2, you calculate a 95 percent confidence limit which is multiplied by --

Q. I'm sorry. I said [redacted] plus or minus [redacted]. You may have misheard me.

A. Oh, I didn't hear the [redacted] if that's what you said.

Q. The point. Yeah, I'm sorry.

MR. DELAFIELD: Same objections.

THE WITNESS: And the same calculations still -- still you do. It's not plus or minus [redacted]. It would be plus or minus something like [redacted].

BY MR. POLLACK:

Q. And that would be 95 percent of the samples?

A. That would be -- would fall in --

MR. DELAFIELD: Same objections.

THE WITNESS: -- in that range.

BY MR. POLLACK:

Q. Okay. So 95 percent of the -- of the samples would fall between [redacted] and [redacted]; is that fair?

MR. DELAFIELD: Objection. Vague. Lacks foundation. Calls for speculation.

THE WITNESS: I forget what number you gave me for the medium purity.

BY MR. POLLACK:

Q. Ah, okay. Let me write it down [redacted].

A. Okay.

Q. And I'm doing a standard deviation of plus or minus [redacted] in my hypothetical.

And my question is whether that means that 95 percent of the samples would fall between [redacted] and [redacted].

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks

foundation.

THE WITNESS: Approximately because I did an approximate calculation of confidence limit but...

BY MR. POLLACK:

Q. Okay. So let me just look back at your paragraph 32 for a second in your declaration, so we don't get confused then.

A. I'm sorry. Paragraph?

Q. 32.

A. Okay.

Q. And so you say here -- this is on page 14. I'm looking at your third sentence, and here you say:

"Although the FDA provides no absolute level of purity required for any drug, based on my experience of approximately 40 years in the pharmaceutical industry interacting with the FDA on regulatory issues, it is commonly assumed that, with rare exception, licensed drugs will have purities in excess of 99%, and often significantly higher."

Did I read that correctly?

A. Yes, you did.

Q. Okay. And you still agree with

that statement?

A. Yes, I do.

Q. Okay. If the Moriarty process is producing [redacted] plus or minus [redacted], wouldn't it meet the standard you just described there in paragraph 32?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Mischaracterizes the document.

THE WITNESS: That's -- that's not a standard. That's -- that's what's commonly occurred. A standard is what's in the spec, what's in the specification of the Certificate of Analysis.

BY MR. POLLACK:

Q. Okay.

A. So that's really what matters.

Q. Right. Okay. Fair enough. And what's in the specification is 98 percent; right?

A. Correct. The lower limit now is 98 percent, yes.

Q. Right. So material made by the Moriarty process, if it has the limits that I just gave of [redacted] plus or minus [redacted], it will 95

percent of the time meet the spec?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation.

THE WITNESS: Based on those, that number and the standard deviation, in my approximate calculation of 90 percent -- 95 percent confidence limits, yes, which is from --

BY MR. POLLACK:

Q. Right. In fact, if we pulled it out to 99 percent confidence limits, we would probably still meet the 98 percent specs?

MR. DELAFIELD: Same objections and outside the scope of his report.

THE WITNESS: Yeah, I can't do that calculation in my head.

BY MR. POLLACK:

Q. Okay.

A. So I don't know what the 99 percent confidence limits will be.

Q. They're going to be greater than 99 percent given my numbers; right?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know. I'd have to do the calculations and I can't do

that one in my head.

BY MR. POLLACK:

Q. Okay. But as you said here, based on your 40 years of experience, if you're in excess of 99 percent, it's not a rule, but as a kind of a sort of rule of thumb or best guess, better than 99 percent is probably going to be fine with the FDA; right?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: No, I wouldn't say that. The rule of thumb would be what's provided in the FDA guidances and, of course, they're guidances. So the FDA can and often does --

BY MR. POLLACK:

Q. Sure.

A. -- tighten them up above 99 percent. That's why I said "in excess of" and so it's what they agree with the manufacturer will be the specification for release.

Q. Right. But before you get to the FDA, when you were at Wyeth or GSK, your team would have to assess based on the purities you were getting what FDA would probably accept;

correct?

A. And --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: And we would -- we would look at the guidance to give us an idea, but it's never a guarantee until the FDA -- until you sit down and discuss with the FDA.

They look at the data. They look at your analysis. They look at the -- the equipment that you're using. They look at the level of detection and, more importantly, the level of quantitation. And it's through that discussion and negotiation that you end up with a specification.

BY MR. POLLACK:

Q. Right. Fair enough. But when your team was working on drug approvals, if you saw, you know, a better than 99 percent, did that give you some confidence that yes, we can go to the FDA and see where that discussion goes?

MR. DELAFIELD: Objection. Vague. Relevance.

THE WITNESS: That depends on

when. 20 years ago, yes, I would think that our teams would go to the FDA with that. I don't believe we'd probably do that now on most drugs, but on some drugs we would go to 99 or maybe even lower.

BY MR. POLLACK:

Q. What about 10 years ago? Would you -- would you go with 99?

MR. DELAFIELD: Same objections.

THE WITNESS: I mean, the -- the criteria get tougher as time goes on and even today, depending on the drug, the FDA, if, for example, if it's a natural product with a very difficult extraction, they go to levels of 85 percent purity. Depends on the drug, the disease.

It's not a property of the drug itself. It's a property of the drug, the disease, the patients, whether there are alternate therapies and how serious a disease is, and those really go into determining what the specification will be in terms of purity.

BY MR. POLLACK:

Q. Okay. I assume in that analysis

the more serious a disease, the lower purity the FDA will accept?

MR. DELAFIELD: Objection. Relevance. Calls for speculation. Outside the scope of his report.

THE WITNESS: It's not that simple. There are serious diseases that have many good therapeutic options, and they may not --

BY MR. POLLACK:

Q. Sure.

A. -- go to that. So that's why I said, it's a very complex dynamic and that's why they issue guidelines and not regulation on these purities. And as you know, there are lots of guidelines on -- from the ICH and the FDA on purity.

Q. Sure. I'm just trying to understand how the guidelines work.

And so for a disease where there isn't or there aren't therapeutic options, is -- is the FDA a little more forgiving about impurities?

MR. DELAFIELD: Objection. Vague. Calls for speculation and outside

the scope of his report.

THE WITNESS: If the disease is very serious, there are few therapeutic options, or if the therapeutic options aren't very good and the FDA believes this is a drug patients should have and you can't get purity to a level that is typically found in guidance, they may relax that standard after negotiation.

But I can tell you, I've seen serious diseases, like cancer, where the FDA wouldn't budge. So it depends on a number of factors, and they take all those things into consideration that I mentioned, including your ability to manufacture a medically necessary drug, and they weigh that.

In addition to what I said earlier, how potent the drug is, which means it has a potent pharmacophore, and whether it's acute use or chronic use. And chronic use with a potent pharmacophore gets greater scrutiny.

So it's a very complicated analysis and assessment that they do which

is why it's the result of often multiple discussions and they -- the amount of data they demand to see before they make that final decision or accept your final recommendation is quite a bit.

BY MR. POLLACK:

Q. Do you know what disease treprostinil treats?

A. Yes.

Q. What disease is that?

A. Pulmonary arterial hypertension.

Q. Is that a serious disease?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I consider that a very serious disease.

BY MR. POLLACK:

Q. Are there a lot of treatment options for pulmonary arterial hypertension?

MR. DELAFIELD: Objection. Vague. Outside the scope of his report.

THE WITNESS: There aren't many and they're not particularly effective. So it is a serious disease.

BY MR. POLLACK:

Q. What about treprostinil? Is it effective for pulmonary arterial hypertension?

MR. DELAFIELD: Same objections.

THE WITNESS: It is effective. It met the negotiated endpoints that the FDA required for approval in this disease.

BY MR. POLLACK:

Q. But people still die anyway of pulmonary arterial hypertension even on treprostinil?

A. They're --

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: Very sadly, yes.

BY MR. POLLACK:

Q. But in 2007, other than treprostinil, there weren't many treatment options for patients with pulmonary arterial hypertension?

MR. DELAFIELD: Same objections.

THE WITNESS: Not very many.

BY MR. POLLACK:

Q. Now, if treprostinil had a purity prior to 2007 of [redacted] percent on average, would

you agree with me that there's not a lot of leeway there to go up? I mean, it's only [redacted] percent?

MR. DELAFIELD: Objection. Calls for speculation. Mischaracterizes documents and vague.

THE WITNESS: If a single lot -- because that's all you can be talking about a single lot -- was [redacted], that's a -- depending on the assay and if it's the -- the reference standard assay HPLC, it -- it actually could be further away from 100 percent than [redacted] because you're basing it on a reference standard, which is not going to be 100 percent.

BY MR. POLLACK:

Q. Well, if the reference standard is not 100 percent, that raises the number; right?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: No. What I said was that that [redacted] percent would be further removed -- [redacted] percent would be further removed from 100 percent. It would be less

than [redacted] percent from 100 because the reference standard is less than 100. So it would be [redacted] percent of the reference standard, and the reference standard is not 100.

BY MR. POLLACK:

Q. Right. Okay. And actually that, we've been talking about reference standards.

Reference standards are just a standard, a known error, in all HPLC assay processes?

MR. DELAFIELD: Objection. Lacks foundation. Vague.

THE WITNESS: It's not a known error. A reference standard has a known purity.

BY MR. POLLACK:

Q. Okay. But scientists were well aware about this issue of reference standards and that the value you get in an HPLC assay analysis, one of the sources of error in all HPLC analysis was reference standard?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: That's not a

source of error. That's inherent in the assay, and it's related to the reference standard and not the equipment or the procedure relevant to the reference standard.

BY MR. POLLACK:

Q. You're saying the reference standard is not part of the HPLC procedure?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: No, because you can do total related substances on an HPLC and that's not a reference standard procedure.

MR. POLLACK: I'm going to mark as Ruffolo Deposition Exhibit 6 a document formerly called UT Exhibit 2035.

(Document marked for identification purposes as Ruffolo Exhibit 6.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. And Ruffolo Exhibit 6, is that one of the documents you relied on in your declaration?

A. Yes, it is.

Q. What is Ruffolo Exhibit 6?

A. The -- it's a guide to reviewers of primarily CMC sections of NDAs on chromatographic procedures of different types.

Q. Can you just very briefly explain what a CMC is?

A. Oh, the chemical, manufacturing and control section of a -- of an NDA. It's a very large and major portion of an NDA.

Q. Right. Very briefly, can you explain what's in the chemistry, manufacturers and control section of a New Drug Application?

MR. DELAFIELD: Objection. Relevance. It's outside the scope of his declaration.

THE WITNESS: I'll do the best I can, but it won't be 100 percent.

It will be the chemical synthesis, the purification procedures, the short-term stability, long-term stability, purity, melting point, the packaging, stability of the packaging, stability of the API, stability of the drug product. Many other things.

And, importantly, the validation of every single assay done on every single part of everything that I just mentioned and the ones I didn't mention, including the equipment and processes for cleaning equipment, cleaning rooms, cleaning. It's a very detailed document.

BY MR. POLLACK:

Q. Descriptions of all the factories and the equipment in the factories?

A. Descriptions and validation --

MR. DELAFIELD: Objection.

THE WITNESS: -- processes used for everything that comes in contact with that drug and every analysis done on that drug.

BY MR. POLLACK:

Q. You mentioned melting point as one of the things that's included in the CMC section.

Why do they have melting point in there?

MR. DELAFIELD: Objection. Vague. Relevance. Outside the scope of his report.

THE WITNESS: Melting point is used as a measure of identity of a compound.

BY MR. POLLACK:

Q. How does that work?

MR. DELAFIELD: Same objections.

THE WITNESS: The FDA wants to be sure that the compound that you say you've made is, in fact, the compound you say you've made, and so they include certain spectral analyses. It could be IR, infrared. It could be Raman spectroscopy. It could be UV and -- and melting points.

Those are characteristics of compounds that help the FDA confirm that what you've said you've made you've actually made.

BY MR. POLLACK:

Q. Okay. Do you know if the melting point is affected by the purity of the compound?

MR. DELAFIELD: Objection. Relevance. Calls for speculation. Outside the scope of his report.

THE WITNESS: There is a relationship to purity and -- between purity

and melting point and it's not an absolute relationship but also crystal form, polymorphs, amorphous forms, solvents, crystallization of solvents, crystallization procedure, all of those and other things affect melting point.

BY MR. POLLACK:

Q. Okay. Let me just ask you.

If I have two solids that are the same crystal form of the same drug and they have different melting points, is there a way to compare their purity based on the melting points?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: As I said, melting point has a relationship to purity, but melting point isn't purity. The FDA doesn't accept melting point as a measure of purity.

BY MR. POLLACK:

Q. Sure.

A. And your question was, if you had a drug with a higher melting point is it more pure?

Q. Well, I said, they're the same crystal form.

A. Same crystal?

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Yeah.

