Watson

Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054
T 862.261.7000
F 862.261.7001
www.watson.com

June 29, 2016

Via FedEx®

General Counsel
United Therapeutics Corporation
55 TW Alexander Drive
Research Triangle Park, NC 27709

General Counsel
United Therapeutics Corporation
1735 Connecticut Ave, N.W., #2
Washington, DC 20009

General Counsel
United Therapeutics Corporation
1040 Spring Street
Silver Spring, MD 20910

Foley& Lardner
Stephen B. Maebius
3000 K Street, N.W., Suite 600
Washington, DC 20007-5109

HIGHLY CONFIDENTIAL

Re: Notification of Certification for U.S. Patent Nos. 9,339,507 and 9,358,240 Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act

Dear Madam or Sir:

Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95, Watson Laboratories, Inc. ("Watson") hereby provides notice of the following information to United Therapeutics Corporation ("United Therapeutics"), as the apparent holder of approved New Drug Application ("NDA") No. 022387 for Tyvaso® (treprostinil) Inhalation Solution, 0.6 mg/ml according to the records of the U.S. Food and Drug Administration ("FDA") and record owner of U.S. Patent Nos. 9,339,507 ("the '507 patent") and 9,358,240 ("the '240 patent) as indicated on the face of the patents.

As a courtesy, Watson is also providing a copy of this Notice Letter and Detailed Statement to Foley & Lardner, c/o Stephen B. Maebius, as the correspondent for the '507 and '240 patents as indicated on the face of the patents.

Pursuant to 21 C.F.R. § 314.95(c), Watson requested from FDA permission to send this notice by means other than registered or certified mail. Specifically, Watson requested that it be allowed to send this notice by FedEx®. FDA granted Watson's request.

I. Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(I) and 21 C.F.R. § 314.95(c)(1), we advise you that FDA has received a Patent Amendment to Abbreviated New Drug Application ("ANDA") from Watson for Treprostinil Inhalation Solution, 0.6 mg/ml. The ANDA contains the required bioavailability and/or bioequivalence data and/or bioequivalence waiver. The Patent Amendment was submitted under 21 U.S.C. § 355(j)(1) and (2)(A), and contains Paragraph IV certifications to obtain approval to engage in the commercial manufacture, use or sale of Treprostinil Inhalation Solution, 0.6 mg/ml before the expiration of U.S. Patent Nos. 9,339,507 and 9,358,240 which are listed in the Patent and Exclusivity Information Addendum of FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book").

II. Pursuant to 21 C.F.R. § 314.95(c)(2), we advise you that FDA has assigned Watson's ANDA the number 208172.

III. Pursuant to 21 C.F.R. § 314.95(c)(3), we advise you that the established name of the drug product that is the subject of Watson's ANDA is Treprostinil Inhalation Solution, 0.6 mg/ml.

IV. Pursuant to 21 C.F.R. § 314.95(c)(4), we advise you that the active ingredient in the proposed drug product is treprostinil; the strength of the proposed drug product is 0.6 mg/ml of treprostinil; and the dosage form of the proposed drug product is inhalation solution.

V. Pursuant to 21 C.F.R. § 314.95(c)(5), we advise you that the patents alleged to be invalid, unenforceable, and/or not infringed in the Paragraph IV certifications are U.S. Patent Nos. 9,339,507 and 9,358,240 which are listed in the Orange Book in connection with United Therapeutics' approved NDA No. 022387 for Tyvaso®. According to information published in the Orange Book, the patents will expire as follows:

U.S. PATENT NO.	EXPIRATION DATE
9,339,507	March 10, 2028
9,358,240	May 5, 2028

VI. Watson alleges, and has certified to FDA, that in Watson's opinion and to the best of its knowledge, U.S. Patent Nos. 9,339,507 and 9,358,240 are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use or sale of the drug product described in Watson's ANDA. Therefore, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(6), Watson's detailed statement of the legal and factual basis for the Paragraph IV certifications set forth in Watson's Patent Amendment is attached hereto and made

a part hereof.

VII. Pursuant to 21 U.S.C. § 355(j)(5)(C), this notice letter includes an Offer of Confidential Access to Application. As required by § 355(j)(5)(C)(i)(III), Watson offers to provide confidential access to certain information from its ANDA No. 208172 for the sole and exclusive purpose of determining whether an infringement action referred to in § 355(j)(5)(B)(iii) can be brought.

Confidential Access to Watson's ANDA No. 208172 shall be governed by the Stipulated Protective Order, entered in Civil Action No. 3:15-cv-05723.

Section 355(j)(5)(C)(i)(III) provides that any request for access that United Therapeutics makes under this Offer of Confidential Access "shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in [this] offer of confidential access" and that the "restrictions and other terms of [this] offer of confidential access shall be considered terms of an enforceable contract." Thus, to the extent that United Therapeutics requests access to Confidential Watson Information, it necessarily accepts the terms and restrictions outlined above.

By providing this Offer of Confidential Access to Application, Watson maintains the right and ability to bring and maintain a Declaratory Judgment action under 28 U.S.C. § 2201 *et seq.*, pursuant to 21 U.S.C. § 355(j)(5)(C).

Very truly yours,

Watson Laboratories, Inc.

By: for B Brown
Joyce Anne Delgaudio
Executive Director, Regulatory Affairs

Enclosure: *Watson's Detailed Factual and Legal Basis for Its Paragraph IV Certifications that U.S. Patent Nos. 9,339,507 and 9,358,240 are Invalid, Unenforceable and/or Not Infringed by the Treprostinil Product Described in Watson's ANDA No. 208172*

ENCLOSURE

Watson's Detailed Factual and Legal Basis for Its Paragraph IV Certifications that U.S. Patent Nos. 9,399,507 and 9,358,240 Are Invalid, Unenforceable and/or Not Infringed by the Treprostinil Product Described in Watson's ANDA No. 208172

I. Introduction

Pursuant to § 505(j)(2)(B)(iv)(II) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95(c)(6), this document is the detailed factual and legal basis for the Paragraph IV certifications of Watson Laboratories, Inc. ("Watson") that, in its opinion and to the best of its knowledge, U.S. Patent Nos. 9,339,507 ("the '507 patent") and 9,358,240 ("the '240 patent") are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the Treprostinil product described in Watson's ANDA No. 208172. Watson specifically reserves the right to raise any additional defenses should litigation ensue.

II. Watson's ANDA Products

The product that is the subject of Watson's ANDA No. 208172 ("Watson ANDA Product" or "Watson ANDA formulation") is a generic version of Tyvaso® (treprostinil) Inhalation Solution, 0.6 mg/ml. Watson's ANDA Product is an inhalation solution containing as the active pharmaceutical ingredient treprostinil. The strength of Watson's ANDA Product is 0.6 mg/ml. Watson will market the Watson ANDA Product for the currently approved indication for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

III. The Orange Book Listed Patents

U.S. PATENT NO.	EXPIRATION DATE
9,339,507	March 10, 2028
9,358,240	May 5, 2028

IV. Legal Principles

A. Claim Construction

A court must first construe claims before determining whether they are valid or infringed. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976, 976 n. 7 (Fed. Cir. 1995) (*en banc*). Claims must be construed the same way for determining validity and infringement. *Amazon.com*, 239 F.3d at 1351.

The claim construction inquiry begins in all cases with the actual words of the claims. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*). Claim terms are to be given their ordinary and customary meanings as they would have been understood by a person of ordinary skill in the art in the context of the patent at the time of the invention, *i.e.*, as of the effective filing date of the patent application. *Id.* at 1312–14. To properly interpret claim terms, the "intrinsic" record, including the claims, the specification, and the prosecution history must be considered. *Id.* at 1314–24. The claims must be read "in view of" and "so as to be consistent with" the specification, which is the "single best guide to the meaning of a disputed term." *Id.* at 1315–1316. The importance of the specification in claim construction derives from its statutory role of providing a "full" and "exact" description of the claimed invention. *Id.* at 1316.

B. Infringement

To literally infringe a United States Letters Patent, an accused product or process must meet each and every limitation of the patent claim exactly, including any functional limitations. *See Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989). Any deviation from the claim precludes a finding of literal infringement. *See, e.g., Cole v. Kimberly-Clark Corp.*, 102 F.3d 524, 532 (Fed. Cir. 1996).

