IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Title:	TREPROSTINIL ADMINISTRATION BY INHALATION (as amended)
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Examiner:	Sara Elizabeth TOWNSLEY
Art Unit:	1629
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SUPPLEMENT AMENDMENT AND REPLY UNDER 37 CFR 1.111

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

Commissioner:

This communication is supplemental to the response filed on November 9, 2015, in response to the Advisory Action dated February 27, 2015, and final Office Action dated October 10, 2014, concerning the above-referenced patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document.

Remarks/Arguments begin on page 5 of this document.

Please amend the application as follows:

AMENDMENTS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-17. (Canceled)

18. (Previously Presented) A method 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 a pulsed ultrasonic nebulizer, wherein said therapeutically effective single event dose comprises from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof, said therapeutically effective single event dose is inhaled in 18 or less breaths by the human.

19.-24. (Canceled)

25. (Previously Presented) The method of claim 18, wherein the single event dose contains from 15 μg to 60 μg of treprostinil or a pharmaceutically acceptable salt thereof.

26-27. (Canceled)

28. (Previously Presented) The method of claim 18, wherein said administering does not significantly disrupt gas exchange in said human.

29. (Previously Presented) The method of claim 18, wherein said administering does not significantly affect heart rate of said human.

30. (Previously Presented) The method of claim 18, wherein said administering does not significantly affect systemic arterial pressure and systemic arterial resistance of said human.

31. (Canceled)

32. (Previously Presented) The method of claim 18, wherein said administering of said therapeutically effective single event dose is performed in 5 or less breaths.

33. (Previously Presented) The method of claim 18, wherein said human receives several therapeutically effective single event doses per day.

34. (Previously Presented) The method of claim 27, wherein the concentration of said treprostinil or a pharmaceutically acceptable salt thereof in the aerosolable solution is 600 µg/ml.

35. (Previously Presented) The method of claim 18, wherein the single event dose is administered in 5 minutes or less.

36. (Previously Presented) The method of claim 27, wherein the single event dose is administered in 5 minutes or less.

37. (Previously Presented) The method of claim 34, wherein the single event dose is administered in 5 minutes or less.

38. (Previously Presented) The method of claim 18, wherein said therapeutically effective single event dose is inhaled in 12 or less breaths by the human.

39. (Previously Presented) The method of claim 27, wherein said therapeutically effective single event dose is inhaled in 12 or less breaths by the human.

40. (Previously Presented) The method of claim 34, wherein said therapeutically effective single event dose is inhaled in 12 or less breaths by the human.

41. (Previously Presented) A method 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 a pulsed ultrasonic nebulizer having a concentration of said treprostinil or a pharmaceutically acceptable salt thereof from 500 µg/m1 to 2000 µg/ml, wherein said therapeutically effective single event dose comprises from 15 µg to 90 µg of treprostinil, or its acid derivative, or a pharmaceutically acceptable salt thereof, said therapeutically effective single event dose being inhaled in 18 or less breaths by the human.

42. (Previously Presented) A method 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 a pulsed ultrasonic nebulizer having a concentration of said treprostinil or a pharmaceutically acceptable salt thereof of 600 µg/ml, wherein said therapeutically effective single event dose comprises from 15 µg to 90 µg of treprostinil, or its acid derivative, or a pharmaceutically acceptable salt thereof, said therapeutically effective single event dose being inhaled in 18 or less breaths by the human.

43. (Previously Presented) The method of claim 18, wherein the pulsed ultrasonic nebulizer comprises an opto-acoustical trigger for timing inspiration by the human to coincide with generation of an aerosol pulse produced by the pulsed ultrasonic nebulizer.

44. (Previously Presented) The method of claim 41, wherein the pulsed ultrasonic nebulizer comprises an opto-acoustical trigger for timing inspiration by the human to coincide with generation of an aerosol pulse produced by the pulsed ultrasonic nebulizer.

45. (Previously Presented) The method of claim 42, wherein the pulsed ultrasonic nebulizer comprises an opto-acoustical trigger for timing inspiration by the human to coincide with generation of an aerosol pulse produced by the pulsed ultrasonic nebulizer.

46. (Previously Presented) The method of claim 18, wherein said administering results in pulmonary vasodilation in the human for longer than 3 hours.

REMARKS

This supplemental response and attached Declarations are filed to supplement the response filed with the RCE on November 9, 2015. To assist the Examiner in considering the original response and this supplemental response, this supplemental response includes the same substantive comments included in the original response and also additional comments based on two newly submitted Declarations. Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Applicants added new claims 41-46 in the previous response filed on November 9, 2015. No further amendments are made in this supplemental response.

Upon entry of the amendments submitted November 9, 2015, claims 18, 25, 28-30, and 32-46 will be pending and subject to examination.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 18, 25, 27-30, and 32-40 stand rejected as obvious over U.S. Published Patent Application No. 2004/0265238 to Chaudry in view of U.S. Patent No. 6,357,671 to Cewers. Applicants respectfully traverse.

To support an obviousness rejection, MPEP § 2143.03 requires "all words of a claim to be considered," and MPEP § 2141.02 requires consideration of the "[claimed] invention and prior art as a whole." Further, the Board of Patent Appeals and Interferences recently confirmed that a proper, post-*KSR* obviousness determination still requires the Office make "a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art." *In re Wada and Murphy*, Appeal 2007-3733 (BPAI Jan. 14, 2008) (citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995)). In sum, it remains well-settled law that an obviousness rejection requires at least a suggestion of all of the claim elements.

The obviousness rejection is improper because the cited references do not teach or suggest all features of the pending claims, including the "single event dose," "18 or less breaths," or a "pulsed ultrasonic nebulizer," as discussed in greater detail below.

