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NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 04/27/2016

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

EXAMINER
TOWNSLEY, SARA ELIZABETH

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 04/27/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/591,200	11/12/2009	Horst Olschewski	080618-0716	4093

TITLE OF INVENTION: Treprostinil administration using a metered dose inhaler

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	07/27/2016

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 04/27/2016
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)

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12/591,200	11/12/2009	Horst Olschewski	080618-0716	4093

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APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	07/27/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
TOWNSLEY, SARA ELIZABETH	1629	514-183000

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. _____

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DATE MAILED: 04/27/2016

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.

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. 12/591,200	Applicant(s) OLSCHEWSKI ET AL.	
	Examiner SARA E. TOWNSLEY	Art Unit 1629	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 *Applicant's replies filed 11/9/2015; 2/2/2016; 3/3/2016; 3/4/2016; and 3/28/2016*.
   ☐ 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 *58-66*. 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 See Continuation Sheet
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20160402* .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SARA E. TOWNSLEY/ Examiner, Art Unit 1629	/JEFFREY S. LUNDGREN/ Supervisory Patent Examiner, Art Unit 1629

Continuation of Attachment(s) 2. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 3/9/2015 and 11/9/2015.

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EXAMINER	
TOWNSLEY, SARA ELIZABETH	
ART UNIT	PAPER NUMBER
1629	

MAIL DATE	DELIVERY MODE
03/19/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 12/591,200	Applicant(s) OLSCHEWSKI ET AL.	
	Examiner SARA E. TOWNSLEY	Art Unit 1629	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/2/2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *18,25,27-30 and 32-40* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *18,25,27-30 and 32-40* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, 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.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *7/2/2013*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

NON-FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed Jul. 2, 2013.

Claim 18 has been amended.

Claims 1-17, 19-24, 26, and 31 have been canceled.

New claims 35-40 have been added.

Thus, claims 18, 25, 27-30, and 32-40 now represent all claims currently pending and under consideration.

Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The rejections and/or objections set forth below are either maintained or newly applied, and constitute the complete set presently applied to the instant claims.

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Jul. 2, 2013 has been entered.

INFORMATION DISCLOSURE STATEMENT

The information disclosure statement (IDS) submitted on Jul. 2, 2013 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Action dated Oct. 17, 2012, on the ground that the references cited therein continue to read on the limitations of the amended claims.

Double Patenting

Claims 18, 25, 27-30, and 32-34 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims **1, 4-13, 15-18, and 52-59 of copending Application No. 11/748,205** in view of Chaudry (US Pub. 2004/0265238), Byron (*Proc. Am. Thorac. Soc*. (1), pp. 321-328, 2004) and Cloutier et al (USPN 6,521,212).

In addition, this rejection is extended to new claims 35-40.

Reference claims 1, 4-13, 15-18, and 52-59 are drawn to methods for treating pulmonary hypertension, comprising administering to a subject in need thereof treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof by a metered dose inhaler, wherein said treprostinil derivative is selected from C_{1-4} alkyl esters of treprostinil and C_{1-4} alkyl amides of treprostinil,

wherein the metered dose inhaler is a soft mist inhaler,

wherein said treprostinil is formulated as a solution, wherein a solvent of the solution comprises water, ethanol or a mixture thereof,

wherein a concentration of the treprostinil ranges from about 500 µg/ml to about 2500 µg/ml, or from about 1000 µg/ml to about 2000 µg/ml,

wherein a dose of the treprostinil administered during a single event ranges from about 15 µg to about 100 µg, or from about 30 µg to about 90 µg, or from about 30 µg to about 60 µg,

wherein said administering does not have a systemic side effect on said subject, wherein the systemic side effect is selected from the group consisting of headache, flush, nausea, and dizziness,

wherein said administering does not disrupt gas exchange in said subject,

wherein said administering does not change heart rate of said subject,

wherein said administering does not affect systemic arterial pressure and systemic arterial resistance,

wherein said administering is carried out in 20 breaths or less breaths in a single event, or 10 or less breaths in a single event, or in 5 or less breaths in a single event,

wherein said administering lasts less than 5 minutes, or less than 1 minute,

wherein said subject is a human being,

wherein said administering comprises administering aerosol particles containing the treprostinil and said particles have a diameter of less than 10 microns, or a diameter of less than 5 microns.

The reference claims do not recite administration with an ultrasonic nebulizer, as recited by examined claims 18 and 27.

Chaudry discloses methods of treating pulmonary hypertension by administering inhalable formulations of treprostinil by way of a metered dose inhaler, a dry powder inhaler, a pressurized aerosol (para. 0052), i.e., a pressurized metered dose inhaler, or via nebulization (para. 0040). Chaudry teaches that any nebulizer is suitable, including ultrasonic nebulizers (para. 0057).