An analysis of literal infringement requires two inquiries: first, the claims must be construed to resolve their proper scope and meaning; and second, it must be determined whether the accused product or process falls exactly within the scope of the properly construed claims. *See Markman*, 52 F.3d at 976; *see also Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364, 1368 (Fed. Cir. 1996). The first inquiry is a legal question for the court; the second inquiry is a factual determination for the fact-finder. *See Markman*, 52 F.3d at 976–80.

Infringement may also be found under the doctrine of equivalents if the accused product or method includes features that are equivalent to each claimed element. *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21, 40 (1997). The determination of equivalency is an objective inquiry applied on an element-by-element basis taking into account the role of each claim element in the context of the claim. *Id.* at 29, 40.

The Supreme Court has not mandated any specific approach to evaluate equivalency. *Id.* at 39-40. Among the recognized approaches that may be applied include the function-way-result test and the insubstantial differences test. *Id.* at 25, 36, 39-40.

There are a number of limitations on the application of the doctrine of equivalents. For example, the doctrine of equivalents cannot be applied so as to effectively eliminate a claim limitation in its entirety. *Id.* at 29. Moreover, limitations may not be afforded a scope of equivalency that effectively results in a claim that does not patentably distinguish the prior art. *See, e.g., Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 683 (Fed. Cir. 1990), overruled on other grounds by *Cardinal Chem. Co. v. Morton Int'l*, 508 U.S. 83 (1993). Additionally, prosecution history estoppel operates to prevent recapture, through the doctrine of equivalents, of coverage of subject matter that was relinquished by amendment or argument during prosecution. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 733-34 (2002).

Although the sale of an apparatus to perform a patented method or process is not a direct infringement of a method or process claim, such a sale may nevertheless constitute an active inducement of infringement under 35 U.S.C. § 271(b) and/or a contributory infringement under 35 U.S.C. § 271(c). *See Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993). "Liability for either active inducement of infringement or for contributory infringement is dependent upon the existence of direct infringement." *Id.*; *see also C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 673 (Fed. Cir. 1990).

Inducement of infringement is actively and knowingly aiding and abetting another's direct infringement of a patent claim. *See id.* at 675; *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). In order to find induced infringement, a patentee must show (i) direct infringement, either literally or under the doctrine of equivalents, (ii) that the alleged indirect infringer actually intended to cause another to directly infringe, (iii) that the alleged indirect infringer knew of the allegedly infringed patents, and (iv) that the alleged indirect infringer knew or should have known that its actions would lead to actual infringement. *See* 35 U.S.C. § 271(b) (2011); *see also DSU Med. Corp.*, 471 F.3d at 1304–05.

Contributory infringement is knowingly making and/or selling a product for use in practicing a patented method or process, when that product is specifically designed for use in infringement of the patented method or process and has no substantial non-infringing uses. *See Preemption Devices, Inc. v. Minn. Mining & Mfg. Co.*, 803 F.2d 1170, 1174 (Fed. Cir. 1986).

C. Invalidity

A patent may be proven invalid by a showing of clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S.Ct. 2238, 2251 (2011).

1. Anticipation

One basis for establishing invalidity is anticipation by the prior art. The general test for anticipation requires that each and every limitation recited in a claim must be found in one item of prior art, either expressly or inherently, and arranged in the item of prior art in the same way as it is claimed, so that the disclosure effectively puts the public in possession of the invention. *Silicon Graphics, Inc. v. ATI Technologies, Inc.*, 607 F.3d 784, 796–97 (Fed. Cir. 2010). A reference will be considered anticipatory if "it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152, 36 U.S.P.Q.2d 1697 (Fed. Cir. 1995).

The law of anticipation does not require that a prior art reference explicitly disclose information that is inevitably present based on the express disclosure of the reference. Thus, "[a]n anticipatory reference … need not duplicate word for word what is in the claims. Anticipation can occur when a claimed limitation is 'inherent' or otherwise implicit in the relevant reference." *Standard Havens Products, Inc. v. Gencor Industries, Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991). In addition, "products of identical chemical composition cannot have mutually exclusive properties." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). A chemical composition and its properties are inseparable. *Id.* Therefore, if the

prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *Id.*

Inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. *Abbott Laboratories v. Baxter Pharmaceutical Products, Inc.*, 471 F.3d 1363, 1367–68 (Fed. Cir. 2006). Thus, with respect to claims to chemical compositions, the discovery of inherent properties of prior compositions that were unknown or unrecognized prior to the alleged invention does not impart patentable novelty on the chemical composition. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("it is immaterial, on the issue of novelty, what inherent properties the alloys have or whether these applicants discovered certain inherent properties").

Further, a party may rely on extrinsic evidence to show a feature not explicitly disclosed in a prior art reference is inherently disclosed in that reference. The Federal Circuit has explained:

> recourse to extrinsic evidence is proper to determine whether a feature, while not explicitly discussed, is necessarily present in a reference. The evidence must make clear that the missing feature is necessarily present, and that it would be so recognized by persons of skill in the relevant art.

Telemac Cellular Corp. v. Topp Telecom, Inc., 247 F.3d 1316, 1328 (Fed. Cir. 2001).

As such, a party asserting inherent anticipation may reference extrinsic evidence beyond the disclosure of the inherently anticipating reference to establish that an inherent feature or property is necessarily present.

2. Obviousness

A patent claim is invalid in view of one or a combination of multiple prior art references if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a)[1] (2011). In determining obviousness, the following four factors must be considered: (1) the scope and content of the prior art; (2) any differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and, (4) any secondary considerations evidencing nonobviousness, such as commercial success, copying, long felt but unsolved needs, failures of others, unexpected results, etc. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966)).

In *KSR*, the U.S. Supreme Court confirmed that, in evaluating obviousness, "an expansive and flexible" approach is to be taken, *i.e.*, "rigid and mandatory formulas" are

[1] 35 U.S.C. 103(a) in its form prior to March 16, 2013 is applicable to the Orange Book Patents, since the filing date of the earliest applications for which the Orange Book Patents are entitled to priority falls before March 16, 2013.

improper. *Id.* at 415, 419. More specifically, the Court stated that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. Additionally, it is likely obvious to: (1) substitute one known element for another in a known structure to yield no more than a predictable result, (2) arrange old elements with each performing its same known function to yield no more than one would expect from the arrangement, (3) make a predictable variation in a known work, when there are design incentives or other market forces prompting the variation (either in the same or a different field) and a person of ordinary skill could have implemented the variation, and (4) use a known technique for improving one device to improve similar devices in the same way, if such use of the technique would be recognized by and within the capability of a person of ordinary skill in the art. *Id.* at 416–417. In these situations, a court must ask "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

Relevant factors in determining the level of ordinary skill in the art include the educational level of active workers in the field, the type of problems encountered in the art, prior art solutions to such problems, the rapidity of innovations in the art, and the sophistication of the technology. *See In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

In order for evidence of secondary considerations of non-obviousness to be given substantial weight, the patentee must demonstrate that there is a nexus between such evidence and the merits of the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–13 (Fed. Cir. 2006). In other words, such evidence must arise from the claimed invention, rather than from extrinsic influences such as unclaimed features, prior art features, marketing activities, FDA requirements, etc. *Id.*

V. Factual and Legal Basis for Watson's Certification

A. U.S. Patent No. 9,339,507 ("the '507 patent"); Treprostinil Administration by Inhalation

U.S. Patent No. 9,339,507 ("the '507 patent") to Olschewski et al. issued May 17, 2016. The '507 patent is entitled "Treprostinil Administration by Inhalation," and is assigned on its face to United Therapeutics Corporation. The application that became the '507 patent was filed with the USPTO on May 11, 2012 and assigned U.S. Patent Application No. 13/469,854 ("the '507 patent application").

1. The Claims of the '507 Patent

The claims of the '507 patent read as follows:

> 1. A kit for treating pulmonary hypertension comprising:
>
> (i) a formulation comprising 200 to 1000 μg/ml treprostinil or a pharmaceutically acceptable salt thereof;
>
> (ii) a pulsed ultrasonic nebulizer comprising an opto-acoustical trigger, configured to
>
> (a) aerosolize a fixed amount of treprostinil per pulse, and

(b) deliver by inhalation a therapeutically effective single event dose of said formulation,

said single event dose comprising 15 μg to 90 μg treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths; and

(iii) instructions for using the pulsed ultrasonic nebulizer with the formulation to treat a patient with pulmonary hypertension by delivering 15 μg to 90 μg treprostinil or a pharmaceutically acceptable salt thereof in 1 to 18 breaths to the patient in the single event dose.