1. The cited references do not teach or suggest the "single event dose" recited in the pending claims

According to the Office Action, the guidance allegedly provided by Chaudry regarding single event dose is found in prophetic example 4, reproduced here in its entirety:

> Example 4
>
> [0097]
>
> 5 Treprostinil sodium 0.1-10.0 mg/ml Sodium Chloride 2.0-10.0 mg/ml Sodium Hydroxide q.s. Citric Acid q.s. Water q.s.
>
> [0098] Example 4 is a prophetic example of a formulation comprising the vasodilator epoprostenol [sic: treprostinil]. Sodium chloride may be added to the solution to adjust tonicity, and sodium hydroxide and citric acid are added to adjust the pH of the solution. The solution of Example 4 may be made by methods known to those of ordinary skill in the art.

At best, this prophetic example gives a range of treprostinil concentration that varies 100-fold with the lowest concentration set at 0.1 mg/mL, *i.e.* 100 µg/mL. Such a wide dosing range is consistent with the prophetic nature of the example and does little to provide guidance to one of skill in the art.

But more importantly, and as explained in the declaration under 37 C.F.R. § 1.132 by Dr. Edmund J. Elder, Jr. ("Elder Declaration"), the "single event dose" comprising "from 15 µg to 90 µg of treprostinil or a pharmaceutically acceptable salt thereof" featured in the pending claims depends on at least two parameters: (1) the concentration of the treprostinil inhalation formulation; and (2) the volume of the formulation delivered through the single event ("delivered volume"). *See* Elder Declaration at ¶ 8. In other words, Example 4, which only describes a broad range of treprostinil concentrations, lacks the information needed for one of ordinary skill in the art to determine how to develop a single event inhalation dose for this example. Specifically, Example 4 describes only broad ranges or concentration and provides no disclosure regarding the delivered volume. Consequently, one of ordinary skill in the art would need to look into Chaudry's disclosure to obtain information, if any, regarding the "delivered volume" during a single inhalation event. Quite simply, prophetic Example 4 alone does not describe the recited "single event dose" or provide sufficient information to render obvious to one of ordinary skill in the art such a "single event dose."

Furthermore, as explained in the Elder Declaration, the "delivered volume" of an inhalable formulation delivered through a single inhalation event by a nebulizer system is based on a number of factors. Those factors, in the case of Chaudry, include the initial volume of the formulation, *i.e.*, the "fill volume," and the residual volume of the formulation that cannot be further delivered through the nebulizer, *i.e.*, the "dead volume." The "delivered volume" can be calculated by subtracting the "dead volume" from the "fill volume". *See* Elder Declaration at ¶¶ 11-12. In other words, one of ordinary skill in the art would need to know both the "dead volume" and the "fill volume" in order to assess the volume of the formulation delivered through a single even inhalation.

Turning to Chaudry's specification, one of ordinary skill in the art would note that Chaudry's paragraph [0060] describes "fill volume" in the form of a laundry list containing many alternative ranges. Nothing in Chaudry's paragraph [0060] describes the corresponding "dead volume." Later, Chaudry's paragraph [0065] describes "dead volume" also in the form of a laundry list of many alternative ranges. Nothing in Chaudry's paragraph [0065] describes the corresponding "fill volume." Thus, as explained in the Elder Declaration, Chaudry's vague disclosure in paragraphs [0060] and [0065] does not allow one of ordinary skill in the art to reasonably assess the "delivered volume" of the formulation in a single event inhalation, especially in light of the many alternative ranges provided in multiple disconnected paragraphs. *See* Elder Declaration at ¶¶ 14-17. Indeed, some of the disclosed alternatives would be inoperative. *Id.* at ¶ 17 ("[T]he combination of certain values selected from the "fill volume" and "dead volume" paragraphs results in a negative volume, which would be undeliverable.").

On the other hand, one of ordinary skill in the art would identify paragraph [0064] as specifically disclosing both "dead volume" and "fill volume" of the nebulizing device used in Chaudry:

> For example, when nebulizing an inhalation solution comprising 2.5 ml or more, about 0.7 ml of the solution remains in the nebulizer system after treatment, though the amount may vary depending on the model of the nebulizer used. In these instances, the individual is not receiving the prescribed dosage or optimum dosage of inhalation medication.

Chaudry at ¶ [0064] (emphasis added); *see also* Elder Declaration at ¶ 18. Thus, Chaudry's paragraph [0064] describes a problem of nebulizing devices in general – insufficient delivery of formulation per inhalation event because of the dead volume. *See* Elder Declaration at ¶ 19. Moreover, one of ordinary skill in the art would understand from paragraph [0064] that a delivery volume of 1.8 mL (2.5 mL fill volume – 0.7 mL dead volume) would lead to the individual "not receiving the prescribed dosage or optimum dosage of inhalation medication," including its exemplary formulations (*e.g.*, prophetic example 4) containing at least 0.1 mg/mL, *i.e.* 100 µg/mL, of treprostinil. Moreover, as noted by Dr. Elder, the insufficiency or inadequacy of 1.8 ml delivery volume is later reconfirmed by Chaudry toward the end of paragraph [0064], stating that:

> For example, in one day, due to the residual medication remaining in the nebulizer system after each treatment, an individual fails to receive approximately 2.1 ml, or more of the prescribed daily amount of medication.

Finally, as explained by Dr. Elder, Chaudry purportedly solves the problem by adjusting filling volume to reduce the dead volume with the ultimate effect of delivering more drug than conventional nebulizers:

> It is believed that the fill volumes of the one or more pulmonary hypertension reducing agents inhalation solutions of the present invention will result in lesser amounts of solution remaining in the nebulizer system after treatment, when compared to conventional inhalation solutions (e.g. 2.5 ml or 3 ml fill volume). Less solution remaining in the nebulizer system means more medication (e.g., one or more pulmonary hypertension reducing agents) administered to the individual during each treatment.