Byron discloses drug delivery devices for inhalation such as metered dose inhalers (MDIs), specifically soft mist MDIs, as recited by the reference claims, as well as ultrasonic nebulizers, as recited by the examined claims, e.g., computer-controlled ultrasonic (piezoelectric) nebulizers that monitor each patient's breathing pattern and administer nebulizer output phased with inspiration (p. 323, left col.).

Because Chaudry teaches that any conventionally known method of administering inhalable medicaments may be used in methods of administering inhalable treprostinil to treat pulmonary hypertension (para. 0052), it would have been predictable to a skilled artisan to administer inhalable treprostinil formulations with either a soft-mist inhaler, as recited by the reference claims, or with an ultrasonic nebulizer, as recited by the examined claims, with a reasonable expectation of success.

In addition, as recognized by MPEP §2144.06, it is *prima facie* obvious to substitute art-recognized equivalents, and an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

This is a provisional obviousness-type double patenting rejection.

RESPONSE TO ARGUMENTS AND EVIDENCE

The Declaration filed on Jul. 2, 2013 under 37 CFR § 1.131(a) is sufficient to overcome the Sandifer reference. Therefore, the rejection under 35 U.S.C. § 103 over Chaudry, Sandifer et al., and Cloutier et al. is withdrawn.

Applicant's arguments filed Jul. 2, 2013 have been fully considered but they are not persuasive.

Specifically, Applicant contends that the references do not disclose a single event dose of 15 to 90 mcg treprostinil which is inhaled in 18 or less breaths, as recited by amended claim 18 (Remarks, pp. 5-6).

These limitations are addressed in the new rejection set forth below.

Applicant further contends that the PTO improperly disregards Applicants' surprising/unexpected results, relying on Sandifer, specifically the claimed method's significant improvement in quality of life for pulmonary hypertension patients due to its substantially greater convenience compared to the only other available inhaled prostacyclin on the market, as shown in the previously filed Rule 132 Declarations of Drs. Rubin and Gotzkowsky (filed on May 23, 2012 and August 10, 2012 respectively) (Remarks, pp. 6-7).

To the extent Applicant's arguments with respect to Sandifer are applicable to the currently cited references, they are addressed in the new rejection set forth below.

Applicant contends that one of ordinary skill in the art would not be able to arrive at the surprising/unexpected result of improved quality of life, nor predict the surprisingly robust patient benefits shown in the previously submitted Rule 132 Declarations by making the changes in the inhalation method that are recited in claim 18, at least because the obviousness analysis was not made explicit (Remarks, p. 8). Specifically, Applicant contends that insufficient factual findings were articulated to establish a *prima facie* case of obviousness under the rationales set forth in MPEP § 2143 (A) and (G) (Remarks, pp. 9-11). In particular, Applicant argues that one of ordinary skill in the art would not have had a reasonable expectation of success to arrive at the dosing regimen recited in claim 18, based on Sandifer (Remarks, p. 11).

To the extent Applicant's arguments with respect to Sandifer are applicable to the currently cited references, they are addressed in the new rejection set forth below.

NEW REJECTIONS

Claim Rejections - 35 USC § 103

1. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 18, 25, 27-30, and 32-40 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chaudry (US Pub. 2004/0265238, cited in the previous action) in view of Cewers (USPN 6,357,671, cited in the action dated Dec. 22, 2011).

Chaudry discloses methods for treating pulmonary hypertension in humans by administering an inhalable formulation comprising at least one hypertension reducing agent, e.g., a vasodilator, in the form of a solution or suspension (abstract). In particular, Chaudry exemplifies an inhalable formulation comprising a pharmaceutically acceptable salt of treprostinil, treprostinil sodium, in a concentration of 0.1-10.0 mg/ml (Example 4), which is preferably administered via nebulization (paras. [0040], para. [0057]).

Chaudry teaches that a nebulized solution is a particular form of an aerosol (para. [0055]), and that administration of a nebulized aerosol is preferred (para. [0053]); thus, it is implicit that the disclosed inhalable formulations are aerosolizable solutions.

Further, Chaudry discloses that prophetic examples 1-4 (including treprostinil, Example 4) are believed to “be suitable for administration via nebulization to an

individual suffering from pulmonary hypertension . . . The objective of these formulations is to provide localized delivery of a pulmonary hypertension reducing agent to a mammal (e.g. humans) in need thereof." Thus, the disclosed compounds, and in particular the exemplified compounds, are presumed to be administrable by inhalation via a nebulizer.