2. The kit of claim 1, wherein the formulation comprises 600 μg/ml of the treprostinil or its pharmaceutically acceptable salt thereof.

3. The kit of claim 1, further comprising instructions for the human not to repeat the single event dose for a period of at least 3 hours.

4. The kit of claim 1, wherein the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose.

5. The kit of claim 1, wherein the fixed amount of treprostinil or its pharmaceutically salt for each breath inhaled by the human comprises at least 5 ng of treprostinil or its pharmaceutically acceptable salt.

6. The kit of claim 2, wherein the fixed amount of treprostinil or its pharmaceutically salt for each breath inhaled by the human comprises at least 5 ng of treprostinil or its pharmaceutically acceptable salt.

7. The kit of claim 1, wherein the single event dose is inhaled in 3 to 18 breaths by the human.

8. The kit of claim 6, wherein the single event dose is inhaled in 3 to 18 breaths by the human.

9. The kit of claim 6, further comprising instructions for the human not to repeat the single event dose for a period of at least 3 hours.

'507 patent at 18:12-52.

B. U.S. Patent No. 9,358,240; Treprostinil Administration by Inhalation

U.S. Patent No. 9,358,240 ("the '240 patent") to Olschewski et al. issued June 7, 2016. The '240 patent is entitled "Treprostinil Administration by Inhalation," and is assigned on its face to United Therapeutics Corporation. The application that became the '240 patent was filed with the USPTO on November 12, 2009 and assigned U.S. Patent Application No. 12/591,200 ("the '240 patent application"). The '240 patent application was a continuation of U.S. Patent Application No. 11/748,205 ("the '205 application"), filed on May 14, 2007 and now abandoned. The '205 application claimed priority to U.S. Provisional Application No. 60/800,016, filed on May 15, 2006.

1. The Claims of the '240 Patent

The claims of the '240 patent read as follows:

> 1. A method of treating pulmonary hypertension comprising:
>
> administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising from 200 to 1000 μg/ml of treprostinil or a pharmaceutically acceptable salt thereof
>
> with a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse,
>
> said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse,
>
> said therapeutically effective single event dose comprising from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths.
>
> 2. The method of claim 1, wherein the formulation comprises 600 μg/ml of the treprostinil or its pharmaceutically acceptable salt thereof.
>
> 3. The method of claim 1, wherein the single event dose is not repeated for a period of at least 3 hours.
>
> 4. The method of claim 1, wherein the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose.
>
> 5. The method of claim 1, wherein the fixed amount of treprostinil or its pharmaceutically salt for each breath inhaled by the human comprises at least 5 μg of treprostinil or its pharmaceutically acceptable salt.
>
> 6. The method of claim 2, wherein the fixed amount of treprostinil or its pharmaceutically salt for each breath inhaled by the human comprises at least 5 μg of treprostinil or its pharmaceutically acceptable salt.
>
> 7. The method of claim 1, wherein the single event dose is inhaled in 3-18 breaths by the human.
>
> 8. The method of claim 6, wherein the single event dose is inhaled in 3-18 breaths by the human.
>
> 9. The method of claim 6, wherein the single event dose is not repeated for a period of at least 3 hours.

'240 patent at 18:2-37.

C. Claim Construction

The claims of the '507 and '240 patents are to be accorded their usual and ordinary meanings to one of ordinary skill in the art as informed by the specification and file history.

D. Non-Infringement Analysis

1. The '507 Patent

(a) Watson's ANDA Product Does Not Directly or Indirectly Infringe the Claims of the '507 Patent.

Claim 1 is the sole independent claim of the '507 patent and reads as follows:

> 1. A kit for treating pulmonary hypertension comprising:
> (i) a formulation comprising 200 to 1000 μg/ml treprostinil or a pharmaceutically acceptable salt thereof;
> (ii) a pulsed ultrasonic nebulizer comprising an opto-acoustical trigger, configured to
> (a) aerosolize a fixed amount of treprostinil per pulse, and
> (b) deliver by inhalation a therapeutically effective single event dose of said formulation,
> said single event dose comprising 15 μg to 90 μg treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths; and
> (iii) instructions for using the pulsed ultrasonic nebulizer with the formulation to treat a patient with pulmonary hypertension by delivering 15 μg to 90 μg treprostinil or a pharmaceutically acceptable salt thereof in 1 to 18 breaths to the patient in the single event dose.

'507 patent at 18:12-28.

The Watson ANDA Product does not literally infringe claim 1 of the '507 patent because the Watson ANDA Product is an ampoule comprising a treprostinil formulation for inhalation and not a kit comprising: (i) a formulation comprising 200 to 1000μg/ml treprostinil; (ii) a pulsed ultrasonic nebulizer; and (iii) instructions for using the pulsed ultrasonic nebulizer with the formulation.

Further, claim 1 cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA Product based on claim vitiation. That is, if claim 1 was expanded to include the Watson ANDA Product, then the entire element of claim 1 requiring a kit comprising a pulsed ultrasonic nebulizer would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc. v. Emtrak, Inc.*, 402 F.3d 1188, 1195 (Fed. Cir. 2005); *Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1358 (Fed. Cir. 2005).

Claims 2-9 of the '507 patent depend, either directly or indirectly, from claim 1 and thereby incorporate all the limitations of claim 1. *See* 35 U.S.C. § 112, ¶ 4 (providing in relevant part "A claim in dependent form shall be construed to incorporate by reference all the limitations

of the claim to which it refers."). *See also Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1358 (Fed. Cir. 2007) ("Instead, claim 4, like its predecessor claim, as attested by the prosecution history, is in dependent form and incorporates the limits of the overarching independent claim." *Id.*); *Wolverine World Wide, Inc. v. Nike, Inc.*, 38 F.3d 1192, 1199 (Fed. Cir. 1994) ("It is axiomatic that dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed." *Id.* (internal citations and quotations omitted)). Therefore, the Watson ANDA Product cannot infringe claims 2-9 of the '507 patent, either literally or under the doctrine of equivalents, for the reasons discussed above regarding claim 1 of the '507 patent.

The manufacture, sale, or distribution of the Watson ANDA Product is not an act of indirect infringement of the '507 patent under a theory of induced infringement and/or contributory infringement, because the use of the Watson ANDA Product with a pulsed ultrasonic nebulizer does not directly infringe the claims of the '507 patent.

It is well-settled law that indirect infringement cannot occur without an act of direct infringement. *See Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 134 S.Ct. 2111, 2118-19 (2014) ("[I]n this case, performance of all the claimed steps cannot be attributed to a single person, so direct infringement never occurred. Limelight cannot be liable for inducing infringement that never came to pass."); *Kendal Co. v. Progressive Medical Technology*, 85 F.3d. 1570, 1573 (Fed. Cir. 1996). It is also well-settled law that the replacement of an unpatented part of a claimed multi-part invention is the lawful right of the owner to repair his property. *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336 (1961); *Kendal*, 85 F.3d at 1574. *See also Special Equipment Co. v. Coe*, 324 U.S. 370 (1925) (the unpatented part of a combination patent may be appropriated by anyone).

In the present situation, a patient will initially obtain the TYVASO® kit from United Therapeutics, the owner of the '507 patent. The TYVASO® kit includes a Nebu-Tec OPTINEB® ultrasonic inhaler, instructions for using the inhaler, and an initial supply of ampoules containing 600 µg/mL of treprostinil. The patent owner is aware that the initial supply of ampoules that are included with the kit will be used by the patient and additional ampoules will be required to continue to use the kit. *See* TYVASO® Prescribing Information at p. 3 (*2.4 Administration*), 12 (*16 How Supplied/Storage and Handling*). Therefore, the patient legally obtained the TYVASO® kit along with the right to obtain replacement ampoules in order to continue to use the TYVASO® kit.

The '507 patent only claims a treprostinil formulation in combination with a kit that includes a nebulizer and instructions, and does not claim a treprostinil formulation alone. Indeed, the '507 patent could not claim only a formulation containing 200-1000µg/mL of treprostinil because formulations containing this range of treprostinil for use in nebulizers were known in the art well before the filing date of the '507 patent. *See generally* Cloutier et al., U.S. Patent No. 6,521,212 ("Cloutier") at 5:22-29 (disclosing an inhalation formulation comprising 500 µg/mL of treprostinil).

