Patent Trial and Appeal Board

A, petition has been filed in Patent Number 9,604,901, Application Number 14/754,932, on March 30, 2020.

The AIA Review Number is IPR2020-00770.

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
14/754,932	9604901	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

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 9,604,901 B2
APPLICATION NO.	: 14/754932
DATED	: March 28, 2017
INVENTOR(S)	: Hitesh Batra et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 17, Claim 1, Line 27, "(c) containing the" should be --(c) contacting the--.

Signed and Sealed this
Sixteenth Day of May, 2017

Michelle K. Lee

Michelle K. Lee
Director of the United States 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®
Patent. No.:	9,604,901
Issue Date:	3/28/2017
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	1865

REQUEST FOR CERTIFICATE OF CORRECTION FOR PTO MISTAKE PURSUANT TO 37 C.F.R. § 1.322(a)

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

Commissioner:

Enclosed, is a Certificate of Correction, Form PTO-1050, for United States Patent Number 9,604,901 issued March 28, 2017. The following Patent Office printing error appears in the issued patent:

IN THE CLAIMS

The exact claim and line number where the error in the issued patent is shown correctly in the application file is

Col. 17, claim 1, line 27, "(c) containing the" should be --(c) contacting the--.

Applicant submits that the above change would not constitute new matter, and correction thereof would not require reexamination.

Pursuant to 37 C.F.R. §1.322, Applicant requests that the enclosed Certificate of Correction be approved.

Although Applicant believes that no fee is required for this Request, the Commissioner is hereby authorized to charge any additional fees which may be required for this Request to Deposit Account No. 19-0741.

Respectfully submitted,

Date APR 11 2017

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

MODIFIED PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	9,604,901
APPLICATION NO.	:	14/754932
DATED	:	3/28/2017
INVENTOR(S)	:	Hitesh BATRA; Sudersan M. TULADHAR; Raju PENMASTA; David A. WALSH

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 17, claim 1, line 27, "(c) containing the" should be --(c) contacting the--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Foley & Lardner LLP
3000 K Street, N.W., Suite 600
Washington, D.C. 20007-5109

4812-9262-0614.1

Electronic Acknowledgement Receipt	
EFS ID:	28891657
Application Number:	14754932
International Application Number:	
Confirmation Number:	1865
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2
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:	080618-1550
Receipt Date:	11-APR-2017
Filing Date:	30-JUN-2015
Time Stamp:	13:22:39
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	Request for Certificate of Correction	ReqCOC.pdf	82104 aa621821b4c31705b86d68f1a81229037aecb4f2	no	3
Warnings:					

Information:	
Total Files Size (in bytes):	82104

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

Mar 10, 2017 03:28:39 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.
14754932	ISSUE.NTF	03/08/2017	080618-1550

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.
14/754,932	03/28/2017	9604901	080618-1550	1865

22428 7590 03/08/2017

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
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 02/14/2017

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

EXAMINER
VALENROD, YEVGENY

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 02/14/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$960	$960	05/15/2017

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 02/14/2017
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.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$960	$960	05/15/2017

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.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

22428 7590 02/14/2017

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

EXAMINER	
VALENROD, YEVGENY	

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 02/14/2017

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. 14/754,932	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 12/21/16*.
   ☐ 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 *1,6 and 8-14*. 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 _____
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 _____.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	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	2/9/2017	YV

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
562	466	2/9/2017	YV

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	2/9/2017	YV
Inventor	2/9/2017	YV
C07C 59/72; 51/08; 51/41; 51/412; 213/08; 405/0075	2/9/2017	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
C07C	59/72; 51/08; 51/41; 51/412; 213/08; 405/0075	2/9/2017	YV
562	466	2/9/2017	YV

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672

Atty. Dkt. No. 080618-1550

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.:	14/754932
Filing Date:	6/30/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation No.:	1865

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

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

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

Invalidity contentions filed against parent U.S. Patent 8,497,393 ("the '393 parent patent") and prior art mentioned therein are being filed in this submission. With respect to certain invalidity contentions that contain "confidential" designations, those documents were previously designated confidential at one time in the litigation, but they are no longer subject to confidentiality, except where certain information has been redacted.

Recent Patent Owner documents are also being cited herein from the related proceeding IPR2016-00006, *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, which involves the same '393 parent patent of the above-captioned patent application. Although these documents were previously submitted, the versions filed with this Statement are new versions of certain documents filed recently in the IPR that have some information unredacted that was previously redacted in prior versions.

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

Atty. Dkt. No. 080618-1550

TIMING OF THE DISCLOSURE

The listed documents are 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 Dec. 21, 2016

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

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**	14/754932
Date Submitted: December 21, 2016				**Filing Date**	6/30/2015
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1672
				Examiner Name	Yevgeny Valenrod
Sheet	1	of	3	Attorney Docket Number	080618-1550

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

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document / Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document 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	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.	
	E2	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.	

Examiner Signature		Date Considered	

4848-0394-1950.1

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**	14/754932
Date Submitted: December 21, 2016				**Filing Date**	6/30/2015
				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	080618-1550

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]
	E3	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.	
	E4	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.	
	E5	Service copy of Third Party Submission dated October 16, 2016, filed but not entered in US 14/754,932 on October 16, 2016, with 6 indicated attachments, 822 pages.	
	E6	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.	
	E7	Defendant Sandoz Inc.'s Invalidity Contention Charts 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.	
	E8	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).	
	E9	Exhibit G, Invalidity Claim Chart for the '393 patent, January 12, 2015, 66 pages.	
	E10	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).	
	E11	Arumugan et al., "A New Purification Process for Pharmaceutical and Chemical Industries," Organic Process Research & Development, 2005, 9:319-320.	
	E12	Burk et al., "An Enantioselective Synthesis of (S)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation," J. Org. Chem., 2003, 68:5731-5734.	
	E13	Eliel et al., Stereochemistry of Organic Compounds, 1994, 322-325.	
	E14	Harwood et al., Experimental organic chemistry: Principles and Practice, 1989, 127-134.	
	E15	Jones, Maitland Jr., Organic Chemistry, 2nd Ed., 2000, 153-155.	
	E16	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.	
	E17	McManus et al., "Tetrazole Analogs of Plant Auxins," J. Org. Chem., 1959, 24:1464-1467.	
	E18	Monson, Richard S., Advanced Organic Synthesis, Methods and Techniques, 1971, 178-188.	

Examiner Signature		Date Considered	

4848-0394-1950.1

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**	14/754932
Date Submitted: December 21, 2016				**Filing Date**	6/30/2015
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1672
				Examiner Name	Yevgeny Valenrod
Sheet	3	of	3	Attorney Docket Number	080618-1550

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]
	E19	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.	
	E20	Olmsted III et al., Chemistry, The Molecular Science, Mosby-Year Book, Inc., Chapter 10 "Effects of Intermolecular Forces," 1994, 428-486.	
	E21	Pavia et al., Introduction to Organic Laboratory Techniques, First Edition, 1998, 648.	
	E22	Physicians' Desk Reference, 59 Edition, 2005, for Bicillin® L-A (penicillin G benzathine suspension), 5 pages.	
	E23	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.	
	E24	REMODULIN® label, 2014, 17 pages.	
	E25	Schoffstall, et al., Microscale and Miniscale Organic Chemistry Laboratory Experiments, 2004, 2nd Ed., 200-202.	
	E26	Sorrell, Thomas N., Organic Chemistry, 1999, 755-758.	
	E27	Wiberg, Laboratory Technique in Organic Chemistry, 1960, 112.	
	E28	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	02/09/2017

4848-0394-1950.1

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**	14/754932
				Filing Date	6/30/2015
Date Submitted: JAN 10 2017				**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	080618-1550

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]
	F1	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	02/09/2017

4821-9333-3824.1

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

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	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	07/28/2015	09/10/2015	02/04/2016	10/14/2016	11/04/2016	02/09/2017			
1	1	✓	=	✓	=	=	=			
	2	✓	=	✓	-	-	-			
	3	✓	=	✓	-	-	-			
	4	✓	-	-	-	-	-			
	5	✓	-	-	-	-	-			
2	6	✓	=	✓	=	=	=			
	7	✓	-	-	-	-	-			
3	8	✓	=	✓	=	=	=			
4	9			✓	=	=	=			
5	10			✓	=	=	=			
6	11			✓	=	=	=			
7	12			✓	=	=	=			
8	13			✓	✓	=	=			
9	14			✓	✓	=	=			

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	2017/02/09 06:34
L2	1	("8242305").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/02/09 06:34
L3	1	("4683330").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/02/09 06:34
L4	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/02/09 06:34
L5	32	((Hitesh) near2 (Batra)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L6	24	((Sudersan) near2 (Tuladhar)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L7	30	((Raju) near2 (Penmasta)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L8	248	((David) near2 (Walsh)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L9	276	L5 or L6 or L7 or L8	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L10	24	L9 and treprostinil	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L11	540	c07c59/72.cpc.	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L12	870	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/02/09 06:34
L13	1283	L11 or L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/02/09 06:34
L14	47	L13 and treprostinil	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34

EAST Search History (Prior Art)

L15	42	L14 and purity	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L16	38	L15 and HPLC	US-PGPUB; USPAT; USOCR	OR	ON	2017/02/09 06:34
L17	1	("6765117").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/02/09 06:34
L18	2	wo "2005007081"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2017/02/09 06:34
L19	4	"9242350"	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2017/02/09 06:34
L20	1	("8242305").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/02/09 06:34
L21	1	("9156786").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2017/02/09 06:34

EAST Search History (Interference)

		<This search history is empty>				

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	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	/	41			I	2013-01-01
C07C		51	/	412			I	2013-01-01
C07C		213	/	08			I	2013-01-01
C07C		405	/	0075			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
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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)	9	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	02/09/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	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)												
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	9	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	02/09/2017	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	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	6														
3	8														
4	9														
5	10														
6	11														
7	12														
8	13														
9	14														

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	9	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	02/09/2017	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
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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.

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22428 7590 02/14/2017
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$960	~~$960~~ $0	05/15/2017

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)**
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☒ 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 February 14, 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 Acknowledgement Receipt	
EFS ID:	28349554
Application Number:	14754932
International Application Number:	
Confirmation Number:	1865
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2
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:	080618-1550
Receipt Date:	14-FEB-2017
Filing Date:	30-JUN-2015
Time Stamp:	13:41:58
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	Issue Fee Payment (PTO-85B)	IFTM.pdf	124943 b99c7a228e8f5ccd7aca3a1d9f12dccf85ae02ed	no	1
Warnings:					

Information:	
Total Files Size (in bytes):	124943

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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.

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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

Feb 14, 2017 03:24:18 AM

Dear PAIR Customer:

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Application	Document	Mailroom Date	Attorney Docket No.
14754932	NOA	02/14/2017	080618-1550
	1449	02/14/2017	080618-1550
	1449	02/14/2017	080618-1550

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Thank you for prompt attention to this notice,

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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22428 7590 02/14/2017
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

OPAP AKIMA-15 FEB 14 2017 PATENT & TRADEMARK OFFICE

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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.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$960	~~$960~~ $0	05/15/2017

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

02/16/2017 MBLANCO1 00000017 14754932
01 FC:1501 960.00 OP

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/
Typed or printed name Stephen B. Maebius
Date February 14, 2017
Registration No. 35,264

02/16/2017 MBLANCO1
Adjustment date: 11/14/2016 INTEPSW 00000339 14754932 -960.00 OP
01 FC:1501

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

Atty. Dkt. No. 080618-1550

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.:	14/754,932
Filing Date:	6/30/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	1865

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/

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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]

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[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

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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:

[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]

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.

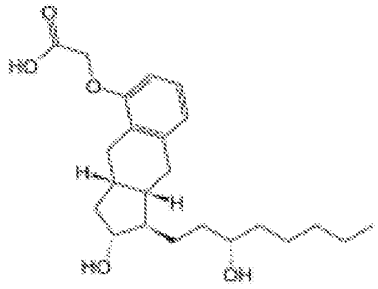
Fourth, Actavis cites Wade to show that physiologically acceptable salts of treprostinil include salts derived from bases such as ammonia, N-methyl-D-glucamine, magnesium, arginine, and lysine. AIC at 49. Once again, however, Actavis fails to provide any detail as to how this is relevant to the obviousness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

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[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.

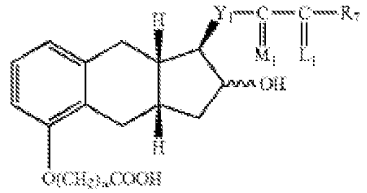
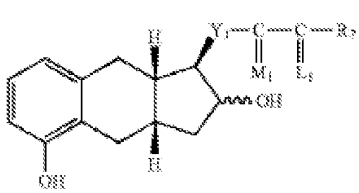
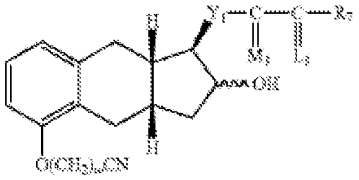
Additionally, the test for sufficiency of written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 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.

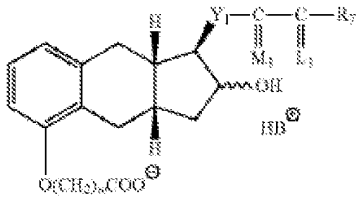
[16] Actavis provides claim 1 as a single limitation and thus does not identify which of the references it lists under claim 1 allegedly disclose each limitation. Actavis has therefore waived arguments regarding the absence of any particular limitation in its cited references including by failing to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

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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

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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

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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

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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

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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

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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

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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

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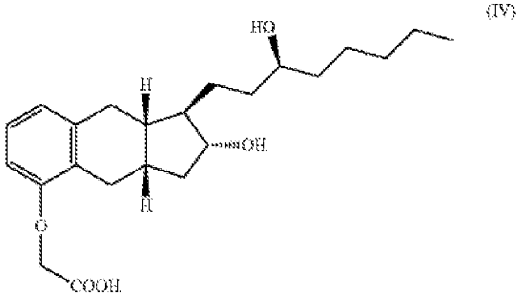
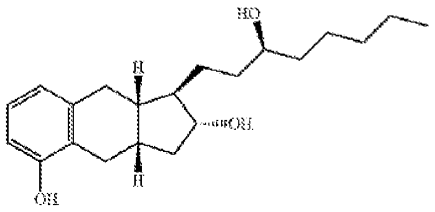
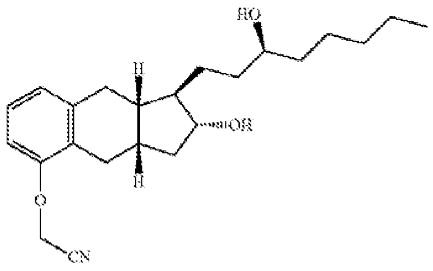
Claim	Representative Deficiencies in Prior Art Disclosure
step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.	independent reason for the obviousness of this claim so no response is 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.

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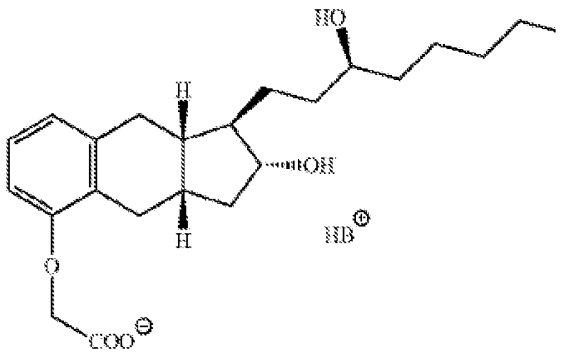
Claim	Representative Deficiencies in Prior Art Disclosure
(b) hydrolyzing the product of formula VI of step (a) with a base, (c) contacting the product of step (h) with a base B to form a salt of formula IV_s, and .  (d) optionally reacting the salt formed in step (c) with an acid to form the compound 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

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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.

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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.

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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

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[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.

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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.

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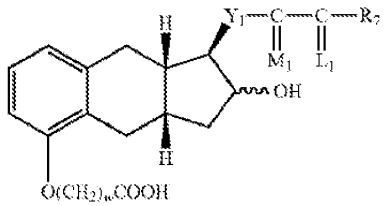
EXHIBIT A

UNITED THERAPEUTICS' RESPONSE TO SANDOZ'S INVALIDITY CONTENTIONS

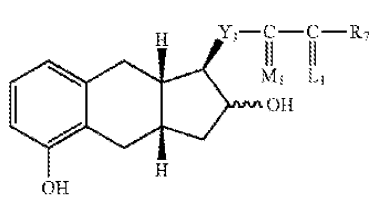
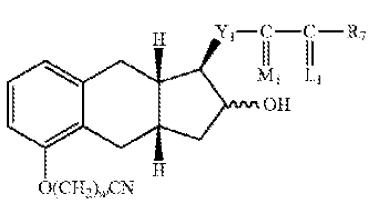
UNITED STATES PATENT NO. 8,497,393[1]

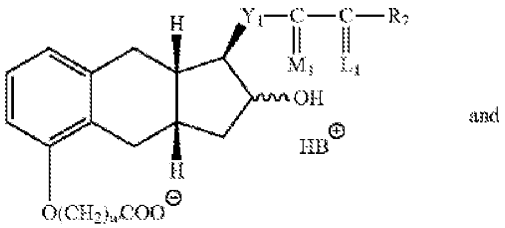
I. Disclosure of Validity Contentions – United States Patent No. 8,497,393

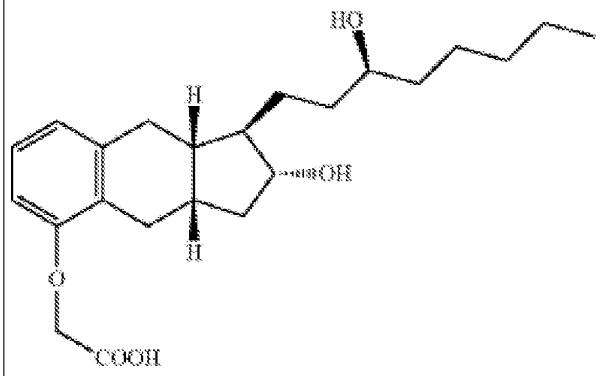
Anticipation and/or Obviousness based on U.S. Patent No. 4,306,075 ("the '075 patent")	
Claim	**Deficiencies in Prior Art**
Claim 1	
1. A product comprising a compound of formula I (I)  or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	The product 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

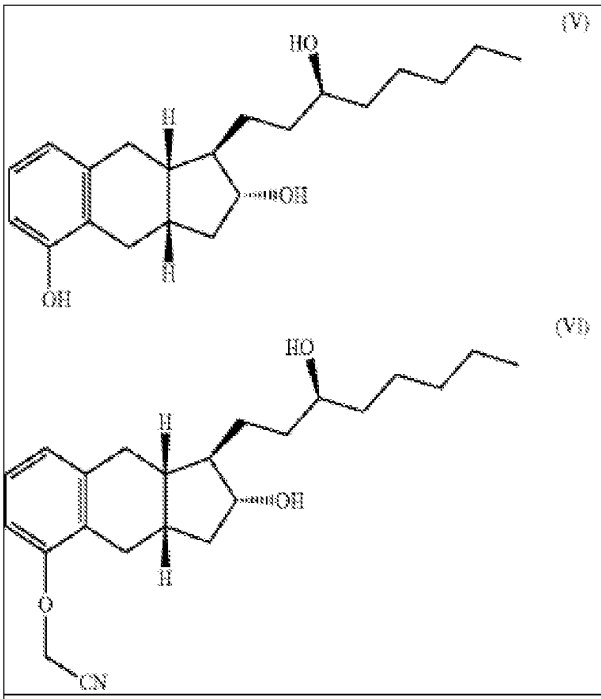
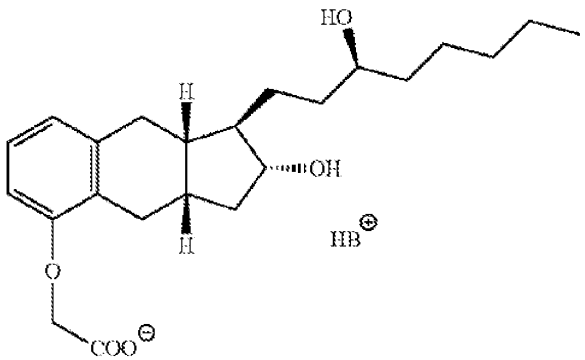
[1] In addition to the references specifically cited herein, United Therapeutics reserves the right to rely on other materials and information including, but not limited to, the references cited by Sandoz in its invalidity contentions, expert opinion, and any additional references uncovered during discovery.

	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

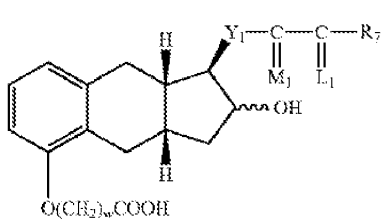
	by the '075 patent synthetic method would be expected to have a different impurity profile than the treprostinil produced by the claimed process of the '393 patent in lower yield.
(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,  (II)  (III) wherein 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_3 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_3 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.	