Chaudry ¶ [0065]. Taken together, Chaudry specifically teaches the amount of medication delivered per nebulizing event as being greater than a conventional nebulizer, *e.g.* at least greater than the 1.8 ml delivery volume described in paragraph [0064]. Elder Declaration at ¶¶20-22. With the lower limit of treprostinil concentration in Chaudry being 100 µg/ml, the single event dose in Chaudry would be at least 180 µg of treprostinil, which is at least two times the upper limit of the single event dose featured in the pending claims, *e.g.*, "from 15 µg to 90 µg" in claim 18. *See* Elder Declaration at ¶ 22. Thus, Chaudry teaches away from the dosage required by the present claims and, specifically, teaches away from reducing the dosage such that one of skill in the art would arrive at the dosage recited in the present claims.

2. The cited references do not teach or suggest the "18 or less breaths" featured in the pending claims

According to the latest Office Action, the guidance allegedly provided by Chaudry regarding the single event inhalation time is found in paragraph [0063]:

> . . . In another alternative embodiment, the fill volumes of the present invention 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.

As explained by Dr. Elder, one of ordinary in the art would interpret the description of times recited in paragraph [0063] as referring to the following two alternative embodiments: (1) reduce each nebulization treatment to about 12, 10, 9, 8, 6, 5, 4, 3 minutes; or (2) reduce each nebulization treatment to less time over conventional nebulizer treatments. *See* Elder Declaration at ¶ 27. This interpretation is consistent with the rest of Chaudry's disclosure of regarding treatment time. For example, paragraph [0067] states:

> . . . The individual continues breathing into the mouthpiece or facemask until the nebulization treatment is finished. This may take about 12, 11, 10, 9, 8, 7, 6, 5, 4 or 3 minutes. In an alternative embodiment, the nebulization treatment is finished when at least substantially all the mist is removed from the nebulizer chamber. This may take about 12, 11, 10, 9, 8, 7, 6, 5, 4, or 3 minutes. . .

The Office, however, interpreted the "or less" in paragraph [0063] as a continuation of "3 minutes", *i.e.*, referring to "less than 3 minutes" of each nebulizing treatment time. As clarified by Dr. Elder, this interpretation would make the "12, 10, 9, 8, 6, 5, 4, 3 minutes, or less" referring not to the reduced inhalation time itself, but to the difference between the reduced inhalation time and the conventional inhalation time - *i.e.* to reduce each nebulization treatment to about 'x' minutes over conventional nebulizer treatments. *See* Elder Declaration at ¶ 28. Without knowing the value of the conventional inhalation time or which of the various concentrations, fill volumes, dead volumes are to be used, one of ordinary skill in the art would not be able to assess what the reduced inhalation time is under the Office's interpretation of paragraph [0063]. *See* Elder Declaration at ¶ 26.

Moreover, as explained by Dr. Elder, one of ordinary skill in the art would understand that (1) the description of reduced inhalation time is general in nature (further generic/non-helpful prophetic teachings), and (2) the purported benefit for the reduced inhalation time is to improve patient compliance as a general result of requiring less time for each inhalation event. *See* Elder Declaration at ¶ 29.

Of course, one of ordinary skill in the art would only consider adopting a reduced single event inhalation time if the reduced inhalation time does not lead to significant side effects. *See* Elder Declaration at ¶ 30. In other words, one of ordinary skill in the art would not adopt the reduced inhalation time taught in Chaudry to improve patient compliance if the reduced inhalation time of a specific active agent would likely lead to adverse side effects.

This desire to avoid adverse events is important in the context of Chaudry. As explained in Applicants' response filed on January 16, 2013, it is known in the art that significant side effects are likely to occur when iloprost, one of the vasodilators specifically listed in Chaudry (paragraph [0026]), is inhaled too quickly. For example, page 17 of Gessler[1] states that:

> "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 $\mu g \cdot mL^{-1}$). In preliminary catherer 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."

Likewise, page 54 of Voswinckel[2] also states that:

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[1] Gessler et al., European Respiratory Journal; 17: 14-19 (2001); Exhibit 5 (Elder Declaration).

[2] Vonswinckel et al., Pulmonary Pharmacology & Therapeutics; 22:50–56 (2009); Exhibit 6 (Elder Declaration).

> "A dose of more than 5 µg iloprost per inhalation or a reduction of inhalation time to less than 3 min induces in most patients considerable systemic prostanoid side effects like hypotension, dizziness, headache, jaw pain, nausea or [diarrhea]."

One of ordinary skill in the art reading Chaudry at the time the present application was filed would be aware of the "considerable" systemic side effects of at least one of the specifically disclosed vasodilators (iloprost) if inhaled too quickly, *e.g.* "2 min" described in Gessler or "less than 3 min" described in Voswinckel. *See* Elder Declaration at ¶ 33. Moreover, one of ordinary skill in the art would recognize that "iloprost" is listed side-by-side as interchangeable with "treprostinil" under the specifically recognized class of "prostacyclin analogs." *See* Chaudry ¶ [0026] ("Vasodilators for use herein also include prostaglandins (Eicosanoids), including prostacyclin (Epoprostenol) and prostacyclin analogs, including Iloprost and Treprostinil, and prodrugs, salts and isomers thereof."). As such, one of ordinary skill in the art would not consider Chaudry's description of its single event inhalation time in paragraph [0063] as referring to "less than 3 minutes," at least not when the inhalable formulation contains iloprost or treprostinil. The specific teachings of Gessler and Voswinckel would cause one of ordinary skill in the art to avoid the shorter inhalation times disclosed by Chaudry assuming the correctness of the Office's interpretation of Chaudry. *See* Elder Declaration at ¶ 34.

In sum, and as supported by the Elder Declaration, the PTO failed to establish a *prima facie* case of obviousness because the cited references do not teach or suggest at least two independent elements of the claimed invention. The cited references do not teach or suggest the "single event dose" and "18 or less breaths" limitations of the pending claims. Accordingly, Applicants request withdrawal of the rejection.