Because the Watson ANDA Product is an unpatented and known disposable part of the kit recited in the claims of the '507 patent, a patient is permitted to obtain the unpatented ampoules from any source, including Watson, for use with a TYVASO® kit that is lawfully

obtained from the '507 patent owner or an authorized distributor. Therefore, there is no act of direct infringement by a patient using the Watson ANDA Product in the OPTINEB® nebulizer provided with the TYVASO® kit, and accordingly, the manufacture, sale, or distribution of the Watson ANDA Product is not an act of indirect infringement of the claims of the '507 patent. *See Kendall*, 85 F.3d at 1570 (holding that the sale of an unpatented disposable sleeve for use with a medical device that applies pressure to a patient's limbs was not an act of contributory infringement of a patent claiming the sleeve as an element of the medical device); *Sage Products, Inc. v. Devon Industries, Inc.*, 45 F.3d 1575 (Fed. Cir. 1995) (holding that the sale of removable inner container liners for use in a disposal device for sharp medical items was not an act of contributory infringement of a patent that claimed the inner container liner as an element of the disposal device); *Everpure, Inc. v. Cuno, Inc.*, 875 F.2d 300 (Fed. Cir. 1989) (holding that the sale of a filter for use in a filtration system was not an act of contributory infringement of a patent that claimed the filter as an element of the filtration system).

2. The '240 Patent

(a) Watson's ANDA Product Does Not Directly Infringe the Claims Of The '240 Patent.

Claim 1 is the sole independent claim of the '240 patent and reads as follows:

> 1. A method of treating pulmonary hypertension comprising:
> administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising from 200 to 1000 μg/ml of treprostinil or a pharmaceutically acceptable salt thereof
> with a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse,
> said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse,
> said therapeutically effective single event dose comprising from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths.

'240 patent at 18:2-16.

The manufacture, sale, and distribution of the Watson ANDA Product does not directly infringe claims 1 of the '240 patent because the manufacture, sale, and distribution of the Watson ANDA Product does not include the step of "administering by inhalation to a human."

Further, claim 1 cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA Product based on claim vitiation. That is, if claim 1 was expanded to include the Watson ANDA Product, then the entire element of claim 1 requiring "administering by inhalation to a human would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc. v. Emtrak, Inc.*, 402 F.3d 1188, 1195 (Fed. Cir. 2005); *Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1358 (Fed. Cir. 2005).

Claims 2-9 of the '240 patent depend, either directly or indirectly, from claim 1 and thereby incorporate all the limitations of claim 1. *See* 35 U.S.C. § 112, ¶ 4 (providing in relevant part "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers."). *See also Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1358 (Fed. Cir. 2007) ("Instead, claim 4, like its predecessor claim, as attested by the prosecution history, is in dependent form and incorporates the limits of the overarching independent claim." *Id.*); *Wolverine World Wide, Inc. v. Nike, Inc.*, 38 F.3d 1192, 1199 (Fed. Cir. 1994) ("It is axiomatic that dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed." *Id.* (internal citations and quotations omitted)). Therefore, the Watson ANDA Product cannot infringe claims 2-9 of the '240 patent, either literally or under the doctrine of equivalents, for the reasons discussed above regarding claim 1 of the '240 patent.

E. Invalidity Analysis

1. Level of Ordinary Skill In The Art

The subject matter of the '507 and '240 patents falls within the medical/pharmaceutical arts. The person of ordinary skill to whom the '507 and '204 patents are directed is a person with at least a B.S. degree or higher in chemistry or related fields such as pharmacology, pharmacy or biochemistry and several years of experience, particularly experience in the development and/or design of inhalation dosage forms. *E.I. DuPont de Demours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), aff'd, 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein, and would have the capability to draw inferences from them.

2. The Scope and Content of the Prior Art

(a) U.S. Patent No. 6,521,212, Method for Treating Peripheral Vascular Disease by Administering Benzindene Prostaglandins by Inhalation, Cloutier et. al.

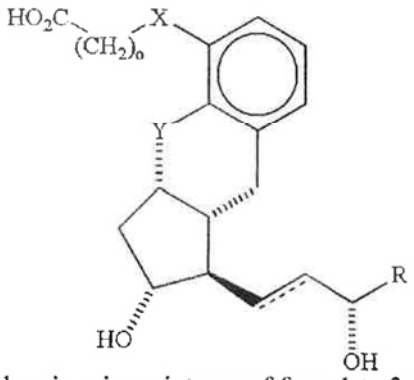
U.S. Patent No. 6,521,212 to Cloutier et al. (hereinafter "Coultier") titled "Method for Treating Peripheral Vascular Disease by Administering Benzindene Prostaglandins by Inhalation," issued February 18, 2003.

Cloutier teaches "a method for treating pulmonary hypertension by administering an effective amount of a benzindene prostaglandin to a mammal in need thereof by inhalation." Cloutier at 3:2-5.

Cloutier also teaches:

> A preferred group of benzindene prostaglandins for delivery by inhalation according to the present invention is as follows:

(I)



wherein a is an integer of from 1 to 3; X and Y, which may be the same or different, are selected from —O— and —CH_2—; R is —$(CH_2)_5$—R^1wherein R^1 is hydrogen or methyl, or R is cyclohexyl, or R is —$CH(CH_3)CH_2C{\equiv}CCH_3$; and the dotted line represents an optional double bond; or a physiologically acceptable salt or acid derivative thereof.

The most preferred benzindene prostaglandin is UT-15, which is 9-deoxy-2′, 9-alpha-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-interphenylene)-13,14-dihydro-prostaglandin F1.

Id. at 4:14-40.[2]

"Inhalation" delivery in the context of this invention refers to the delivery of the active ingredient or combination of active ingredients through a respiratory passage, wherein the mammal in need of the active ingredient(s) inhales the active ingredient(s) through the mammal's airways, such as the nose or mouth.

Id. at 4:41-46.

A preferred solution for administration by inhalation with a nebulizer includes a sterile solution of UT-15 comprising UT-15, sodium citrate, citric acid, sodium hydroxide, sodium chloride, and meta-cresol. A more preferred solution is prepared by mixing 0.125 grams UT-15, 1.25 grams hydrous sodium citrate, 0.125 grams of anhydrous citric acid, 0.05 grams of sodium hydroxide, and approximately 250 ml of water for injection.

Id. at 5:22-29.[3]

---

[2] UT-15 is also known as treprostinil *See* TYVASO® Prescribing Information; '507 patent at 5:32-34.
[3] This preferred solution for inhalation described by Cloutier contains 500 μg/mL of treprostinil.

> Benzindene prostaglandins, including UT-15 and its salts or esters, further exhibit vasodilatory action on blood vessels and therefore have a particular utility as anti-hypertensives for the treatment of high blood pressure in mammals, including man.

Id. at 6:11-15.

> In accordance with the present invention, a benzindene prostaglandin is delivered by inhalation to a patient in need thereof in a "therapeutically effective amount". A "therapeutically effective amount" refers to that amount that has therapeutic effects on the condition intended to be treated or prevented. . . . The precise amount that is considered effective for a particular therapeutic purpose will, of course, depend upon the specific circumstances of the patient being treated and the magnitude of effect desired by the patient's doctor. Titration to effect may be used to determine proper dosage.

Id. at 6:56-7:3.

> Further known uses of UT-15 include treatment of peripheral vascular disease (covered in co-pending application Serial No. 09/190,450, now U.S. Pat. No. 6,054,486, the entire contents of which are incorporated by reference herein). In the case of treating peripheral vascular disease by inhalation of a benzindene prostaglandin of the present invention, the dosage for inhalation, taking into account that some of the active ingredient is breathed out and not taken into the bloodstream, should be sufficient to deliver an amount that is equivalent to a daily infusion dose in the range of 25 µg to 250 mg; typically from 0.5 tg to 2.5 mg, preferably from 7 µg to 285 µg, per day per kilogram bodyweight. For example, an intravenous dose in the range 0.5 µg to 1.5 mg per kilogram bodyweight per day may conveniently be administered as an infusion of from 0.5 ng to 1.0 µg per kilogram bodyweight per minute. A preferred dosage is 10 ng/kg/min.

Id. at 5:51-66.