A. Yeah, in the same crystal form? Perhaps, perhaps not.

Q. What's the relationship -- you said there's relationship between melting point and purity?

A. Yes.

Q. What's the relationship?

MR. DELAFIELD: Same objections.

THE WITNESS: Often higher melting points have higher purities, but that's not necessarily the case. And when I reviewed all of the -- the Certificate of Analysis sheets on the specs, you can see many examples where higher levels of purity didn't have a higher melting point.

BY MR. POLLACK:

Q. You didn't put an opinion in your declaration on that, though; correct?

A. No. As I said, my -- my task was

to deal on long-felt need and so I didn't comment on that.

Q. Okay.

A. But if I had, I would have commented in the way I've told you and which, in fact, I believe is consistent with Dr. Williams' assessments with melting point.

Q. You can look at Exhibit 6, Ruffolo Exhibit 6. If you could turn to page 12.

And you reviewed this exhibit in detail, right, before creating your opinion?

A. Yes, I did.

Q. Okay. You said first paragraph, that first full paragraph, it says "With UVD detectors."

A. I'm sorry. I don't -- I don't see that. I must -- I'm on page 12.

Q. Page 12.

A. Oh, there are two page 12s.

Q. Ah, I'm sorry. Yes. I'm looking at the one that's sort of typed at the bottom.

A. Okay. I have it. Okay.

Q. I think it also says --

A. I'm sorry.

Q. -- page 9 in the smaller.

A. Yeah, I see it.

Q. No, you're right.

A. Yeah.

Q. There's two -- there's two different numbers on there so it's confusing.

A. Yeah. Okay.

Q. So it's the one that says P.12.

A. I see that. Okay.

Q. And you see there's a first full paragraph that says "With UV detectors."

Is it -- well, let me ask you. UV detectors. Those are the kind of detectors that are used in HPLC assay analysis?

A. Oh.

MR. DELAFIELD: Objection. Outside the scope of his report. Vague. Calls for speculation.

THE WITNESS: Lots of different types of detectors can be used with almost any spectra -- spectra photographic.

BY MR. POLLACK:

Q. Sure.

A. So it's one of them.

Q. For example, in Moriarty, Moriarty used a UV detection?

A. Are you saying --

MR. DELAFIELD: Same objections.

THE WITNESS: I don't remember that.

MR. POLLACK: I got to do my own work now.

I'm going to mark as Ruffolo Deposition Exhibit 7 a document formerly known as Exhibit 1004. It's an article from the Journal of Organic Chemistry by Moriarty and others.

(Document marked for identification purposes as Ruffolo Exhibit 7.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. And this is what we've been referring to as the Moriarty article?

A. Yes.

Q. And I think if you turn to the very last page, it says -- I'm going to create ambiguity here, but the one that says page 13 in the bottom right-hand corner.

A. I see it, yes.

Q. It's also known as 1902.

A. Okay.

Q. Page 1902 from the original article.

Looking at page 1902, also known as page 13, does Moriarty report there on the purity of treprostinil that he made according to the Moriarty process?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: So you're referring to what? I'm sorry.

BY MR. POLLACK:

Q. I just asked: Does he report on the purity of treprostinil made by the Moriarty process?

MR. DELAFIELD: Same objections.

THE WITNESS: There is a purity of 99.7 percent listed.

BY MR. POLLACK:

Q. Okay. And does he say there that it was done by HPLC?

MR. DELAFIELD: Same objections.

THE WITNESS: It says it was done by HPLC.

BY MR. POLLACK:

Q. Okay. And prior to that, does he -- does he indicate that UV was used?

MR. DELAFIELD: Same objections.

THE WITNESS: Prior to that. Can -- can you --

BY MR. POLLACK:

Q. Just before the words "HPLC." I'm not -- I'm not trying to --

A. Where HPLC is methanol --

MR. DELAFIELD: Same objections.

THE WITNESS: -- 217 nanometers.

BY MR. POLLACK:

Q. You see the words "UV" before that?

A. No.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. No, you don't?

A. Oh, UV. I see. Yes, I'm sorry.

Q. Okay.

A. Yeah.

Q. Based on your review, can you tell me whether or not he used UV detection for HPLC?

A. Yes.

MR. DELAFIELD: Same objections.

THE WITNESS: It appears he did.

BY MR. POLLACK:

Q. Okay. Let me ask you.

The analyses that United Therapeutics did for HPLC analysis, do you know whether they used UV detectors?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: I'd have to, just as with Moriarty, I'd have to -- I'd have to go back and check.

BY MR. POLLACK:

Q. Okay. You didn't look into that?

MR. DELAFIELD: Same objections.

THE WITNESS: I probably did. I don't remember. It would be common to do that, but I don't -- I don't remember.

BY MR. POLLACK:

Q. What about in the '393 patent? Do you know whether they used UV detection?

MR. DELAFIELD: Objection. Vague. Outside the scope of his report.

THE WITNESS: (Reviewing document). Unless you see it listed

someplace, I don't see it, but I'm, you know, I could read the whole thing to find out, and I don't know if it says.

BY MR. POLLACK:

Q. Yeah, I haven't seen it. I was just wondering --

A. I don't -- I don't know.

Q. -- if you had any knowledge.

A. I don't know.

Q. Okay. What about when United Therapeutics looks at total related impurities? Do you know whether they're using UV detection for those impurities?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: I don't know. That will be in the CMC section, but I don't recall.

BY MR. POLLACK:

Q. But it would be fairly typical to use UV as a detection?

A. It would --

MR. DELAFIELD: Objection. Vague. Calls for speculation.

Mischaracterizes his testimony.

THE WITNESS: It would be -- it would be common --

BY MR. POLLACK:

Q. Yeah.

A. -- to do that.

Q. Let me ask you if the following sentence from Exhibit 6 is one you can agree with.

"With UV detectors" --

A. I'm sorry. Exhibit?

Q. And this is on page 12. Yeah.

A. Oh, oh, that's the same document. Okay.

Q. Yeah. This is the Reviewer Guidance --

A. Yeah, got it.

Q. -- Validation of Chromatographic Methods.

A. Okay.

Q. Just to make things clear, this comes from the Center For Drug Evaluation and Research?

A. Yes.

Q. That's a branch of the United

States Food and Drug Administration?

A. Yes, that's CEDR, part of the FDA.

Q. Right. They're the ones who actually decide drug approvals within the FDA?

MR. DELAFIELD: Objection. Calls for speculation.

THE WITNESS: For small molecules and, yes, for those types of drugs, yes.

BY MR. POLLACK:

Q. Right. And treprostinil is a small molecule. It's not a biomolecule?

A. Correct.

MR. DELAFIELD: Objection. Vague.

BY MR. POLLACK:

Q. So the CEDR, these are the kinds of people, this is a group that would approve a drug like treprostinil?

A. I --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I assume --

MR. DELAFIELD: Lacks foundation.

THE WITNESS: I assume treprostinil went through CEDR.

BY MR. POLLACK:

Q. Well, I think you earlier were referring to an NDA rather than a BLA based on that?

A. That's -- that's correct.

Q. Does that indicate that, therefore, it went through CEDR?

MR. DELAFIELD: Same objections.

THE WITNESS: It can -- when a drug is used with a device, as this one, it can go through the device division, too. I don't know if it did. I have no -- no reason to believe it, but I don't know.

BY MR. POLLACK:

Q. Okay. So CEDR says here on page 12 of the document, and by that I mean the P.12:

"With UV detectors, it is difficult to assure the detection precision of low level compounds due to potential gradual loss of sensitivity of detector lamps with age or noise level variation by detector manufacturer."

Do you agree with that statement?

A. I agree with that statement, but in

the CMC section, as I said, all instrumentation has to be validated and go through, and these are things that would be specified to assure the FDA that this isn't happening.

The F -- that's why they're giving this guidance to their reviewers to make sure that that is in there. You couldn't use an old lamp. You couldn't use a device -- a machine with a high noise level because that will affect what they care about, which is the level of quantitation and level of detection.

Q. Okay. But noise level is something that really is only a problem when you're trying to detect very small amounts of signal in materials?

MR. DELAFIELD: Objection. Vague. Lacks foundation. Outside the scope of his report.

THE WITNESS: Not -- not only. It depends on the signal from -- the magnitude of the signal from even the agent you're looking at. If it doesn't give a very powerful signal, then the inherent noise could affect that, too.

BY MR. POLLACK:

Q. Sure. But if I have a sample where, you know, [redacted] percent of it is my drug and [redacted] percent of it is an impurity, it's more likely I'm going to have noise problems with the [redacted] percent rather than the [redacted], is that generally the case?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: That would generally be the case.

BY MR. POLLACK:

Q. And then one of the other things they say here. It's kind of interesting. Going a couple sentences later.

A. Uh-huh.

Q. It says:

"With no reference standard for given impurity or means to assure detectability, extraneous peaks could disappear and appear."

Do you agree with that statement?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Yes, that's why

the FDA on these types of analyses for release specifications have reference standards so that that doesn't happen.

BY MR. POLLACK:

Q. Right. So reference standards, they're actually preferred in doing HPLC analysis?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: They are preferred and almost always insisted on by the FDA.

BY MR. POLLACK:

Q. Okay. Let's go back to Ruffolo Exhibit 5, and that's the letter that used to be known as Exhibit 2006, from United Therapeutics to Norman Stockbridge dated January 2, 2009.

A. Exhibit 5?

Q. Exhibit 5.

A. Yeah, I have that.

Q. I want to look at a statement that United Therapeutics made to the FDA.

If you look on page 3, if you look at the second full paragraph, the third

paragraph on the page, beginning with the words "In conclusion."

Do you see where I am?

A. Yes, I do.

Q. Okay. It says:

"In conclusion, the lots of treprostinil API produced by the new process in Silver Spring are of the same high quality impurity as the commercial lots of API produced by the existing process at the Chicago facility."

Did I read that correctly?

A. Yes, you did.

Q. Okay. And I'm correct that the commercial lots of API produced by the existing process of the Chicago facility, that refers to what we've -- we've been calling the [redacted]?

MR. DELAFIELD: Objection. Calls for speculation.

THE WITNESS: I'm sorry. Could you repeat that?

BY MR. POLLACK:

Q. Yes. The -- where it says here the commercial lots of active pharmaceutical

ingredient produced by the "[redacted]" at the Chicago facility, that refers to what we've been calling the [redacted]?

MR. DELAFIELD: Same objection.

THE WITNESS: Yes.

BY MR. POLLACK:

Q. Okay. And the "[redacted]" in the Silver Spring facility, that refers to the process we've been calling the [redacted]?

A. Yes, that's my understanding.

Q. Okay. And what the -- what United Therapeutics is representing to the FDA here is that the treprostinil made by the '393 process has the same quality and purity as API made by the Moriarty process; isn't that what this says?

MR. DELAFIELD: Objection. Mischaracterizes --

BY MR. POLLACK:

Q. In simpler English?

A. Yeah.

MR. DELAFIELD: Mischaracterizes this document.

THE WITNESS: It says same high purity. They both could have high purity

and -- and it's pretty clear from the analyses that I've seen that the purity of '393 process is higher than Moriarty, but that doesn't mean that they're both not highly, highly pure.

BY MR. POLLACK:

Q. Okay. They're not making a representation here in this conclusion that the [redacted] process is superior to the -- the [redacted], that is, the '393 process is superior to the Moriarty process in that sentence?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: There are no purity levels given and I don't know when the -- the recognition for the high level of purity was made, but also I don't think that changes the fact that both could be high purity. One is higher than the other.

BY MR. POLLACK:

Q. Okay. Now, let me turn to some of the other representations they made.

If you can go to page 6.

A. Yes.

Q. And you're going to need to look at page 5 as well because, unfortunately, they didn't repeat the headings of the table.

A. Okay.

Q. Okay. So let me go through the headings on page 5. So the first column is labeled "Test."

Do you see that?

A. Yes.

Q. Okay. And that refers to whatever test or category is described underneath --

A. Uh-huh.

Q. -- is that fair?

A. Yes.

Q. Okay. And the second column is called "Currently Approved Specification"?

A. Yes.

Q. Okay. And that refers to the Moriarty process?

A. That's correct.

Q. And the third column is called -- is called "Proposed New Specification"?

A. Yes.

Q. Okay. And that refers to the '393 process?

A. That's correct.

Q. And if we go to page 6, under the Test column -- and feel free if you want to write these column headings on top. If you remember, that's fine.

A. Okay.

Q. So the first column, the Test column, you see it has a chromatographic purity HPLC.

Do you see that row?

A. Yes, I do.

Q. Okay. And then in that row is a set of named impurities?

A. Yes, I see.

Q. Okay. And these were the purities that -- the impurities that United Therapeutics was able to see in its HPLC instrument?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: These are the specifications for those purities. The minimum specifications for allowable levels of these impurities in -- in the product.

