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EXAMINER	
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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 *4/28/2014*.

☐ 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5a) Of the above claim(s) _____ is/are withdrawn from consideration.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 *6/13/2014*.

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

4) ☐ Other: _____.

FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed Apr. 28, 2014.

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.

STATUS OF THE CLAIMS

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

No claims have been amended, and no new claims have been added.

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

INFORMATION DISCLOSURE STATEMENT

The information disclosure statement (IDS) submitted on Jun. 13, 2014 was filed after the mailing date of the non-final action on Mar. 19, 2014. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered.

MAINTAINED REJECTIONS

The following rejections are maintained from the previous Office Action dated Mar. 19, 2014, on the ground that the references cited therein continue to read on the limitations of the amended claims.

Claim Rejections - 35 USC § 103

Claims 18, 25, 27-30, and 32-40 stand rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chaudry (US Pub. 2004/0265238) in view of Cewers (USPN 6,357,671).

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; claim 44), which is preferably administered via nebulization (paras. [0040], para. [0057]; claims 27-29).

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 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; claim 44), 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 aerosol 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.

While Chaudry discloses ultrasonic nebulizers and breath-actuated nebulizers (claim 29), the reference does not explicitly 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).

Double Patenting

Claims 18, 25, 27-30, and 32-40 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).

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

Applicant's arguments filed Apr. 28, 2014 have been fully considered but they are not persuasive.

With respect to the rejection under 35 U.S.C. § 103, Applicant contends that a *prima facie* case of obviousness has not been established, because, using the same references, a similar or identical rejection could be made with respect to iloprost; yet a single event dose of iloprost cannot be administered with a pulsed ultrasonic nebulizer in 18 or less breaths, which indicates that the PTO's logic is deficient (Remarks, pp. 4-

5). In other words, Applicant's traversal of the rejection is based on the thesis that Chaudry and Cewers are equally applicable to iloprost and treprostinil (Remarks, p. 6).

However, this is insufficient to rebut the rejection. To clarify, the instant claims are drawn to methods of treating pulmonary hypertension by administering treprostinil with a pulsed ultrasonic nebulizer in 18 or less breaths. Search and examination is directed to the claimed invention, which does not encompass iloprost. Thus, the relevance of whether the same combination of references also teaches other distinct, unrecited embodiments is unclear.

Alternatively, Applicant contends that the fact that a single event dose of treprostinil can be administered with a pulsed ultrasonic nebulizer in 18 breaths or less, while iloprost cannot, represents surprising results that could not be expected based on the cited references (Remarks, pp. 6-7), citing the Gessler reference (of record) and Example 2 of the instant specification.

First, Gessler et al. compared administration of iloprost by jet nebulizer versus ultrasonic nebulizer. "Based on the data of the physical characterization, the inhalation time for delivery of an equivalent iloprost dose at the mouthpiece (2.8 µg) was reduced from 12 min with the jet nebulizer system to 2 min with the ultrasonic nebulizer, when retaining the same concentration of the iloprost solution (10 µg/mL). In preliminary catheter investigations, however, some increase in systemic side effects was observed when administering the total iloprost dose of 2.8 µg via the inhalation route for such a short time period. Therefore we reduced the iloprost concentration from 10 µg/ml to 5 µg/ml when employing the ultrasonic nebulizer, and consequently doubled the inhalation

time to 4 min with this device. This inhalation protocol was generally well tolerated. Furthermore, by diluting the solution, drug waste in the dead space of the nebulizer was reduced" (p. 17, col. 2).

Thus, Gessler et al. report that 2.8 µg iloprost can be administered via ultrasonic nebulizer in 2 min, at a concentration of 10 µg/ml (with some increase in side effects), or in 4 min, at a concentration of 5 µg/ml (without an increase in side effects).

Gessler et al. conclude that, due to the markedly higher efficiency and output of the ultrasonic device, wastage of drug is largely avoided and duration of inhalation can be shortened to one-third (from 12 minutes to 4 minutes), with comparable haemodynamic effects and without enforcing side effects (abstract; p. 19, col. 1).

Therefore, Gessler et al. provides a reason to select an ultrasonic nebulizer over other devices, such as a jet nebulizer, and thus supports the teaching of Chaudry, which discloses that administration of a nebulized aerosol is preferred (para. [0053]) and discloses exemplary ultrasonic nebulizers (para. [0057]; claim 29).