> It has been discovered that aerosolized UT-15 has both greater potency and efficacy relative to attenuating chemically induced pulmonary hypertension as shown by an increase in pulmonary vascular resistance. Furthermore, aerosolized UT-15 has a greater potency as compared to intravascularly administered UT-15, since the actual amount of UT-15 delivered via aerosolization delivery is only a fraction (10-50%) of the dosage delivered intravascularly. While the mechanism(s) that accounts

for the greater potency and efficacy for aerosolized UT-15 is unknown, it can be hypothesized that a low "first-pass" uptake via intravenous infusion of UT-15 could be at least partially responsible. A low first-pass uptake would thus allow the majority of the drug to be made available to the peripheral circulation (including the coronary circulation), which would increase the heart rate and cardiac output.

Aerosolized UT-15 has no apparent peripheral effects, such as on the heart rate or cardiac output, as compared to intravascular UT-15 during pulmonary vascular hypertension by chemical inducement. This is particularly beneficial for those patients that are near right heart failure and where peripheral vasodilation would exacerbate the challenge to the right heart.

Id. at 8:5-27.

Example V

CONSTRICTED INTRAVENOUS AND AEROSOLIZED UT-15 DOSE RESPONSE

Two separate experiments were conducted to determine the dose response effects of intravenously infused UT-15 and aerosolized UT-15 during U44069 induced pulmonary hypertension. After a 30 minute baseline was established, U44069 was infused intravenously at a rate of 1 ng per kg per min. For the intravenous administration of UT-15 and after allowing the sheep to achieve a steady-state for 30-60 minutes, a dose-response to intravenous UT-15 was similar to that set forth in Example IV. For the aerosolized administration of UT-15 and after allowing the sheep to achieve a steady-state for 30-60 minutes, a dose-response to intravenous UT-15 was similar to that set forth in Example IV. In each experimental protocol, UT-15 was administered to three sheep for 30 minutes and to the other three sheep for 60 minutes.

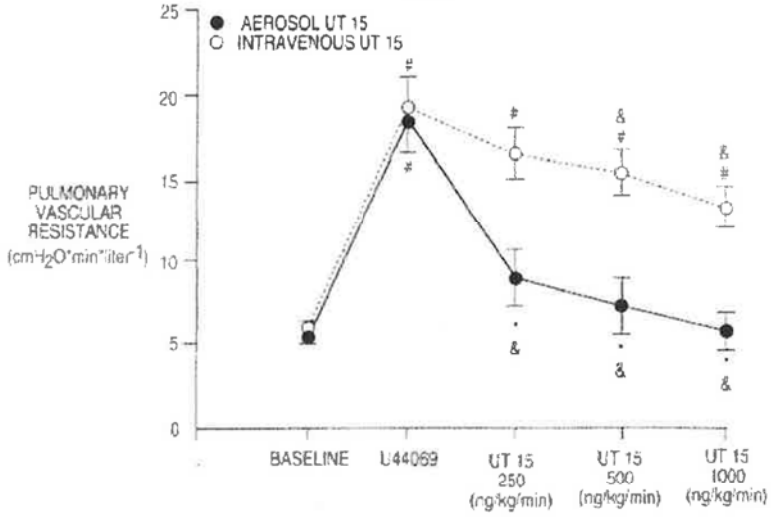
No differences were found between 30 minute and 60 minute UT-15 delivery at each of the three rates of administration. The effects of U44069 and the subsequent dose-response effects of UT-15 during U44069 infusion on heart rate are shown in FIG. 10. Intravenous UT-15 caused heart rate to increase above the values during U44069 conditions, whereas aerosolized UT-15 had no effect on heart rate. . . .

. . . .

FIG. 16 graphically demonstrates the overall effects of intravenous and aerosol delivery of UT-15 on pulmonary vascular resistance during U44069. It shows that pulmonary vascular resistance, while being significantly attenuated by both intravascularly infused and aerosolized UT-15, was more affected by aerosolized UT-15. In particular, U44069 caused a dramatic increase in PVR, which was significantly attenuated at 500 and 1000 ng per kg per min for intravenously infused UT-15. Aerosolized UT-15 caused PVR to decrease such that there was no significant difference for any of the three delivery rates relative to the baseline PVR. Interestingly, the time at which intravenous and aerosol UT-15 began to attenuate the increase in PVR were very similarly (4-5 minutes), whereas the off response for aerosolized UT-15 was much longer than intravenous UT-15 (43 vs. 12 minutes).

Id. at 11:51-12:20, 12:62-13:10.

FIG. 16



Id. at Fig. 16.

Example III

EFFECTS OF AEROSOLIZED UT-15 GIVEN AT HIGH DOSES ON BASELINE HEMODYNAMICS

Baseline measurements consisted of 30 minutes of monitoring during vehicle/saline aerosolization (0.28 ml/min). After baseline measurements, the vehicle/saline solution in the

aerosol delivery system was replaced with the stock UT-15 solution (500 ng/ml) and was aerosolized at 0.28 ml/min for 90 minutes.

FIG. 2 depicts the only statistically altered variables observed after 90 minutes of high dose aerosolized UT-15 (3800-5700 ng per kg per min). PSYS decreased by 7.5%, PPA decreased by approximately 18%, and PVR decreased by approximately 19% relative to their respective baseline values.

These data are important in that this would indicate that, unlike intravenously infused UT-15, aerosolized UT-15 can be given in high doses without significant non-lung effects, i.e., heart rate, cardiac output. The aerosol delivery of UT-15 for these experiments is approximately 15-27 times that of the effective minimal tested dose of 250 ng per kg per min shown in FIG. 16.

Id. at 10:32-57.

What is claimed is:

1. A method of treating peripheral vascular disease comprising administering to a mammal in need thereof by inhalation a formulation comprising a therapeutically effective amount of a benzindene prostaglandin.

. . . .

3. The method of claim 2, wherein said benzindene prostaglandin is UT-15.

4. The method of claim 3, wherein said aerosolized form comprises droplets less than 10 micrometers in diameter, said droplets comprising said UT-15 in a suitable pharmacologically-acceptable liquid carrier.

5. The method of claim 1, wherein the mammal is a human.

. . . .

12. The method of claim 1, wherein said aerosolized administration of benzindene prostaglandin has no effect on heart rate.

Id. at 13:16-14:29.

(b) Mueller et al., *Inhaled Iloprost in the Management of Pulmonary Hypertension in Infants Undergoing Congenital Heart Surgery*, European Journal of Anesthesiology, 21(suppl. 33):3, Abstract No. 084 (June 2004) ("Mueller")

Mueller published in June of 2004.

Mueller teaches the aerosolized administration of the benzindene prostaglandin, iloprost, with the Nebu-Tec OPTINEB® ultrasonic nebulizer. *See* Mueller.

Specifically Mueller teaches:

> The use of aerosolized Iloprost has shown to be safe and effective in adults with pulmonary hypertension. However, no data is available about intra-operative use of inhaled iloprost in infants <1 year with pulmonary hypertension undergoing cardiac surgery.
>
> Method. Eight infants . . . undergoing cardiac surgery with CPB . . . were included in this case-control-study. After weaning of CPB, infants . . . received inhaled iloprost (2.5 μg kg^{-1} over 15 min) using an ultrasonic nebulizer (Optineb®, Nebu-Tec, Elsenfeld, Germany). Mean pulmonary artery pressure (MPAP) and mean arterial pressure (MAP) were measured . . . .
>
> . . . .
>
> Discussion. A single dose inhaled iloprost decreases MPAP/MAP in infants after weaning off CPB by 21% and 25% after 30 min and 60 min, respectively. . . . Inhaled iloprost may therefore be an alternative for selective pulmonary vasodilation in infants undergoing cardiac surgery because it is effective, easy to use and long acting.

Id.

(c) U.S. Patent Application Publication No. 2004/0265238, Inhalable Formulations for Treating Pulmonary Hypertensions and Methods of Using Same, Chandry

U.S. Patent Application Publication No. 2004/0265238 to Chandry (hereinafter "Chandry") titled "Inhalable Formulations for Treating Pulmonary Hypertensions and Methods of Using Same," published on December 30, 2004.

Chaudry teaches kits for the aerosolized administration of a prostaglandin, such as treprostinil, to treat pulmonary hypertension.