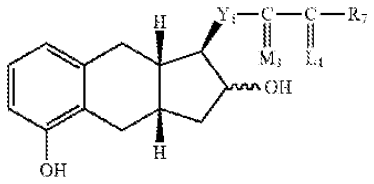
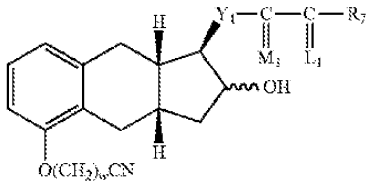
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	The only difference between claim 16 and claim 8 of the '393 patent is their dependence of claims 9 and 1, respectively. Thus, each of the arguments for claim 8 is applicable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

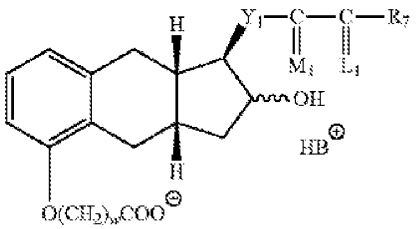
Anticipation and/or Obviousness based on U.S. Patent No. 4,668,814 ("the '814 patent") and European Patent Publication No. 0159784A1 ("EP '784")	
Claim	**Deficiencies in Prior Art**
Claim 1	
1. A product comprising a compound of formula I  (I) or a pharmaceutically acceptable salt thereof, wherein said 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

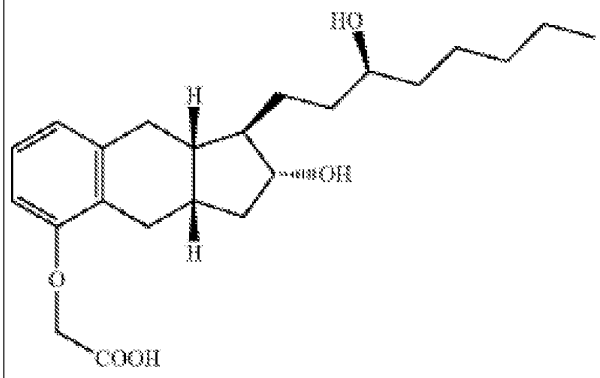
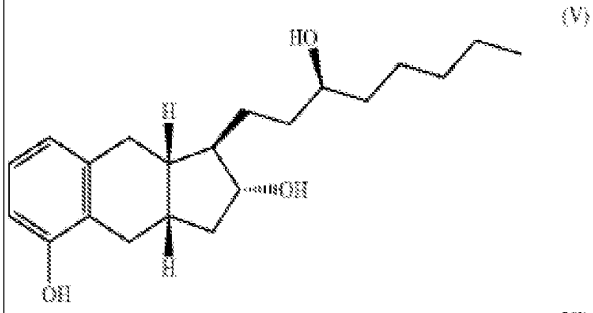
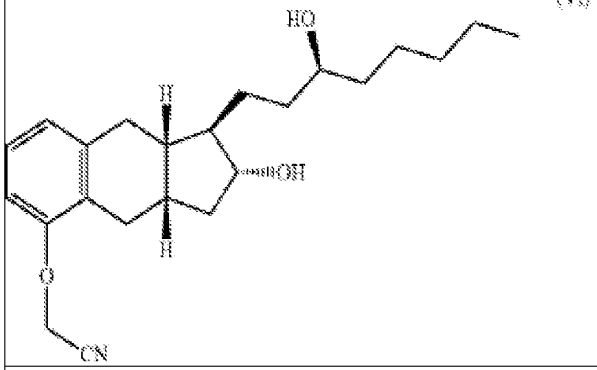
[2] UTC reserves the right to use the entire documents Sandoz cited in their narrative contention response.

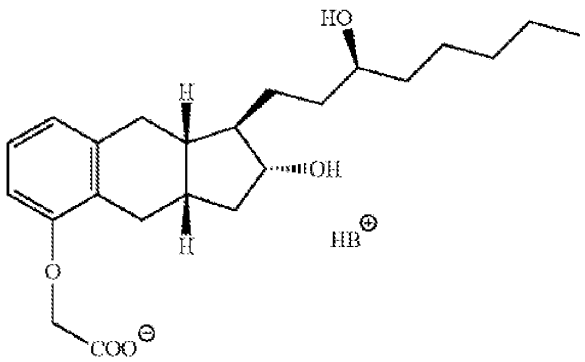
	makes clear that the product of the '814 patent was inadequate even with additional purification techniques not disclosed in the references themselves. Additionally, the lots produced by the prior Upjohn optimized synthesis have a different impurity profile, different average optical rotation, and lower 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

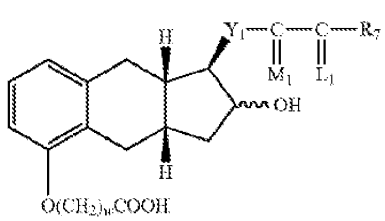
	referring to that route as well. Sandoz' previous Invalidity Contentions operate as an admission of a party opponent, and confirm that even Sandoz itself recognizes the validity of the '393 patent, and the superiority of the product produced by the claimed process of the '393 patent. For these reasons,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

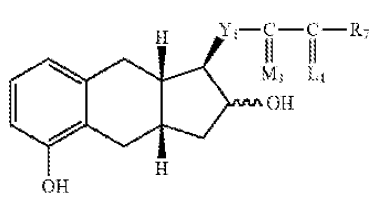
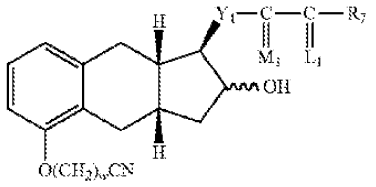
or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising	Claim 1 of the '393 patent is not anticipated by the Moriarty references because the product produced by the claimed method is different from the product of the Moriarty references. While the chemical 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

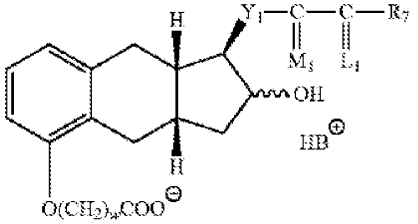
[4] UTC reserves the right to use the entire documents Sandoz cited in their narrative contention response.

	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-

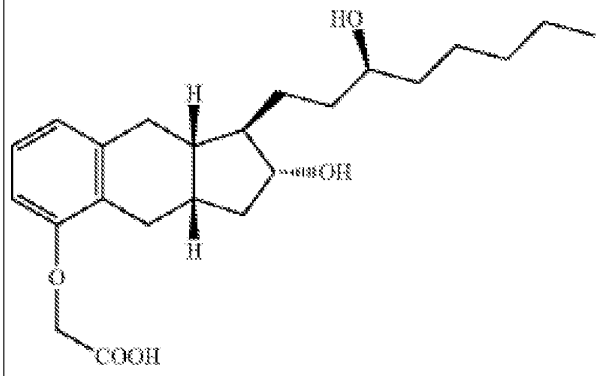
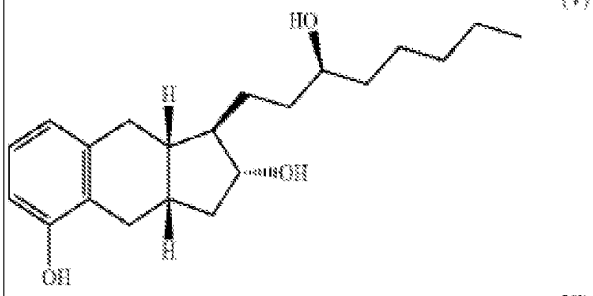
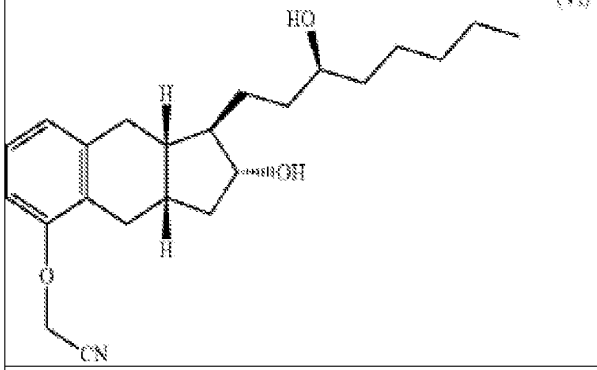
	Sand-Rem01156295-302; *see also*, UTC-Sand-Rem00062013. Other documents also indicate the types of impurities present, level of impurities, yields and other information about these and other lots made by the Moriarty process. See, e.g., UTC-Sand-Rem01096537, PTX-100a, UTC-Sand-Rem00001673-702; UTC-Sand-Rem00804699-707; 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-

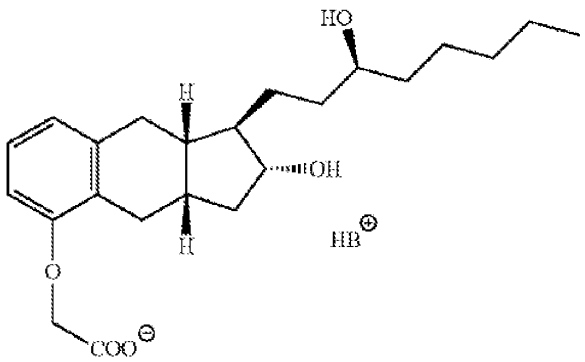
[5] The documents cited herein for batches of treprostinil made by the '117 patent process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information 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.

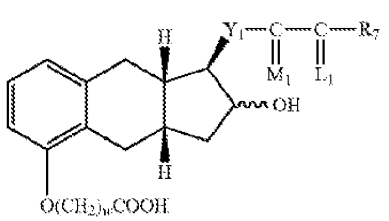
	Rem01096533 ("The following chart lists in detail the changes that occurred in the process between Chicago [using Moriarty process] and Silver Spring [using '393 process]. In Silver Spring, the diethanolamine salt was introduced as a purification step and the batch size was increased from [redacted] 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%

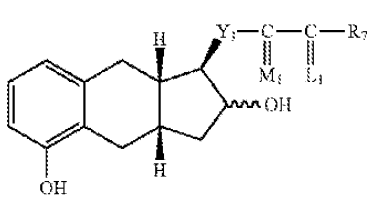
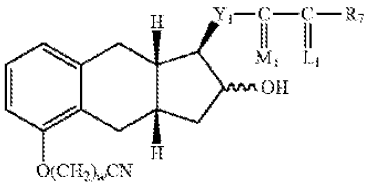
[7] UTC reserves the right to use the entire documents Sandoz cited in their narrative contention response.

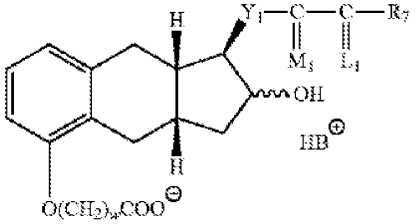
	[redacted] impurity and <0.05% [redacted] impurity. UTC-Sand-Rem01096535-36. This is a very low amount for these impurities given that these were the first few batches made with the process. The last six years of Moriarty batches made, however, had more impurities on average per impurity of several impurities 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

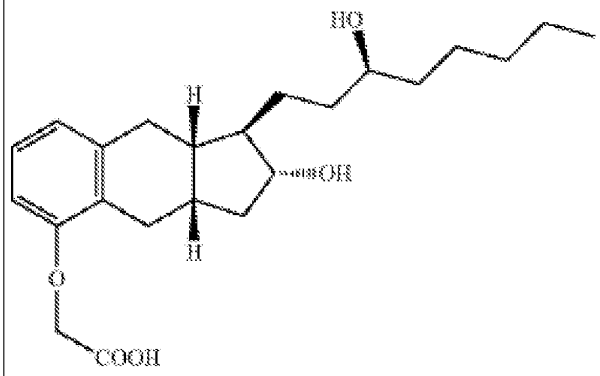
[8] The documents cited herein for batches of treprostinil made by the '117 patent process and by the '393 patent process are illustrative examples. Discovery in this case has just started and expert discovery has not started. Thus, UTC reserves the right to cite additional documents showing information 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.

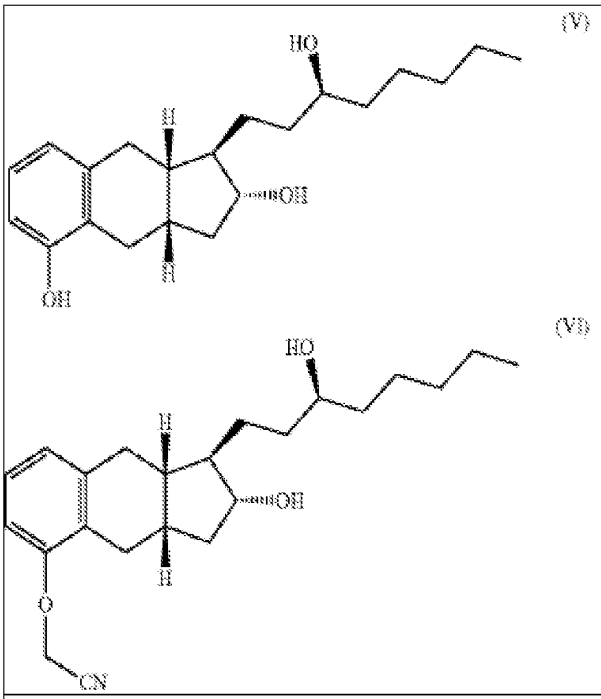
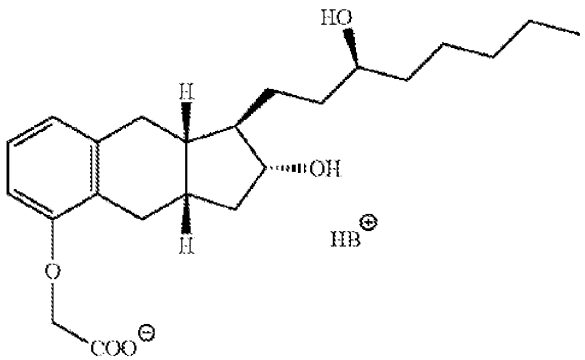
	99.9% compared to 99% for the Moriarty process. *Id.* A person of ordinary skill in the art would therefore understand that any improvements in the commercial lots of treprostinil made using the '393 patent synthesis is further magnified over the Moriarty synthesis products given the difference in scale. 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.

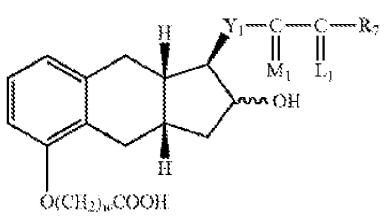
Y_1 is trans-CH=CH—, cis-CH=CH—, —$CH_2(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3; R_7 is (1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive, (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that 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

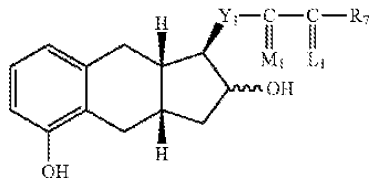
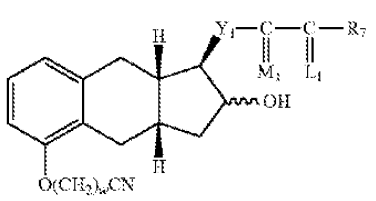
	Anderson reference.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	Sandoz fails to identify any disclosure of step (d) in the Phares or Anderson reference. The Moriarty 2004 reference similarly does not disclose the treprostinil diethanolamine salt 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.

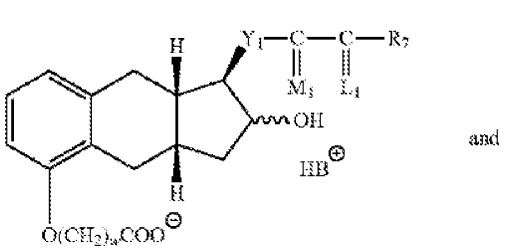
is KOH or NaOH.	
Claim 8	
8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).	Moriarty 2004 indicates that column chromatography is used to purify the compound of formula (III). Similarly, Phares does not disclose the details of 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.

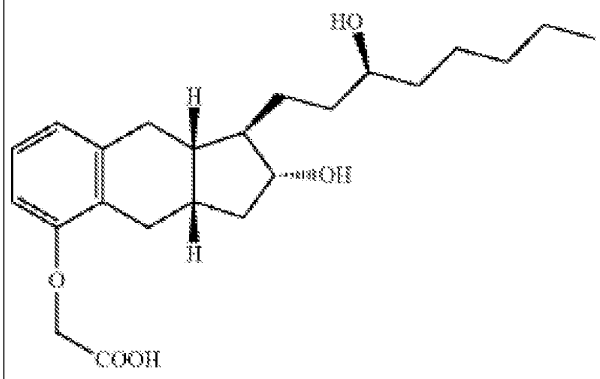
	
(b) hydrolyzing the product of formula VI of step (a) with a base,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to 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.

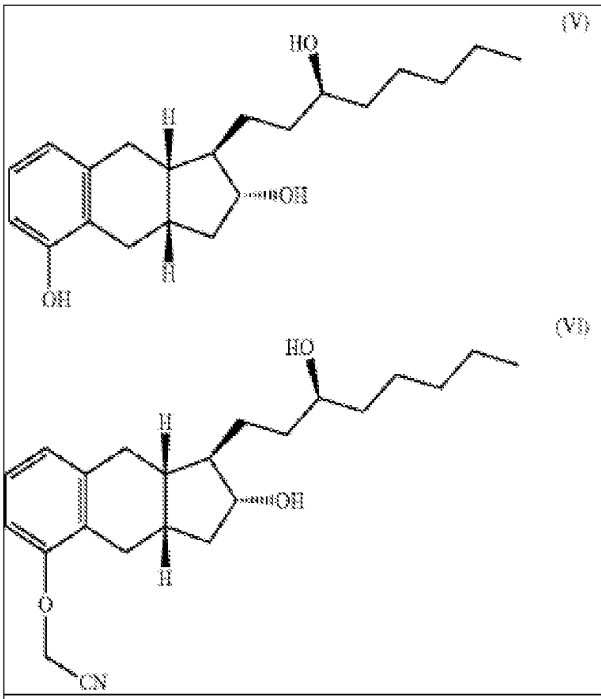
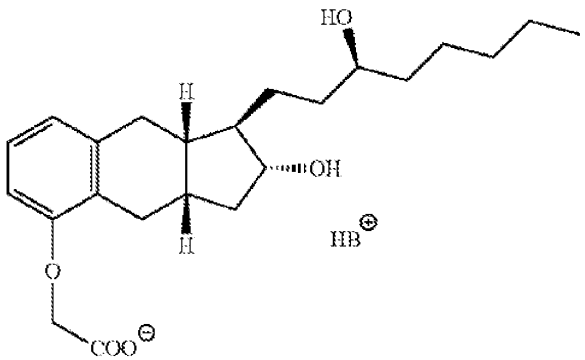
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	The only difference between claim 16 and claim 8 of the '393 patent is their dependence of claims 9 and 1, respectively. Thus, each of the arguments for claim 8 are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

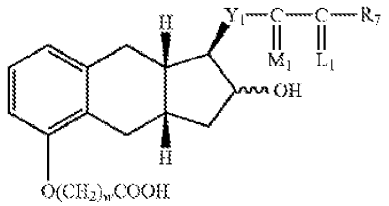
	references regarding the purity, impurity profiles, synthesis or composition of the drug product. As previously discussed, none of these references anticipate and/or render obvious any claim of the '393 patent. See, '075 patent, '814 patent references, and Moriarty references charts above.
(b) alkylating 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.

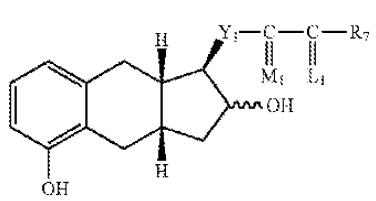
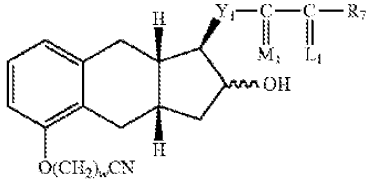
(2) 2-(2-furyl)ethyl, (3) 2-(3-thienyl)ethoxy, or (4) 3-thienyloxymethyl; M_1 is α-OH:β-R_5 or α-R_5β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 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

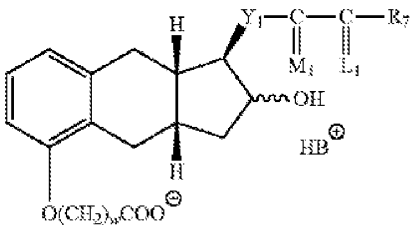
not include purifying the compound of formula (III) produced in step (a).	this claim for the same reasons as the '117 patent and Moriarty 2004 do not anticipate and/or render obvious the claim. See claim 1, above. See also '117 patent and Moriarty 2004 charts above.
Claim 9	
9. A product comprising a 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,	

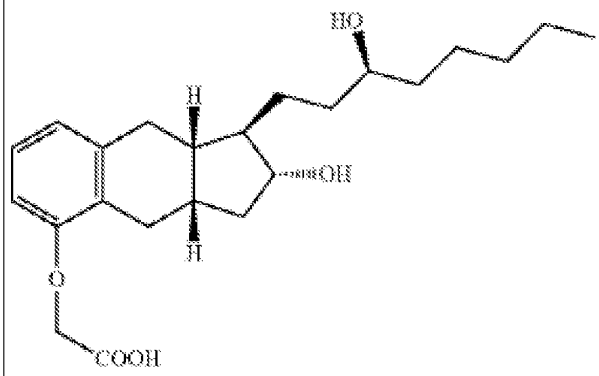
	
(b) hydrolyzing the product of formula VI of step (a) with a base,	The only difference between claim 9 and claim 1 of the '393 patent is the structures shown are limited to the synthesis of treprostinil and not related prostacyclin analogues. Thus, each of the arguments for claim 1 are applicable to 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.