Next, Example 2 of the instant specification, study (i), compared administration of iloprost and treprostinil with a pulsed ultrasonic nebulizer at an inhaled dose of 7.5 µg (paras. [0068]-[0071]). "In study (i) it was shown that the inhalation of treprostinil and iloprost in similar doses resulted in a comparable maximum pulmonary vasodilatory effect. However, marked differences in the response profile were noted. The onset of the pulmonary vasodilatory effect of inhaled treprostinil was delayed compared to iloprost, but lasted considerably longer, with the PVR decrease continuing beyond the one-hour observation period. Although the average dose of treprostinil was higher than

the iloprost dose, no systemic effects were noted after treprostinil inhalation, whereas flush and transient SAP decrease, accompanied by more prominent cardiac output increase, occurred after iloprost inhalation" (para. [0087]).

The occasionally observed mild side effects of iloprost inhalation at the given dose (transient flush, headache) were not observed with inhaled treprostinil (para. [0078]). Inhaled treprostinil is advantageous to inhaled iloprost in terms of duration of effect and systemic side effects (para. [0069]).

Thus, the results presented in the instant specification demonstrate that it is possible to administer both iloprost and treprostinil via pulsed ultrasonic nebulizer – which would have been expected in view of Gessler et al. – but that treprostinil has certain advantages over iloprost, such as reduced or no side effects at higher doses.

The question is whether these results are truly unexpected, or simply the natural outcome of following the guidance and direction provided in the prior art.

As recognized by MPEP §716.02(c)(II), "[e]xpected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). Analogously, in *Pfizer v. Apotex*, 82 USPQ2d 1321 (Fed. Cir. 2007), the Court held that

> the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer **merely had to verify through routine testing**. *Merck*, 874 F.2d at 809. . . . [O]ur conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, **and merely had to verify that expectation** [emphasis added].
>
> We find this case analogous to the optimization of a range or other variable within the claims that flows from the "normal desire of scientists or artisans to improve upon what is

> already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (determining where in a disclosed set of percentage ranges the optimum combination of percentages lies is *prima facie* obvious). In *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955), our predecessor court set forth the rule that the discovery of an optimum value of a variable in a known process is usually obvious. 82 USPQ2d at 1335.

As noted in the previous action, the rationale to administer treprostinil with an ultrasonic nebulizer is that Chaudry exemplifies only four formulations for inhalation (which do not include iloprost), one of which is treprostinil (Example 4), and specifically identifies ultrasonic nebulizers as a suitable delivery device (para. [0057]). Notably, Chaudry claims both of these features:

> 27. A method of treating pulmonary hypertension in a mammal, said method comprising the step of administering to said mammal a formulation comprising a therapeutically effective amount of a hypertension reducing agent, wherein said hypertension reducing agent is at least one of an ACEI, ARB, beta-blocker, calcium-channel blocker or vasodilator, and wherein said formulation is suitable for administration via inhalation.
>
> 28. The method of claim 27, wherein said formulation is administered via nebulization to said mammal.
>
> 29. The method of claim 28, wherein said formulation is administered via jet nebulizer, **ultrasonic nebulizer or breath-actuated nebulizer** to said mammal.
>
> 44. An inhalable formulation for the treatment of pulmonary hypertension, said formulation comprising about 0.1-10.0 mg/ml **Treprostinil** sodium, about 2.0-10.0 mg/ml, Sodium Chloride, Sodium Hydroxide, Citric Acid and water, wherein said formulation is suitable for administration via nebulization to a mammal in need thereof.

With this guidance, a skilled artisan would have had a reasonable expectation of success of arriving at the claimed drug/device combination by routine experimentation, even if such experimentation required trial and error, took a long time, or required significant resources, which does not necessarily make it undue. The legal standard to establish a *prima facie* case of obviousness requires a reasonable, not *guaranteed*, expectation of success; and does not require specific guidance pointing to the *optimum* embodiment.

Applicant further contends that additional secondary considerations are presented, specifically, (1) that the claimed drug/device combination (TYVASO) has been approved by the FDA; and (2) the commercial success of TYVASO (Remarks, pp. 6-9)

(1) Regarding FDA approval of TYVASO (Applicant's formulation of treprostinil for inhalation using the OPTINEB IR pulsed ultrasonic nebulizer), Applicant cites *Leo Pharmaceutical Products Ltd. v. Teresa Stanek Rea* (Fed. Cir. 2013), which held that "[w]hile FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness. . . . Here, FDA approval highlights that Leo Pharmaceutical's formulation is truly storage stable, something that the prior art formulations did not achieve" (Remarks, p. 7 and p. 9).