Specifically, Chaudry teaches:

> In one preferred embodiment, the present invention provides a formulation for the treatment of pulmonary hypertension in a mammal (e.g., humans), wherein the formulation is suitable for administration via inhalation. Preferably, the formulation of the present invention is suitable for administration via nebulization. The formulations of the present invention comprise a therapeutically effective amount of a hypertension reducing agent. Hypertension reducing agents suitable for use in the present formulations include ACEI, ARBs, beta-blockers, calcium-channel blockers or vasodilators, or any combination thereof. In one alternative embodiment, the formulation of the present invention comprises a combination of two or more hypertension reducing agents.
>
> . . . .
>
> The present invention also relates to a method for treating pulmonary hypertension in a mammal, which includes animals or humans. In one embodiment, the method of the present invention comprises the step of administering the formulation of the present invention to a mammal in need thereof. In one embodiment, the method of the present invention further comprises the step of administering another therapy or pharmaceutical agent useful to or related to the treatment of pulmonary hypertension. Such therapies and/or pharmaceutical agents including, for example, anticoagulants and diuretics.
>
> Additionally, the present invention is directed to a kit for treating pulmonary hypertension in a mammal. In one embodiment, the kit of the present invention comprises the formulation of the present invention. In another embodiment, the formulation of the kit is premeasured, premixed and prepackaged. In an alternative embodiment, the kit further comprises instructions for administering the formulation.

Chaudry at [0017]-[0020].

> As used herein, the term "vasodilator" means any pharmaceutical agent that causes dilation of blood vessels. . . . Vasodilators for use herein also include prostaglandins (Eicosanoids), including prostacyclin (Epoprostenol) and prostacyclin analogs, including Iloprost and Treprostinil . . . .

Id. at [0026].

> The formulations of the present invention may be administered in a variety of ways, preferably by inhalation. For

example, the present formulations may be administered to an individual in need thereof by way of an inhaler, e.g., metered dose inhaler or a dry powder inhaler, an insufflator, a nebulizer or any other conventionally known method of administering inhalable medicaments. Preferably, the formulation of the present invention is administered by nebulization. In one alternative embodiment, the formulations of the present invention may be administered by way of a pressurized aerosol comprising, separately, a hypertension-reducing agent, or salt or an ester thereof with at least a suitable propellant or with a surfactant or a mixture of surfactants. Any conventionally known propellant may be used.

. . . .

Also provided herein are combinations containing a composition provided herein and a nebulizer. The combinations can be packaged as kits, which optionally contain other components, including instructions for use of the nebulizer. Any nebulizer is contemplated for use in the kits and methods provided herein. In particular, the nebulizers for use herein nebulize liquid formulations, including the compositions provided herein, containing no propellant. The nebulizer may produce the nebulized mist by any method known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or vibration. The nebulizer may further have an internal baffle. The internal baffle, together with the housing of the nebulizer, selectively removes large droplets from the mist by impaction and allows the droplets to return to the reservoir. The fine aerosol droplets thus produced are entrained into the lung by the inhaling air/oxygen.

. . . .

Nebulizers for use herein include, but are not limited to, jet nebulizers (optionally sold with compressors), ultrasonic nebulizers, and others. Exemplary jet nebulizers for use herein include Pari LC plus/ProNeb, Pari LC plus/ProNeb Turbo, Pari LC plus/Dura Neb 1000 & 2000, Pari LC plus/Walkhaler, Pari LC plus/Pari Master, Pari LC star, Omron CompAir XL Portable Nebulizer System (NE-C18 and JetAir Disposable nebulizer), Omron CompAir Elite Compressor Nebulizer System (NE-C21 and Elite Air Reusable Nebilizer [sic]), Pari LC Plus or Pari LC Star nebulizer with Proneb Ultra compressor, Pulmo-aide, Pulmo-aide LT, Pulmo-aide traveler, Invacare Passport, Inspiration Healthdyne 626, Pulmo-Neb Traverier, DeVilbiss 646, Whisper Jet, Acorn 11, Misty-Neb, Allied aerosol, Schuco Home Care, Lexan Plasic Pocet Neb, SideStream Hand Held Neb, Mobil Mist, Up-Draft, Up-Draft 11, T Up-Draft, ISO-NEB, AVA-NEB, Micro Mist, and PulmoMate. Exemplary ultrasonic nebulizers for use

herein include MicroAir, UltraAir, Siemens Ultra Nebulizer 145, CompAir, Pulmosonic, Scout, 5003 Ultrasonic Neb, 5110 Ultrasonic Neb, 5004 Desk Ultrasonic Nebulizer, Mystique Ultrasonic, Luminscope's Ultrasonic Nebulizer, Medisana Ultrasonic Nebulizer, Microstat Ultrasonic Nebulizer, and MABISMist Hand Held Ultrasonic Nebulizer. Other nebulizers for use herein include 5000 Electromagnetic Neb, 5001 Electromagnetic Neb 5002 Rotary Piston Neb, Lumineb I Piston Nebulizer 5500, Aeroneb' Portable Nebulizer System, Aerodose" Inhaler, and AeroEclipse Breath Actuated Nebulizer.

Pharmaceutical compositions containing a pulmonary hypertension reducing agent for administration via nebulization are provided. The compositions may be sterile filtered and filled in vials, including unit dose vials providing sterile unit dose formulations which are used in a nebulizer and suitably nebulized. Each unit dose vial may be sterile and suitably nebulized without contaminating other vials or the next dose.

Id. at [0052]-[0058].

Drugs administered by nebulization could play a major role in the treatment of pulmonary hypertension. However, a possible drawback of nebulization therapy is the number of times it must be performed each day, and the amount of time each treatment takes. For example, an individual may be required to receive 4 doses of inhalation solution per day by nebulization. In some instances, each nebulizer treatment takes about 15 minutes, or more to deliver a 2.5 ml fill volume of a bronchodilator, though the amount of time may vary depending on the model of the nebulizer used. The time requirements for nebulization therapy can be burdensome, and cause individuals to skip required dosages during the day. The impact of not following the prescribed dosage regimen could compromise the individual's condition.

In one alternative embodiment, the volume of the one or more pulmonary hypertension reducing agents inhalation solutions of the present invention is about 0.1 ml to about 2.25 ml, or about 0.1 ml to about 2 ml, or about 1 ml to about 2 ml, or about 1.5 ml to about 2 ml, preferably about 1 ml, about 1.5 ml, about 2.0 ml, or about 2.25 ml while no clinical trials or other experiments were carried out on these fill volumes, it is believed that such volumes are more beneficial over conventional nebulizer fill volumes solutions (e.g. 2.5 ml or 3.0 ml fill volume) because they will enable the individual to receive more medication (e.g., one or more pulmonary hypertension reducing agents) in less time during each

nebulization treatment. Also, it is believed that the fill volumes of the present invention will minimize common handling complications with nebulizer therapy, and it may extend the life of the nebulizer.

In one alternative embodiment, the above fill volumes of the present invention may reduce the time of each nebulization treatment by at least 20%, 30%, 40%, 50%, 60%, 70% or 80% or more over conventional nebulizer treatments (e.g. 2.5 ml or 3 ml fill volume). 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.

Id. at [0061]-[0063].

In an alternative embodiment, the present invention also comprises a device for use in the relief of symptoms associated with pulmonary hypertension, including bronchospasm. Such device may take the form of a label, written instructions or any other form incorporating indicia thereon. The device may comprise indicia which indicates that a patient suffering from symptoms associated with pulmonary hypertension can be treated with at least one prepackaged, sterile, premixed, premeasured and/or BAC-free inhalation solution comprising a unit dose of a therapeutically effective amount of one or more pulmonary hypertension reducing agents in a single vial. The inhalation solution being suitable for nebulization in a nebulizer. The device may also comprise indicia which provides instructions for utilizing the inhalation solution to treat said symptoms in patients.

Id. at [0070].

In another alternative embodiment, the method of the present invention comprises the step of administering to a mammal in need thereof an inhalation solution comprising a therapeutically effective amount of a hypertension-reducing pharmaceutical agent, wherein the inhalation solution is administered via nebulizer, such nebulizer including, but not limited to, a jet nebulizer, ultrasonic nebulizer and breath-actuated nebulizer. Preferably, the nebulizer is a jet nebulizer connected to an air compressor with adequate air flow. The nebulizer being equipped with a mouthpiece or suitable face mask.

Id. at [0077].

Example 4

Epoprostenol sodium	[illegible] mg/ml
Sodium Chloride	[illegible] mg/ml
Sodium Hydroxide	q.s.
Citric Acid	q.s.
Water	q.s.

Example 4 is a prophetic example of a formulation comprising the vasodilator epoprostenol. 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.

Id. at [0097]-[0098].

(d) Gessler et al., *Ultrasonic versus Jet Nebulization of Iloprost in Severe Pulmonary Hypertension*, European Respiratory Journal, 17:14-19 (2001) ("Gessler")

Gessler published in 2001.