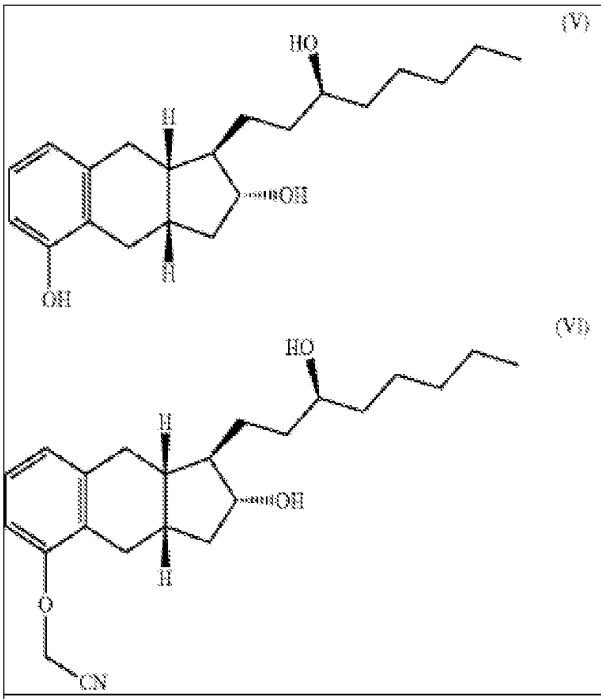
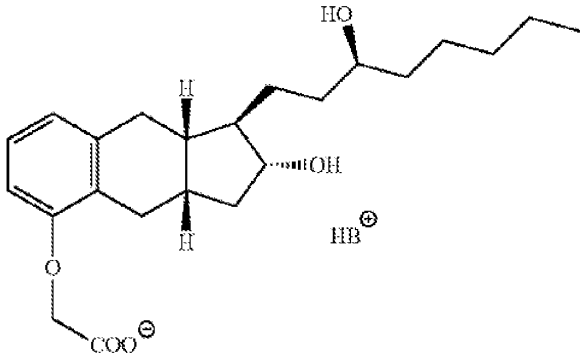
Claim 16	
16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).	The only difference between claim 16 and claim 8 of the '393 patent is their dependence of claims 9 and 1, respectively. Thus, each of the arguments for claim 8 are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

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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

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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.

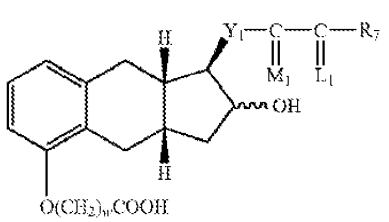
Lastly, both Teva's lack of enablement and written description defenses are based solely on what UTC argues and Teva provides no analysis of any alleged lack of enablement or written description regardless of what UTC's arguments may be. Indeed, UTC already provided responses to Teva's first Invalidity 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.

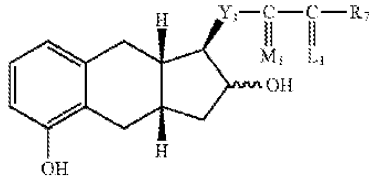
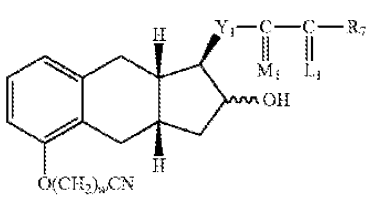
Claim	Deficiencies in Prior Art
	Specifically, Teva alleges to the extent that the Moriarty references do not anticipate the '393 patent, the claims would be rendered obvious by one or more of the Moriarty references in combination with one or more of Monson (1971), Eliel (1994), Jones (1971 or 2000), 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.

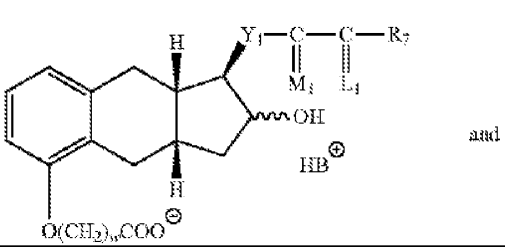
Claim	Deficiencies in Prior Art
	First, Teva cites Lin, Aristoff, and McManus for the contention that alkylation using chlorolacetonitrile and subsequent hydrolysis to carboxylic acid was known, but fails to indicate how this is relevant to the obviousness analysis as the '393 patent itself references 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

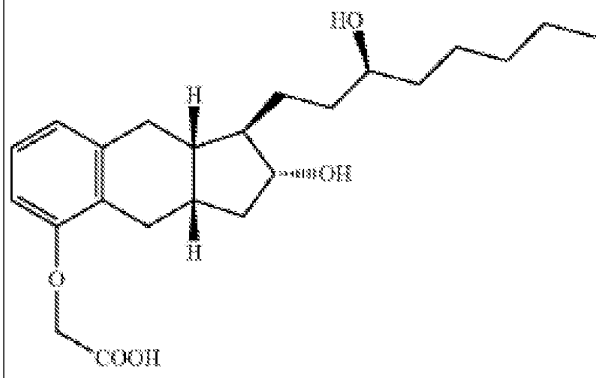
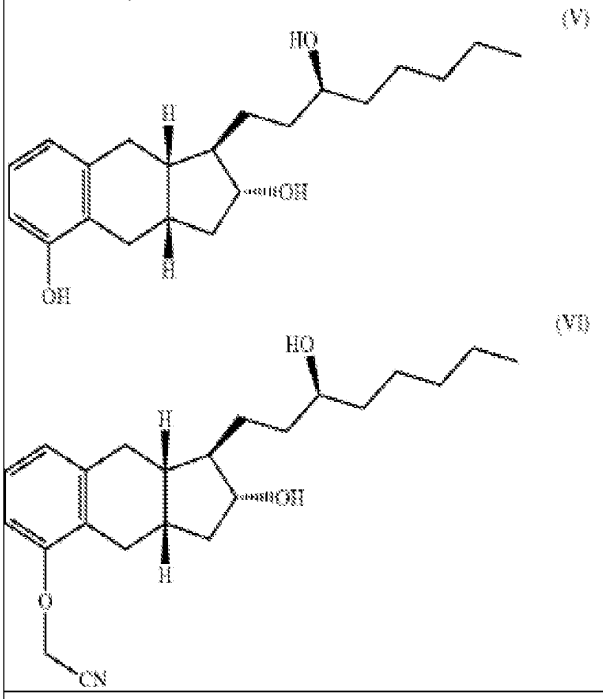
Claim	Deficiencies in Prior Art
	are very different than the claims of the '393 patent and would result in a different product. Moreover, the '117 patent does not specifically disclose treprostinil diethanolamine salt. *See Astellas Pharma, Inc. v. Ranbaxy Inc.*, No. CIV.A.05 2563 MLC, 2007 WL 576341, 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

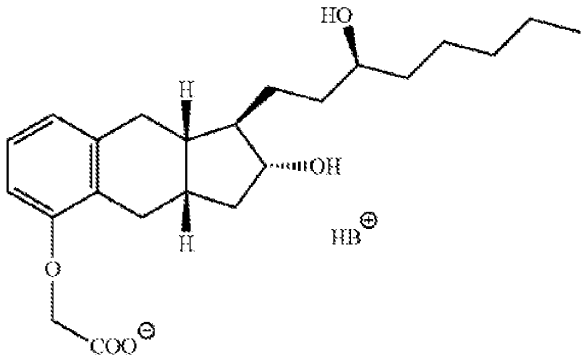
Claim	Deficiencies in Prior Art
	or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. 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.

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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.

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[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

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[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

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[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.

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[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

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[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").

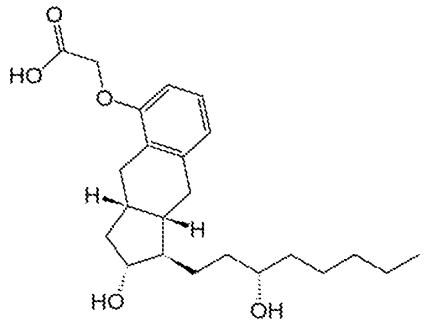
[30] Priscinzano, Piperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909): High Affinity Ligands for the Dopamine Transporter, J. Med. Chem. 2002, 45, 4371-4374 ("Priscinzano")

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.

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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.

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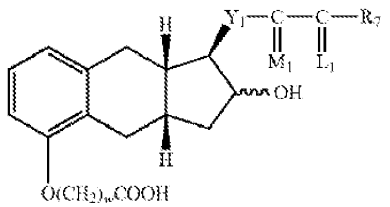
EXHIBIT C

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

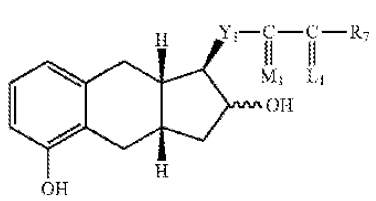
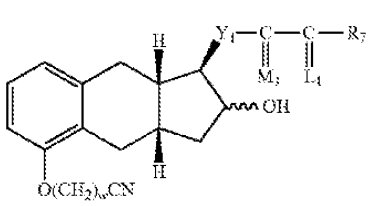
Claim	Deficiencies in Prior Art
	already-formed free acid disclosed in the Moriarty references, and Watson has failed to establish that a skilled artisan would have carried out steps necessary to inherently obtain the claimed products. Thus, Watson fails to establish prima facie case that claims 6, 10, 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.

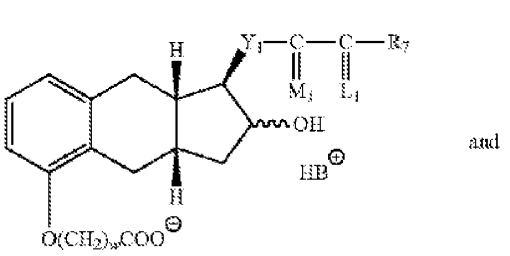
Claim	Deficiencies in Prior Art
	See, e.g., United Therapeutics Corp. v. Sandoz, Inc., Civil Action No. 3:14-cv-05499-PGS-LHG (D.N.J. 2014); *United Therapeutics Corp. v. Teva Pharma*, Civil Action No. 3:14-cv-05498-PGS-LHG (D.N.J. 2014). As stated, above, the '393 patent product and process is currently 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

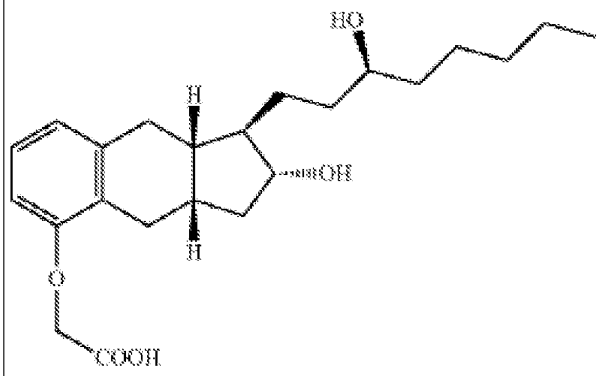
Claim	Deficiencies in Prior Art
I_s  (I$_s$) and	limitation separately.
(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.	*See*, claim 1. Watson provides no additional citations or information regarding this claim limitation as the claim chart provided 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

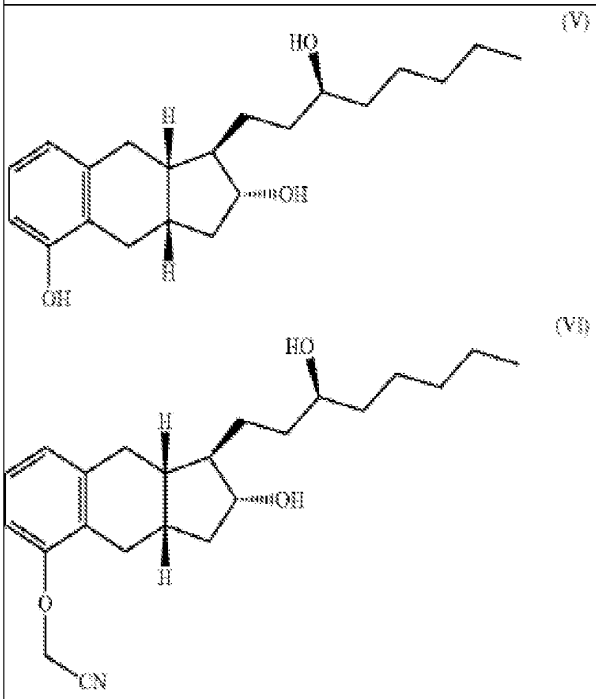
Claim	Deficiencies in Prior Art
	Office explicitly considered that claim in relation to the Moriarty 2004 reference and allowed the '393 patent. '393 Patent File History, Office Action dated May 15, 2013 (UTC_WAT_00001465-1470); Office Action Response dated June 5, 2013 (UTC_WAT_00001477-1485); Notice 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

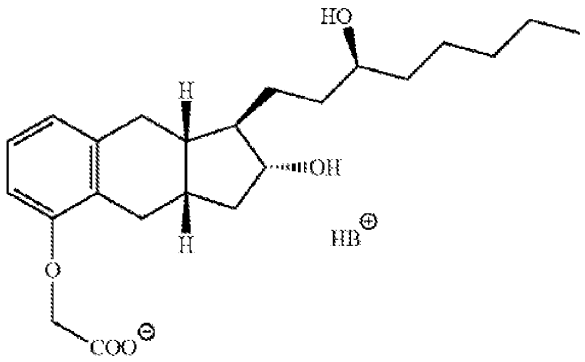
Claim	Deficiencies in Prior Art
	description.
Claim 3	
The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.	*See*, claim 1. UTC incorporates by reference all arguments regarding Claim 1 above. Watson provides no additional citations or information 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:	28022586
Application Number:	14754932
International Application Number:	
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Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Strawderman
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	NtfRltProc.pdf	52080 8967160f1c896991b0ae092c15223462fc766e15	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):	1532504		

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**	14/754932
Date Submitted: JAN 10 2017				**Filing Date**	6/30/2015
				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	080618-1550

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]
	F1	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	

4821-9333-3824.1

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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.

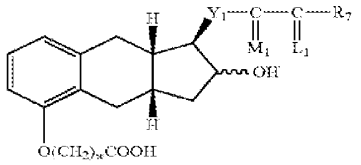
[redacted]

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.

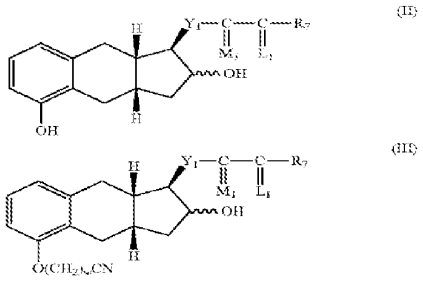
The '393 patent has twenty-two claims, including independent claims 1 and 9, all of which are asserted against Watson. Claims 1-22 are product-by-process claims directed to treprostinil or its pharmaceutically acceptable salt. The claimed process involves the alkylation of a triol compound to a benzindene 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

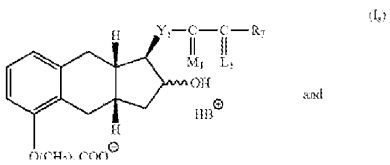
(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive,

(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.

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.

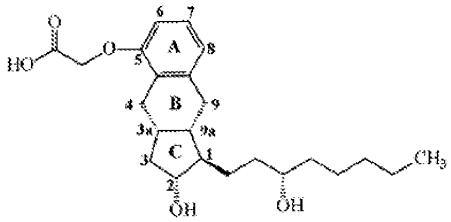
a. The '117 Patent

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.

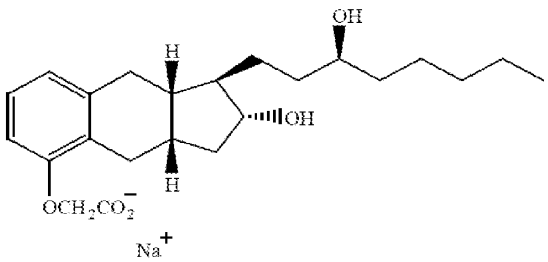


7

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.

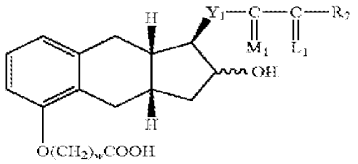
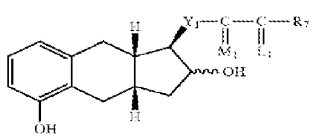
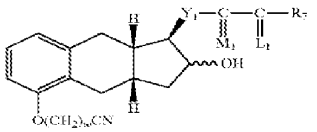
Here, the '117 and '393 patents share at least one common inventor (Raju Penmasta) and the same owner (United Therapeutics Corporation). The claims of the '117 patent are directed to the same subject matter, treprostinil and its pharmacologically acceptable salt form. *See* '117 patent, claims 1–4. There 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

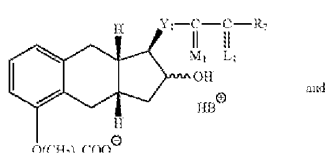
POSA and the prior art. Therefore, for the reasons explained in more detail above in the anticipation and obviousness analyses, the '393 patent is invalid for obviousness type double patenting over the '117 patent.

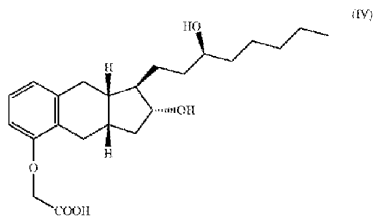
4. Claims 1-22 Of The '393 Patent Are Not Enabled Or Fail To Meet The Written Description Requirement.

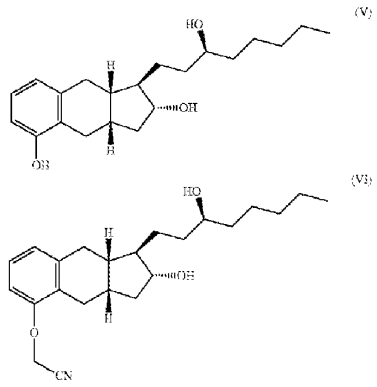
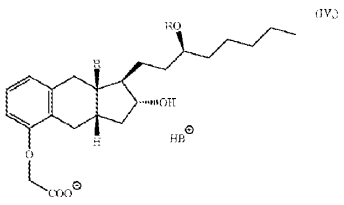
As discussed in the previous sections, it would have been obvious for a POSA to practice the claimed invention by applying known procedures described in the prior art. But if plaintiff contends that it would have required undue experimentation for a POSA to apply these prior art procedures to obtain 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

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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:

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Attorneys for Plaintiff United Therapeutics Corporation

/s/ Liza M. Walsh
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Dated: December 11, 2015

Electronic Acknowledgement Receipt	
EFS ID:	28022644
Application Number:	14754932
International Application Number:	
Confirmation Number:	1865
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2
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:	080618-1550
Receipt Date:	10-JAN-2017
Filing Date:	30-JUN-2015
Time Stamp:	14:38:45
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	155124 c03b92fbdb035c949ebac5eeee5a6bb288768624	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):	507592		

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.:	14/754932
Filing Date:	6/30/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation No.:	1865

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. Information not related to the '393 patent has been 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.:	14/754932
Appl. Filing Date:	6/30/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	1865

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:

[ ] Amendment/Reply.

[ ] Affidavit(s)/Declaration(s).

[**X**] Information Disclosure Statement.

[**X**] Form PTO/SB/08 with copies of listed references.

[ ] PTO/SB/424 - Request for Prioritized Examination.

[ ] Other Documents

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):							$1,700.00	=	$1,700.00
Total Claims:	9	-	20	=	0	x	$80.00	=	$0.00
Independents	1	-	3	=	0	x	$420.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$780.00	=	$0.00
CLAIMS FEE TOTAL:								=	$1,700.00

[ ] 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:		$1,700.00
	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:		$1,700.00

The above-identified fees of $1,700.00 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. 21, 2016

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
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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®
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Filing Date:	6/30/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation No.:	1865

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

Invalidity contentions filed against parent U.S. Patent 8,497,393 ("the '393 parent patent") and prior art mentioned therein are being filed in this submission. With respect to certain invalidity contentions that contain "confidential" designations, those documents were previously designated confidential at one time in the litigation, but they are no longer subject to confidentiality, except where certain information has been redacted.