BY MR. POLLACK:

Q. Right. Right.

A. The API. API.

Q. I'm just -- I'm just saying, yeah, before we get to the spec part.

A. Yeah.

Q. Just in the Test column, that's a list of the impurities that United Therapeutics saw on their particular HPLC column?

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document.

THE WITNESS: Those are the average characteristic impurities that you see in their analysis.

BY MR. POLLACK:

Q. Yeah. Okay. And if an impurity for some reason doesn't separate out on their particular HPLC column, we wouldn't see that impurity listed here?

MR. DELAFIELD: Same objections. Calls for speculation.

THE WITNESS: I'm not sure I agree. Could you repeat that?

BY MR. POLLACK:

Q. Sure. If an impurity doesn't separate out from the other ingredients in the particular HPLC column material that they

selected, we wouldn't see that impurity listed here?

MR. DELAFIELD: Same objections.

THE WITNESS: That's not true.

BY MR. POLLACK:

Q. That's not true?

A. No.

Q. Okay. So you're saying HPLC can separate all impurities from other impurities --

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. -- regardless of what column is used?

MR. DELAFIELD: Objection. Mischaracterizes testimony.

THE WITNESS: No.

MR. DELAFIELD: Calls for speculation.

THE WITNESS: The FDA requires that you actually conclude that there are not two superimposing peaks, and so they have an assurance of that in the CMC part of the document as part of all of that validation that I mentioned earlier.

BY MR. POLLACK:

Q. What if an impurity comes out at about the same retention time as the API itself?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Would they be able to separate that?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: The FDA would force you to use a different column with a different bedding that did separate them. The FDA will insist that you confirm that there are no overlapping peaks.

BY MR. POLLACK:

Q. Even if you don't know if the impurity is there, they would do that?

MR. DELAFIELD: Same objections.

THE WITNESS: You actually have to go look. So when you report a peak, you have to assure them that there are not -- that there's only one material there under that peak. And there are various tests you

can do to show them, and you do have to show them that. That's part of the validation for using the technique.

BY MR. POLLACK:

Q. Do you know whether that was done for treprostinil?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know. If they had two drugs under one peak, it would have been done. It would be required.

BY MR. POLLACK:

Q. But for treprostinil you don't know?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know, but because I don't recall the -- that part of the CMC, but I do know that United Therapeutics would have to show them that there are not two peaks occurring at the same retention time with one masking the other.

And you have to show that by convincing evidence, and there are ways to do that and that's part of the validation of the assay that the FDA requires that United

Therapeutics would have had to have been done.

BY MR. POLLACK:

Q. Okay. You haven't reviewed, though, the CMC other than this letter?

A. I reviewed -- no, that's not true. I reviewed quite a bit of the CMC, but I didn't review it all. It would be too much for a single person to review.

Q. You didn't attach the CMC to your declaration?

A. No, I did not attach the CMC to my declaration.

Q. Okay. That's not listed in your materials you reviewed in your -- in the paragraph you have on that in your declaration?

MR. DELAFIELD: Objection. Mischaracterizes declaration.

THE WITNESS: I don't -- I don't recall if there are CMC sections in my declaration, but I have reviewed parts of the CMC as part of those documents that I mentioned that were sent to me by counsel.

BY MR. POLLACK:

Q. Which -- which parts did you

review?

MR. DELAFIELD: Objection.

Relevance.

THE WITNESS: I reviewed the Certificates of Analysis and I reviewed the injectable NDA component showing how those analyses were done and the calculations that were used. And there was, I think, an ND -- annual NDA update or something like that that I reviewed. So I did review components of the CMC.

MR. POLLACK: Counsel, I'm going to request that production of all sections of the CMC and any other documents that Dr. Ruffolo reviewed that haven't been produced so far.

MR. DELAFIELD: I believe we've produced everything. I think he's only been shown things that we've produced, so...

BY MR. POLLACK:

Q. So the sections of the CMC you're referring to, were those ones that Dr. Williams relied upon?

MR. DELAFIELD: Objection.

Calls for speculation.

THE WITNESS: I think you have to ask Dr. Williams that. I don't know what he -- what he did, what he looked at.

MR. POLLACK: Counsel, are there any documents that he reviewed that were not attached as exhibits provided to the PTAB?

MR. DELAFIELD: No, we haven't reviewed anything other than what's been an exhibit.

MR. POLLACK: What's been an exhibit to PTAB?

MR. DELAFIELD: Yeah.

BY MR. POLLACK:

Q. Okay. All right. Let's take a look at these.

MR. DELAFIELD: One thing. He mentioned that he reviewed the label. I don't think the label is an exhibit. So the label for treprostinil.

MR. POLLACK: Okay.

MR. DELAFIELD: All right.

MR. POLLACK: Would be the only?

MR. DELAFIELD: Yeah.

MR. POLLACK: If you could produce the label that he reviewed then.

MR. DELAFIELD: Okay. We'll take it under advisement.

BY MR. POLLACK:

Q. So let's look at the second column.

A. Yes.

Q. And the second column, that is specifications --

A. Yes.

Q. -- for each of the impurities for the Moriarty process; is that correct?

A. Yes, that's correct.

Q. Okay. And the third -- third column, those are specifications for impurities for the '393 process; correct?

A. That's correct.

Q. Okay. And am I also correct that the specification for the impurities in the Moriarty process are identical for every single impurity to the specifications for the '393 process?

A. Yes.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The specification limits are the same for both processes.

BY MR. POLLACK:

Q. Do you know whether on this document United Therapeutics listed every impurity for which a peak was observed?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: I'm sorry. Would you repeat that?

BY MR. POLLACK:

Q. Yeah. Do you know whether on this document United Therapeutics listed every impurity for which a peak was observed?

MR. DELAFIELD: Same objections.

THE WITNESS: They do list unidentified impurities, which are peaks, and if the level of that impurity rose to a level of requiring identification, it would have been identified. That would have been a requirement.

BY MR. POLLACK:

Q. Right. Now, the final sum there at the bottom, it says "total related substances"?

A. Yes, I see that.

Q. Okay. What is it -- why does it use the term "related"? Are there unrelated

substances?

MR. DELAFIELD: Objection.

Vague.

THE WITNESS: I don't -- I don't recall the exact definition of total related substances. I would have to go research that. Remember, this is not something I prepared for.

BY MR. POLLACK:

Q. Sure.

A. This is, you know, here mainly for -- for the -- for the need. So I'd have to go -- I'd have to go look up and see exactly what the regulatory definition of that is.

Q. Okay. You didn't look into that as part of your opinion?

A. No, I didn't look into -- into that.

Q. Okay. Now, the names of some of these substances are a little, I think, funny. There's one called 1AU90.

A. Yes.

Q. What is that?

MR. DELAFIELD: Objection.

Outside the scope of his report.

THE WITNESS: Somebody would have to show me the chemical structure on that.

BY MR. POLLACK:

Q. Well, this -- do you think anyone knows the chemical structure of that?

A. Oh, yes.

Q. You do?

MR. DELAFIELD: Objection. Argumentative.

THE WITNESS: The -- if it rose to the level of reporting threshold, it would have to be reported.

BY MR. POLLACK:

Q. Sure. What's the reporting threshold?

A. Well, .05 and -- and .1 would be the identification threshold and they would have to identify it.

Q. If it's greater than .1?

A. Yeah.

Q. Yeah. Do you know if any of these which have just code names have a greater than .1?

A. Oh, I -- I don't know.

Q. Okay. Do you know whether 1AU90 was identified by United Therapeutics?

MR. DELAFIELD: Objection. Vague. Outside the scope of his report.

THE WITNESS: I don't know. You're, again, asking me questions outside of what I prepared for.

BY MR. POLLACK:

Q. I mean, this is one of the documents you are heavily relying on. That's why I'm asking you.

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, but you're asking me questions that are not related to unfelt need. So --

BY MR. POLLACK:

Q. Your unfelt need has to do with purity; correct?

A. It has to do with increases in purity.

Q. Right. Okay.

A. Yeah.

Q. So I'm asking about the impurities here.

A. Yeah.

Q. Okay.

MR. DELAFIELD: Objection. Outside the scope of his report here.

BY MR. POLLACK:

Q. Outside the group of us here, who are privileged to see this, do you think any member of the public knows what 1AU90 is?

MR. DELAFIELD: Objection. Calls for speculation. Argumentative.

THE WITNESS: I don't know, but I would assume not, but that's just an assumption.

BY MR. POLLACK:

Q. By the way, do you have -- do you have any reason to believe that in 2007 -- that's when this patent was filed, two years before this document was created -- do you have any evidence that United Therapeutics had any idea what impurities were in treprostinil made by the '393 process?

A. Before?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Before 2009. In 2007 where the '393 patent was filed -- first filed.

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: Because I reviewed all of the -- the lot specifications on the Certificate of Analysis, these were present before 2007 as well as after.

BY MR. POLLACK:

Q. Okay. In the '393 patent, is there any mention of what impurities are present or any of these names or similar names?

A. Can I refer to the patent?

Q. Please.

A. (Reviewing document).

Okay. Can you repeat the question, please?

Q. Is there any evidence in the '393 patent regarding what impurities were in the treprostinil made in the '393 patent?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Outside the scope of his report.

THE WITNESS: I didn't see this list reproduced there.

BY MR. POLLACK:

Q. Okay. Was -- was there any kind of

list of what impurities were in the treprostinil made in the '393 patent?

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. In the patent itself?

A. Without reading the whole thing, I see primarily purities of the parent compound, which is what I believe the invention is related to. And -- and so I see comparisons between the old process and new process with purities, but -- but I don't see, unless I've missed it, I don't see the impurities.

Q. Right. All that information -- all the information in the '393 patent is related to the parent compound?

A. The overall purity of the parent compound.

Q. Right. And that compound is, well, treprostinil or one of those other compounds that are -- that are in there, the diethanolamine salt or the other ones that are in the claim?

MR. DELAFIELD: Objection. Compound.

THE WITNESS: The -- yes.

BY MR. POLLACK:

Q. I want to go back to your paragraph 32. There's something else there I was confused about. It's on page 14 of your declaration.

A. Okay. I have it.

Q. And that's Ruffolo Exhibit 3.

If you go about halfway down the page, it says:

"There is so much concern with the purity of drug substance and drug product that the highest level of purity possible should be achieved, even if that means changing the synthetic method as has been done in the '393 patent."

Do you see that?

A. Yes, I see that.

Q. Okay. And then in -- this is what confuses me.

In paragraph 57 -- it's on page 27 of your declaration -- you say in the last sentence:

"My personal experience has been that when considering the safety and toxicology profiles of impurities, it is often more

efficient to reduce the levels of impurities in the drug substance by altering or changing the synthetic method."

Do you see that?

A. Yes, I do.

Q. Okay. So here you're saying change the synthetic method but in 32 --

A. I'm saying exactly the same thing.

Q. Same thing. Okay. Oh, I see what confused me.

But then you say "as has been done in the '393 patent."

So I guess what I was wondering is: How has the synthetic method changed in the -- in the '393 patent?

A. The number of steps was reduced. The purification of the nitrile was taken out. The starting material was changed. The efficiency of the system was increased. The purity, of course, was increased. Fewer solvents were used.

And there's a list of -- in the patent, which I could probably find, of things that were changed and improved by the process.

Q. Yeah. Can you find me that list?

A. (Reviewing document).

On column 5 about line 36 or 37.

"The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity."

Q. Okay. Yeah. I didn't see any list there of some of the changes that you described, like the elimination of the purification of the nitrile or --

A. I just said that. It's in that

paragraph. They -- they specifically state:

"For example, the purification by common chromatography is eliminated."

That's for the nitrile.

Q. Oh, okay. Thanks. Thanks for clarifying that.

A. Yeah.

Q. And eliminating that purification of the nitrile, how does that affect the purity of the treprostinil?

MR. DELAFIELD: Objection. Calls for speculation. Outside the scope of his declaration.

THE WITNESS: I don't know how that affects the purity. I'd have to -- have to look into that, but it certainly is related to the efficiency and the -- the faster speed of the reaction, easier to operate, and -- and be more economical. That's -- that's quite significant.

BY MR. POLLACK:

Q. What about the change in solvents? How does that -- does that affect the purity?

MR. DELAFIELD: Same objections.

THE WITNESS: I give a similar

answer.

I can't tell what the solvent impact would be on the purity level, but it would certainly be relevant to the easier to operate, the greener, the faster component and, you know, so that's what that would be relevant to.

BY MR. POLLACK:

Q. Okay. Let me ask you, though, changing the solvents. That's something that you're not sure how much it does it, but it's something that might affect the purity?

MR. DELAFIELD: Objection. Calls for speculation. Outside the scope of his report. Vague.

THE WITNESS: I don't know.