3. The cited references do not teach or suggest a pulsed ultrasonic nebulizer recited in the pending claims.

The Office acknowledges on page 10, lines 5-6, of the Final Office Action that Chaudry does not teach a pulsed ultrasonic nebulizer recited in claim 18. To remedy these deficiencies of Chaudry, the Office relies on Cewers. Cewers, however, is far removed from the pulsed ultrasonic nebulizer of the present claims that controls the amount of drug administered per inhalation event, and it does not suggest the use of an "opto-acoustical trigger" as recited in

dependent claims 43-45. The Office appears to have misapprehended certain aspects of Cewers, so the following remarks provide a more detailed explanation of Cewers.

The present specification defines the pulsed ultrasonic nebulizer in paragraph [0070] as "mimicking a metered dose inhaler." A metered dose inhaler is defined in paragraph [0040] as an inhaler "capable of delivering a metered or bolus dose of a respiratory drug to the lungs." This is achieved by the pulsed ultrasonic nebulizer through a "pulse" of aerosol production followed by a pause, as described in paragraph [0078] with the exemplary Optineb nebulizer, which allows the human to breathe in each pulse and exhale during a pause before the next breath is taken. The present claims recite a number of breaths that correspond to the number of pulses of aerosol, which, taken together with the recited concentration range, makes it possible to control the dosage delivered to the human (15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof as recited in claim 18). In addition, the opto-acoustical trigger of claims 43-45 further improves accuracy by facilitating "inspiration by the human to coincide with generation of an aerosol pulse produced by the pulsed ultrasonic nebulizer."

Although Cewers does have intermittent nebulization periods, there is no suggestion that any of these nebulization periods would correspond to a timed "pulse" of aerosol that is inhaled in one breath by the patient as presently claimed. To the contrary, Cewers expressly states that the time periods during which nebulization is stopped are simply to allow measurement of liquid volume inside the nebulizing chamber:

> The variation is such that nebulization periods, during which high amplitude ultrasound are emitted which are sufficient to cause nebulization, alternate with measurement periods, during which only ultrasound sonar pulses are emitted having an amplitude, insufficient to affect i.e. disturb, the location of the upper boundary 6 to a measurable extent.
>
> During a measurement period a trigger signal is sent to the sonar detection stage 11, corresponding to the oscillator 2 being driven, to generate an ultrasonic sonar pulse. The trigger signal, which may conveniently be provided either by the controller unit 12 or the driver 10, initiates the start of timing by the timer circuitry. The time measurement is stopped when the receipt of a reflected component of the generated ultrasonic pulse is detected at the oscillator 2.

Cewers, col. 3, ll. 21-33 (emphasis supplied). A trigger signal is used when nebulization stops in order to start the measurement period with an ultrasonic sonar pulse. Thus, Cewers discloses that the liquid level information obtained during a first and a second measurement period may be compared to determine the amount of liquid nebulized during the intervening nebulization period

to provide dose information. Cewers at col. 3, 11. 51-63. The dose information is determined by an emitted acoustic pulse reflected into the chamber that is used in a manner similar to sonar detection to determine the amount of drug remaining in the chamber. Cewers at col. 3 11.1-9 and claim 1. Such a pulse is a "feedback" pulse, meaning that a reflected sound wave is used to give the depth of fluid that remains in the nebulization chamber and has no impact on the dose delivered, nor does it guide the human subject to coordinate inhalation of each breath so that it coincides with the generation of a pulse of aerosol. Cewers at col. 2 11. 56-61.

Unlike the device disclosed in Cewers, a pulsed ultrasonic nebulizer offers a distinct advantage of reducing waste of the nebulized drug. A pulsed ultrasonic nebulizer generates pulses of aerosol spaced apart in time that correspond to each breath inhaled by a human. The pulses allow inspiration of each pulse, and the pauses in between prevent drug being wasted when inspiration is not occurring while a human exhales. The pauses also reduce the risk that persons will be unintentionally exposed to drug that is not inhaled, "thereby providing exact dosage." *See* Specification at paragraph 74.

The presently claimed methods use a pulsed ultrasonic nebulizer with a starting solution of treprostinil having a certain drug concentration range. The pauses between pulses of aerosol allow the human to inhale a precise amount of drug that varies between 15 to 90 micrograms in 18 or less breaths. By contrast, Cewers uses acoustical pulses to determine the depth of liquid inside the nebulizer chamber for calculating how much drug remains. Measuring how much drug was given or how much remains is not a teaching of a "pulsed ultrasonic nebulizer" capable of delivering the dose range recited in the present claims using a certain number of breaths in one event.

4. The cited references are non-enabling as to the presently claimed methods

Prior art that is non-enabling cannot anticipate or render obvious a claimed invention. Specifically, in *Impax Laboratories v. Aventis Pharmaceuticals*, 545 F.3d 1312 (Fed. Cir. 2008), the Court held that a "[a] method for treating a mammal with amyotrophic lateral sclerosis, comprising the step of administering to said mammal in recognized need of said treatment an effective amount of 2-amino-6-(trifluoromethoxy)benzothiazole or a pharmaceutically acceptable salt thereof" was not anticipated by a non-enabling generic reference. The brand

name of the claimed compound is "riluzole." *Impax*, 545 F.3d at 1312. Thus, the patent claims at issue in *Impax*, like those currently pending in the present application, are directed to a method of treating a specific disease with a specific compound.