Recent Patent Owner documents are also being cited herein from the related proceeding IPR2016-00006, *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, which involves the same '393 parent patent of the above-captioned patent application. Although these documents were previously submitted, the versions filed with this Statement are new versions of certain documents filed recently in the IPR that have some information unredacted that was previously redacted in prior versions.

TIMING OF THE DISCLOSURE

The listed documents are 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 Dec. 21, 2016

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

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/754932
Date Submitted: December 21, 2016				**Filing Date**	6/30/2015
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1672
				Examiner Name	Yevgeny Valenrod
Sheet	1	of	3	Attorney Docket Number	080618-1550

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

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document / Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document 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	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.	
	E2	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.	

Examiner Signature		Date Considered	

4848-0394-1950.1

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/754932
Date Submitted: December 21, 2016				**Filing Date**	6/30/2015
				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	080618-1550

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]
	E3	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.	
	E4	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.	
	E5	Service copy of Third Party Submission dated October 16, 2016, filed but not entered in US 14/754,932 on October 16, 2016, with 6 indicated attachments, 822 pages.	
	E6	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.	
	E7	Defendant Sandoz Inc.'s Invalidity Contention Charts 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.	
	E8	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).	
	E9	Exhibit G, Invalidity Claim Chart for the '393 patent, January 12, 2015, 66 pages.	
	E10	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).	
	E11	Arumugan et al., "A New Purification Process for Pharmaceutical and Chemical Industries," Organic Process Research & Development, 2005, 9:319-320.	
	E12	Burk et al., "An Enantioselective Synthesis of (S)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation," J. Org. Chem., 2003, 68:5731-5734.	
	E13	Eliel et al., Stereochemistry of Organic Compounds, 1994, 322-325.	
	E14	Harwood et al., Experimental organic chemistry: Principles and Practice, 1989, 127-134.	
	E15	Jones, Maitland Jr., Organic Chemistry, 2nd Ed., 2000, 153-155.	
	E16	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.	
	E17	McManus et al., "Tetrazole Analogs of Plant Auxins," J. Org. Chem., 1959, 24:1464-1467.	
	E18	Monson, Richard S., Advanced Organic Synthesis, Methods and Techniques, 1971, 178-188.	

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Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/754932
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				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1672
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Sheet	3	of	3	Attorney Docket Number	080618-1550

NON PATENT LITERATURE DOCUMENTS			
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	E19	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.	
	E20	Olmsted III et al., Chemistry, The Molecular Science, Mosby-Year Book, Inc., Chapter 10 "Effects of Intermolecular Forces," 1994, 428-486.	
	E21	Pavia et al., Introduction to Organic Laboratory Techniques, First Edition, 1998, 648.	
	E22	Physicians' Desk Reference, 59 Edition, 2005, for Bicillin® L-A (penicillin G benzathine suspension), 5 pages.	
	E23	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.	
	E24	REMODULIN® label, 2014, 17 pages.	
	E25	Schoffstall, et al., Microscale and Miniscale Organic Chemistry Laboratory Experiments, 2004, 2nd Ed., 200-202.	
	E26	Sorrell, Thomas N., Organic Chemistry, 1999, 755-758.	
	E27	Wiberg, Laboratory Technique in Organic Chemistry, 1960, 112.	
	E28	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		Date Considered	

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

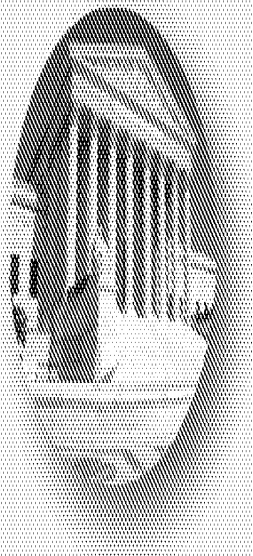
5 Obviousness

- Phares and Moriarty
- Kawakami and Moriarty
- Dependent Claims 6, 10, 21 & 22

6 Claim Construction

1 Legal Concepts

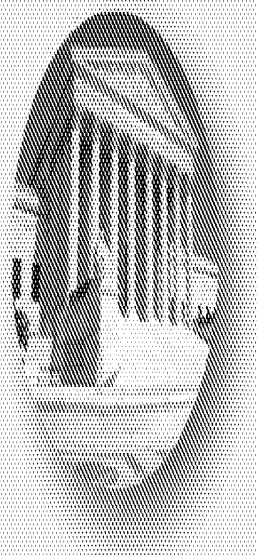
Legal Concepts



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)

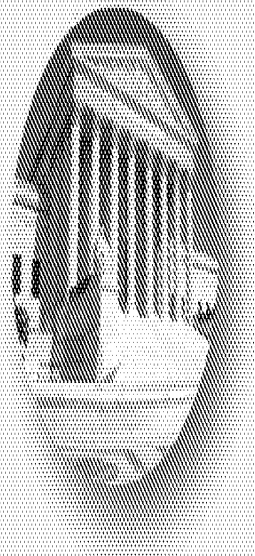
Legal Concepts



"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)

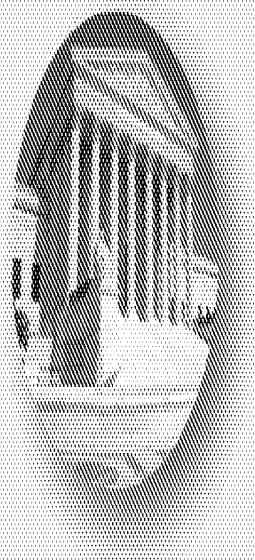
Legal Concepts



"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)

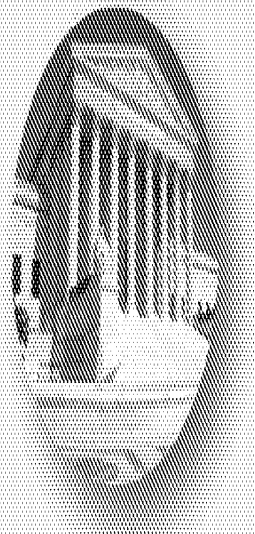
Legal Concepts



"[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)

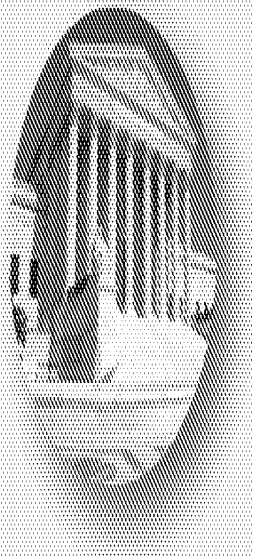
Legal Concepts



"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

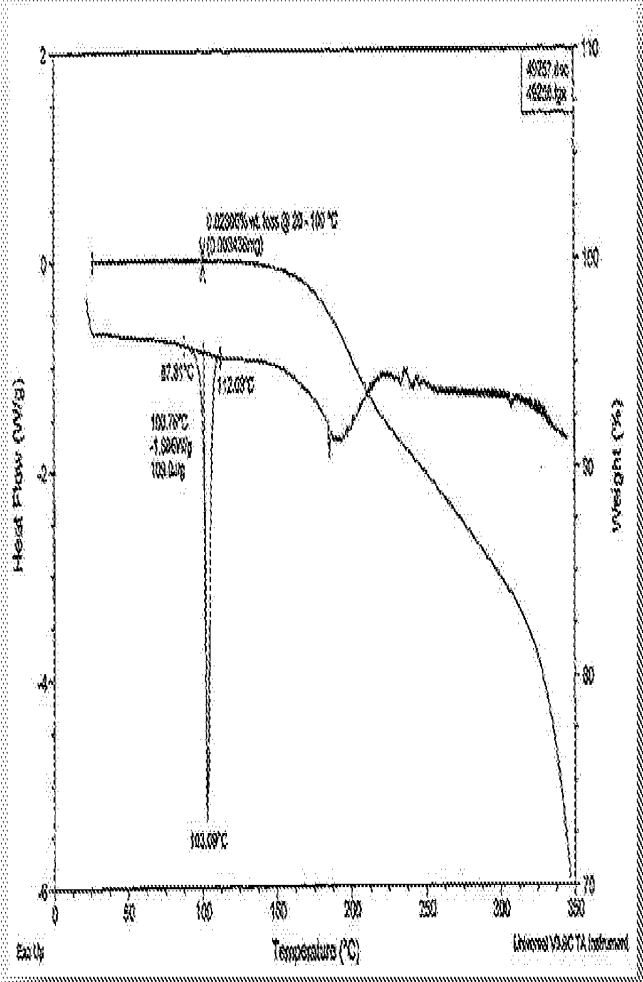
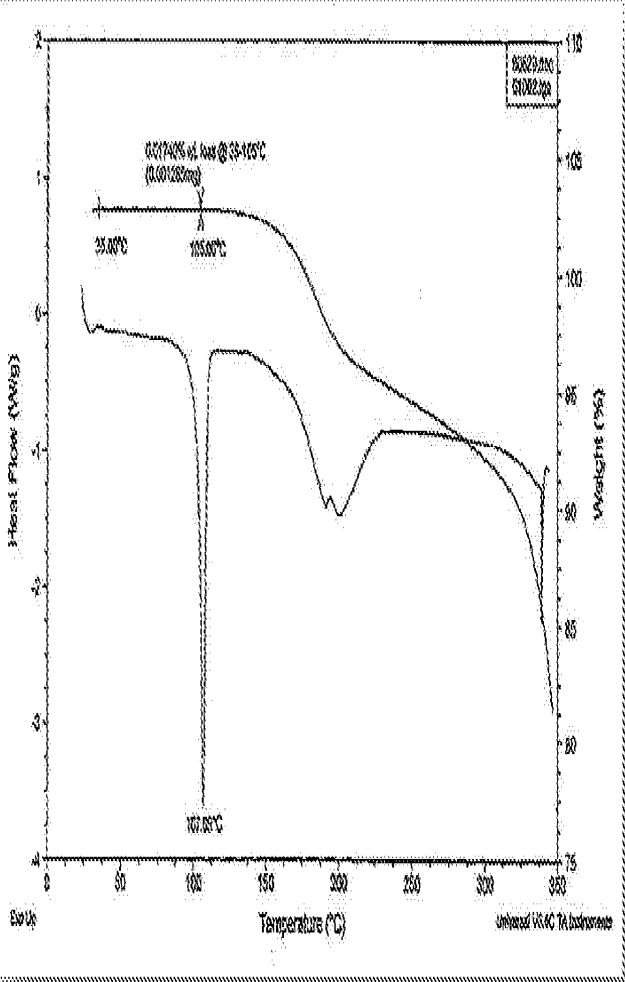


Figure 21



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

3

Ex. 2006 at 3

3 Overview

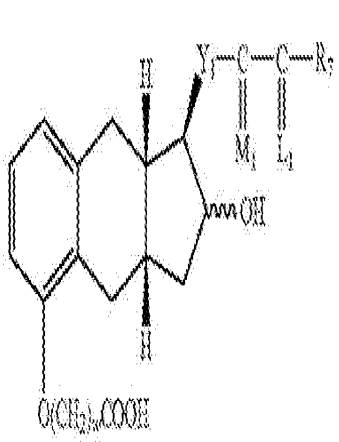
Overview

Independent Claims

Claim 1

What is claimed is:

1. A product comprising a compound of formula I

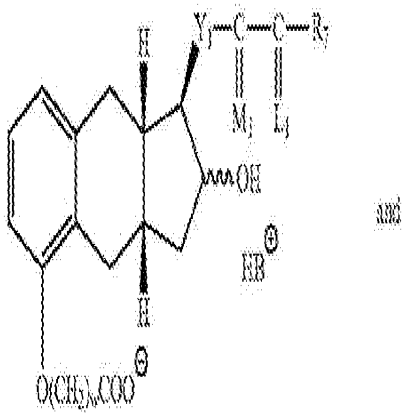


or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

(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_a,



and

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

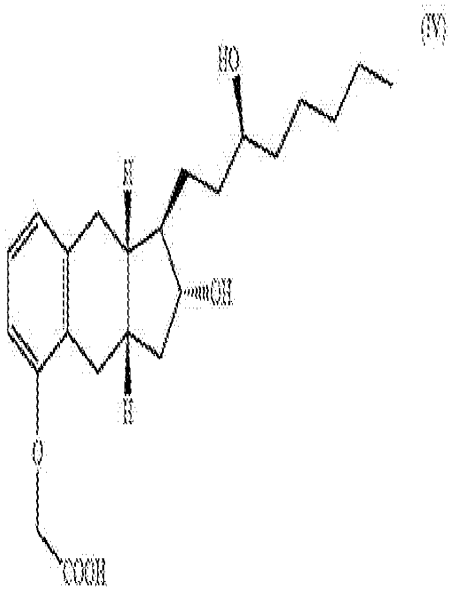
Ex. 1001 ("'393 Patent") at 11-12

Overview

Independent Claims

Claim 9

9. A product comprising a compound having formula IV

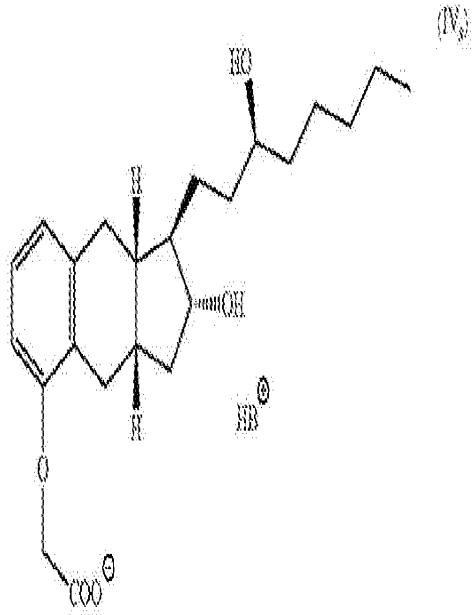


or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

(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

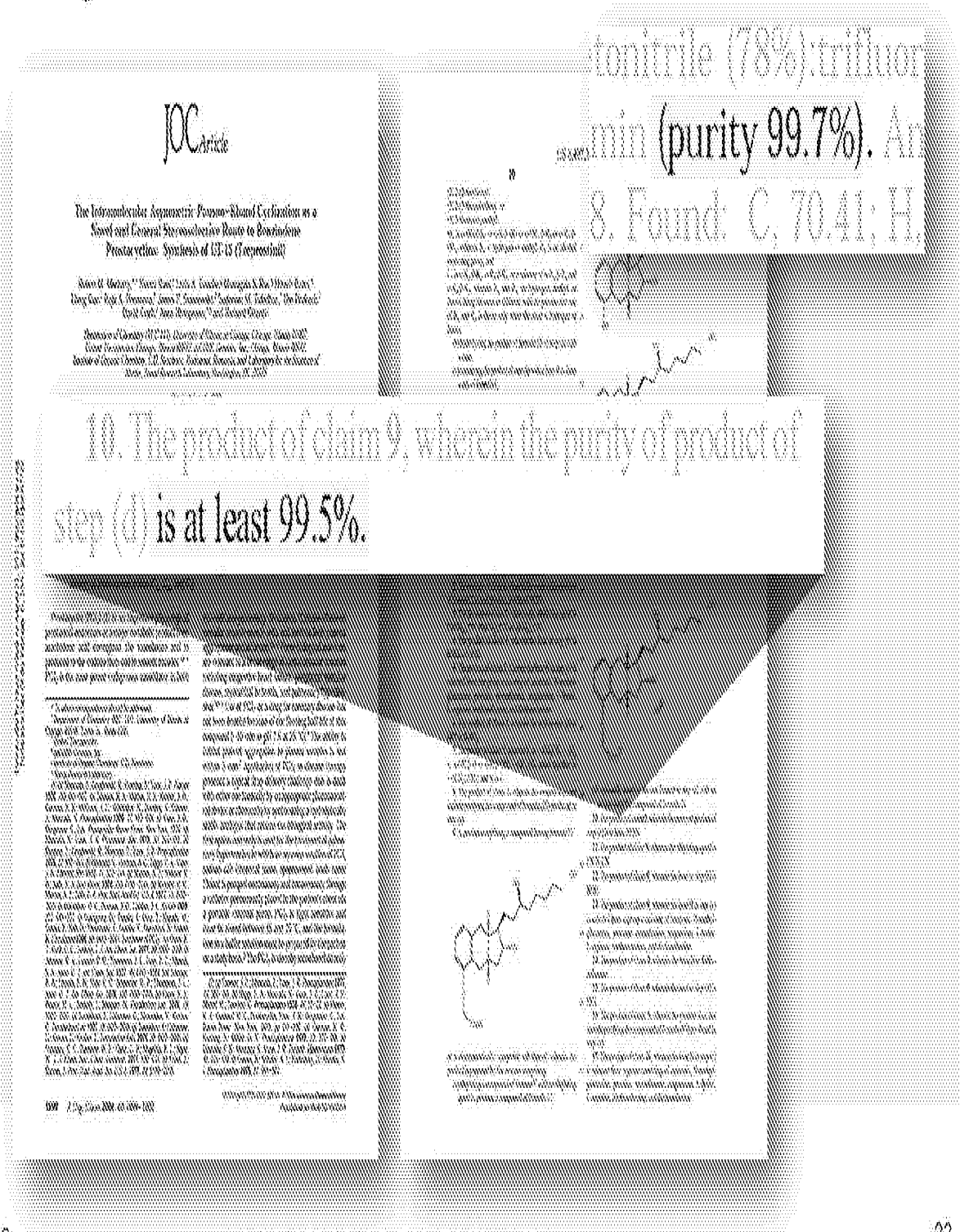
The Intramolecular Asymmetric Passerini–Ugi Combination as a Novel and General Stereoselective Route to Bendazolone Peptidomimetics: Synthesis of GT-15 (Tryptostatin B)

JOC Article

tonitrile (78%):trifluor
min (purity 99.7%). An
8. Found: C, 70.41; H,

Overview

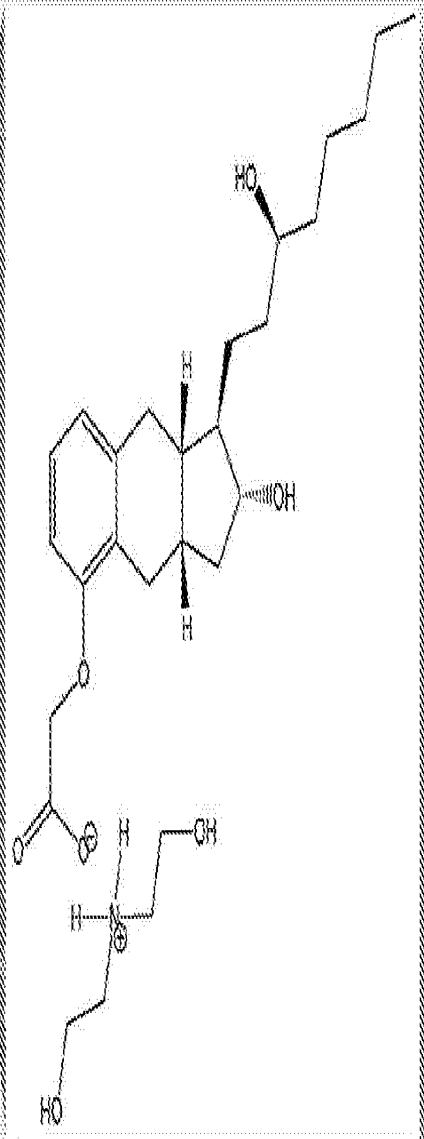
Prior Art: Moriarty



Overview

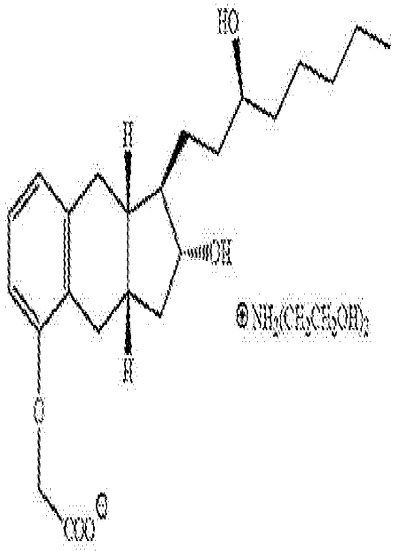
Prior Art: Phares

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.