BY MR. POLLACK:

Q. Okay.

A. It might, it might not.

Q. It might or it might not; is that right?

A. Yes, that's what I said. I'm sorry.

Q. Yeah, okay. That's fine. My hearing is going. (Laugh).

A. No. It happens to all of us.

Q. And the same for eliminating the purification of the nitrile. That might or might not affect the purity?

MR. DELAFIELD: Same objections.

THE WITNESS: I -- I don't know. That's what you asked, I think, two or three questions ago. I don't -- I don't know. I haven't seen that assessment done.

BY MR. POLLACK:

Q. Okay. But it could. It's a possibility?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know.

MR. POLLACK: Okay. I'm going to mark as Ruffolo Deposition Exhibit 8 a document formerly known as UT Exhibit 2047. It's the "Guidance for Industry on Non-Penicillin Beta-Lactam Drugs."

(Document marked for identification purposes as Ruffolo Exhibit 8.)

THE WITNESS: Thank you.

MR. POLLACK: And I'm going to mark one more exhibit while we're at it.

This will be Ruffolo Deposition Exhibit 9 formerly known as UT Exhibit 2048.

(Document marked for identification purposes as Ruffolo Exhibit 9.)

BY MR. POLLACK:

Q. And Ruffolo Exhibit 9 is an article called "Clinical Pharmacology of Human Insulin."

Are these, Dr. Ruffolo, these two documents that you relied upon in writing your declaration?

A. Yes, they are.

Q. All right. Starting with Exhibit 8, the non-penicillin beta-lactam drugs?

A. Uh-huh. Yes.

Q. Why did you rely on this document?

A. In putting together my -- my report, which relates to the importance of high purity and some of the risks of having impurities even in highly pure drugs, I gave examples that are known so that that -- and these are widely known examples -- that confirm that some impurities that one wouldn't even anticipate could be extremely risky and present

high risk to patients.

Q. What's this example?

A. This example?

Q. Yes. I'm sorry.

A. The --

Q. What is the example in Ruffolo Deposition Exhibit 8?

A. So in -- when I first started my career, penicillins and beta-lactams in general, which would include cephalosporins, were manufactured by, for example, my first company Lilly, which was the worldwide leader in antibiotics at the time, but they made many other drugs.

And as part of the CMC section in an NDA, you have to show how you cleaned the room, sterilized the equipment, and -- and, you know, run into basically an aseptic room when you manufacture another drug so there's not cross-contamination.

With respect to penicillins, even when you do that, penicillins just by being airborne can contaminate other products you make in the same building. And what was learned was that that minute contamination,

which you can't even quantify it's so low, produced allergic reactions ranging from very minor to very severe anaphylaxis, resulting in death, and because beta-lactams in general are so highly sensitizing to the immune systems of some people. And this is just what might be existing in a cleaned laboratory in the air.

So the FDA first, and then other agencies following shortly thereafter, mandated that you couldn't make a penicillin even in the same building, no matter how much you cleaned that building. You couldn't manufacture any other drug except another penicillin in a building and, of course, you can imagine the difficulty that creates to have a solely dedicated building only for penicillins and you have all these other drugs you manufacture.

And so that's what this guideline is. It was the regulators and ultimately the global regulators and, as you can see, the ICH that -- that -- that mandated completely different facilities had to be used. And it -- and so those are very, very low levels of contamination that you, as I say, you can't measure.

And it even got so significant that when we ordered AP -- starting materials, for example, for other companies, we always had to ask, are there rooms different from penicillin? Because they're not making a drug. They're just making an intermediate.

And then, finally, many of these companies that supply intermediates and starting materials would even advertise themselves as non-penicillin producing companies. So that's an example of how dangerous a safe drug, penicillin, can be as a contaminant.

Q. Right. In fact, for beta-lactams, those companies that are still making them, they require interlocks right into the buildings?

A. Now they've made a concession. They went from completely different buildings, totally separate buildings, and now with improvements in air handling, filtration systems, if you have in one building rooms with completely different ventilation systems that are physically isolated and separate, you now can do it in the same building, but that's

rarely done.

People still use separate buildings, but you have to have -- again, they relaxed the requirement. You can do it in the same building but completely different -- your interlocking systems that have absolutely no chance of crossover and that even includes air intake, so...

Q. Right. And the workers have to actually change their clothes as they go in and out?

A. Yeah. Well, they have to do that that anyway, no matter -- no matter what. When you walk into a plant that makes any drug, not just penicillin, the workers have to go through pressure locks, change their clothes, and then go through other double door pressure locks. There are several double door pressure locks to get into any manufacturing facility.

Q. To get into the United States?

A. That's correct.

Q. I don't want to scare you, but you haven't seen what it's like in India, but that's another day.

A. But in India, you know -- well,

okay. Okay.

Q. (Laugh).

A. So that's -- that's what that's about.

Q. Right. Because beta-lactams, those are drugs that come from a biological source?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: Most are synthetic now and don't come from a biologic source.

BY MR. POLLACK:

Q. Right. But initially there was a biologic source?

A. Well --

MR. DELAFIELD: Same objection.

THE WITNESS: -- way back penicillin was isolated. The pharmacophore that I discussed earlier was isolated, and you would put different decoration on it to change it into different antibiotics with different spectra. Now they're synthetic. They're entirely synthetic and have been for many, many years.

BY MR. POLLACK:

Q. Treprostinil, though, as far as you

know, there isn't a compound like penicillin that requires that kind of isolation in the manufacture of treprostinil; is that fair?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: Well, I don't know what I don't know and there are unidentified peaks, as we've discussed earlier, and -- and as we also talked about, there could be peaks below level of detection of a -- of an HPLC. And I don't know what those are.

I have no reason to believe it would be this, but the point of this in my document was to highlight that even very safe impurities can be dangerous because penicillin is clearly a safe drug. You give --

BY MR. POLLACK:

Q. Not for me but maybe for others. (Laugh).

A. Yes, that's unfortunate, but it is very safe. You give now -- when I worked in Children's Hospital, they used to give 5 million units. The first people to get penicillin in World War II got 10,000 units.

So it's a very safe drug, but as a contaminant that you can't even detect, it can be very dangerous.

Q. For those who are allergic?

A. For those who are allergic.

Q. And looking at your second exhibit here, Exhibit Ruffolo 9.

A. Uh-huh.

Q. This is about insulin?

A. Yes.

Q. Okay. And insulin is a bio -- it's a biodrug; right? It's not a small molecule?

MR. DELAFIELD: Objection. Calls for speculation. Lack of foundation.

THE WITNESS: Insulin is a biologic. It's a large molecule.

BY MR. POLLACK:

Q. And for insulin, the concern, I understand, is the E. coli bacteria?

A. It wasn't the bacteria. It was residual impurities from the bacteria in which the insulin was made.

Q. Referring to antigens from the -- from the bacteria?

A. They would --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: They would or could be antigens, and it was a very high purified -- highly purified product.

MR. DELAFIELD: Counsel, I hate to interrupt.

MR. POLLACK: No.

MR. DELAFIELD: Do you mind if we take a break? He has to catch a flight and I wouldn't mind going to the bathroom.

MR. POLLACK: Yeah. Okay. Yeah. No problem like that.

THE VIDEOGRAPHER: The time is 3:13 p.m. This completes Media Unit No. 3. We are off the record.

(Recess - 3:14 p.m. - 3:21 p.m.)

(Mr. Maebius no longer present.)

THE VIDEOGRAPHER: The time is 3:21 p.m. This begins Media Unit No. 4. We're on the record. Please proceed, counsel.

BY MR. POLLACK:

Q. Okay. We were talking about Ruffolo Deposition Exhibit 9 before the break.

A. Yes.

Q. This is about the biomolecule insulin?

A. That's correct.

Q. Correct. And the concern here was about certain antigens from E. coli that could end up in the insulin?

A. Yes, that's correct.

Q. And that's because E. coli were involved in the production of the -- of the insulin?

A. Yeah. Yes, they were.

Q. In manufacturing treprostinil, am I correct there are no biological agents that are used in manufacturing treprostinil?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: This, again, was an example of trace contaminants that can be potentially dangerous. But if you do look in the manufacturing process of treprostinil and you look into the specifications, example listed right here in the 2009 letter in the specifications that were sent to the FDA showing an increase in the level of --

of purity, you can see that they were looking at endotoxins, which can only come from bacteria, as well as total aerobic count, total yeast count, E. coli, Salmonella, pseudomonas, staphyloncus.

So these are -- the reason they're here is they can cause the same kind of allergic reaction that we saw with human insulin.

BY MR. POLLACK:

Q. Well, these are all lists, if you look at the microbial limits, right, these you would see for any drug? These are all lists of microbes that cause disease; right?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Well --

MR. DELAFIELD: Mischaracterizes the document.

BY MR. POLLACK:

Q. Staph?

A. E. coli is the same as in the example I gave.

Q. Sure.

A. And so it was given as an example

of how a trace contaminant from a microbe can produce adverse events, and that's the same logic in the specification for treprostinil and many other drugs.

Q. Sure. But treprostinil is not made from biologic agents of any kind?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: No, it is not made from a bio -- a cell.

BY MR. POLLACK:

Q. Right. And the concern here on page 6 where it says "microbial limits," that's about the sterility of the facilities, something we -- one always looks at?

MR. DELAFIELD: I'm sorry. Page 6 of what?

MR. POLLACK: Yeah. Page 6 of -- you are right -- Deposition Exhibit 5 formerly known as Exhibit 2006 on page 6.

BY MR. POLLACK:

Q. The microbial limits on this document have to do with the sterility of the facilities; isn't that correct?

MR. DELAFIELD: Objection.

Mischaracterizes the document. Lacks foundation.

THE WITNESS: Yeah, or airborne contaminants, as we discussed, with -- with non- -- with penicillins. They could come in through any process.

In fact, in the ICH guidelines on purity, they specifically point out that every single step of every single drug can introduce contaminants and impurities, including every single instrument or vessel. So that's why it's important.

BY MR. POLLACK:

Q. Okay. But looking at this document, there's nothing on here about penicillin or other beta-lactam antibiotics on Ruffolo Deposition Exhibit 5?

A. No, and they weren't intended to. As I said, the examples I gave for contaminants was to show that contaminants that you didn't know were there or you believed were safe or that were there in extremely low and undetectable levels can have significant effects that lead to serious adverse effects. So that's really what these were about.

Q. Right.

A. And that's also what these numbers in the table on page 6 are related to. They could be introduced the same way. Trace penicillin contaminants can be introduced into a product.

But the examples that I gave that you just cite in these last two exhibits was just to show the significance and why the FDA is so concerned about contaminants and why there is an unfelt need to increase purity.

Q. Let me ask you.

Both of these exhibits, Deposition Exhibit 8 and Exhibit 9, these are examples of contaminants, as you called it, that affect the immune system; correct?

MR. DELAFIELD: Objection. Calls for speculation. Vague.

BY MR. POLLACK:

Q. These are contaminants that create an immune response. That's why they're a problem?

MR. DELAFIELD: Same objections.

THE WITNESS: In the case of penicillin, it's a sensitization of the

immune system after penicillin acts as a hapten binding to a protein.

BY MR. POLLACK:

Q. And let me try to put that in simpler English.

A. Oh.

Q. Some people are allergic to penicillin?

A. That's -- okay.

Q. Is that right?

A. That's -- that's correct.

Q. Right. And it sets off their immune system?

A. Yeah. Yes.

Q. Okay.

A. But you can be allergic to anything, and as you look at FDA labels for virtually any drugs, one of the precautions is don't take if you're allergic to any of the components in it. So that that's a very common occurrence.

Q. But penicillin it is agreed that a fair percentage of the population is allergic to, while other drugs it's a little more rare?

MR. DELAFIELD: Objection.

Lacks foundation. Vague.

THE WITNESS: It's -- it's not that necessarily that the allergic reaction is more rare with other drugs. It can be less severe. So there's a difference between the frequency of allergic and the severity and that's, of course, penicillin and contaminants.

BY MR. POLLACK:

Q. And similarly with the -- with the E. coli antigens, that's an issue also involving the immune system in Deposition Exhibit 9?

A. Yes. That would be antigens that would -- antigens that would cause an immune response.

Q. Let me ask you.

Looking at the -- let's go back to -- I guess we were already looking at it -- Ruffolo Deposition Exhibit 5 at page 6.

A. Okay. Yes.

Q. Do you know if any of these listed chromatographic impurities have any adverse effects in humans?

MR. DELAFIELD: Objection.

Vague.

BY MR. POLLACK:

Q. And if so, what are they?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know.

What I can tell you is that if you review the FDA label, there are a host of adverse effects produced or observed in patients who are taking treprostinil.