Impax argued at trial that the claims at issue are invalid because they are anticipated by the '940 patent, describing a generic "formula I compound," which "includes riluzole as a formula I compound, suggests that formula I compounds may be used to treat ALS, and provides some dosage information." *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 496 F.Supp. 2d 428 (D. Del. 2007). The trial court disagreed, finding that the '940 patent actually names riluzole "so to exclude it from the claimed invention or to identify it as a 'raw' or starting material for the synthesis of other compounds." *Impax*, 496 F.Supp 2d at 432. However, the trial court also pointed to a number of additional factors that led away from enablement, stating that "[m]oreover, the dosage guidelines are broad and not specific to any of the hundreds of formula I compounds of the claimed invention or to any of the listed disease." *Id.* The Court further notes that "there are no working examples in the patent for the treatment of ALS with riluzole." *Id.* Finally, the Court concludes that "'[b]ecause the link between riluzole and the treatment of ALS is speculative and undue experimentation would be required to establish such a link, the Court cannot conclude that the '940 patent is enabled." *Id.*

On appeal, the Federal Circuit affirmed the district court's decision, stating that "the district court applied the proper enablement standard and correctly determined that the '940 patent is not an enabling prior art reference and that it does not anticipate claims 1-5 of the '814 patent." *Impax*, 545 F.3d at 1315. Specifically, the Court noted that the district court relied on the following factors: (1) "excessive experimentation would have been necessary to practice the invention;" (2) "formula I of the alleged prior art discloses hundreds or thousands of compounds and several diseases;" (3) "the trial court did not find the dosage information in the disclosure to teach a proper treatment" and (4) "the noted the absence of working examples." *Id.* The Federal Circuit itself concluded that "the '940 patent's dosage guidelines are broad and general without sufficient direction or guidance to prescribe a treatment regimen" and that "[t]he alleged prior art also contains no working examples." *Id.* Thus, the Court held that "each component of the claimed invention – identifying riluzole as a treatment for ALS and devising dosage parameters – would require undue experimentation based on the teachings of the '940 patent." *Id.*

5. Secondary considerations support the non-obviousness of the pending claims

Even if the Office Action had established *prima facie* obviousness, which it does not as discussed above, the challenged claims are nevertheless patentable based on the extensive objective evidence of nonobviousness ("secondary considerations"). *See* MPEP §§ 716.01(A), 2141(V), 2145. According to MPEP 716.01(b),

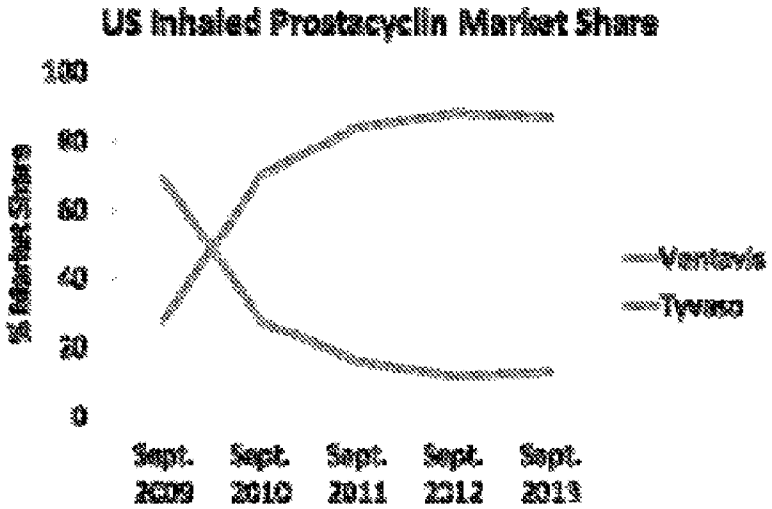
> To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed, and therefore the examiner must determine whether there is a nexus between the merits of the claimed invention and the evidence of secondary considerations. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 305 n.42, 227 USPQ 657, 673-674 n. 42 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). The term "nexus" designates a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 7 USPQ2d 1222 (Fed. Cir.), cert. denied, 488 U.S. 956 (1988).

Applicants submit herewith a second declaration under 37 C.F.R. § 1.132 by Dr. Roham T. Zamanian ("Second Zamanian Declaration") to supplement Dr. Zamanian's earlier declaration ("First Zamanian Declaration"). The Zamanian Declarations are based on the commercial product Tyvaso® (treprostinil) Inhalation Solution, which is an embodiment of the claimed invention approved by FDA for use in treating pulmonary hypertension. Dr. Zamanian's declarations provide strong evidence of commercial success and unexpected results and explain the nexus between the secondary considerations and the technical features of the pending claims, as discussed in greater detail below.

Commercial Success

Tyvaso®, an embodiment of the pending claims, has enjoyed significant commercial success since sales began in September 2009. This is supported by: (a) the total dollar amount of sales revenue generated from the Tyvaso® product; and (b) the Tyvaso® product's growth in market share from 2009 to 2014. According to Dr. Zamanian, Tyvaso®, upon launch, quickly became the preferred option over Ventavis®. *See* First Zamanian Declaration at ¶ 18. Provided below is a chart comparing market shares between Tyvaso® and Ventavis®, which is an FDA-approved and commercially available inhalable product containing iloprost for treating

pulmonary hypertension. As clearly shown in the comparison chart, the tradeoff market share and dominance of Tyvaso® over Ventavis® provides unequivocal evidence of commercial success. *See* First Zamanian Declaration at ¶¶ 18-19; *see also* Second Zamanian Declaration at ¶¶ 13-16.



More importantly, this tradeoff in market share dominance of Tyvaso® over Ventavis® results from the clinical advantages that Tyvaso® has over Ventavis®. *See* Second Zamanian Declaration at ¶¶ 13-15. In particular, the clinical advantages of Tyvaso® over Ventavis® are direct results of: a) dosing regimen of Tyvaso® compared to Ventavis®; and b) the pulsed ultrasonic nebulizer used with Tyvaso® compared to Ventavis®. *See* First Zamanian Declaration at ¶¶ 20-24 and ¶¶ 25-28.