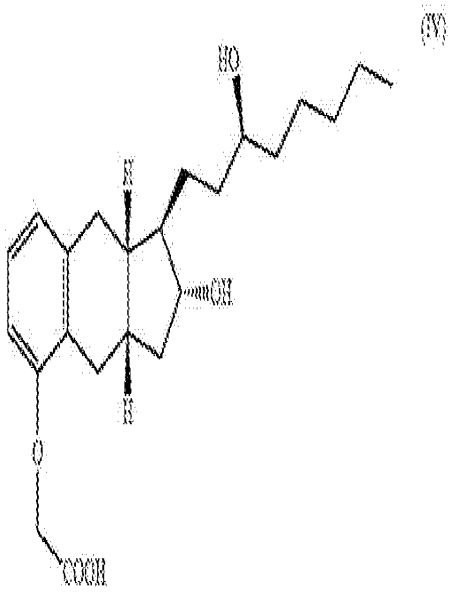
4 Anticipation

Anticipation

Independent Claims

Claim 9

9. A product comprising a compound having formula IV

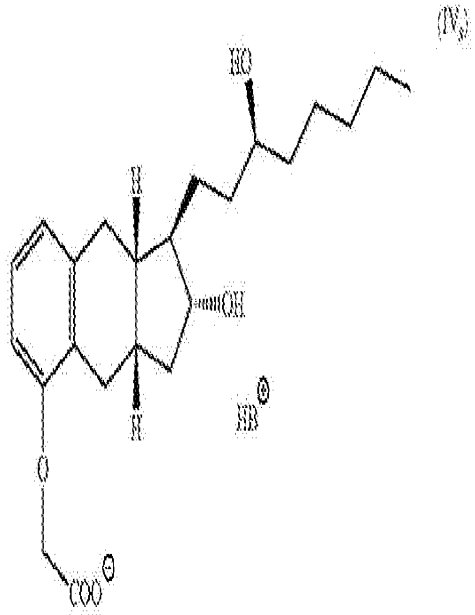


or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

(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

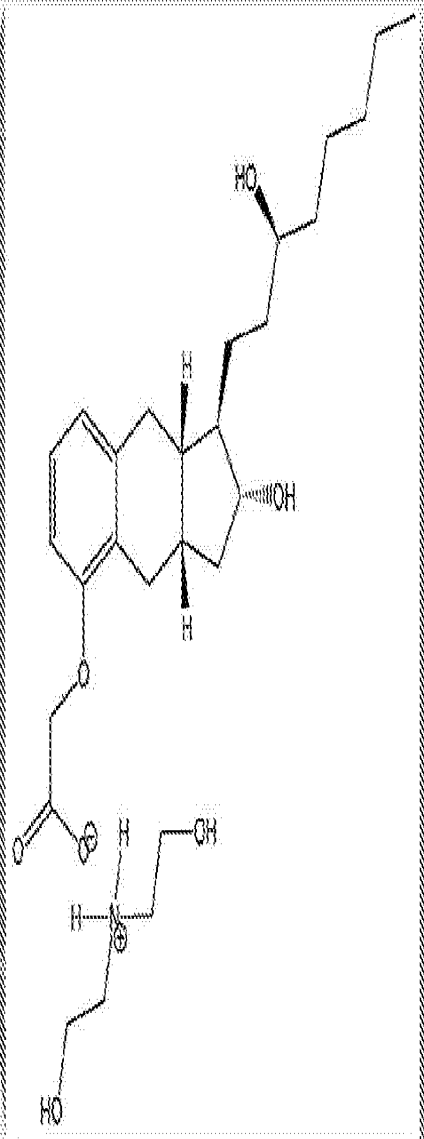


(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

Anticipation

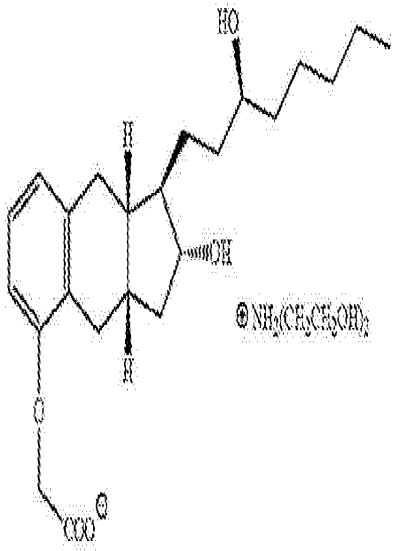
Prior Art: Phares

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.

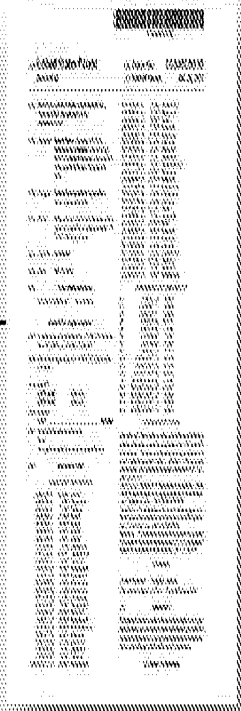
In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

Ex. 1005 ("Phares") at 99 (Claim 49); Ex. 1001 at 6 ('393 Patent) col.8 ll. 47-63.

Anticipation

'393 Patent/Phares Melting Points

Ex. 1001: '393 Patent



Example 3

Batch 1: 104.3-106.3 °C

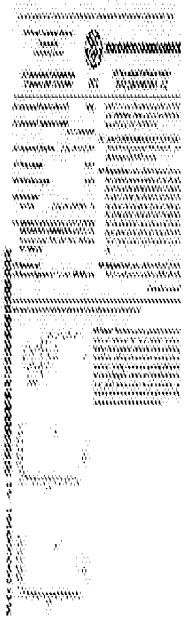
Batch 3: 104.7-106.6 °C

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

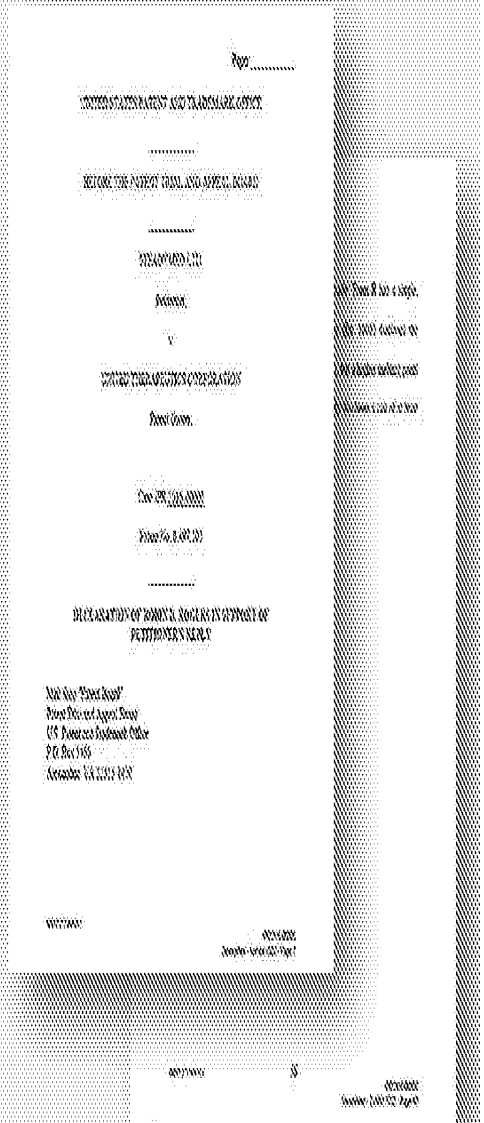
Ex. 1001 at 8-9 ('393 Patent) col 12-13; Ex. 1005 ("Phares") at 91, 121

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.) 158:25-157:2

Anticipation

Prior Art: Phares

Dr. Williams relied on "Adhiyaman reference" (Ex. 2030), which he initially believed showed different melting points for same crystal form.

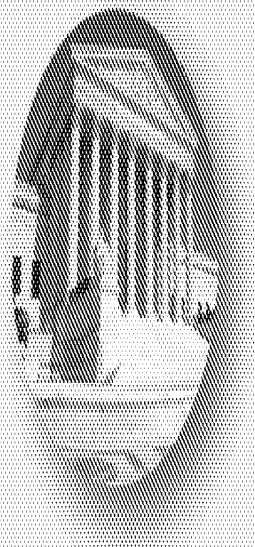
Q. Okay. So each of these is really a different crystal form of the same drug; is that fair?

A. I think that's fair."

Ex. 2059 (Williams Dep.) 180:17-20

Anticipation

Process can be Different

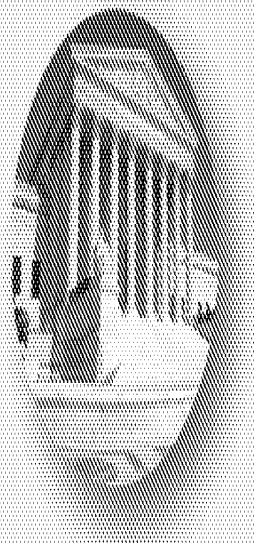


"If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985)

Anticipation

Starting Material Irrelevant

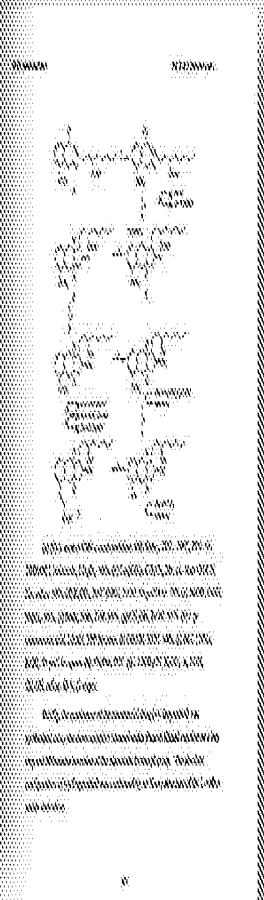


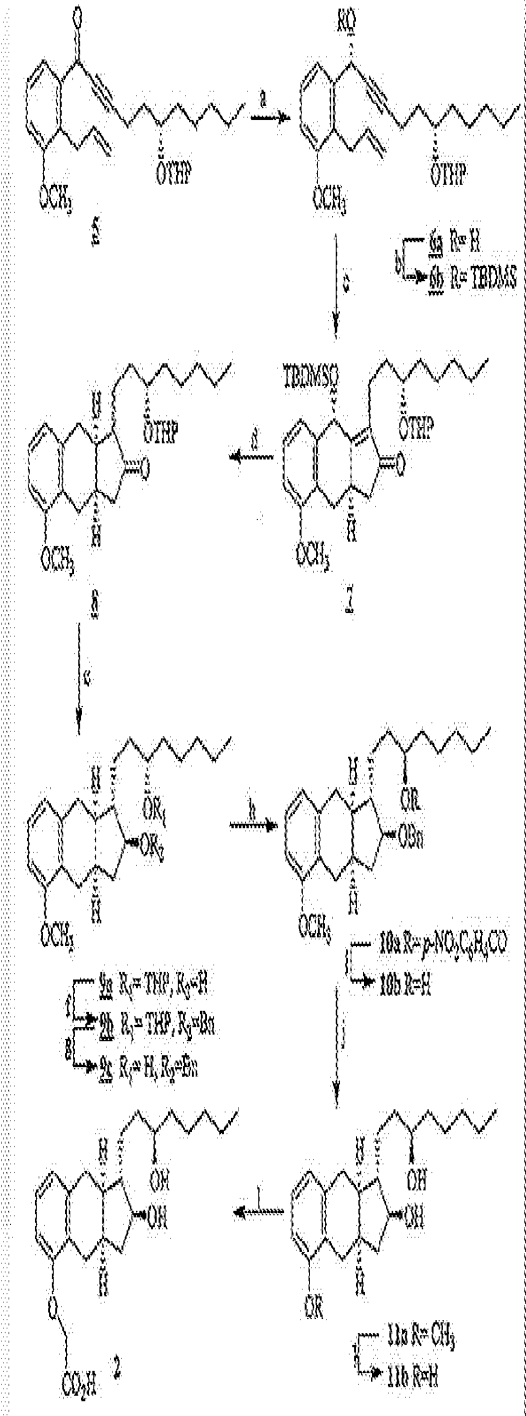
"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step.... One need not know that the 14-hydroxy was derived from 8α as opposed to 8β to answer that question."

Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1353 (Fed. Cir. 2016)

Anticipation

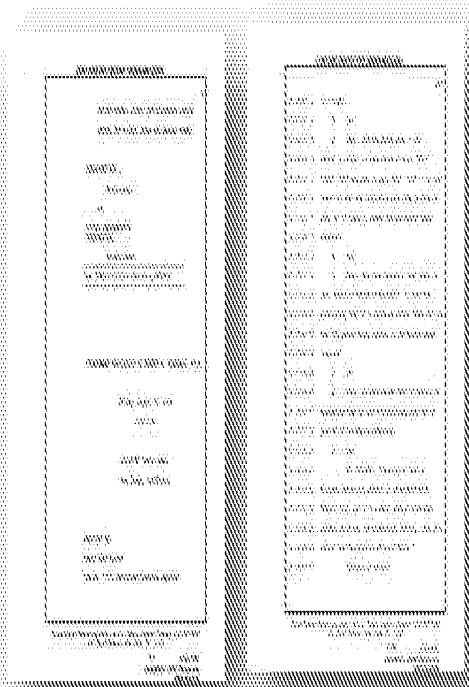
Prior Art: Phares





Anticipation

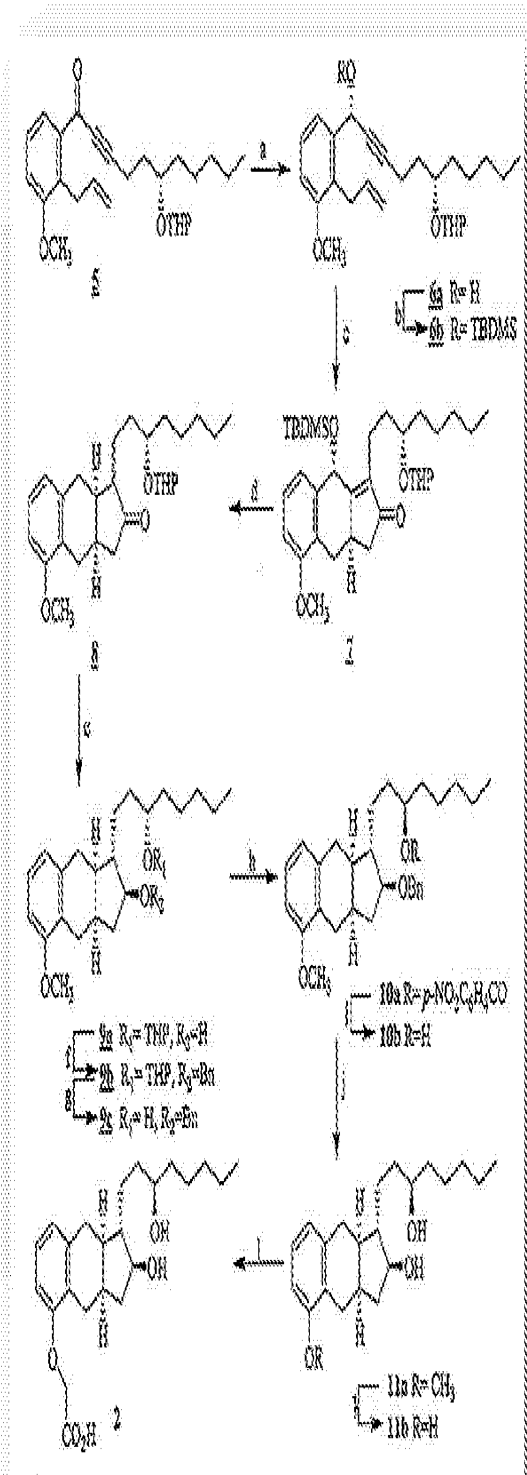
Prior Art: Phares



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.

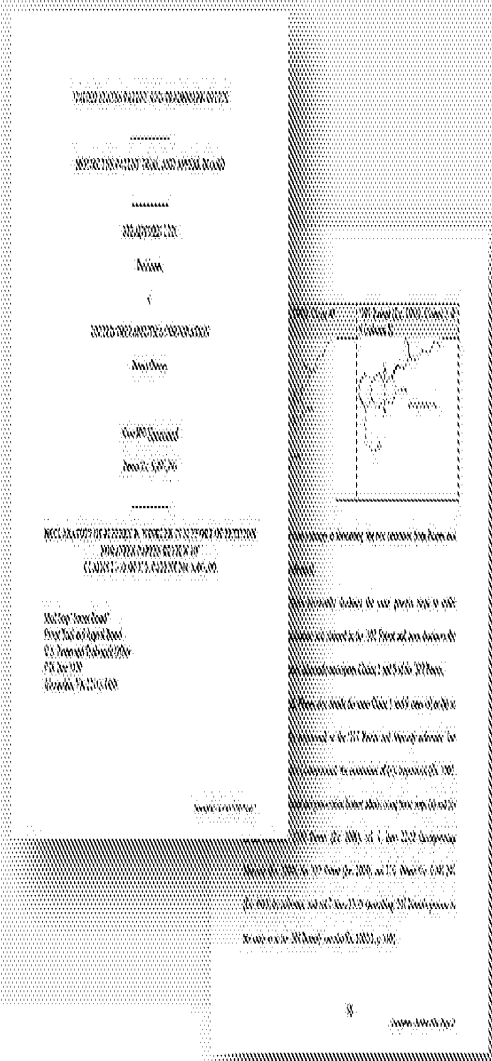
Ex. 2059 (Williams Dep.) 190: 16-19



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 %

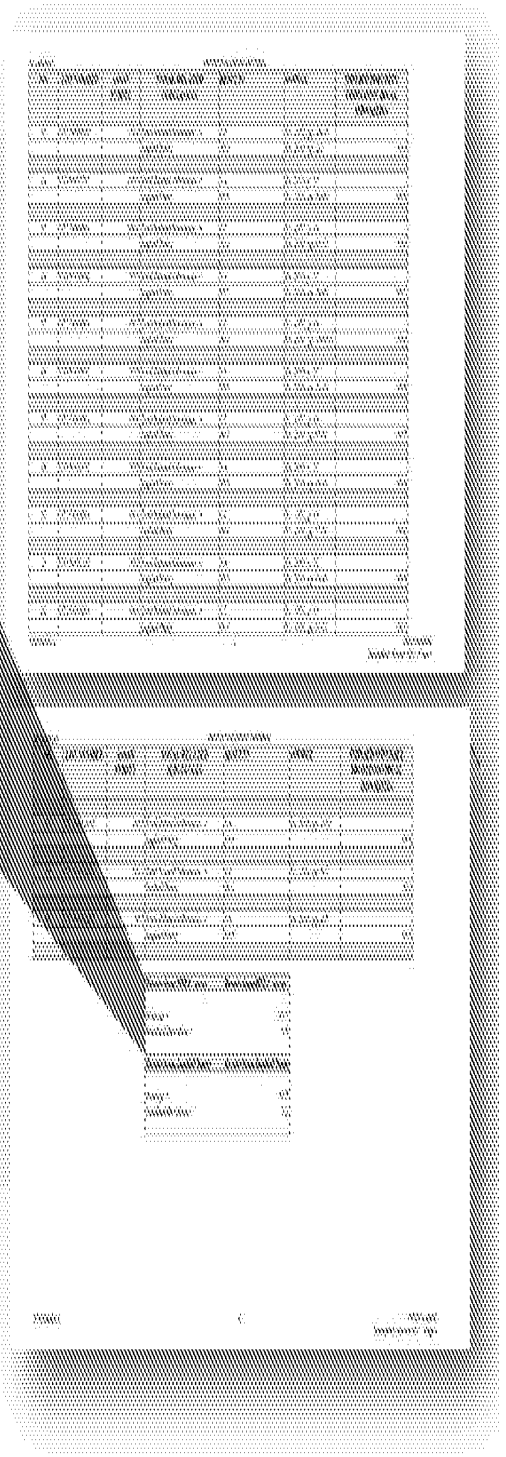
Ex. 1002 at 249 (Walsh Declaration)

Ex. 2036 ("Phares") at 5; Ex. 1002 at 249 ("393 Patent Prosecution")

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 45 samples)

Anticipation

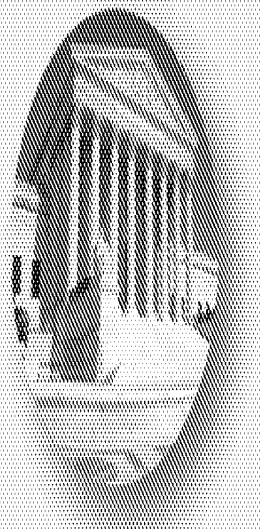
Key Scientific Concepts: HPLC and Purity

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



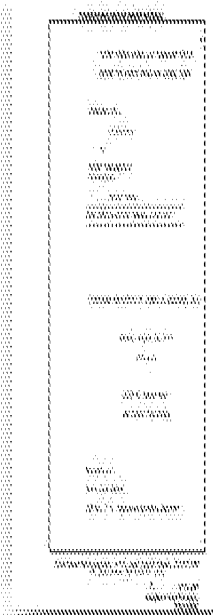
"[I]f the process by which a product is made imparts '**structural** and **functional differences**' distinguishing the claimed product from the prior art, then those differences 'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'"

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.

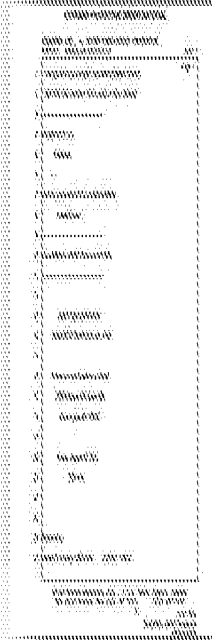
BY MR. POLLACK:

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.