BY MR. POLLACK:

Q. Sure.

A. And --

Q. But they're taking purified treprostinil?

A. Well, the purified treprostinil still has impurities, and if it's made by the '393 process, it has fewer of them, but there's still some there and including those maybe you don't see.

And the -- I lost my train of thought when you asked that second question. What was the question you asked for?

Q. Yes. I was asking about the effects of any of these listed impurities. What were those?

MR. DELAFIELD: Same objections.

THE WITNESS: Oh, yes, I remember my point.

In the FDA label, there are adverse events, serious adverse events listed, and the FDA breaks them down into two categories.

One that's -- one category are those adverse events that are related to the pharmacology or an extension of the pharmacology of treprostinil, which would be prostaglandin-like activity, and the others don't have an attributable cause.

BY MR. POLLACK:

Q. Does that mean they could be due to the treprostinil itself?

A. Or they -- it could be due to the treprostinil itself or it could be due to a contaminant or it could be due to something else, but the FDA never really knows. They only know what they think is due to the extension of the pharmacology, and it's based on that that they have this desire for impurities to be as low as possible and practical.

Q. Did you review -- in forming your opinion on the effect of impurities, did you review adverse event reports for treprostinil for the Remodulin product sold by United Therapeutics?

A. I reviewed the adverse events in the label, and -- and those include adverse events observed in clinical trials and also after market. So that that's what I reviewed.

Q. Okay. But did you review individual adverse event reports that were provided to the FDA?

A. No, I didn't review that section of the NDA.

Q. Okay. Do you know whether there were any changes in the adverse event reports after United Therapeutics changed its process of making treprostinil?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That would be a very difficult thing to do and is rarely done. Most adverse events occur at a low level and the possibility of seeing a difference statistically -- and the FDA --

the FDA would only -- only change a label based on data that solid -- is very low and that's the case with any process change or even any increase in purity.

So you wouldn't expect to see that, and at the time you file a change in manufacturing, for example, to give you a decrease in purity, you would not have that information because you don't repeat clinical trials. You repeat and you do studies to match purity standards and release specifications.

BY MR. POLLACK:

Q. Okay. But as far as you know, from the adverse events reports, there's nothing indicating that there was some change in adverse events over time?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: Nobody would know that, and I didn't review the adverse events reports -- adverse event reports.

BY MR. POLLACK:

Q. Go back to your declaration, Ruffolo Deposition Exhibit 3.

A. Okay.

Q. If you could turn to paragraph 70.

A. Okay.

Q. And I'm looking on page 35. Near the end of that paragraph, you say here:

"Additionally, as shown by the 175 batch records, the average purity of the treprostinil product prepared by the process of the '393 patent is 99.71% while the average purity of the Moriarty product is 99.05%."

Do you see that?

A. Yes, I do.

Q. Where did those two numbers come from?

A. Those would have come from Dr. Williams.

Q. Okay. That's not something you calculated?

A. No.

Q. Okay.

A. I didn't calculate that.

Q. And then it says in the next sentence:

"Thus, the average purity of the treprostinil product prepared by the process of

the '393 patent has a 0.7% higher average purity than the Moriarty product."

How did you determine that?

A. That I also believe was from Dr. Williams.

Q. Okay. Do you know where that .7 percent number came from?

A. I believe it came from -- I don't remember. It came either from his analysis or from his declaration.

Q. Okay.

A. I'm not sure.

Q. I guess I was wondering: Do you know if that came from taking 99.71 and subtracting the 99.05?

A. That's -- that's what I believe he did.

Q. Okay.

A. Yes.

Q. You're not certain, though, but that's what you think he did?

A. Yes, that's what I believe he did.

Q. In view -- in your view, is that a correct way to compare the purity?

A. Because he compared apples to

apples and had the same -- compared the same analyses on total related substances, yes, I think that's a valid assessment of the difference.

Q. Earlier you and I were talking about standard deviation --

A. Uh-huh.

Q. -- and confidence intervals.

Do you remember that?

A. Yes, I do.

Q. Okay. What role does standard deviation and confidence intervals play in making the comparison between the two purities?

MR. DELAFIELD: Objection. Vague. Relevance. Outside the scope of his report.

THE WITNESS: Any measurement of means can have associated with it a standard error or standard deviation and from which you can calculate a confidence interval and -- and that would be used to show a statistically significant difference between two pools of numbers.

BY MR. POLLACK:

Q. You may recall this as well.

There's no standard deviation reported by Dr. Williams for these averages.

If the confidence interval significantly overlapped, how would that affect your conclusion about the differences between the purity?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Relevance. Outside the scope of his report.

THE WITNESS: It wouldn't change my interpretation because there would still be a numerically higher number level of purity with the Moriarty process -- with the -- excuse me -- '393 process and that also translated to a -- what did I have? -- [redacted] some odd percent reduction in impurities, and that's a number that is impressive and regulators would like to see.

BY MR. POLLACK:

Q. That reduction you just described, the [redacted] some percent, that's based on these two numbers here, isn't it?

A. Yes.

Q. Okay. And earlier in one of your -- in your answer just two answers ago,

you used the word "statistical significance" I believe?

A. Yes.

Q. What were you referring to?

A. Numbers can differ and when they differ by what's called a statistical significance that's assuming a 95 percent probability, that's called statistical significance, and when they don't, it's called a trend.

Q. If you only see a trend, what conclusions can you draw from the difference between numbers that are only a trend, as you called it?

MR. DELAFIELD: Objection. Vague. Relevance. Calls for speculation and outside the scope of his report.

THE WITNESS: The trends that are not statistically significant don't mean that they're not real. I think the more important part is based on these data, the FDA agreed to change the specification for purity from a mean of 99 percent to a mean of 100 percent, resulting in a higher quality product.

BY MR. POLLACK:

Q. Actually, didn't they change the specification from 98 percent to 102?

A. That's --

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document.

THE WITNESS: That's the range. I was talking about the mean centered around that.

BY MR. POLLACK:

Q. Okay.

A. But we can talk about both because the answer is the same.

If you have a mean purity of 99 percent that they move up to 100, that's a higher quality product. If you take the lower level of 97 percent and move it up to 98 percent, which is what the FDA did.

Q. Right. Did the FDA do that or did United Therapeutics do that?

A. Oh, United Therapeutics made the request and the FDA, which doesn't have to do it and they don't make changes that they don't believe are -- are not important. The FDA approved, agreed and approved those changes to

the FDA's standard. It met their long-felt need, and they made that change.

Q. The FDA made that change or United Therapeutics made that change?

A. United Therapeutics --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: -- can't make a change. They can only propose a change. Only the FDA can make a change.

BY MR. POLLACK:

Q. At the time that United Therapeutics was making an -- making an amendment to their application, they were asking to move, factories, correct from Chicago to Silver Spring?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: I don't recall the timing. I think the document, the letter suggests that they were about the same time.

BY MR. POLLACK:

Q. Actually, the letter is about the change --

A. Yeah. Okay.

Q. -- of the factory from Chicago to Silver Spring; correct?

A. I think so, yes.

Q. Yes. And the letter is also about the -- that's a major change, by the way, moving from one factory to another; right?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That is considered a major change.

BY MR. POLLACK:

Q. Yes. And in addition, they -- the people at United Therapeutics decided that they would change what [redacted] were used for the process; right?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: United Therapeutics decided to change the process, and as part of that change in process, they also changed the [redacted].

BY MR. POLLACK:

Q. Right. Now, changing [redacted] has nothing to do with what's discussed in the '393 patent; correct?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: Sorry. Could you say that again, please?

BY MR. POLLACK:

Q. Yeah. A change in [redacted] that has nothing to do with what's discussed in the '393 patent?

A. The '393 patent describes a change in process from a more lengthy process to a much abbreviated process, and as part of that process, the starting material changed from whatever it was in Moriarty many, many, many steps earlier to the benzindene triol.

So, yes, both the process and the starting material did change, and that's the subject of the patent.

Q. The [redacted] change, though, was not; right? In the patent, they describe making the product from other materials, correct, not from benzindene triol?

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document.

THE WITNESS: It's my understanding that the starting material of

the '393 process in the patent is the benzindene triol.

BY MR. POLLACK:

Q. The patent describe -- doesn't describe using materials to make the benzindene triol as well?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: When I -- when I look at the process, for example, in Example 1, it looks to me like the starting material is benzindene triol. That's one of the four compounds that occur in the entire process and that to me seems very different than the Moriarty process.

BY MR. POLLACK:

Q. The Moriarty process doesn't go through benzindene triol?

MR. DELAFIELD: Objection. Calls for speculation.

THE WITNESS: Your question --

MR. DELAFIELD: Lack of foundation.

THE WITNESS: -- was the starting material, and the starting material

in the Moriarty process is not the benzindene triol. It's something many, many steps earlier.

BY MR. POLLACK:

Q. And if we look at the '393 patent at column 7?

A. Yes.

Q. There's a formula there 10.

Do you see that?

A. Formula?

Q. It's in column 10. It says "X." There's an X and under that it's X11. It's around line 20.

A. Oh, I see. Yes, I see that.

Q. Isn't that the starting material for the process described in the '393 patent?

MR. DELAFIELD: Objection. Vague. Outside the scope of his report. Lacks foundation.

THE WITNESS: When I look at the steps that they're talking about -- steps A, B, C, and D -- they start at the benzindene triol, not at compound X.

BY MR. POLLACK:

Q. Sure. So you're saying the claims

only claim that part of the process; correct?

A. Yes.

MR. DELAFIELD: Objection. Vague.

THE WITNESS: And I, you know, again, am not a lawyer.

BY MR. POLLACK:

Q. Right.

A. I wasn't prepared for this, but it looks to me like the process that they're patenting is starting at benzindene triol and ending with treprostinil free acid.

Q. Okay. You understand that in the patent it describes the process as starting from compound 10?

MR. DELAFIELD: Objection. Vague. Lacks foundation.

THE WITNESS: That's not my understanding. I see that they're referring to that reaction from another patent and I -- that to me doesn't look like the starting material for this process, nor is it what they told the FDA was their new process.

The new process started with benzindene triol, which is a major change,

and then, of course, the [redacted] of that [redacted], which was going to be [redacted] and none of that involves this material.

BY MR. POLLACK:

Q. Right.

A. Compound X.

Q. And one of the issues is, it's going to be [redacted]. So now the United Therapeutics doesn't have [redacted] over how some [redacted] is [redacted] the [redacted] [redacted]; correct?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation.

THE WITNESS: No, that's not correct.

BY MR. POLLACK:

Q. Okay. Explain to me.

A. In the letter where the -- the 2009 letter where UTC is requesting this change in process as well as a change in [redacted] [redacted], both of which are major changes, the FDA is so concerned about purity, as we've said all day, that they were worried about the

purity of the [redacted] and carryover of any impurities into the final product. It's a major change. That's a very difficult question.

And the response you can see shows that the [redacted] of the [redacted] was subject to specifications that were put in place by the [redacted] that matched [redacted] specifications for [redacted].

So they did have [redacted] over that [redacted] and that's basically what the FDA was asking and that's what satisfied the FDA and allowed them to start this new process starting benzindene triol.

Q. Right. But United Therapeutics is not -- they're getting a [redacted] from that [redacted], but they're [redacted]; is that fair?

MR. DELAFIELD: Objection.

BY MR. POLLACK:

Q. Of the [redacted]?

MR. DELAFIELD: Objection. Vague. Calls for speculation. Lacks foundation. Outside the scope of his

report.

THE WITNESS: It's been my experience that when a late-stage [redacted] is [redacted] and [redacted] we actually place somebody at that [redacted] to make sure that the [redacted], which as it turns out happened to be [redacted] by definition.

So it's not as if the material is [redacted], [redacted], and then just put into a reaction. The material [redacted] the [redacted], the [redacted] at the site where you [redacted] it, and then the first thing you do when you [redacted] the [redacted] is [redacted] the [redacted] in-house as well.

BY MR. POLLACK:

Q. By the way, do you know whether the [redacted] United Therapeutics' [redacted], do you know whether or not they used the process described in [redacted]?

MR. DELAFIELD: Same objections.

THE WITNESS: Again, I wasn't prepared to go into detail on that and it's not something I was asked to comment about,

but in that letter, they -- UTC indicates that the process is -- I don't remember -- either the same or virtually the same.

BY MR. POLLACK:

Q. Okay. Do you know where that is in the letter?

A. I can find it.

Q. Is that the bottom -- bottom of the first page that you're referring to?

A. (Reviewing document).

Yes, beginning on the bottom of page 1 and extending through about the first third of page 2.

Q. Okay. So I'm right. I think I'm right. One of the things that needs to get -- one of the changes that needs to get approved here as a major amendment is that the [redacted] is now being [redacted] from a [redacted] called [redacted] or [redacted] called [redacted]; is that right?

A. Yes.

Q. Okay. And so the FDA is approving all of these changes; right? The change in factory, the change -- and the change in [redacted] and the change in crystallization in

the process?