Nexus between Commercial Success and Pending Claims

As for the dosing regimen, "[b]ecause of the pharmacodynamic differences between iloprost and treprostinil, Tyvaso® does not need to be administered as frequently as Ventavis®, leading to higher patient compliance." *See* First Zamanian Declaration at ¶ 20. "Tyvaso® (inhaled treprostinil) has a much longer half-life when inhaled by human subjects suffering from pulmonary hypertension. This allows Tyvaso® to be administered markedly less frequently - about 1 to 4 times a day." *See* First Zamanian Declaration at ¶ 22.

More importantly, the single event dosing of "from 15 μg to 90 μg of treprostinil" and the single inhalation event of "18 or less breaths" features in the pending claims combine to provide a dosing regimen that benefits from the unique pharmacodynamic profile of treprostinil to achieve the higher patient compliance, an insight of the present application heretofore unknown. *See* Second Zamanian Declaration at ¶ 14. In contrast, "Ventavis® (inhaled iloprost) has a half-life between 20-25 min. As a result, Ventavis® needs to be used 6-9 times a day, as frequent as every 2 hours." In Dr. Zamanian's practice, he has "found that patients are more likely to comply with a regimen that requires less frequent administrations; thus, Tyvaso® has been preferable." *See* First Zamanian Declaration at ¶ 23. These observations are not limited to Dr. Zamanian's practice. One study reported that "the transition from inhaled iloprost to inhaled treprostinil resulted in a time savings of approximately 1.4 h per day." Bourge et al., Cardiovascular Therapeutics 31:38-44 (2013) at 42 (emphasis added) (attached). Indeed, patients transitioning from inhaled iloprost to inhaled treprostinil had improved six-minute walk distances (a common metric to assess pulmonary hypertension), improved patient satisfaction, and improved quality of life. *Id.* at 42-43. These benefits are the result of the dosage characteristics recited in the pending claims. *Id.* Thus, the Zamanian Declarations support the requisite nexus between the commercial success of Tyvaso® and the technical features of the pending claims, including the single event dosing of "from 15 μg to 90 μg of treprostinil" and the single inhalation event of "18 or less breaths."

Turning to the pulsed ultrasonic nebulizer used with Tyvaso® over an adaptive aerosol delivery (AAD) nebulizer employed with Ventavis®, Dr. Zamanian states that "[t]he differences in the devices used to administer each drug also results in higher patient preference and

compliance with Tyvaso®," *See* First Zamanian Declaration at ¶ 25. In particular, the "pulsed ultrasonic nebulizer" and the single inhalation event of "18 or less breaths" features in the pending claims combine to provide a more effective and beneficial inhalation event that also contributes to the higher patient compliance compared to the nebulizer and inhalation duration used in existing product, an insight of the present application heretofore unknown. *See* Second Zamanian Declaration at ¶ 15.

As stated by Dr. Zamanian, "Ventavis® employs an adaptive aerosol delivery (AAD) nebulizer. See Ventavis® Patient Brochure (EXHIBIT 5). Such a device adjusts the dose amount to the volume of the breath the patient takes in. Thus, the duration of use of the device is dependent on the patient's breathing. This can lead to the time engagement required to deliver the drug ranging from 10-20 min, depending on the AAD device." *See* First Zamanian Declaration at ¶ 26. "Tyvaso® employs a pulsed ultrasonic nebulizer, as indicated in the pending claims. See Tyvaso® Patient Brochure (EXHIBIT 6). With this device, the dose is a fixed bolus dose per breath; thus, the dosing is based on breath number, e.g. 18 breaths or less as claimed. *Id*; *see also* specification at paragraphs [0040], [0070], and [0078]." *See* First Zamanian Declaration at ¶ 27. According to Dr. Zamanian, in his clinical practice, he has "found that this results in a better patient experience and, thus, higher patient compliance." *See* First Zamanian Declaration at ¶ 28. Thus, the Zamanian Declarations support the requisite nexus between the commercial success of Tyvaso® and the technical features of the pending claims, including the pulsed ultrasonic nebulizer and the single inhalation event of "18 or less breaths."

Unexpected Results

According to Dr. Zamanian, "aerosolized treprostinil administered according to the instant claims has a dose dependent and longer pharmacokinetic effect than would not be expected based on iloprost." *See* First Zamanian Declaration at ¶ 29. "As noted in paragraph [0081], while the maximum effect of aerosolized iloprost and treprostinil on pulmonary vascular resistance (PVR) was comparable, treatment with treprostinil achieved this maximum effect much sooner and lasted for a longer duration compared to treatment with iloprost. Further, while iloprost is known to reduce systemic arterial pressure (SAP), Figure 6C demonstrates that

administration of treprostinil does not result in this same reduction of SAP." *See* First Zamanian Declaration at¶ 30. "Regardless of pulse number in which dose was administered, administration of aerosolized treprostinil resulted in no significant effect on SAP. Of particular clinical interest is the high reduction of PVR achieved in a three-pulse administration of 15 μg of treprostinil, which appears to have the most modest impact on SAP based on Figures 10 and 11." *See* First Zamanian Declaration at ¶ 31. "These data suggest that treprostinil is far more pulmonary selective than iloprost: a result that would have been unexpected as of May 15, 2006." *See* First Zamanian Declaration at ¶ 32.

Nexus between Unexpected Results and Pending Claims

As stated by Dr. Zamanian, "[a]lthough not expected as of May 15, 2006, Tyvaso® is clinically superior to Ventavis® and preferred to Ventavis® for at least the above mentioned reasons. Further, the claimed method employing inhaled treprostinil results in unexpected benefits for treatment of pulmonary hypertension." *See* First Zamanian Declaration at ¶ 33; *see also* Second Zamanian Declaration at ¶¶ 17. In other words, the Tyvaso®'s unexpected clinical superiority over Ventavis® is not only attributable treprostinil's unexpected pharmacodynamic and pharmacokinetic properties recognized in the present application, it is also attributable to the technical features of the pending claims that combine to take advantage of treprostinil's unexpected pharmacodynamic and pharmacokinetic properties. *See* Second Zamanian Declaration at ¶ 19-20.