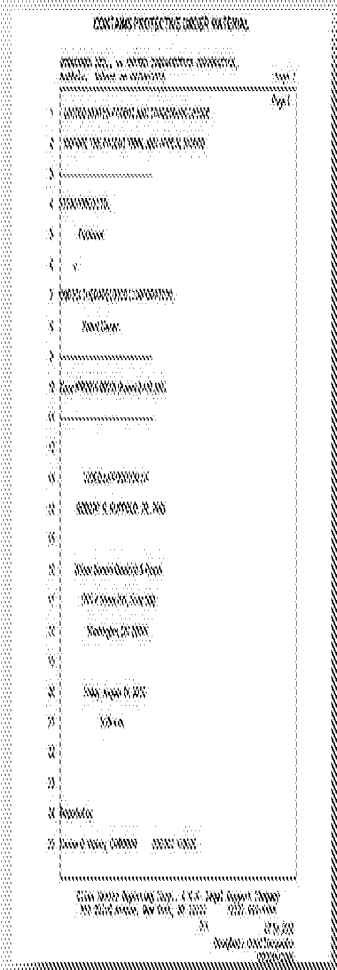
Ex. 2058 (Ruffolo Dep.) 257:22-258:3

Ex. 2059 (Williams Dep. at 47; Ex. 2058 (Ruffolo Dep.) at 66

Ex. 1035, Sandoz v. United Therapeutics, IPR2019-00896

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

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

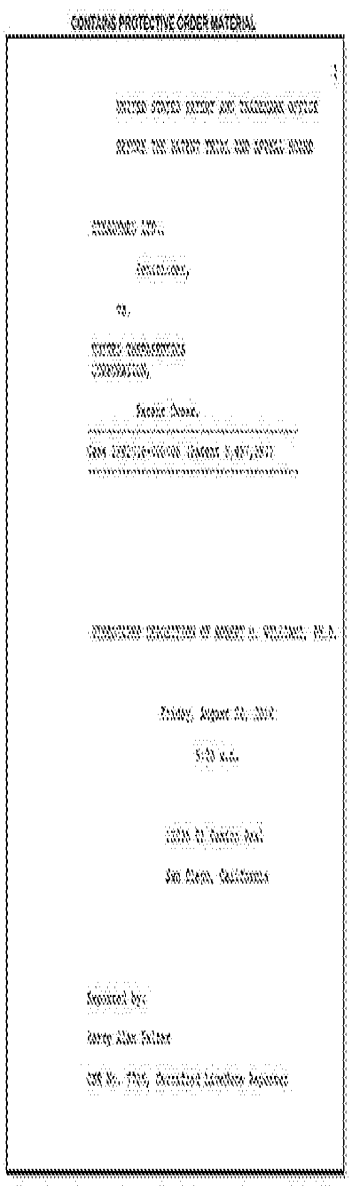
Phares and Moriarty

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 IPR2020-00770 (Patent 9,630,903 B2)

DEPOSITION OF ROBERT A. WILLIAMS, M.D.

Friday, August 21, 2020

9:03 a.m.

12230 El Camino Real

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.

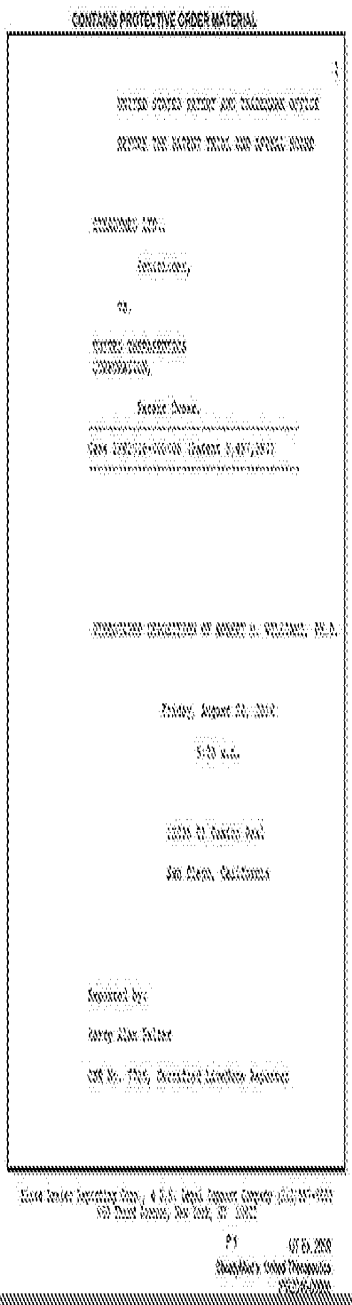
Ex. 2059 (Williams Dep.) 244:10-21

Ex. 2059 (Williams Dep.) at 240, 244

Ex. 1029 Sandoz/Mylan v. United Therapeutics, IPR2015-00933

Obviousness: Phares & Moriarty

Reasonable Expectation of Success


CONTAINS PROTECTIVE ORDER MATERIAL

Friday, August 31, 2012

Ex. 2059 (Williams Dep.) at 94:1-12.

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 --

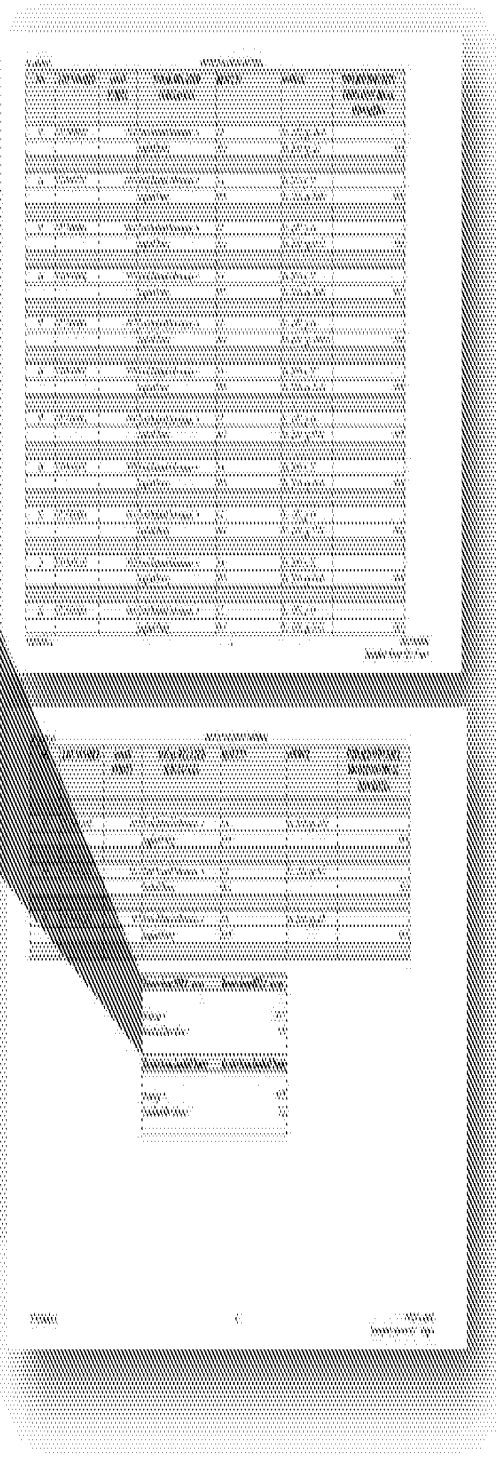
Q Of course.

A -- by chromatography to 99.99999 percent if you wanted to --

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 45 samples)

Obviousness: Phares & Moriarty

Reasonable Expectation of Success

JOC Article

The Intramolecular Asymmetric Pauson–Khand Cyclization as a Novel and General Stereoselective Route to Bicyclenone Prostacyclins: Synthesis of cTI-15 (Treprostinil)

tonitrile (78%):trifluor
min (purity 99.7%). An
8. Found: C, 70.41; H,

5 Obviousness

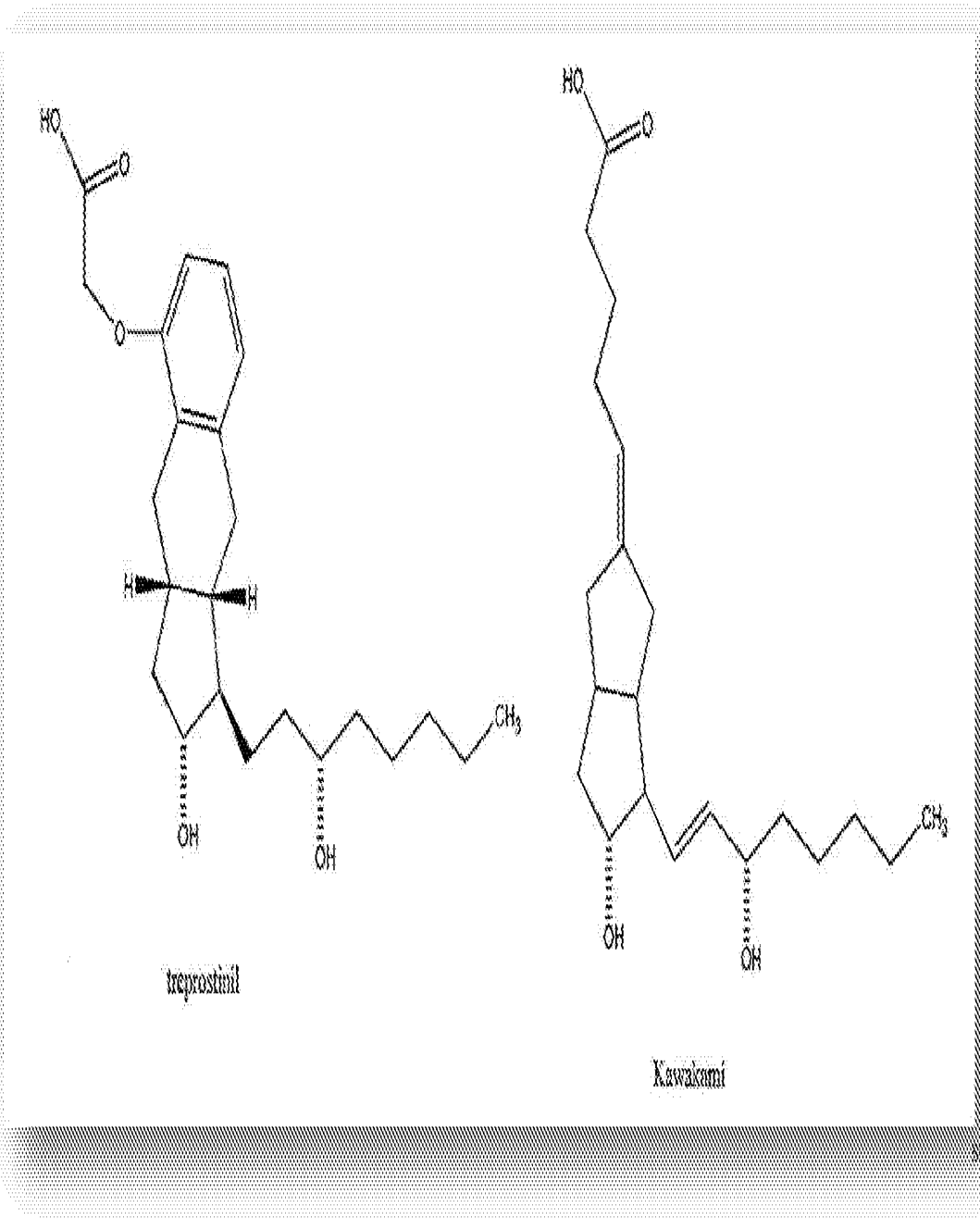
Phares and Moriarty

Kawakami and Moriarty

Dependent claims 6, 10, 15, 21, and 22

Obviousness: Kawakami & Moriarty

Motivation to Combine

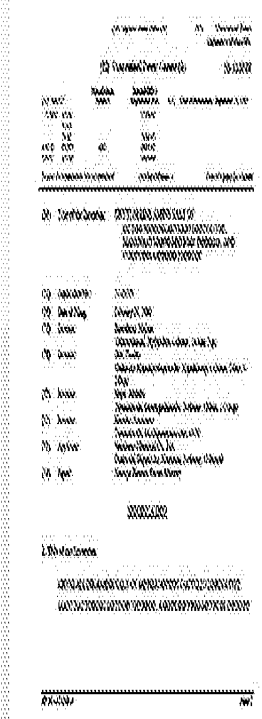


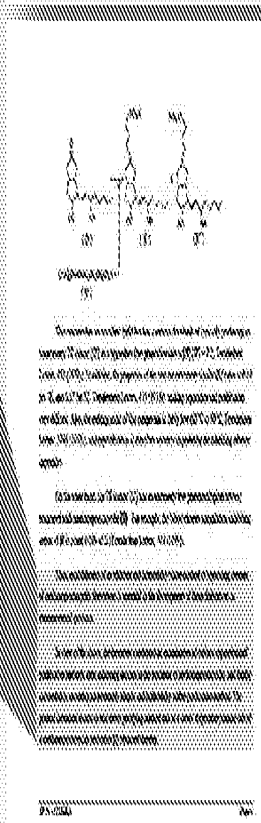
Obviousness: Kawakami & Moriarty

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.

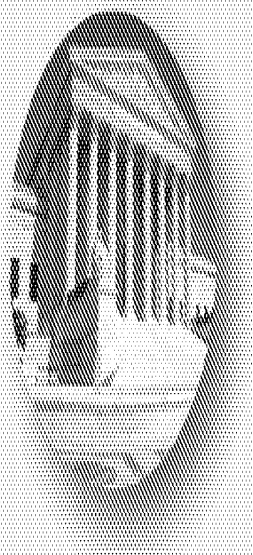
In view of the above, the inventors conducted an examination of various separation and purification methods after achieving success in the synthesis of methanoprostacyclin, and finally succeeded in inventing an extremely simple and industrially viable purification method. The present invention relates to this novel purifying method and to a novel dicyclohexylamine salt of a methanoprostacyclin derivative [I] obtained thereby.





Obviousness: Kawakami & Moriarty

Motivation to Combine

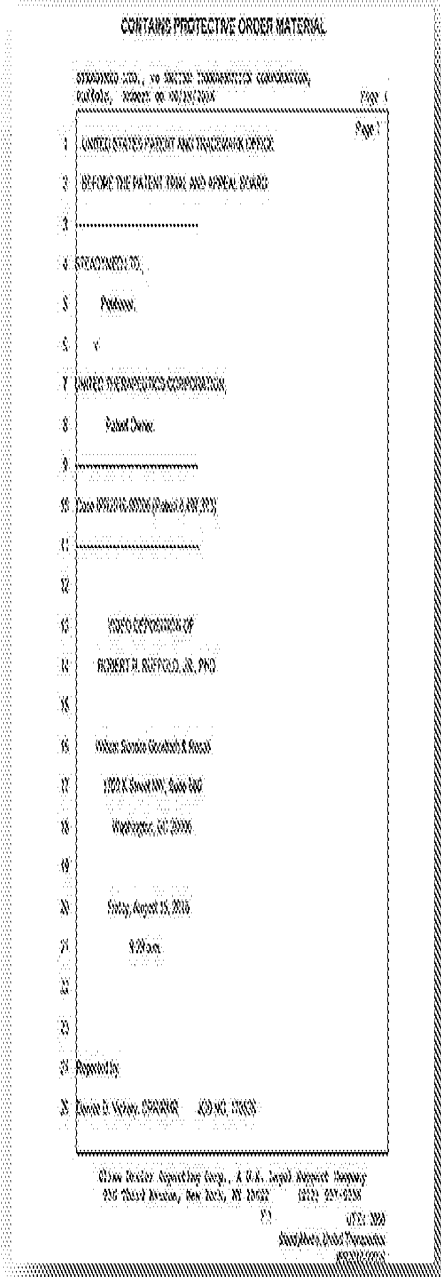


"[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."

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.

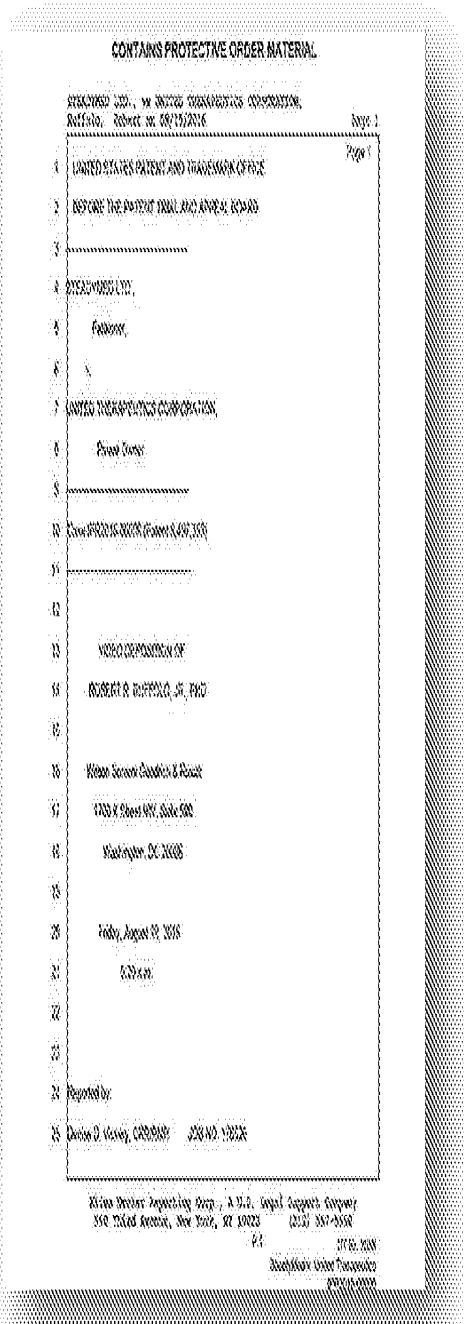
Q. And when did you go to college?

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

Page 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Petitioner,

v.

Patent Owner

VIDEO DEPOSITION OF

ROBERT B. 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. Kelly, CSR/RMR/CRR JOB NO. 119226

Veritext Deposition & Video Services (NY)

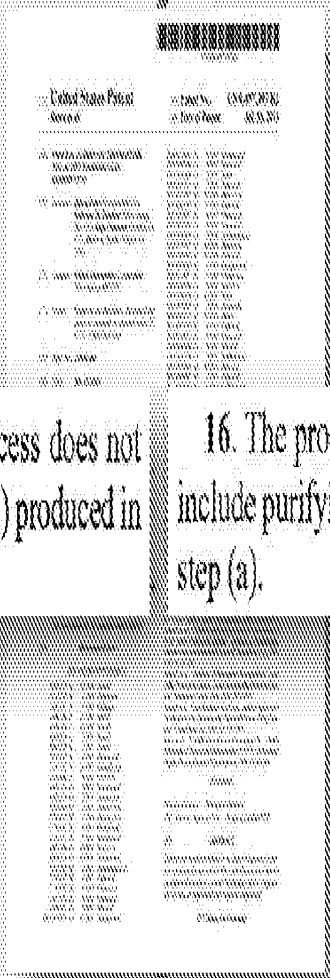
> Q. Okay. Was -- was there any kind of list of what impurities were in the treprostinil made in the '393 patent?
>
> BY MR. POLLACK:
>
> Q. In the patent itself?
>
> A. Without reading the whole thing, I see primarily purities of the parent compound, which is what I believe the invention is related 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).