In this regard, Applicant argues that, as in *Leo*, the FDA approval of TYVASO's more convenient dosing regimen is probative evidence of unobviousness, showing "something that the prior art formulations did not achieve." While Chaudry suggests that any prostacyclin listed in paragraph [0026] (iloprost, epoprostenol or treprostinil) is

interchangeably administered with a nebulizer, the results turned out completely different. Epoprostenol is not even on the market in inhaled form; and iloprost (VENTAVIS), while approved by the FDA, has been far less successful because of the more convenient dosing regimen that was surprisingly possible for treprostinil (TYVASO). As Dr. Rubin explained in his Rule 132 Declaration, one of ordinary skill in the art would not have expected to be successful at achieving the approved dosage regimen of TYVASO, based on a variety of factors, including unknown effects of high treprostinil concentration in the solution to be aerosolized, number of breaths per event, and potential side effects resulting from higher drug doses (Remarks, pp. 9-10).

As recognized by MPEP §716.02, where Applicant alleges unexpected results, any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (differences in sedative and anticholinergic effects between prior art and claimed antidepressants were not unexpected).

Here, Chaudry discloses that the formulations disclosed therein represent an improvement over conventional means for treating pulmonary hypertension, “because the delivery of the hypertension-reducing agent would be localized to the user's pulmonary system, as opposed to systemic delivery. It is believed that localized therapy may increase bioavailability as well as increased efficacy and/or prolonged therapeutic effect. Due to increased bioavailability, the present formulations may contain lower dosages of the hypertension-reducing agents while effectively treating pulmonary

hypertension. Additionally, it is believed that localized therapy may result in a decrease in side-effects due to lower dosages and a decrease in patient discomfort and inconvenience due to the less invasive or time-consuming systemic delivery method" (para. [0036]).

Chaudry further discloses "a method of facilitating patient care, reducing medication error, reducing nebulizer treatment time, improving the efficiency and efficacy of nebulizing therapy or enhancing therapeutic compliance of an individual suffering from pulmonary hypertension" (para. [0067]). In addition, Chaudry discloses that other features "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, Chaudry discloses, teaches, and suggests all of the advantages and benefits cited by Applicant, while the examples and claims would have led a skilled artisan to only four active agents, which include treprostinil.

In addition, evidence of secondary considerations does not always overcome a *prima facie* case of obviousness. "Good science and useful contributions do not necessarily result in patentability." *PharmaStem Therapeutics. v. Viacell*, 491 F.3d 1342 at 1364 (Fed. Cir. 2007). "Even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification

was within the capabilities of one skilled in the art. *Pfizer v. Apotex*, 82 USPQ2d 1321 at 1338 (Fed. Cir. 2007, citing *In re Aller*, 220 F.2d at 456).

Finally, it is noted that the claims are not limited to the device (OPTINEB-IR) used in the TYVASO combination which has received FDA approval, but rather encompass any and all pulsed ultrasonic nebulizers.

As recognized by MPEP §716.02(d),

> Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness **must be commensurate in scope with the claims which the evidence is offered to support**." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980).

(2) As evidence of commercial success, Applicant presents a plot comparing market shares for VENTAVIS (a solution containing iloprost for inhalation via INEB AAD® (Adaptive Aerosol Delivery) System), and TYVASO (Applicant's formulation of treprostinil for inhalation using the OPTINEB IR pulsed ultrasonic nebulizer) (pp. 11-12), which shows that TYVASO took away the majority of the US market for inhaled prostacyclins from VENTAVIS in a single year. Applicant contends that this dramatic commercial success is attributable directly to the differences of the claimed invention over the prior art (Remarks, p. 12).

However, as recognized by MPEP § 716.03, Applicant bears the burden of proof of establishing a nexus between the claimed invention and evidence of commercial success, which has not been met. Specifically, it must be shown that the alleged commercial success is a direct result of the claimed features of the invention, and not a

result of, e.g., heavy promotion, marketing, or advertising. Further, objective evidence of nonobviousness, including commercial success, must be commensurate in scope with the claims, which are not limited to OPTINEB-IR, but rather encompass any pulsed ultrasonic nebulizer.

For the foregoing reasons, the rejections of claims 18, 25, 27-30, and 32-40, under 35 U.S.C. § 103 and on the ground of obviousness-type double patenting, are maintained.

CONCLUSION

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

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

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, Jeff 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.

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