Gessler teaches the aerosolized administration of the benzindene prostaglandin iloprost with a jet nebulizer and an ultrasonic nebulizer for the treatment of pulmonary hypertension.

Specifically, Gessler teaches:

> [I]n a controlled study continuous prostacyclin infusion was shown to improve exercise capacity and survival in patients suffering from severe PPH [pulmonary hypertension]. Disadvantages of this intraveneous approach are the lack of pulmonary selectivity, giving way to systemic side effects, as well as infectious complications related to the long-term use of an intravenous catheter.
>
> In a recent approach to overcome these shortcomings, aerosolization of the stable prostacyclin analogue iloprost was employed for pulmonary vasodilation in both PPH and severe SPH. . . .
>
> In all previous studies investigating short-term or long-term iloprost nebulization, a continuous output jet nebulizer with a reservoir and filter system was used. However, the limited output of this device requires long inhalation periods of 12-15 min for delivery of an adequate iloprost dose for pulmonary vasodilation.

> Moreover, the therapeutic use of iloprost aerosolization in pulmonary hypertension demands multiple daily inhalation manoeuvres, since the pulmonary vasodilatory effects of each single inhalation levels off within ~1 h, thus resulting in a total duration of inhalation of up to 3 h per day. . . . Therefore, a reduction of inhalation time with the use of a more efficient nebulizer system will markedly improve iloprost aerosol therapy. A recently developed ultrasonic nebulizer device might offer the possibility to overcome these limitations. . . .
>
> . . . .
>
> . . . The jet nebulizer system investigated in this study (Ilo-Neb™, Nebu-Tec company, Elsenfeld, Germany) . . . . For the ultrasonic nebulizer system (Multisonic Compact™, Schill company, Probstzella, Germany) . . .
>
> . . . To mimic aerosol inhalation in patients, a volunteer performed the inhalation manoeuvres through the filter at the mouthpiece (tidal volume ~ 1.5 L, breathing frequency ~ 11 min^{-1} . . .).

Gessler at pp. 14-15.

> The physical parameters of both nebulizers are shown in table 1. . . . 61% of the generated aerosol was lost within the jet nebulizer device, compared to only 14% in the ultrasonic device. Based on these data, the "standard" iloprost aerosol application, as investigated in previous clinical studies with employment of the currently tested jet nebulizer device, was calculated to result in a total iloprost dose at the mouthpiece of 2.8 µg (12 min inhalation period, iloprost concentration 10 $\mu g \cdot mL^{-1}$). To achieve an equivalent dose when using the ultrasonic nebulizer device, the iloprost concentration was reduced to 5 $\mu g \cdot mL^{-1}$ and the inhalation time to 4 min to match the higher output at the mouthpiece of the ultrasonic nebulizer.
>
> . . . .

Table 1. – Comparison of physical parameters of the nebulizer devices

	Jet nebulizer system	Ultrasonic nebulizer system
MMAD µm	3.2±0.1	3.9±0.2
Gsd	1.8±0.0	1.6±0.1
Total output of nebulizer µL·min^{-1}	60±7	163±15
Output at mouthpiece µL·min^{-1}	23±3	140±13
Efficiency %	39±3	86±5

Data are presented as mean±SD; n=6. MMAD: mass median aerodynamic diameter; Gsd: geometric standard deviation.

Id. at pp. 16-17.

The total output of the ultrasonic nebulizer (163 µL·min^{-1}) is 2.7 times higher than that of the jet nebulizer. The difference between the two systems is even more pronounced with regard to the output at mouthpiece: this parameter, describing the amount of aerosol delivered *de facto* to the inhaling patient, is more than six times higher in the ultrasonic nebulizer system as compared to the jet nebulizer. This is mainly due to a notable aerosol loss at the inspiration valve of the jet nebulizer device (fig. 1), with preferential deposition of large particles. The design of the ultrasonic nebulizer does not require any valve in the inspiratory aerosol flow, leading to a high efficiency of the device: 86% of the total aerosol output is available at the mouthpiece for inhalation. Moreover, the ultrasonic device offers, due to its compact construction, the advantage of an easy handling and maintenance, as compared to the jet nebulizer.

Id. at p. 17.

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^{-1}). 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 a short time period. Therefore, we reduced the iloprost concentration from 10 µg·mL^{-1} to 5 µg·mL^{-1} when employing the ultrasonic nebulizer, and consequently doubled the inhalation time to 4 min with this device.

Id.

> In conclusion, ultrasonic nebulization is suitable for inhalation of iloprost in severe pulmonary hypertension, inducing preferential pulmonary vasodilation. Markedly higher efficiency and output of the currently investigated ultrasonic device, in comparison to a standard jet aerosolization technique, avoids wastage of drug and allows shortening of the inhalation time to ~30%, with comparable haemodynamic effects. The delivery of a standard iloprost dose of 2.8 µg in the notably reduced inhalation time did not induce side effects and was well tolerated by all patients. Long-term use of the ultrasonic nebulization device, performed in selected patients beyond the scope of the present study, as yet has shown no technical drawbacks. Thus employment of ultrasonic aerosol generation offers more effective alveolar deposition of vasoactive drugs in severe pulmonary hypertension, as compared to conventional jet nebulization.

Id. at p. 19.

(e) Nebu-Tec, OPTINEB® website ("OPTINEB® website")

The OPTINEB® website was available to the public at least as early December 2002.[4]

The OPTINEB® website provides information on various nebulizers manufactured and sold by Nebu-Tec, including the OPTINEB® device.

Specifically the OPTINEB® website, under the section "Fields of Therapy Usage," states:

> Pulmonary Hypertension
> Ani-fungal Prevention
> Muccoviszidosis
>
> All non-oily substances (medication) can be nebulized

OPTINEB® website at "Therapy Usage."

The OPTINEB® website also provides an instruction guide for the OPTINEB microprocessor controlled mobile ultrasonic nebulizer that states in relevant part:

> 3.1 Functional Description
>
> The ultrasonic nebulizer is equipped with a timer that is switched ON-OFF with a sensor button. A second Start-Stop sensor button is used to switch on the production of aerosol or to

[4] The OPTINEB® website was obtained from the *Wayback Machine* available from archive.org, which is a website that maintains a historical archive of webpages as they existed at a particular point in time.

interrupt it, and then resumed by pressing the button again. This is possible until the set timer period has elapsed. By pressing both buttons simultaneously you will enter the programming mode of the timer where you can change the inhalation times upward or downward by pressing one of the buttons. After 5 seconds the set time will automatically be stored. The unit is equipped with a multifunctional indicator light which shows the operating condition.

3.2 Functioning at Spontaneus [sic] Respiration

If the inhalation device is in operation it continuously produces aerosol. The generated mist can be inhaled by the patient through the mouthpiece. The inhalation and exhalation take place over the mouthpiece and is controlled by the valves installed inside the filter shell that cannot be interchanged. These filters prevent any leakage of aerosol into the air and thus form a closed system of the nebulizer unit.

. . . .

7.1 Using Your OPTINEB® Ultrasonic Nebulizer:

. . . .

7.11 To switch-on the nebulizer, press the On/OFF sensor button (multifunctional indicator light is yellow).

7.12 To start the nebulizer, press the Start/Stop sensor button, nebulization will begin (multifunctional indicator light is green).

IMPORTANT

If you interrupt the inhalation do not forget to stop the nebulization by pressing the Start/Stop button again (multifunctional indicator light is yellow).

Restart the nebulizer after the break by pressing the Start/Stop button again (multifunctional indicator light is green).

. . . .

7.13 Place the mouthpiece in your mouth and inhale the medicated aerosol over the inhalation filter and the valve by taking a slow deep breath. The exhalation also takes place over the mouthpiece and the exhalation filter with valve (the inhalation instruction: 'The Right Way to Inhale' is available separately).

> 7.14 Continue to inhale until the set timer period has expired (acoustic signal), or the medication was entirely nebulized.

Id. at "Instruction Guide."

The OPTINEB® website also indicates that the total output of the OPTINEB® ultrasonic nebulizer is 173±3 μL/min. *See id.* at "Particle Size."