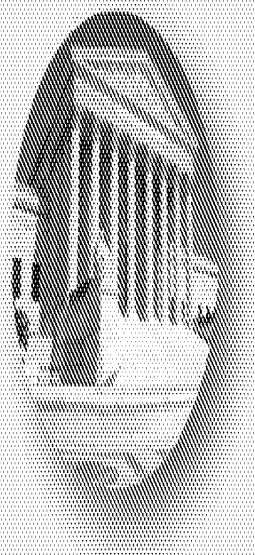


Claim 16

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

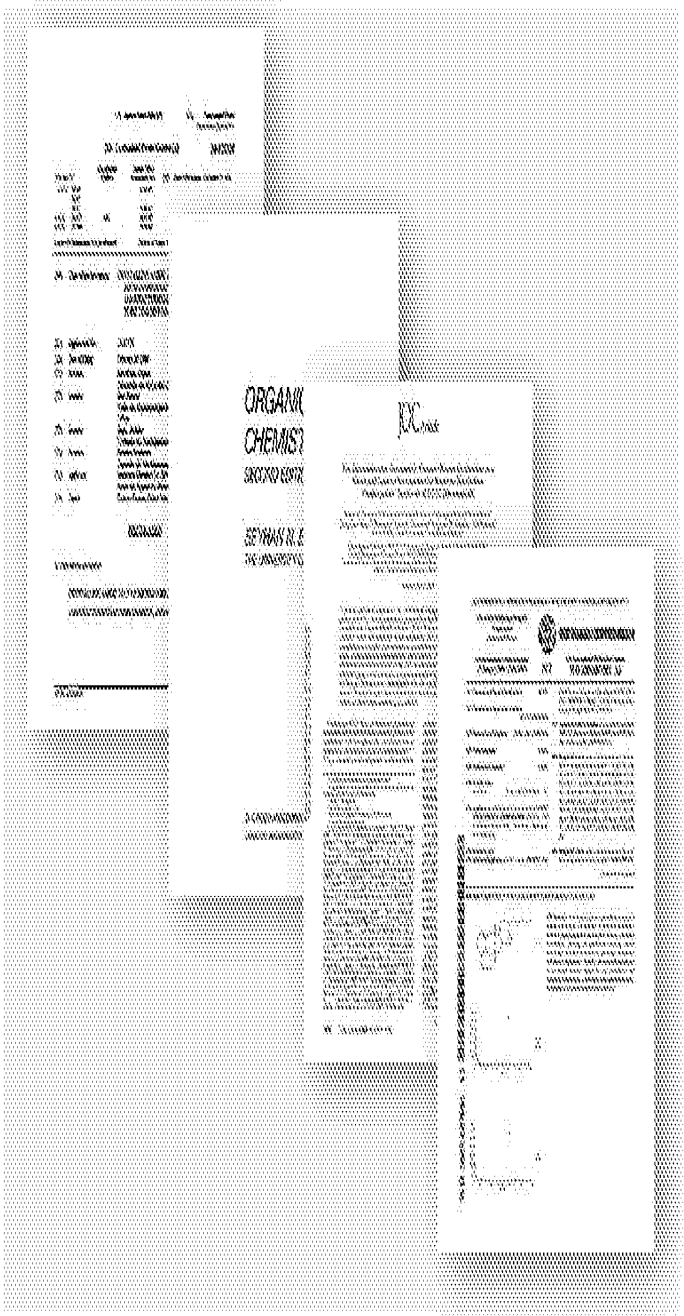
Phares and Moriarty

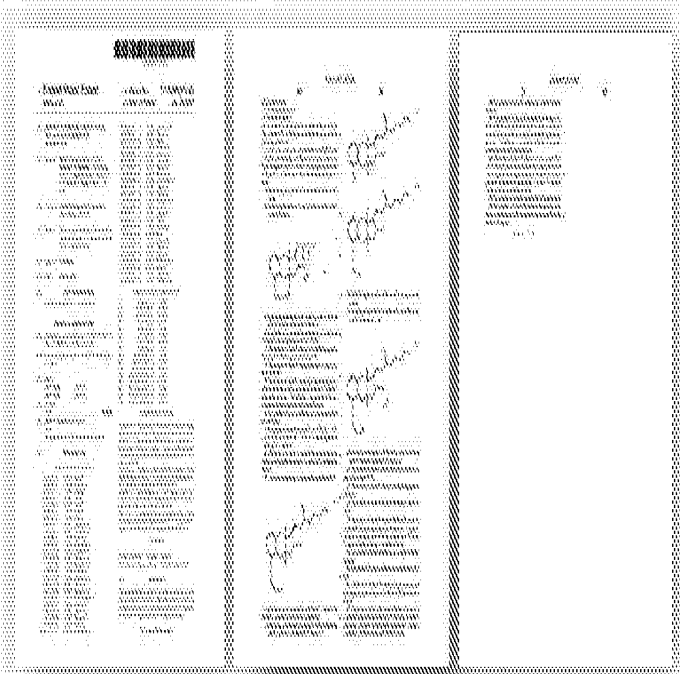
Kawakami and Moriarty

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.

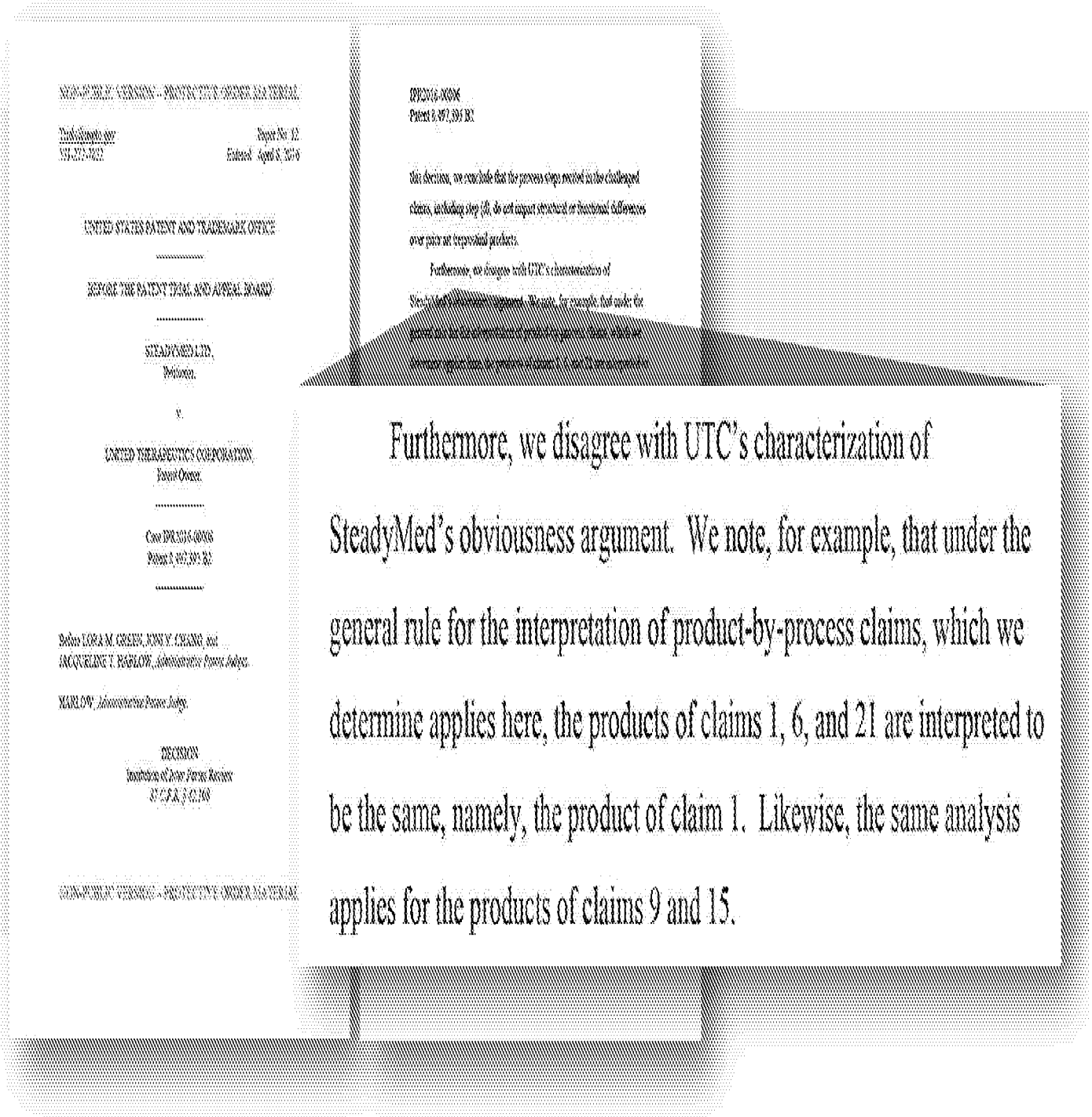
22. The product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

Ex. 1007 (Kawakami), Ex. 1004, Ex. 1006 (Ege), Ex. 1005 (Phares), Ex. 1001

Ex. 1025; Sandoz/Mylan v. United Therapeutics, IPR2019-00326

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Kawakami with Moriarty, Phares and Ege

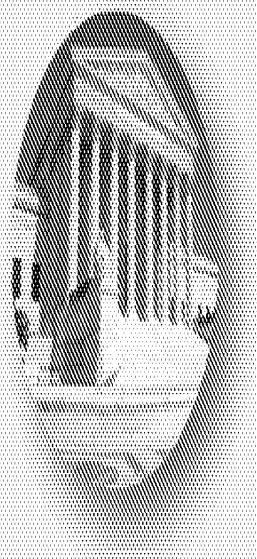


Furthermore, we disagree with UTC's characterization of SteadyMed's obviousness argument. We note, for example, that under the general rule for the interpretation of product-by-process claims, which we determine applies here, the products of claims 1, 6, and 21 are interpreted to be the same, namely, 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



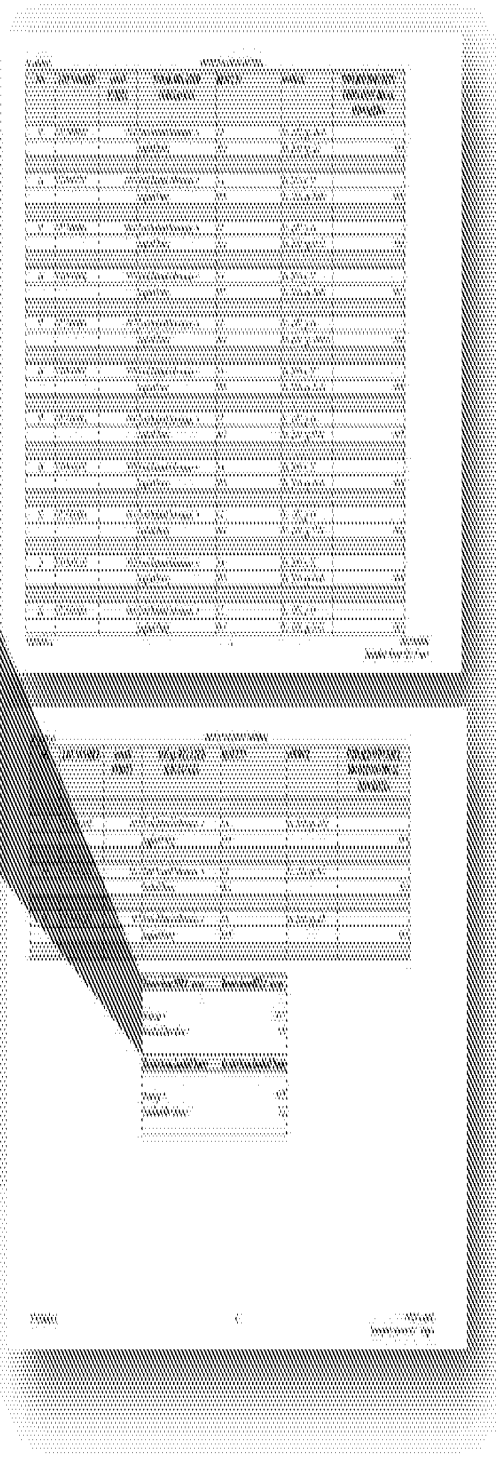
"Purdue claimed the end product; it did not claim a particular method for creating that product, such as the use of hydrogenation after the salting step...."

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



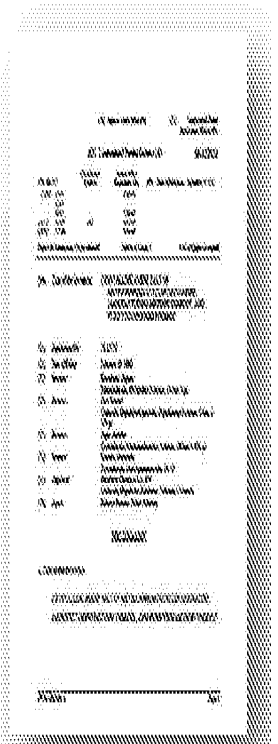
99.7 ± 0.5 %

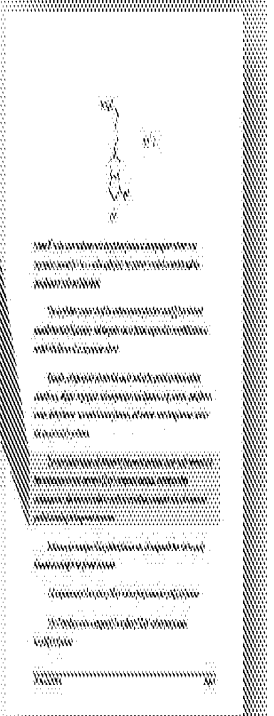
Ex. 1021 at 5 (Moriarty, average of 45 samples)

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.

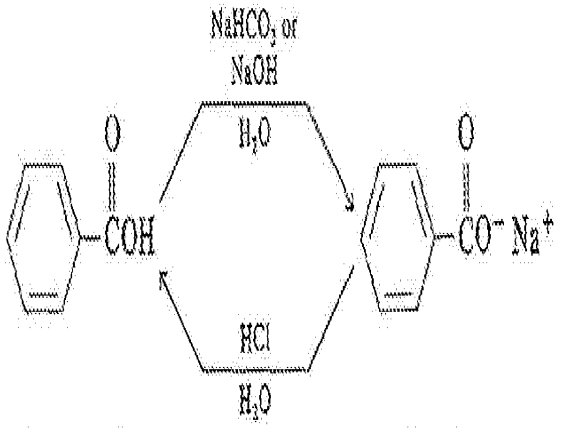




Obviousness: Dependent Claims 6, 10, 15, 21 & 22

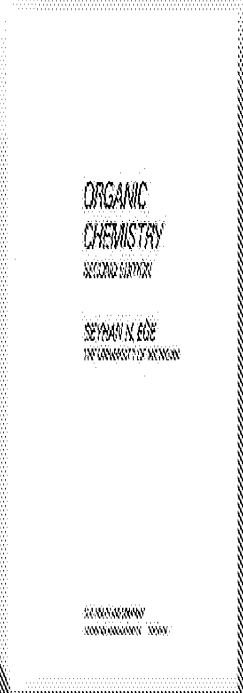
Prior Art Used Same Process

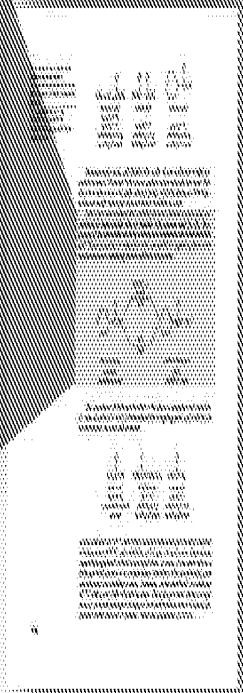
Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base (p. 95). Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.



benzoic acid
covalent,
insoluble in water

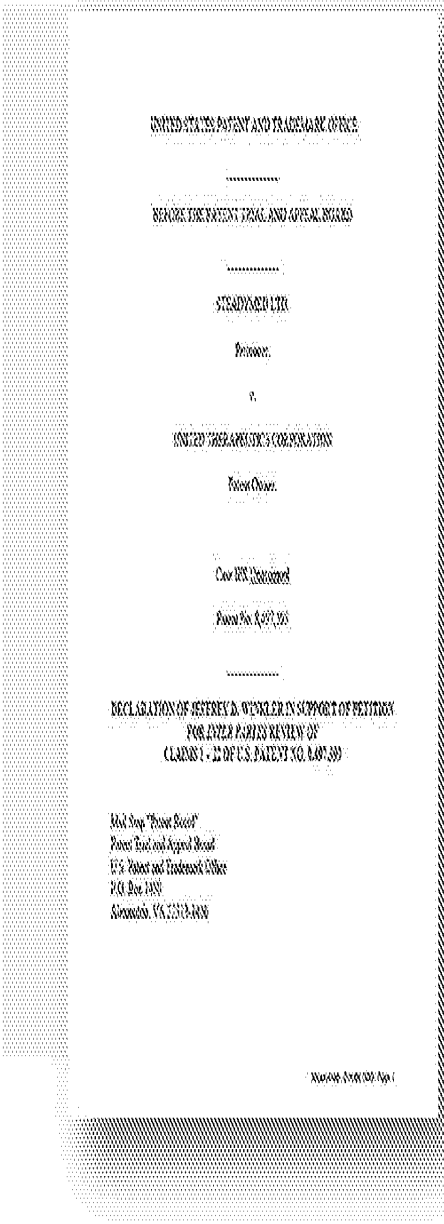
sodium benzoate
ionic,
soluble in water





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 REINHOLD 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

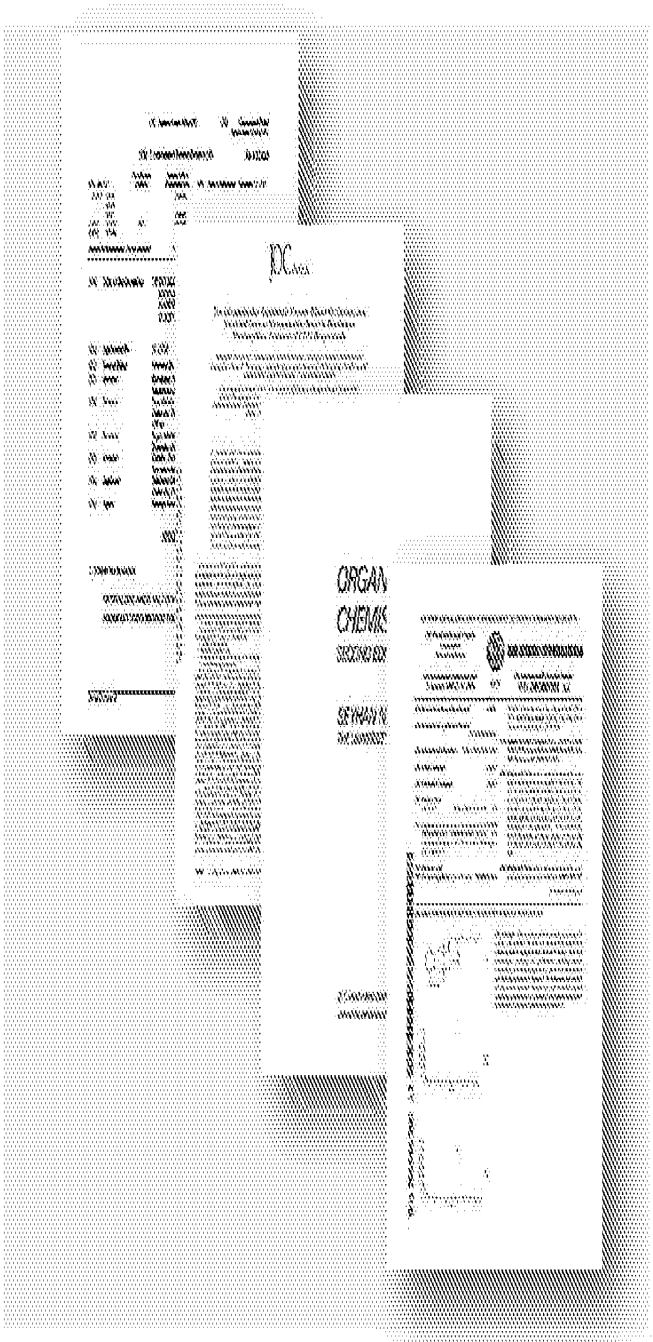
Attorney Docket No.:

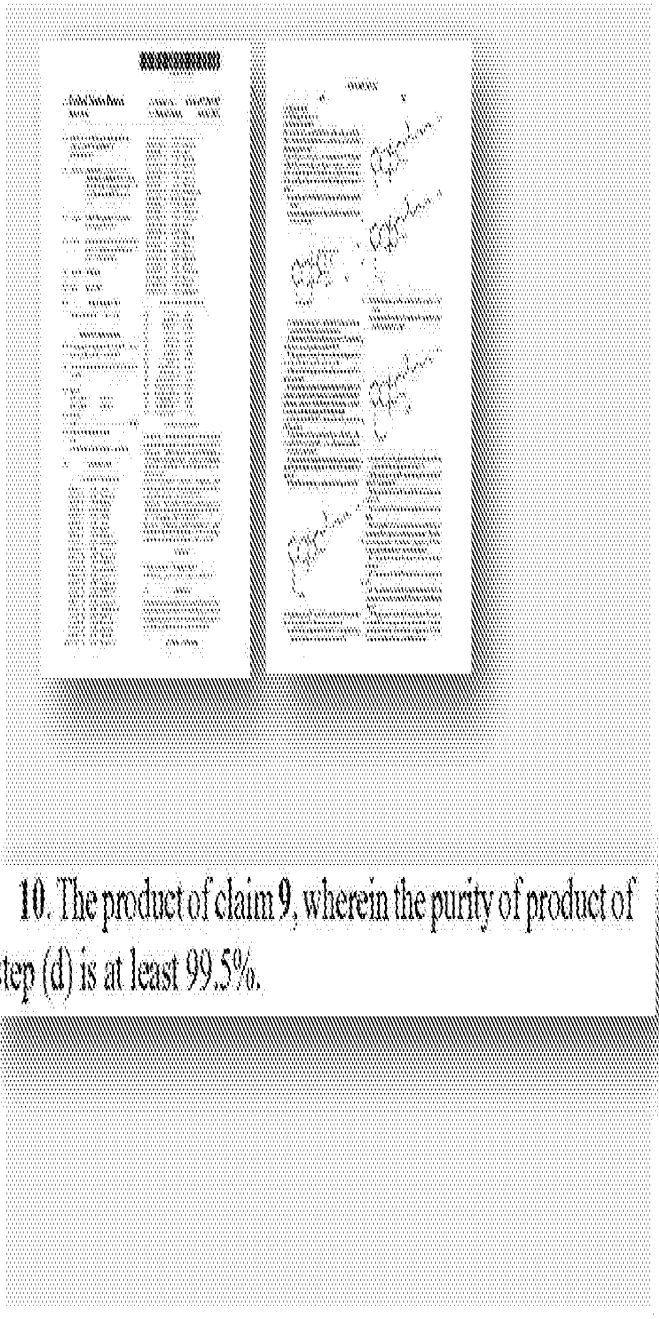
40. A person of ordinary skill in the art would recognize that the formation of a carboxylate salt, by the addition of a weak base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in steps (c) and (d), is standard chemistry purification – *i.e.*, organic chemistry 101.