As discussed above, the single event dosing of "from 15 μg to 90 μg of treprostinil" and the single inhalation event of "18 or less breaths" features in the pending claims combine to provide a dosing regimen that benefits from the unique pharmacodynamic profile of treprostinil to achieve the higher patient compliance. *See* Second Zamanian Declaration at ¶ 21. In addition, the "pulsed ultrasonic nebulizer" and the single inhalation event of "18 or less breaths" features in the pending claims also combine to provide a more effective and beneficial inhalation event that also contributes to the higher patient compliance. *Id.* Thus, Dr. Zamanian's Declarations supports the requisite nexus between the unexpected clinical results of Tyvaso® and the technical features of the pending claims.

In sum, Applicants request withdrawal of the rejection in view of evidence of secondary considerations of non-obviousness provided in the Zamanian Declarations.

6. New claims 41 and 42

New claims 41 and 42 are patentable over the cited references because these claims include all the elements of claim 18, which is patentable over Chaudry and Cewers for the reasons discussed above. In addition, claims 41 and 42 are patentable over Chaudry and Cewers because one of ordinary skill in the art would not have arrived at the particular treprostinil concentrations recited for use with the pulsed ultrasonic nebulizer of these claims. As noted above, Chaudry's prophetic example 4 teaches a concentration range varying between 0.1 and 10 mg/ml, but it gives no information about the number of breaths per dosing event or the type of inhalation device. Nothing in Chaudry or Cewers or the combination thereof would have led one of ordinary skill in the art to select the type of device in the present claims, the number of breaths and the particular concentration of claims 41 and 42.

7. New claim 43-45

New claims 43-45 are patentable over the cited references because they depend on claims 18, 41 and 42, which are patentable over Chaudry and Cewers for the reasons discussed above. In addition, claim 43-45 are patentable over the cited prior art because Chaudry and Cewers do not teach or suggest "an opto-acoustical trigger for timing inspiration by the human to coincide with generation of an aerosol pulse produced by the pulsed ultrasonic nebulizer." Although Cewers mentions a "trigger" in column 3, lines 28-33, as shown above, Cewers' trigger is totally different from the opto-acoustical trigger recited in claims 43-45. The trigger in Cewers is used to trigger a timing interval for measuring the liquid level <u>inside the nebulization chamber</u> using an ultrasound pulse while nebulization is stopped. Thus, it has no relationship whatsoever to "timing inspiration by the human to coincide with generation of an aerosol pulse."

8. New claim 46

New claim 46 is patentable over the cited references because it depends on claim 18, which is patentable over Chaudry and Cewers for the reasons discussed above. In addition, claim 46 is patentable over the cited prior art because Chaudry and Cewers do not teach that administering of treprostinil by inhalation can achieve pulmonary vasodilation in the human for longer than 3 hours. Applicants respectfully submit that one of ordinary skill in the art would not expect such results based on the cited references.

DOUBLE PATENTING REJECTION

Claims 18, 25, 27-30 and 32-34 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1, 4-17, and 52-59 of co-pending Application No. 11/748,205 in view of Chaudry et al. (US Pub. No. 2004/0265328), Byron (Proc. Am. Thor. Soc. (1), pp. 321-328, 2004) and Cloutier et al. (USPN 6,521,212).

This rejection should be withdrawn in view of abandonment of U.S. Application No. 11/748,205.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition

for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: Feb. 2, 2016

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Horst OLSCHEWSKI et al.
Title:	TREPROSTINIL ADMINISTRATION BY INHALATION
Appl. No.:	12/591,200
Filing Date:	11/12/2009
Examiner:	Sara Elizabeth Townsley
Art Unit:	1629
Confirmation Number:	4093

SECOND DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. ROHAM T. ZAMANIAN

I, Dr. Roham T. Zamanian, hereby declare:

1. I received a Bachelor of Science and a Doctor of Medicine from the University of California, Irvine, where I also completed my internship, residency, and a fellowship in pulmonary medicine and critical care. I completed a second fellowship in pulmonary medicine and critical care at Stanford University Medical Center where I am now an Associate Professor of Medicine and Director of the Adult Pulmonary Hypertension Program.

2. I am board certified in both internal and pulmonary medicine and have served as an investigator in a number of clinical trials of pulmonary hypertension drug trials, which are listed in my CV. *See* EXHIBIT 1 of my previous Declaration submitted November 9, 2015.

3. My research focuses on strategies for management of pulmonary hypertension, and I have a number of publications in these areas – listed in my CV. *See* EXHIBIT 1 of my previous Declaration submitted November 9, 2015.

4. I am a paid consultant for United Therapeutics, the assignee of the above-identified patent application, in connection with this matter. My compensation does not depend on the content of my opinions or the disposition of this application.

5. Prior to consulting for United Therapeutics, I was a principal investigator in the "Aspire" registry comparing the incidence of respiratory tract adverse events in patients treated with United Therapeutics' product – Tyvaso® – with other FDA approved pulmonary hypertension therapies. Stanford University has also received compensation from United Therapeutics for my work as an investigator on the CONFRONT and FREEDOM M trials.

I. The Cited References

6. I have read and am familiar with the Office Action dated October 10, 2014 in U.S. Patent Application No. 12/591,200 as well as the disclosure and claims of the subject application. I am also familiar with the references cited in the Office Action.

7. I understand the claims of U.S. Patent Application No. 12/591,200 are directed to a method 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 a pulsed ultrasonic nebulizer, wherein said therapeutically effective single event dose comprises from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof, said therapeutically effective single event dose is inhaled in 18 or less breaths by the human.