Thus, Chaudry discloses a method of treating pulmonary hypertension comprising administering by inhalation to a human in need thereof a therapeutically effective dose of an inhalable formulation with an ultrasonic nebulizer, as recited by claim 18.

The inhalable formulation of Chaudry Example 4 comprises treprostinil sodium in a concentration of 0.1-10.0 mg/ml (Example 4), which encompasses the range of 500-2500 mcg/ml (= 0.5-2.5 mg/ml) as recited by claim 27.

Chaudry further discloses that a therapeutically effective amount of the hypertension-reducing agent (e.g., treprostinil) may include from about, e.g.,

- 0.51 mg/ml to about 1.00 mg/ml (510 – 1000 mcg/ml);
- 1.01 mg/ml to about 1.50 mg/ml (1010 – 1500 mcg/ml); and
- 1.51 mg/ml to about 2.00 mg/ml (1510 – 2000 mcg/ml)

(para. [0037]). These concentration ranges fall squarely within the claimed range of 500 – 2500 mcg/ml, as recited by claim 27.

Chaudry also teaches that "[t]he solution of Example 4 may be made by methods known to those of ordinary skill in the art" (para. [0098]). In other words, the reference

itself teaches that any concentration within the exemplified range can be arrived at by routine experimentation.

Therefore, a skilled artisan would have had a reasonable expectation of success of treating pulmonary hypertension by administering by inhalation an aerosolable solution of treprostinil at a concentration of 600 mcg/ml (0.6 mg/ml), as recited by claim 34.

Chaudry teaches other embodiments in which the dose of the inhalation solution may be administered 1, 2, 3, 4, 5, 6, 7, or 8 times per day by nebulization, i.e., several times per day, as recited by claim 33. Chaudry also teaches that nebulizer fill volumes may be adjusted to reduce each nebulization treatment to about, e.g., 5, 4, 3 minutes, or less (para. [0063]), as recited by claims 35-37.

Chaudry does not specifically teach inhalation administration of a therapeutically effective single event dose of treprostinil

- in an amount of 15 to 90 mcg, as recited by claim 18,
- in an amount of 15 to 60 mcg, as recited by claim 25;
- in 18 or less breaths, as recited by claim 18;
- in 12 or less breaths, as recited by claims 38-40; or
- in 5 or less breaths, as recited by claim 32.

However, Chaudry discloses inhalation administration by ultrasonic nebulizer of therapeutically effective doses of treprostinil, in the concentration ranges noted above. The dose administered during a “single event," i.e., a single breath, depends on factors such as, e.g., the concentration of the solution used, the volume of solution the device is

calibrated to dispense with each “puff,” the patient’s condition and capabilities, and the judgment of the treating physician. These factors also influence the number of breaths administered in a given treatment interval, and the number of intervals per day.

Chaudry teaches embodiments in which the disclosed fill volumes “may reduce each nebulization treatment to about 12, 10, 9, 8, 6, 5, 4, 3 minutes, or less over conventional nebulizer treatments (e.g. 2.5 ml or 3.0 ml fill volume). Reducing the amount of time to complete the treatment means individuals will be more likely to comply with the prescribed dosing regimen and achieve optimal benefit from the medication prescribed" (para. [0063]). Reducing the amount of time to complete the treatment implies a higher drug concentration, so that a given amount of drug is delivered in a shorter time interval and/or fewer breaths

Chaudry teach that other features of the disclosed invention include “improved user compliance and quality of life as compared to conventional treatments for pulmonary hypertension. While the level of compliance of any pulmonary hypertension treatment depends in part on the motivation of the user and the skill of the individual dispensing the treatment, compliance nevertheless may be improved by controlling factors such as the ease with which the treatment may be administered, as well as the desirability of receiving the treatment” (para. [0082]).

Thus, a skilled artisan would have had a reasonable expectation of success of optimizing the drug concentration and increasing the dose in order to reduce the amount of time, and hence, the number of breaths to complete the treatment, such as 18 or 12 or 5 breaths, because Chaudry teaches that treatment can be completed in 3

minutes or less, and that reducing the duration of the treatment enhances patient compliance.

Further, it would have been within the judgment of an ordinarily skilled clinician to optimize the treprostinil concentration and dose, the frequency and duration of administration, and/or the number of breaths of the formulation inhaled, because these are result-effective variables which can be modified and adjusted by routine experimentation, as taught by Chaudry. As recognized by MPEP § 2144.05,

> *Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).*

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the concentration, single-event dosage, frequency, and duration of inhaled treprostinil administration to treat pulmonary hypertension with a reasonable expectation of success, because Chaudry discloses drug concentration ranges overlapping those claimed, which may be modified by methods known to those of ordinary skill in the art; and Chaudry discloses treatment intervals which read on or encompass those claimed, and teaches the advantage that reducing the amount of time, and hence, the number of breaths, to complete treatment enhances patient compliance.