A. And process and starting material, yes.

Q. So there's a large number of changes in here instead of three changes, big changes?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: There were -- these are considered major changes, and so UTC had to go through all of the documentation necessary to satisfy the FDA because this is a major concern of the FDA because of ultimately quality of the material produced and purity.

And, again, in the three questions raised by the FDA, two of them had to deal with purity.

BY MR. POLLACK:

Q. Right. One of those had to do with the purity of the benzindene triol; right?

A. One of those was the purity of the benzindene triol and the concern by the FDA of the carry-through of any impurities in the benzindene triol to the final product. That's

how concerned they are about purity and contaminants.

Q. Right.

A. And they were obviously satisfied by the fact that the process were the same and the release specs remained the same for [redacted], and then also the fact that there was a higher level of purity by this new process. That was considered significant enough by the FDA to allow a change to the drug specification.

Q. You keep saying the FDA considered it significant enough.

Can you show me where in the letter they said they thought it was significant?

A. No, it doesn't say that in the letter. The fact that they approved it when they don't like to make changes unless they're considered important. You can't simply change it yourself.

And when you submit this change for approval, it involves a great, great, great deal of analysis by the FDA. It takes a long time, a lot of people and, again, they have to balance that between their desire to increase

purity and their belief that you can make this product consistently so that there are no drug shortages.

Q. And that last reason, the drug shortages, that's why they allow, for example, a purity of 98 percent?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation.

THE WITNESS: The -- the FDA, again because of their strong desire to have the highest levels of purity as possible, and I keep saying practical, the practical part is to make sure that they get the highest level of purity, which they obviously we're happy with.

They made -- they approved the change, but they would not have approved that if they thought the company couldn't make the material or that a subsequent company, after the drug loses its patent, couldn't make that material, which would result in drug shortages.

BY MR. POLLACK:

Q. But, in fact, all the material made under the [redacted] process, at least all the

material we've seen, met the 98 percent standard, didn't it?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation.

THE WITNESS: Well, all of the batches, I don't know whether they all met that. I'd have to go look at the data. I don't know what the variability was and, you know, I reviewed 170 something Certificates of Analysis. I don't remember if any did or didn't. So I don't know.

BY MR. POLLACK:

Q. Okay. I'll represent to you that all of the ones made under the [redacted] process made the 98 percent level.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Given that, how does that affect your opinion?

A. That doesn't change my opinion at all. Because when the FDA agrees to allow a mean range to center from 99 to 100 percent and a lower level from 97 to 98 percent, they are assured of having a higher quality product than would have been allowed under the other

guidelines, and that makes them feel good. That's what they shoot for. That's their -- it's an unfelt need or the -- I'm blanking on the words. That's what their need is. That's what they desire.

MR. POLLACK: Let's -- let's take a break for 10 minutes. I want to look at --

THE WITNESS: Okay.

MR. POLLACK: -- what other things we want to ask you?

THE WITNESS: Sure. Okay.

MR. POLLACK: Why don't you guys out.

THE WITNESS: Yeah, I'll leave.

THE VIDEOGRAPHER: The time is 4:03 p.m. We're going off the record.

(Recess - 4:03 p.m. - 4:21 p.m.)

(Document marked for identification purposes as Ruffolo Exhibit 10.)

THE VIDEOGRAPHER: The time is 4:21 p.m. We're back on the record. Please proceed, counsel.

MR. POLLACK: Okay.

BY MR. POLLACK:

Q. Welcome back.

A. Thank you.

Q. I've already marked as Ruffolo Deposition Exhibit 10 a letter from the Department of Health and Human Services, the FDA -- Food and Drug Administration to United Therapeutics Corporation, Dean Bunce, Executive Vice President of Regulatory Affairs and Compliance, dated March 10, 2014 regarding the drug Remodulin.

A. Thank you.

Q. Let me just ask you first. Am I correct that this is a -- that Deposition Exhibit 10 is a letter from the FDA to United Therapeutics Corporation?

A. Yes, it is.

Q. Okay. And the letter is dated March 10, 2014?

MR. DELAFIELD: Objection. And I object to this exhibit that it hasn't been submitted to the Patent Office yet and it's beyond the scope of his declaration. And relevance.

THE WITNESS: The -- you asked

about the date?

BY MR. POLLACK:

Q. The date, yeah.

A. But, you know, this is a problem with -- and I've had it with many FDA documents. It can't find the date. I see a stamped date. I don't know whether that's when it was received. So I don't -- I don't know anything. I can't confirm the date.

Q. Okay. You haven't seen that kind of stamp on all of the FDA's official documents?

A. No.

Q. No? Okay.

A. No.

Q. Remodulin. You see the name Remodulin?

A. Yes.

Q. Okay. That's the -- that's United Therapeutics treprostinil product?

A. Yes.

Q. Yes? Okay.

And now you haven't reviewed this letter before; is that -- is that correct?

A. No, I've never seen this.

Q. Okay. But you see this is a letter responding to a citizen's petition? You see that in the first sentence?

MR. DELAFIELD: Objection. Vague. Relevance. Beyond the scope of his declaration.

THE WITNESS: (Reviewing document). I see that it says it's a citizen's petition.

BY MR. POLLACK:

Q. Okay. It's a letter responding to a citizen's --

A. Yeah.

Q. -- petition; right?

A. Yeah.

Q. And it's a citizen's petition that was filed by United Therapeutics?

MR. DELAFIELD: Objection. Relevance. Beyond the scope of his declaration.

THE WITNESS: I don't -- I don't know.

BY MR. POLLACK:

Q. Well, it says there; right?

"This letter responds to a

citizen's petition submitted to the FDA by United Therapeutics Corp."

Did I read that correctly?

A. You -- yes, you did.

Q. Okay. Do you have any reason to believe it's -- that United Therapeutics Corp. did not file a citizen's petition?

A. I don't know.

MR. DELAFIELD: Objection.

THE WITNESS: Did they?

MR. DELAFIELD: I'd just like to enter a standing objection for any questions relating to this regarding relevance and that it's outside the scope of his declaration.

THE WITNESS: And I, you know, I don't know what United Therapeutics did. You know, I guess if they're responding to it, they probably did, but I don't -- I don't know. I have no idea what this is about.

BY MR. POLLACK:

Q. Okay. You know -- do you know what a citizen's petition is?

MR. DELAFIELD: Objection.

Outside the scope of his testimony and lacks foundation.

THE WITNESS: I've heard -- I've heard the word a number of times. I actually don't really know what it means.

BY MR. POLLACK:

Q. Okay.

A. It's -- despite my experience, I don't -- I never had to deal with one. So I really don't know what -- exactly what it is.

Q. Okay. I mean, I assume when you were at Wyeth they did file citizen's petitions with the FDA?

MR. DELAFIELD: Objection. Lacks foundation. Vague.

THE WITNESS: I assume they did. Again, I'm familiar with the words, but I'm not familiar with what it is --

BY MR. POLLACK:

Q. Okay.

A. -- and what was done with them.

Q. Okay. Are you aware that a citizen's petition is part of the -- a process of challenging regulatory approvals at the FDA?

MR. DELAFIELD: Objection.

Lacks foundation. Same objections as before.

THE WITNESS: I was not familiar with that. I haven't seen many of them, and I don't know --

BY MR. POLLACK:

Q. Okay.

A. -- what that is.

Q. So this goes beyond your regulatory expertise?

A. This?

Q. Citizen's petitions.

A. Citizen's? Yes, I would say this goes beyond my regulatory expertise.

Q. Okay. If you could turn to -- indulge me and turn to page 8 of Ruffolo Deposition Exhibit 10.

A. Oh.

Q. This one.

A. Oh, oh, oh. I'm sorry.

Q. If you could turn to page 8.

A. 8. Okay. (Pause). Okay.

Q. Let me ask you this first.

Are you aware that -- are you -- are you aware of what the Orange Book is?

MR. DELAFIELD: Objection. Relevance. Outside the scope of his declaration.

THE WITNESS: I have heard of the Orange Book. I have a little bit of knowledge, but I -- it's not something that I've paid a lot of attention to. So it's -- I put that in the same category of -- of the citizen's petition.

Most of my regulatory experience focuses on regulations, guidelines, approval, and -- and that goes not just for the FDA, but the three major agencies in the world, EMA and PMDA.

And I know the Orange Book has something to do with patents, but as I said, I'm not a patent lawyer and I don't really follow that very much. So that also is beyond my area of expertise in regulatory.

BY MR. POLLACK:

Q. Okay. But let me ask you this.

Were you aware that in filing a New Drug Application, the drug companies that you worked for are required to file a list of patents that covered the drug in the New Drug

Application?

MR. DELAFIELD: Same objections.

THE WITNESS: I am aware of that.

BY MR. POLLACK:

Q. Okay. And were you aware that those patents would then get listed in something called the Orange Book, which today is just a website?

MR. DELAFIELD: The same objections.

THE WITNESS: I was not aware of that.

BY MR. POLLACK:

Q. Okay. But you're aware that patents are filed with New Drug Applications?

MR. DELAFIELD: Same objections.

THE WITNESS: Yes, I was.

BY MR. POLLACK:

Q. Okay. And are you aware regarding whether or not United Therapeutics filed any patents with the FDA in their NDA for Remodulin?

MR. DELAFIELD: Objection. Relevance. Outside the scope of his

declaration.

THE WITNESS: Not -- not -- no, I don't know that. Again, as I said, I was focused on -- on need and -- and I haven't had a chance to look at this, think about this. And even if I did, this falls outside my area of expertise.

BY MR. POLLACK:

Q. Let me ask you this.

Have you compared the claims of the '393 patent to United Therapeutics' Remodulin product?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: I'm sorry?

BY MR. POLLACK:

Q. Yes. Have you compared the patent claims in the '393 patent to United Therapeutics' Remodulin product?

MR. DELAFIELD: Same objection.

THE WITNESS: You have to clarify. Compare what and how?

BY MR. POLLACK:

Q. Oh, okay. So by that I mean, did you go through, say, claim 9, compare the

element -- do you know what the elements of a claim are?

A. Sorry.

Q. Okay.

A. I'm not a patent attorney. I...

Q. Did you compare the language in claim 9 to United Therapeutics' treprostinil product?

MR. DELAFIELD: Same objection.

THE WITNESS: Still I don't know how -- what you mean "compare." Compare to what?

BY MR. POLLACK:

Q. I'll see if I can make it simpler.

Did you analyze claim 9 and determine whether it covers United Therapeutics' Remodulin product?

MR. DELAFIELD: Same objection.

THE WITNESS: I -- again, I'm still not quite sure what you mean but, you know, that wasn't what I was asked to do, and I don't believe I did make any comparison like that.

BY MR. POLLACK:

Q. Do you know if anyone else in this

case made that comparison?

A. No.

MR. DELAFIELD: Same objection.

THE WITNESS: I haven't spoken to anyone outside of Mr. Delafield.

BY MR. POLLACK:

Q. Okay. All right. If we can turn back to page 8 in Ruffolo Deposition Exhibit 10.

A. Yes.

Q. And as you'll see here, the issue is whether a generic treprostinil injection product can emit material that's on the Remodulin label and, in particular, the use of something called a "high pH glycine diluent."

Do you see that?

MR. DELAFIELD: Objection. Outside the scope of his declaration. Lacks foundation.

THE WITNESS: I mean, I can't interpret that. I'd have -- even if I had read this, I may not be able to interpret it. But is there a section you would like me to read?

BY MR. POLLACK:

Q. Why don't you feel free to read this section starting from the word "Discussion" on the page before.

A. "Discussion." Oh.

Q. Yep.

A. (Reviewing document). Okay.

Q. Have you read enough or you want to read more?

A. I don't know. It depends on your question.

Q. Okay. Fair enough.

Do you understand from this that United Therapeutics was allowed by the agency to add to their label for Remodulin (treprostinil) information about using a high pH glycine diluent to reduce the risk of BSIs?

MR. DELAFIELD: Objection. Mischaracterizes the document. Relevance. Outside the scope of his declaration.

THE WITNESS: No, I wasn't aware of that. The section I read didn't define BSIs and, again, I focused on long-felt need with respect to purity and I -- and impurities and I didn't see anything here related to any of that.

So I really don't know what this letter is in response to and I don't understand. Here we're talking about drug product and that wasn't the focus of my review. It was on --

BY MR. POLLACK:

Q. Uh-huh.

A. It was on contaminants and impurities in the synthesis of API. So I'm sorry. I don't even know how to respond.

Q. Yeah. I'm not going to ask you about BSIs and whether that's true or anything else.

A. Yeah.

Q. I just wanted to know is, you know, based on the letter, is it -- is it the case that the FDA had allowed United Therapeutics to add to their label information about the use of high pH glycine diluent?