8. I have reviewed US 2004/0265238 (Chaudry) and U.S. Patent No. 6,357,671 (Cewers) cited in the Office Action, in addition to further references pertinent in the art regarding inhaled pulmonary hypertension treatment – specifically those references cited herein and attached as EXHIBITS 2-7.

9. Chaudry broadly relates to inhalable formulations for treating pulmonary hypertension and methods of using the same, see, *e.g.* title. Among the list of hypertension reducing agents included the extensive list of paragraphs [0022]-[0027] are treprostinil and iloprost. Both compounds are cited among examples of vasodilators in paragraph [0026] that may ostensibly be used interchangeably with any other compound disclosed in the paragraph.

10. An exemplary embodiment of the claimed invention comprising treprostinil is FDA approved for use with pulmonary hypertension and available on the market as Tyvaso®. An inhalable formulation for treating pulmonary hypertension containing iloprost, Ventavis®, is also FDA approved and currently available on the market.

11. I am aware that a claimed invention can be considered nonobvious in view of prior art based on objective evidence of nonobviousness ("secondary considerations"). I have also been informed that such secondary considerations can include commercial success attributable to the claimed features and unexpected results. I also understand that for such evidence to be relevant, there must be a sufficient nexus between the evidence of secondary considerations and the features of the claims.

12. I am familiar with the Tyvaso® product and its clinical use to treat pulmonary hypertension. I understand that the invention recited in the pending claims is implemented in the Tyvaso® product, which has enjoyed significant commercial success and produced unexpected clinical results, both directly attributable to the technical features of the pending claims.

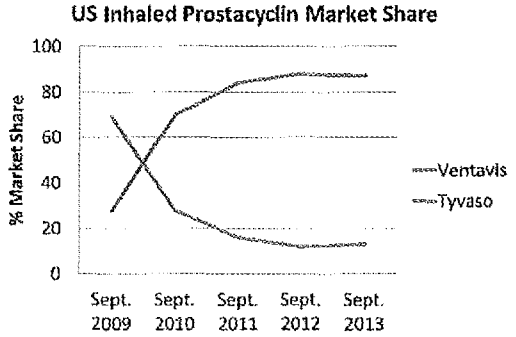
II. Commercial Success

13. Tyvaso® has seen a rapid increase in market share growth since its introduction. See "US Inhaled Prostacyclin Market Share" chart, reproduced above. The commercial success of the Tyvaso® product is directly attributable to features recited in the pending claims.

14. First, the commercial success of Tyvaso® directly results from its unique dosing regimen. In particular, the single event dosing of "from 15 μg to 90 μg of treprostinil" and the single inhalation event of "18 or less breaths" feature in the pending claims combine to provide a dosing regimen that benefits from the unique pharmacodynamic profile of treprostinil to achieve the higher patient compliance. This unique dosing regimen and its clinical effect have not been recognized by either Chaudry or the art in general.

15. Second, the commercial success of Tyvaso® direct results from the pulsed ultrasonic nebulizer used with Tyvaso®. In particular, the "pulsed ultrasonic nebulizer" and the single inhalation event of "18 or less breaths" featured in the pending claims combine to provide a more effective and beneficial inhalation event that also contributes to the higher patient compliance compared to the nebulizer and inhalation duration used in the onyly other existing inhaled product (Ventavis®). This unique dosing regimen and its clinical effect have not been recognized by either Chaudry or the art in general.

16. There is a clear nexus between the commercial success of Tyvaso® and the technical features of the pending claims, including the single event dosing of "from 15 μg to 90 μg



of treprostinil", the single inhalation event of "18 or less breaths," and the pulsed ultrasonic nebulizer.

III. Unexpected Results

17. As explained in my previous Declaration, at the time of the present application, iloprost and treprostinil are two alternative prostacyclin analogues. *See, e.g.* Chaudry at paragraph [0026]. While both iloprost and treprostinil have similar maximum effect on pulmonary vascular resistance (PVR), the effect on PVR is longer sustained by treprostinil than by iloprost. Moreover, they have differential effects on systemic arterial pressure (SAP). *See* Fig. 5, 6 and 7.

18. Tyvaso® (inhalable treprostinil) is preferred over Ventavis® (inhalable iloprost), as evidenced in the tradeoff market share shown in the chart above. In my clinical experience, this results from clinicians' awareness of its higher patient compliance and its favorable hemodynamic/clinical profile.

19. The present application recognizes unique pharmacodynamic and pharmacokinetic properties of treprostinil. However, mere recognition of those fundamental properties would not by itself produce the unexpected clinical result seen in the Tyvaso® product.

20. Tyvaso®'s unexpected clinical superiority over Ventavis® is not only attributable treprostinil's unexpected pharmacodynamic and pharmacokinetic properties recognized in the present application, it is also attributable to the technical features of the pending claims that combine to translate treprostinil's unexpected pharmacodynamic and pharmacokinetic properties into its unexpected clinical results.

21. In particular, the single event dosing of "from 15 μg to 90 μg of treprostinil" and the single inhalation event of "18 or less breaths" featured in the pending claims combine to provide a dosing regimen that benefits from the unique pharmacodynamic profile of treprostinil to achieve the higher patient compliance. In addition, the "pulsed ultrasonic

nebulizer" and the single inhalation event of "18 or less breaths" feature in the pending claims also combine to provide a more effective and beneficial inhalation event that also contributes to the higher patient compliance.

22. Thus, there is a clear nexus between the unexpected clinical results of Tyvaso® and the specific technical features of the pending claims, including the single event dosing of "from 15 μg to 90 μg of treprostinil", the single inhalation event of "18 or less breaths," and the use of a pulsed ultrasonic nebulizer that give rise to the unexpected clinical results observed with Tyvaso®.

IV. Concluding Statements

23. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 1st day of February, 2016.

MD

Dr. Roham T. Zamanian