Thus, Chaudry discloses, teaches, and suggests methods of treating pulmonary hypertension comprising administering by inhalation to a human in need thereof a therapeutically effective single event dose of an inhalable formulation with an ultrasonic

nebulizer, wherein said therapeutically effective single event dose comprises from 15 mcg to 60 mcg or 90 mcg of treprostinil and is inhaled in 18, 12, or 5 or less breaths, as recited by claims 18, 32, and 38-40;

wherein the treprostinil is inhaled in 5 minutes or less, as recited by claims 35-37;

wherein the ultrasonic nebulizer comprises an aerosolable solution having a concentration of treprostinil from 500 mcg/ml to 2500 mcg/ml, specifically 600 mcg/ml, as recited by claims 27 and 34, respectively; and

wherein the human receives several therapeutically effective single event doses per day, as recited by claim 33.

Regarding claims 28-30, as evidenced by, e.g., the instant specification, it is intrinsic in the methods disclosed by Chaudry that treprostinil administered by inhalation does not significantly disrupt gas exchange, as recited by claim 28 (para. [0015]; Fig. 2); does not significantly affect heart rate, as recited by claim 29 (para. [0015]; Fig. 2); and does not significantly affect systemic arterial pressure and systemic arterial resistance (para. [0014]; Fig. 1), as recited by claim 30.

By disclosing inhalation administration of a therapeutically effective amount of treprostinil to a patient in need of such treatment to treat pulmonary hypertension, the resulting physiological responses, as recited by claims 28-30, are intrinsic in the methods of Chaudry, even if those effects or responses were not known or appreciated. As evidenced by, e.g., the data presented in Figures 1 and 2 of the instant specification, carrying out the methods taught by Chaudry produces the claimed results.

All the molecular and cellular mechanisms by which a compound exerts its therapeutic effects are intrinsic in the methods of Chaudry, and occur each time treprostinil in the claimed amounts is administered by inhalation to the patient population in need of treatment for pulmonary hypertension, regardless of whether anyone was aware of those molecular and cellular mechanisms.

A novel use of a known compound can be patentable. However, the instant claims do not recite a novel use of a known compound, but rather a previously unknown property of known compounds known to treat the same conditions in the same patient population.

The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites the use of a known compound in a known method and the "use" is directed to a result or property of that compound, then the claim is anticipated. *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601 (CCPA 1978) affirmed the rejection of claims 1 and 6, directed to methods of effecting nonaddictive analgesia, which were anticipated by the applied prior art which disclosed the same compounds for effecting analgesia, but which was silent as to addiction. The court affirmed the rejection on the grounds that the applicants had merely found a new property of the compound and such a discovery did not constitute a new use. 197 USPQ 601, 607.

Claims 28-30 recite intrinsic results that naturally flow from administering inhaled treprostinil to a human in the claimed amounts to treat pulmonary hypertension. While

the references do not show a specific recognition of those results, their discovery is tantamount only to finding a new property intrinsic in carrying out an old method. Because reference teaches methods of administering the same compound in the same amounts to treat the same condition in the same patient population, the physiological effects of such administration are intrinsic in the methods of Chaudry.

Chaudry does not disclose pulsed ultrasonic nebulizers, as recited by claim 18.

Cewers discloses ultrasonic nebulizers for the delivery of controlled doses of medication to a patient (col. 1, lines 5-26), wherein the aerosol is delivered in pulses separated by intervals during which no nebulization occurs (claim 1), i.e., a "pulsed ultrasonic nebulizer," as recited by claim 18.

A skilled artisan would have been motivated to treat pulmonary hypertension by administering treprostinil with a pulsed ultrasonic nebulizer, as disclosed by Cewers, with a reasonable expectation of success, because Chaudry teaches that any ultrasonic nebulizer is contemplated for use (para. [0054]).

As recognized by MPEP §2143, combining prior art elements according to known methods to yield predictable results would motivate the skilled artisan to modify the references with a reasonable expectation of success. The rationale to support a conclusion of *prima facie* obviousness is that all the claimed elements were known in the prior art, and a skilled artisan could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. See *KSR Int'l Co. v. Teleflex Inc.* (550 U.S. 398, 409).

CONCLUSION

Claims 18, 25, 27-30, and 32-40 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. TOWNSLEY whose telephone number is 571-270-7672. The examiner can normally be reached on Mon-Fri from 9:00 am to 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren, can be reached at 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SARA E. TOWNSLEY/
Examiner, Art Unit 1629