MR. DELAFIELD: Objection. Relevance. Calls for speculation. Mischaracterizes the document and outside the scope of his declaration.

THE WITNESS: And what was your question?

BY MR. POLLACK:

Q. Yeah. I was just asking whether or not United Therapeutics was allowed by the FDA to add information about the use of a high pH glycine diluent, whatever that may be, to their -- to their label.

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know anything about that at all, and reading a couple of paragraphs on this letter that don't even define some of the abbreviations used, I can't -- I can't do anything with this. This doesn't mean anything to me.

BY MR. POLLACK:

Q. Well, do you see -- let's take a look at the second full paragraph on page 8.

A. The which? The --

Q. The one beginning with "More the point." "More to the point." I want to a take a look at the second sentence. Do you see there it says:

"When we approve the addition of this information to Remodulin's label in September 2013."

Do you see where I'm reading?

A. Yes, I do.

Q. Okay. Reading that, am I correct that the FDA approved adding certain information to Remodulin -- that's the same product we've been talking about -- to the labeling of Remodulin; is that fair?

MR. DELAFIELD: Same objections.

THE WITNESS: I guess so. I don't know.

BY MR. POLLACK:

Q. Okay. That's what the letter says; right?

A. That's --

MR. DELAFIELD: Same objection.

BY MR. POLLACK:

Q. I know you don't know independently, but in the letter that's what it says?

MR. DELAFIELD: Same objection.

THE WITNESS: That's what, two sentences out of a 10-page letter I never saw before that's related to something I didn't prepare for. It doesn't mean anything to me.

BY MR. POLLACK:

Q. Okay.

A. In fact, the only thing that means anything to me is the signature of Janet Woodcock, who's a good friend of mine.

Q. Okay. That's the same Janet Woodcock --

A. Yes.

Q. -- that you refer to in your declaration?

A. Correct.

Q. She's the author of this letter?

A. She's the signatory of this letter.

Q. Letter is issued with her approval; correct?

A. That's correct.

Q. Okay. And if we go back to page 8?

A. Okay.

Q. Okay. In Janet Woodcock's letter, she says "We" and by 'we' she's referring to the FDA?

MR. DELAFIELD: Objection. Calls for speculation. Lacks foundation. Relevance. Outside the scope of his declaration.

THE WITNESS: Which "we"? "We

did not take these acts"?

BY MR. POLLACK:

Q. Yes, or we did -- all of the "we's." "We approved." "We did so in the interest."

That's referring to the FDA; right?

MR. DELAFIELD: Same objections.

THE WITNESS: I guess so. I suppose she would.

BY MR. POLLACK:

Q. Right? It's a letter from the FDA; is that fair?

A. Yeah.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. Okay. And it says here --

A. I should point out.

Q. Uh-huh.

A. Letters come from the FDA that don't represent the entire FDA opinion. During the entire NDA process, you get letters from the FDA. That's -- that's a --

Q. Yeah. This is an official response to a citizen's petition?

MR. DELAFIELD: Same objection.

THE WITNESS: Again, I don't know.

BY MR. POLLACK:

Q. You don't know what those are?

A. Yeah. I'm sorry.

Q. Okay. And they say here they made a label change; right?

They did so in the interest of "providing healthcare providers with up-to-date information on the use of high glycine diluents and not out of the concern that the administration of IV treprostinil with a neutral diluent should always be avoided because it poses a risk to patients. The agency had been concerned about the safety of neutral diluents" -- I'm sorry.

"If the agency had been concerned about the safety of neutral diluents, it could have revised the labeling to require the use of high pH glycine diluents only and taken steps to raise awareness about the effect that choice of diluent has on the risk of BSIs."

Now, in the case of the changes that we're talking about here that were approved by the FDA, the manufacturing changes,

those changes don't even appear on the label; correct?

MR. DELAFIELD: Same objections.

THE WITNESS: That's correct.

BY MR. POLLACK:

Q. Right. Here we're talking about changes that were approved by the agency that do appear on the label; correct?

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know. I don't remember it from the label. I reviewed the label. I don't remember this.

BY MR. POLLACK:

Q. Okay. But here the agency is saying, just because we approved it on the label, that doesn't mean we endorsed your statements about the effect of these high pH glycine diluents; isn't that what they're saying?

MR. DELAFIELD: Objection. Vague. Mischaracterizes the document. Relevance. Lacks foundation. Outside the scope of his declaration.

THE WITNESS: To be honest, I don't know what the agency is saying here.

You know, I'm sorry. In a 10-page letter, looking at a couple of paragraphs, I don't know what they mean. I don't know what they're referring to. I don't know what their intent is. And this is an area that I have not been involved with before.

BY MR. POLLACK:

Q. Okay. Well, you said you had some regulatory expertise.

Based on your regulatory expertise, can you explain what's being described here?

MR. DELAFIELD: Same objections. Asked and answered.

THE WITNESS: I said I had a great deal of regulatory expertise. But I also said that I didn't know everything about regulatory affairs and that there were people in regulatory affairs that knew more than me and many who knew less, but this is something that I have not had to deal with.

And this is -- again, I don't know what this is.

BY MR. POLLACK:

Q. Okay. I'm only asking this because earlier I believe you stated the opinion that

by approving United Therapeutics' changes from 97 to 98 percent, the FDA was endorsing that as a change in purity. And you seem to have the expertise to opine on that or that was your view that there was an endorsement, or maybe I misunderstood you.

And yet here you're not able to tell me whether the FDA considers an approval, as they did here, to be an endorsement.

A. They --

MR. DELAFIELD: Objection. Mischaracterizes testimony. Relevance and outside the scope of his declaration.

THE WITNESS: The area I testified to before I've had a great deal of experience in at every level with the FDA.

BY MR. POLLACK:

Q. Uh-huh.

A. This I have not had any experience and I know for -- I know that the FDA does not like to make changes in specifications unless they believe they are significant. I don't know what Janet is saying about whatever label -- labeling change she's talking about.

Q. Well, you said earlier that you had

reviewed the label?

A. I did review the label, yeah.

Q. Okay. If you reviewed the label, you saw a discussion about what diluents should be used with Remodulin?

MR. DELAFIELD: Objection. Lacks foundation.

THE WITNESS: It --

MR. DELAFIELD: Outside the scope of his declaration. Relevance.

THE WITNESS: Well, and because it was outside the scope, it's not an area that I would have focused on. I focused on other parts of the label, and I do know a good deal about labeling negotiations as far as NDA approval.

This in citizen's petition I don't -- is an area that I have not been involved with, not focused on, and I don't have the experience in. What I testified to I have great deal of experience in. Sorry.

BY MR. POLLACK:

Q. Yeah. Okay. But in regard to whether or not the FDA endorses statements made by applicants, what's your evidence of that?

MR. DELAFIELD: Objection. Mischaracterizes his testimony. Relevance.

THE WITNESS: The applicant can't make a change without the FDA's agreement and approval.

BY MR. POLLACK:

Q. Uh-huh.

A. And when they do that in the context of a specification, they wouldn't permit it if they didn't believe it was significant and important enough to do so.

I have no idea what this letter is talking about, and I don't even understand the argument that's being made here. Again, maybe if I studied this for a couple of days but, you know, this is not something I've seen or been involved with.

Q. Okay. But you don't have any statements, articles, documents, evidencing that the FDA endorses statements made by applicants merely because they approved the change?

MR. DELAFIELD: Objection. Vague. Asked and answered. Relevance.

THE WITNESS: The FDA doesn't

allow change unless they agreed with that change and approved that change. That's their job.

BY MR. POLLACK:

Q. Sure.

A. And with respect to specifications and release of batches and all of the pre-NDA work and NDA work, their approval is required and that approval is so important that it's what allows you to sell a new product. That's a big deal.

Q. Uh-huh.

A. So that acknowledgement by the FDA is important, it has a legal meaning, and it's not done trivially.

Q. Okay. I understand that.

A. So --

Q. But that's not what I asked you.

A. Well, but, again, I have no idea what you're asking me. I'm sorry.

Q. Oh. I was asking if you had any --

A. I can't say it in any other words.

Q. Sure. I was asking if you had any documentation regarding the statement you just made. Not -- not your -- not your opinion but

what -- do you have any documents with those statements on them from the FDA? Do you have any other written materials from anyone --

A. Well --

Q. -- supporting those statements?

MR. DELAFIELD: Same objections. Compound.

THE WITNESS: There are numerous documents that define the changes that we spoke about earlier, and I've referenced those, on how sponsors deal with the FDA and what the FDA requires.

So, yes, there are documents that lay out what the FDA requires.

And as I said earlier, the changes that were made by UTC with respect to the manufacturing process, the starting material, those are defined in FDA and ICH documents as major changes requiring validation, documentation, and ultimately approval by the FDA.

So, yeah, those documents exist, and I've cited them.

BY MR. POLLACK:

Q. Well, actually --

A. This is --

Q. Uh-huh.

A. You know, again, I don't even know what this is.

Q. This is just a document regarding the same product that we're talking about in this case; right?

MR. DELAFIELD: Objection. Argumentative.

THE WITNESS: Yeah. It's --

BY MR. POLLACK:

Q. Yeah. Okay.

A. I understand from the title it's the same product we're talking about, but I don't know what they're talking about.

Q. Okay. Looking back at Exhibit -- what was called Exhibit 2006, the letter from the --

A. Oh, yeah.

Q. -- from United Therapeutics to the FDA.

As we discussed earlier, there were two other major amendments that were made; right? One regarding the [redacted] of the product and one regarding the location of the

facility?

MR. DELAFIELD: Objection. Mischaracterizes the document.

THE WITNESS: Yes, that's correct.

BY MR. POLLACK:

Q. Okay. Given that those -- those two were changes requiring major amendments in the first place, how do we know that changing the spec from 97 to 98 was also a major amendment? Is there any indication that they considered that to be a major amendment?

A. Sure.

MR. DELAFIELD: Objection. Compound. Vague.

BY MR. POLLACK:

Q. What's the indication?

A. You -- the documents that I've cited consider those changes to be amendment. They specifically address changes in specifications.

Q. Can you -- can you show me where it says that a change in purity from 97 to 98 percent is considered a major amendment?

A. They wouldn't have listed something

as a change in purity from 97 to 98 percent. That's not what guidelines do. They talk about changes in specifications, which that would -- would be.

Q. Okay. Can you show me where they say a change -- in the documents you've cited -- a change increasing the minimum HPLC assay purity is a major amendment?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: The increasing the stringency of a -- of a specification is not a major amendment. What is a major amendment was the change in the process, the change in the starting material. Those are major changes, and those major changes resulted in an increase in purity that the FDA ultimately approved.

MR. POLLACK: I'm going to mark as Ruffolo Deposition Exhibit 11.

(Document marked for identification purposes as Ruffolo Exhibit 11.)

THE WITNESS: Thank you.

BY MR. POLLACK:

Q. Ruffolo -- and Ruffolo 11 is a document entitled "Patent Owner Response to Petition."

A. Yes.

Q. Have you seen this document before?

A. Yes, I believe I have.

Q. Okay. When did you see this document?

A. I saw this maybe a year ago. Oh, I'm sorry. This is the response. This is not the --

Q. Yeah. I don't want to trick you or anything.

A. Right. Yeah.

Q. If you turn to the last page?

A. Yeah.

Q. You'll see it's dated July 6, 2016?

A. Oh, okay. Sorry. I would have read this in the last couple of weeks.

Q. Oh, okay. Were you involved at all in creating Ruffolo Deposition Exhibit 11?

A. No, I was not --

Q. Okay.

A. -- involved in the creation of this document.

Q. Okay. And had you read this document at any time before you wrote your final draft of your declaration?

A. I don't believe so because I believe my document was submitted on this day because it was the day before a family vacation where I had to finish mine. So I don't know if I could have read this in advance.

Q. Okay. Let me ask you.

Did you read any prior drafts of Ruffolo Deposition Exhibit 11?

A. Oh. No.

Q. Okay.

A. No.

Q. So Ruffolo Deposition Exhibit 11 you first read in preparation for today's deposition?

A. Yes, that's correct.

Q. Okay. Was there anything in Ruffolo Deposition Exhibit 11 that you disagreed with?

A. Could you be more specific?

Q. Well, did you see any mistakes or -- let me start with that. Did you see any mistakes in Ruffolo Deposition Exhibit 11?

A. Not that I recall.

Q. Okay. Did you see opinions or statements that you thought were maybe just slightly inaccurate?

A. Can you be more specific on whose opinions you're talking about?

Q. Yeah. Any of the opinions that were written in here by -- this was submitted -- this was submitted by United Therapeutics.

A. I understand.

Q. Okay.

A. Yeah.

Q. Were any of the statements in here -- I assume this was -- these were written by United Therapeutics attorneys.

Were there any statements in this document that you looked at and said, well, I don't know if I completely agree with --

A. Okay.

Q. -- that statement?

MR. DELAFIELD: Objection. Vague.