Ex. 1009 (Winkler Decl. at 12) ¶ 40

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Kawakami with Moriarty, Phares, and Eje





10. The product of claim **9**, wherein the purity of product of step (d) is at least 99.5%.

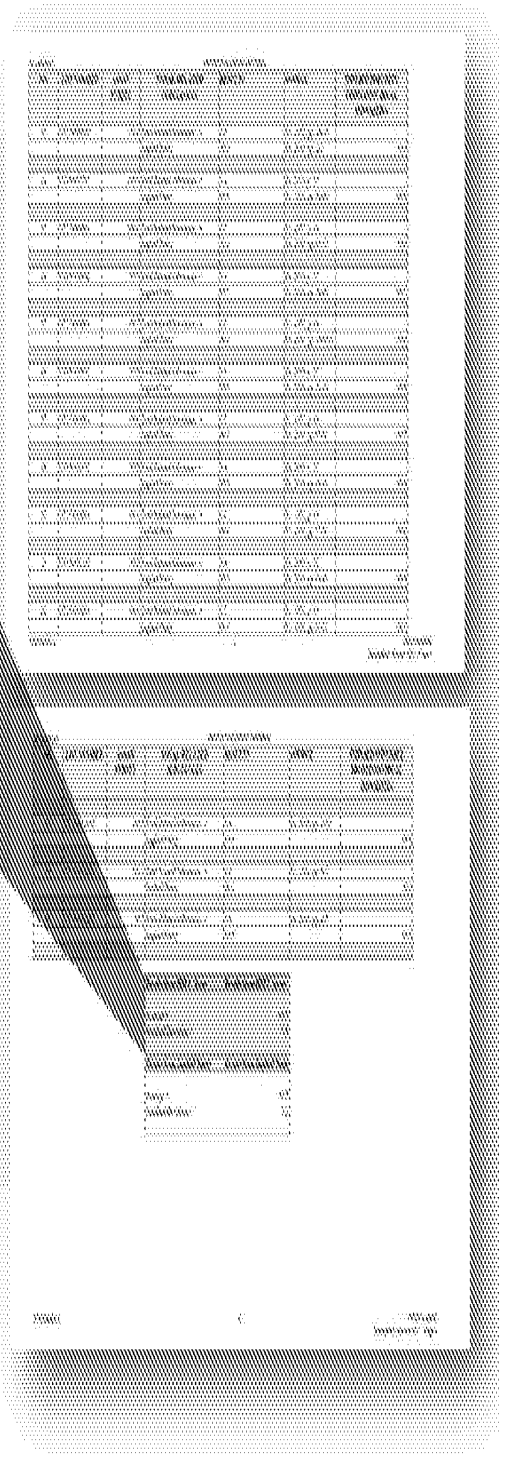
Ex. 1007 (Kawakami); Ex. 1004, Ex. 1008 (Eje); Ex. 1005 (Phares); Ex. 1001

Ex. 1020; Sandoz Inc. v. United Therapeutics Corp., IPR2019-00885

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 45 samples)

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

Prior Art Made Same Product

Obviousness: Dependent Claims 6, 10, 15, 21 & 22

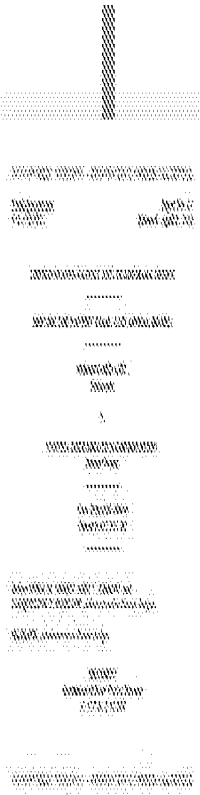
Conclusions

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"

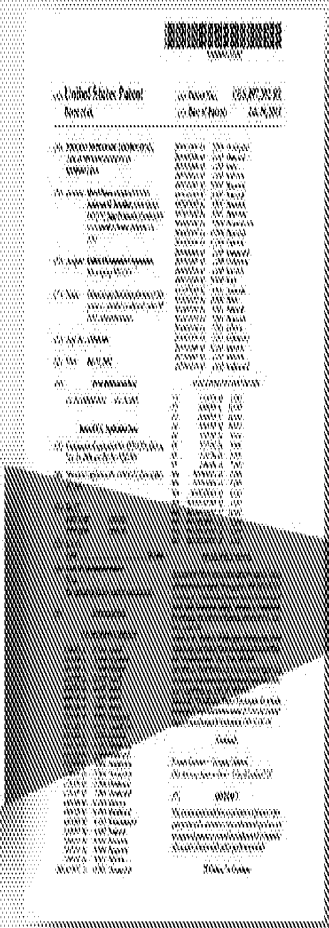
The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by

Institution Decision, Paper No. 12, at 12

Claim Construction

"Comprising"

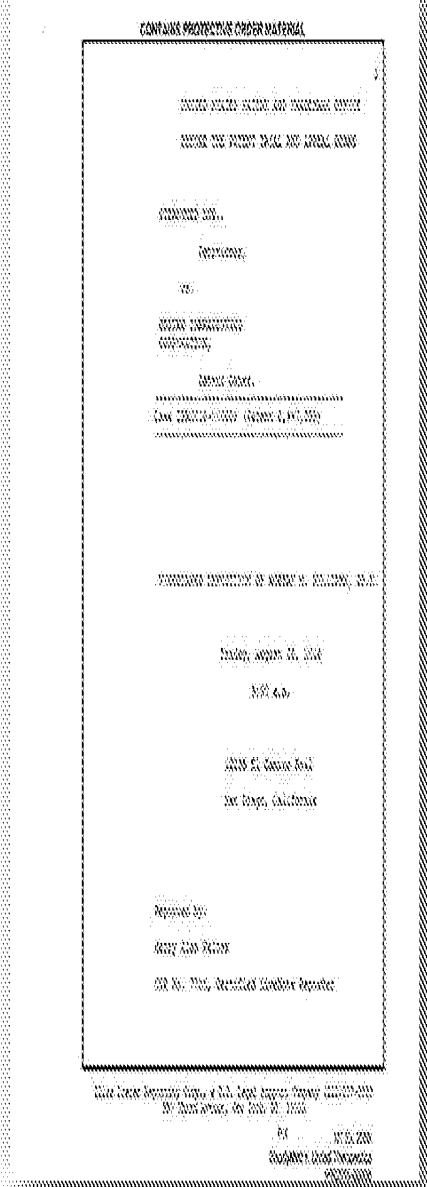
The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.



Ex. 1001 at 4

Claim Construction

"Product"


CONTAINS PROTECTIVE ORDER MATERIAL

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.

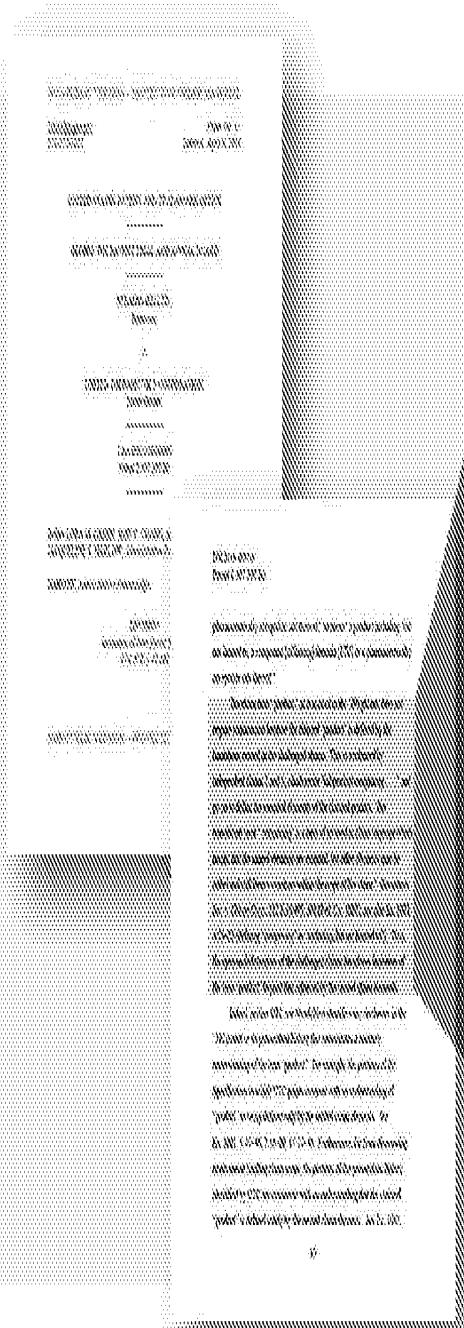
Q. Okay. Let me ask you: In the '393 patent, do you see any place where the '393 patent says: I'm going to define the word "product" for this patent? Do you see that anywhere in there?

A. I don't recall it being defined, other than its plain, ordinary meaning as it's understood, as I just explained.

Ex. 2059 at 248:4-249:6

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

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TABLE OF AUTHORITIES

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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.

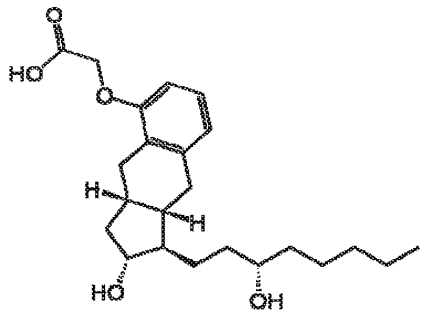
Indeed, the only example given in Eğe is of benzoic acid – a very simple aromatic acid that is quite different from the structure of treprostinil, as it has no chiral centers and therefore no stereoisomeric impurities. *Id.* at ¶108. Given that Eğe only predicts the removal of neutral and basic compounds 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

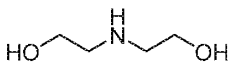
multiple chiral centers such as treprostinil could be isolated from entirely different impurities and then converted back to the free acid form. *Id.*

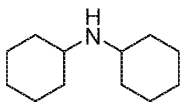
Thus, the purification of treprostinil from its stereoisomers and related impurities is quite different from the purification of the methanoprostacyclin derivative from its structural isomer – the compositions are not improved in the *same way*.

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.





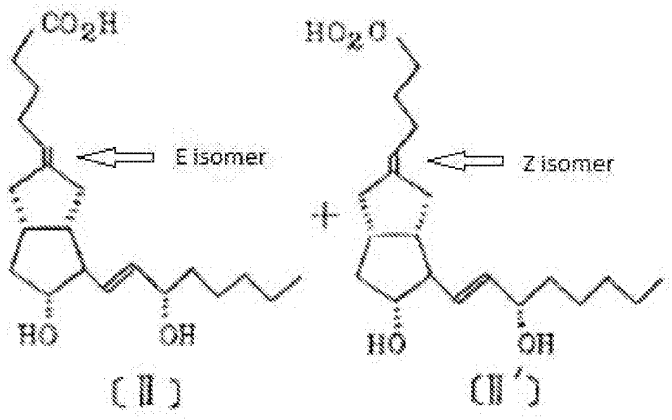
Diethanolamine **dicyclohexyl amine**

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]

United Therapeutics

[redacted]

[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]

UT Ex. 2006
SteadyMed v. United Therapeutics
IPR2016-00006

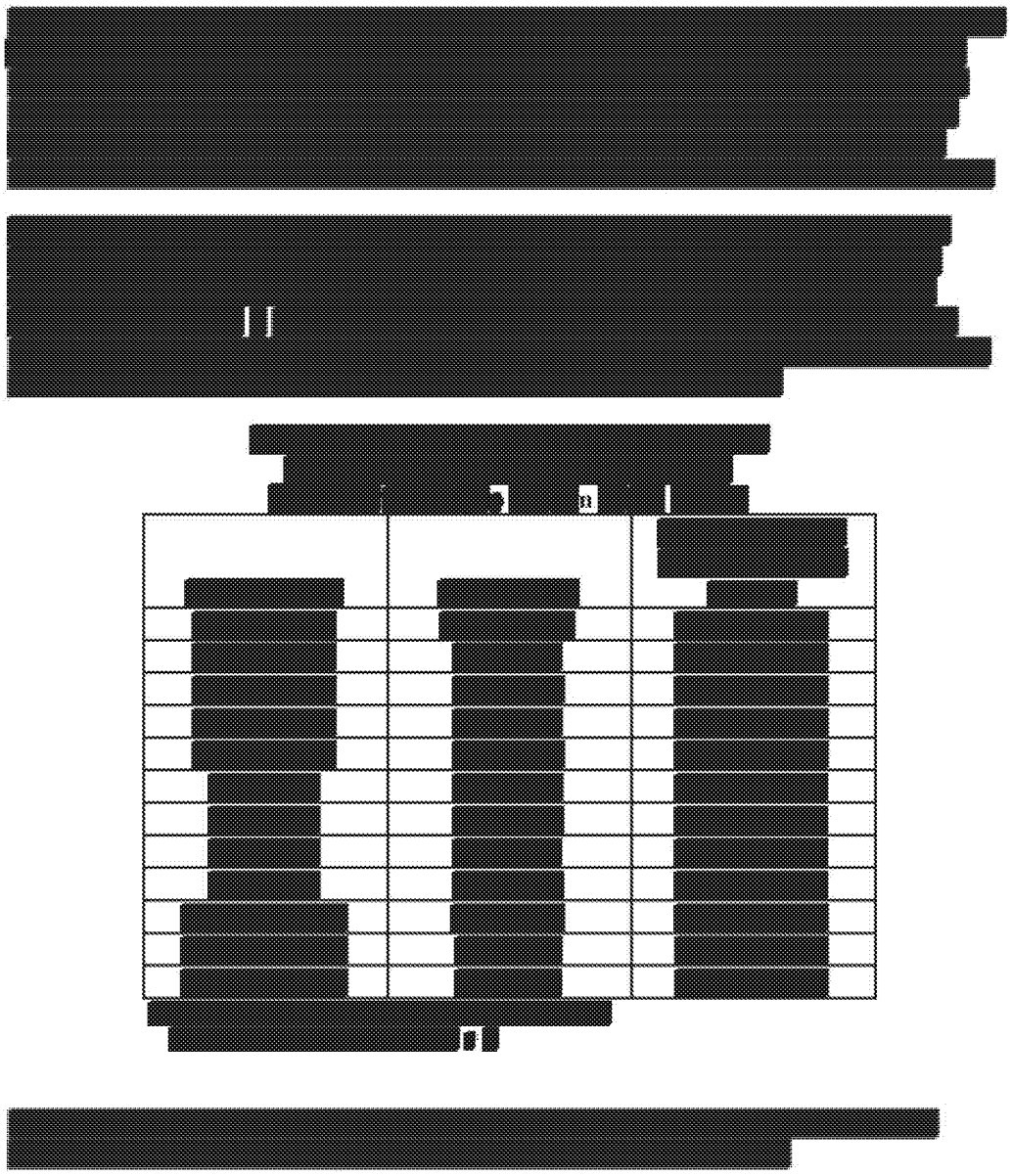
[redacted]

IPR2020-00770
United Therapeutics EX2007

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

[redacted]

[redacted]



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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

DECLARATION OF ROBERT M. WILLIAMS, Ph.D., IN SUPPORT OF PATENT OWNER RESPONSE TO PETITION

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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

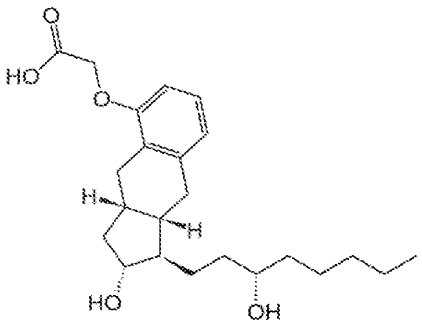
of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds." Ex. 1008 at 8. This disclosure, however, would not have provided a POSA with a motivation to make the treprostinil free acid disclosed in Moriarty, convert that to the salt form of Phares, 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.

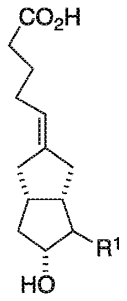
109. Indeed, given that Eğe predicts that only neutral and basic impurities would be removed, the actual average impurity profile for the '393 patent product is an unexpected result given that some but not all neutral impurities are removed as well as some but not all acidic impurities. *See*, Section 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

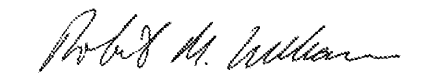
carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure. For this additional reason, Claims 6 and 15 would not have been rendered obvious by any combination of Phares, Moriarty, Kawakami 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
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0.1
Ex. 2037, p. 44
0
0
0.06
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0.05
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0.13
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Ex. 2037, pp. 195-196
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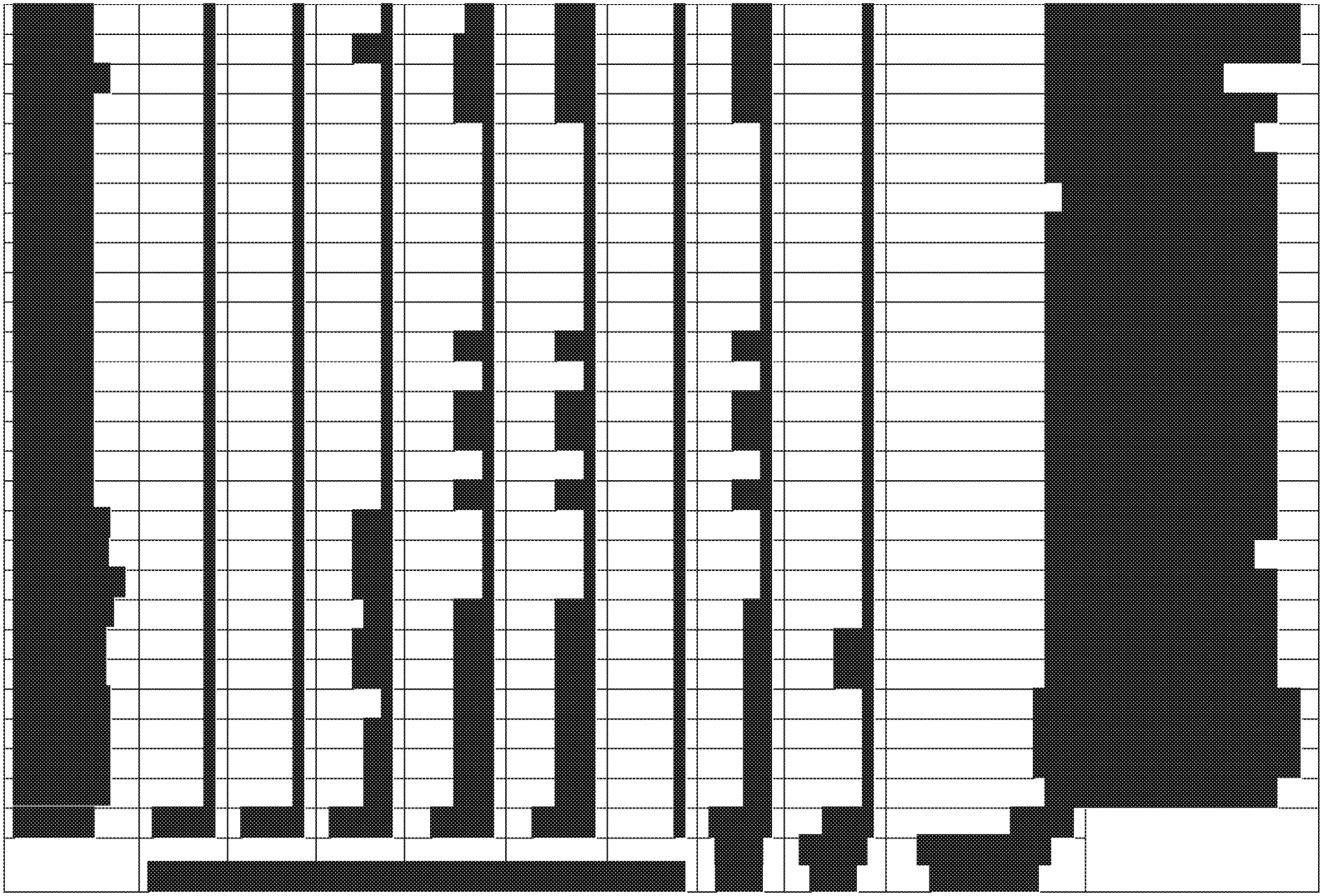
4851-2371-9220.1
P. 50



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.)

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ERRATA SHEET

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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

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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"

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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: ____

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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

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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

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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