THE WITNESS: This document, as I recall, quotes some opinions from -- from either Dr. Winkler or from the -- the Board,

that Board.

BY MR. POLLACK:

Q. The Board? The Board that's -- that's hearing this case?

A. Many of those I wouldn't have agreed with.

Q. Okay.

A. Obviously the opinions that relate to mine --

Q. Uh-huh.

A. -- my declaration and the opinions that relate to Dr. Williams' declaration I do agree with.

Q. Okay. So there was nothing -- there were no statements in here that United Therapeutics was advancing that you thought, I don't -- I don't completely with that?

A. Not that I recall.

MR. DELAFIELD: Objection. Asked and answered.

BY MR. POLLACK:

Q. Let me just -- I just wanted to check one thing with you.

If you turn to page 34?

A. Okay.

Q. At the top of the page, this is under a heading that says "The '393 Patent Product is Structurally and Functionally Distinct from Moriarty's Product."

A. Yes, I see that.

Q. Okay. Do you know what that means?

A. I believe I do.

Q. What -- what does it mean?

A. "Structurally different" I believe means a difference in the chemical that was produced as a result of the reaction, and "functionally" I believe means the clinical or perhaps patient significance. That's -- that's my understanding.

Q. Is there a difference between the approved Moriarty treprostinil product that was shown clinically that's different from the '393 product?

MR. DELAFIELD: Objection. Vague. Compound. Outside the scope of his declaration.

THE WITNESS: Not -- not to my knowledge.

BY MR. POLLACK:

Q. And you said that -- we were

mentioning structurally.

Is there a difference between the structure of treprostinil as made by the Moriarty product and the structure of treprostinil as made by the '393 patent?

A. Yeah. As I -- as I indicated, structure to me represents the result of the chemical reaction, and the purity of the material produced by '393 is higher and the levels of all but one of the impurities are lower in the '393 process compared to Moriarty.

Q. Let me ask you a hypothetical.

If the -- here you point out that the difference in purity is .7 percent; right?

A. That's --

MR. DELAFIELD: Objection. Vague.

THE WITNESS: That's -- yes, that's from my declaration.

BY MR. POLLACK:

Q. Okay. Is that a fair characterization of your declaration that's made on page 34? A .7 percent difference in average purity?

A. Yes, I believe it is.

Q. Okay. And in your view, is that being used to show that the '393 product is structurally different from the Moriarty product?

A. Yes, in that it contains two-thirds less impurity than the Moriarty process.

Q. Okay. Let me ask you.

If instead of .7 percent difference, what if the difference was [redacted] percent? Would that still be a structural difference, in your view?

MR. DELAFIELD: Objection. Calls for speculation. Outside the scope of his declaration.

THE WITNESS: If it was [redacted], that would represent about a [redacted] percent reduction. Yeah, that -- that would be important to me.

BY MR. POLLACK:

Q. Okay. What about a [redacted] percent difference? Would that be a structural difference, in your view?

MR. DELAFIELD: Same objections.

THE WITNESS: That would be about a [redacted] percent -- would be, yeah, [redacted]

percent reduction in overall impurities. Maybe. I don't know. I'd have to think about that.

BY MR. POLLACK:

Q. Okay. What if it were a [redacted] percent difference in impurity? Would that -- between the '393 and treprostinil product, would that be a structural difference, in your view?

MR. DELAFIELD: Same objections.

THE WITNESS: Well, certainly if I have to think about [redacted], I'd have to think about [redacted], and I haven't thought about that.

BY MR. POLLACK:

Q. Do you -- you're giving an opinion that .7 is a structural difference.

I'm trying to figure out where is that borderline between structural difference and one that's not a structural difference.

MR. DELAFIELD: Same objections.

THE WITNESS: I don't know, but I do believe that a [redacted] percent reduction in -- in purity is. I don't know what the cutoff is at the low end, but I'm confident that [redacted] percent reduction in purity is.

BY MR. POLLACK:

Q. Okay. Are there -- is there a number that I could give you that you would agree that that would be too small a difference to make a structural difference?

MR. DELAFIELD: Objection. Relevance. Outside the scope. Lacks foundation.

THE WITNESS: You know, not -- if you're asking me can I set the lower limit?

BY MR. POLLACK:

Q. Yeah.

A. I'm telling you, I'd have to think about that. I haven't thought about that, and I don't know off the top of my head what it would be.

Q. In your view, is there no lower limit?

MR. DELAFIELD: Objection. Asked and answered.

THE WITNESS: There is a lower limit to everything. I just don't know where it is off the top of my head.

BY MR. POLLACK:

Q. You haven't thought of that?

A. No.

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. What if there were no difference in the average purity for the Moriarty process and the '393 process? How would your [redacted] change then?

MR. DELAFIELD: Objection. Vague. Calls for speculation.

THE WITNESS: Well, first off, there isn't no difference. There is a difference in the purity of treprostinil that's higher and a difference in the overall level of impurities that are lower in the '393 process. So the hypothetical doesn't mean anything to me.

BY MR. POLLACK:

Q. I understand, but I'm asking you to give an opinion based on my hypothetical and you're here as an expert. So --

MR. DELAFIELD: Same objections.

BY MR. POLLACK:

Q. -- I'd like to you do that.

A. So if you're asking me are two

identical preparations?

Q. Uh-huh.

A. Is there a difference between two identical preparations?

Q. Well, they're two different processes; right?

A. Well --

Q. But let's say they give around the same average purity.

A. Then there could be a difference depending on which contaminant -- which contaminants are or aren't different, which ones are elevated or which are lower, and I wouldn't know that in a hypothetical example.

Q. How come you don't know that?

MR. DELAFIELD: Objection.

THE WITNESS: Because I can't --

MR. DELAFIELD: Calls for speculation.

THE WITNESS: Because I can't make it up.

BY MR. POLLACK:

Q. Okay.

A. You're asking me to make up information that doesn't exist and I -- that's

not how I think.

Q. So, in your opinion, it's not just a difference in purity, but also the exact identity of each of those impurities that --

A. Sure.

Q. -- matters to the claim?

A. Sure.

MR. DELAFIELD: Objection. Calls for speculation.

BY MR. POLLACK:

Q. Okay.

A. Absolutely. Absolutely. It's what I referred to as the -- the characteristic impurities.

Just to give you an example. If two processes that were different and had exactly the same purity, but one of them had a very high level of one single impurity. It would be very high that made up all of that impurity, and the other one had much lower levels. You bet that would make a difference.

Q. Right. Wouldn't that depend on the FDA, the guidelines, how --

A. Of course.

Q. Whether or not that impurity

mattered? So it may make no difference at all; isn't that right?

MR. DELAFIELD: Objection. Vague. Incomplete hypothetical. Calls for speculation.

THE WITNESS: You know, if the purity was [redacted] percent and that [redacted] percent was all one single peak, that would get a great deal of attention by all those groups you said: the FDA, the reviewers, and including the company itself.

BY MR. POLLACK:

Q. All right. But that's not the case for the Moriarty process?

MR. DELAFIELD: Same objections.

THE WITNESS: The Moriarty process doesn't fit your hypothetical example where you ask me to make up data.

BY MR. POLLACK:

Q. Uh-huh.

A. The Moriarty process produces [redacted] plus fold increase in impurities compared to '393 and that I'm more comfortable with because that's real and not made up.

Q. Okay. Yeah, but I'm just asking

that weren't real, you know, how far would your opinion go?

MR. DELAFIELD: Objection. Calls for speculation. Outside his expert evaluation.

THE WITNESS: Well, I mean, as I said, I can't off the top of my head think of that.

But in the example that you gave me where you required me to make up data, which is something scientists don't really do well, at least not good scientists -- we go on real information like this .7 percent data, you know -- I have difficulty answering that question.

And I gave you an example of made-up data that you requested where it would make a big deal, a big difference but, I mean, I guess you can ask me to make up data all day long and I could come up with lots of silly examples where it would make a difference. And I'm happy to do that if you like. It's just not something I do for a living.

BY MR. POLLACK:

Q. All right. No further questions.

A. Thank you.

MR. DELAFIELD: I have no questions.

MR. POLLACK: Thanks so much for your time.

THE WITNESS: Thank you. Thank you.

THE VIDEOGRAPHER: The time is 5:11 p.m. This concludes today's audiovisual deposition of Dr. Robert R. Ruffolo. We're off the record.

(Off the stenographic record.)

THE REPORTER: Mr. Delafield, do you wish a copy of the transcript?

MR. DELAFIELD: Yes, if I could get it expedited.

MR. POLLACK: I need it expedited.

THE REPORTER: What time frame?

MR. POLLACK: Three days.

THE REPORTER: Do you wish a rough?

MR. DELAFIELD: I want one.

MR. POLLACK: Sure. Yeah, I'll

get a rough, too.

MR. DELAFIELD: If I could get expedited, both the rough and final.

THE REPORTER: When do you want the final?

MR. DELAFIELD: When can I get it?

THE REPORTER: Three days.

MR. DELAFIELD: Okay. If that's the quickest, yes.

(Signature having not been waived, the taking of the deposition concluded at 5:11 p.m.)

* * *

ERRATA SHEET

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

Page No._____Line No._____Change to:_____

_____

DECLARATION UNDER PENALTY OF PERJURY

I declare under penalty of perjury that I have read the entire transcript of my Deposition taken in the captioned matter or the same has been read to me, and the same is true and accurate, save and except for changes and/or corrections, if any, as indicated by me on the DEPOSITION ERRATA SHEET hereof, with the understanding that I offer these changes as if still under oath.

Signed on the _____ day of _____, 2016.

_____

ROBERT R. RUFFOLO, JR., PHD

CERTIFICATE OF REPORTER

DISTRICT OF COLUMBIA)

I, DENISE D. VICKERY, CRR/RMR and Notary Public, hereby certify the witness was by me first duly sworn to testify to the truth; that the foregoing deposition was taken at the time and place stated herein; and that the said deposition was recorded stenographically by me and thereafter reduced to printing under my direction; that said deposition is a true record of the testimony given by said witness.

I certify the inspection, reading and signing of said deposition were NOT waived by counsel for the respective parties and by the witness; and that I am not a relative or employee of any of the parties, or a relative or employee of either counsel, and I am in no way interested directly or indirectly in this action.

Denise D. Vickery, CRR/RMR

My Commission expires February 14, 2018

P.330

P.331
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.332
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.333
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.334
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.335
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.336
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.337
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.338
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.339

P.340
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.341

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.342
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.343

P.344

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.345
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.346
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.347

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.348

P.349

P.350

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.351
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.352
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.353

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.354
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.355
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.356

U

P.357
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.358

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

P.359

ERRATA SHEET

Page No. 8 Line No. 4 Change to: "and" to "am"

Page No. 10 Line No. 9 Change to: "Trandolapril" To "Trandilapril"

Page No. 10 Line No. 10 Change to: "Trandolapril" To "Trandilapril"

Page No. 10 Line No. 11 Change to: "Trandolapril" To "Trandilapril"

Page No. 83 Line No. 21 Change to: "Their" To "There are"

Page No. 113 Line No. 19 Change to: "reactive" To "reacted"

Page No. 142 Line No. 15 Change to: "purity" To "impurity"

Page No. 142 Line No. 17 Change to: "purity" To "impurity"

Page No. 164 Line No. 24 Change to: "a" to "an"

Page No. 204 Line No. 20 Change to: "Spectra photographic" To "Spectrophotometric"

Page No. 245 Line No. 3 Change to: "for" To "from"

P.360
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

ERRATA SHEET

Page No. 261 Line No. 7-8 Change to: "a decrease" To "an increase" (mispoke)

Page No. 284 Line No. 6 Change to: "It" To "I"

Page No. 318 Line No. 25 Change to: "purity" To "impurity"

Page No. 320 Line No. 12 Change to: "no" To "any"

Page No. 323 Line No. 7 Change to: "90" To "99"

Page No. ____ Line No. ____ Change to: ____

Page No. ____ Line No. ____ Change to: ____

Page No. ____ Line No. ____ Change to: ____

Page No. ____ Line No. ____ Change to: ____

Page No. ____ Line No. ____ Change to: ____

Page No. ____ Line No. ____ Change to: ____

P.361
UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006

DECLARATION UNDER PENALTY OF PERJURY

I declare under penalty of perjury that I have read the entire transcript of my Deposition taken in the captioned matter or the same has been read to me, and the same is true and accurate, save and except for changes and/or corrections, if any, as indicated by me on the DEPOSITION ERRATA SHEET hereof, with the understanding that I offer these changes as if still under oath.

Signed on the 1st day of September, 2016.

ROBERT R. RUFFOLO, JR., PHD

P.362

UT Ex. 2058
SteadyMed v. United Therapeutics
IPR2016-00006