(f) General Knowledge Relating to Treprostinil

Prior to the earliest priority date of the '507 and '240 patents, a skilled artisan would have been aware of numerous references that described general knowledge regarding the inhalation of treprostinil and related analogs. For example, a skilled artisan would have been aware of Badesh et al., *Prostanoid Therapy for Pulmonary Arterial Hypertension*, Journal of the American College of Cardiology, 43(12):Suppl. S (2004) ("Badesh"). Badesh teaches that treprostinil and iloprost are useful to treat pulmonary hypertension and that treprostinil has a half-life of about 3 hours and iloprost has a half-life of 20-25 minutes. *See* Badesh at 58S-59S. *See also* Sandifer et al., *Potent Effects of Aerosol Compared with Intravenous Treprostinil on the Pulmonary Circulation*, J. Appl. Physiol., 99:2363-2368 (2005) ("Sandifer") ("Treprostinil also has a longer half-life than prostacyclin and iloprost"). Sandifer appears to report the same experiments contained in the Examples of Cloutier, but also states:

> To achieve an effect in sheep, it was necessary to administer doses of treprostinil that were much higher than those used in treating patients, regardless of the route of delivery. . . .
>
> . . . .
>
> It is clear from this study and others that aerosolized delivery of prostacyclin analogs can reverse acute pulmonary vasoconstriction with minimal systemic side effects. Furthermore, when similar doses of intravenous and aerosolized medication have been used, the effects of aerosol are similar to or greater than systemically administered drug. . . .
>
> . . . .
>
> . . . Duration of action of prostacyclin is short, requiring an unrealistic frequency of administration for clinical use, but development of analogs (e.g., treprostinil) or formulations that are long acting could make this approach feasible.

Sandifer at p. 2367. *See also* Sandifer et al., *Effects of Aerosol vs IV UT-15 on Prostaglandin H2 Analog-Induced Pulmonary Hypertension in Sheep*, Chest, 616S (2005) ("Sandifer II"); Lee et al., *Current Treatment Strategies for Pulmonary Arterial Hypertension*, Journal of Internal Medicine, 199-215 (2005) ("Lee").

Other references that describe the state of the art include:

- Booke et al., *Prostaglandins in Patients with Pulmonary Hypertension: The Route of Administration*, Anesth. Analg., 86:914-920 (1998) ("Booke")

- Olschewski et al., *Aerosolized Prostacyclin and Iloprost in Severe Pulmonary Hypertension*, Annals of Internal Medicine, 124(9):820-824 (1996) ("Olschewski")

- Hallioglu et al., *Comparison of Acute Hemodynamic Effects of Aerosolized and Intravenous Iloprost in Secondary Pulmonary Hypertension in Children with Congenital Heart Disease*, Am. J. Cardiol., 92(8):1007-1009 (2003) ("Hallioglu")

- *VENTA*-NEB®-ir AICI brochure

3. The '507 Patent

Claims 1-9 of the '507 patent are invalid under 35 U.S.C. § 103(a) as obvious over Cloutier et al., U.S. Patent No. 6,521,212 ("Cloutier") combined with (i) Mueller et al., *Inhaled Iloprost in the Management of Pulmonary Hypertension in Infants Undergoing Congenital Heart Surgery*, European Journal of Anesthesiology, 21(suppl. 33):3, Abstract No. 084 (June 2004) ("Mueller"); (ii) Chaudry, U.S. Patent Application Publication No. 2004/0265238 ("Chaudry"); (iii) Gessler et al., *Ultrasonic versus Jet Nebulization of Iloprost in Severe Pulmonary Hypertension*, European Respiratory Journal, 17:14-19 (2001) ("Gessler"); and/or (iv) the Nebu-Tec, OPTINEB® website ("OPTINEB® website"). Any differences between the claims of the '507 patent and the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website are mere process optimizations that a skilled artisan could easily undertake based upon the general knowledge in the art regarding aerosolized administration of treprostinil.

Claim 1 of the '507 patent reads:

> 1. A kit for treating pulmonary hypertension comprising:
> (i) a formulation comprising 200 to 1000 μg/ml treprostinil or a pharmaceutically acceptable salt thereof;
> (ii) a pulsed ultrasonic nebulizer comprising an opto-acoustical trigger, configured to
> (a) aerosolize a fixed amount of treprostinil per pulse, and
> (b) deliver by inhalation a therapeutically effective single event dose of said formulation,
> said single event dose comprising 15 μg to 90 μg treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths; and
> (iii) instructions for using the pulsed ultrasonic nebulizer with the formulation to treat a patient with pulmonary hypertension by delivering 15 μg to 90 μg treprostinil or a pharmaceutically acceptable salt thereof in 1 to 18 breaths to the patient in the single event dose.

Cloutier claims methods for treating pulmonary hypertension comprising the aerosolized administration of treprostinil to humans.

Cloutier describes the aerosol administration of a treprostinil formulation comprising 500 µg/mL of treprostinil to treat pulmonary hypertension. Cloutier teaches a wide range of doses to obtain a therapeutic effect and exemplifies the administration of 262.5 µg, 525 µg, and 1050 µg of treprostinil to sheep over a 30 minute interval using a jet nebulizer.[5] Cloutier at 9:4-12. Figure 16 of Cloutier shows that these doses are effective and that the decrease in pulmonary vascular resistance with increasing dose is relatively minor. More importantly, Cloutier teaches that "the time at which intravenous and aerosol UT-15 [treprostinil] began to attenuate the increase in PVR were very similarly (4-5 minutes), whereas the off response for aerosolized UT-15 was much longer than intravenous UT-15." Cloutier at 13:7-10.

Cloutier further teaches high doses of treprostinil can be administered via inhalation without significantly effecting non-lung parameters such as heart rate and cardiac output. *See id.* at 10:50-57.

Cloutier teaches that formulations containing a dose of treprostinil of 250 ng/kg/minute, 500 ng/kg/minute, and 1,000 ng/kg/minute were administered to sheep (weighing 35 kg) at a nebulization rate of 0.28 mL per minute via tracheostromy. *See id.* at 9:4-12, 11:7-14. Thus, in view of Cloutier's teaching that aerosol treprostinil began to attenuate the increase in pulmonary vascular resistance after 4-5 minutes, Cloutier demonstrates that therapeutic effects for an administration of 250 ng/kg/minute were present after 35-43.75 µg of treprostinil was administered; therapeutic effects for an administration of 500 ng/kg/minute were present after 70-87.5 µg of treprostinil was administered; and therapeutic effects for an administration of 1,000 ng/kg/minute were present after 140-175 µg of treprostinil was administered disclosing a range overlapping with the claimed single event dose.[6]

Accordingly, Cloutier teaches all the essential elements of the claims of the '507 patent except for the use of a pulsed ultrasonic nebulizer with an opto-acoustical trigger or the administration of a therapeutically effective dose of treprostinil in 1-18 breaths. These features are taught by the secondary references. Specifically, ultrasonic nebulizers are taught by Mueller, Chaudry, Gessler, and the OPTINEB® website. Moreover, Mueller and the OPTINEB® website specifically identify the exact ultrasonic nebulizer employed in the examples of the '507 patent.[7]

---

[5] Although the specific nebulizer is not mentioned in the examples of Cloutier, Watson believes that the data generated in Examples III-V of Cloutier was obtained by using a jet nebulizer, specifically AM-601 Medicator Aerosol Delivery System, manufactured by Healthline Medical of Baldwin Park, Ca. (*see* U.S. 2008/0095711 at [0058] (stating that the AM-601 is a jet nebulizer)). This belief is based on the fact that the foregoing nebulizer is the only nebulizer mentioned in Cloutier (5:30-36); Example 1 states that the test solutions were prepared in larger volumes to account for "void" volume or the amount typically left in a jet nebulizer (9:7-12) and Sandifer which reports the results of the same experiments as Cloutier and states the treprostinil solution was administered with a "Healthline Medical AM-601 Medicator Aerosol Delivery System" (Sandifer at p. 2364).

[6] A skilled artisan would understand that these values are not absolute because the aerosolizd delivery only delivers about 1—50% of the expected value. Cloutier at 8:10-12 ("the actual amount of UT-15 delivered via aerosolization is only a fraction (10-50%) of the dosage delivered intravascularly"). *See also* Gessler at p. 15 ("limited efficiency of the jet nebulizer system causes a notable waste of drug.")

[7] The same device employed in the examples of the '507 patent, which is reported to have an "opto-acoustical trigger," is employed in Mueller and the OPTINEB® website.

In addition, the recitation of 1-18 breaths is nothing more than an inherent/optimized feature that occurs from using the specific treprostinil compositions of Cloutier in the known ultrasonic nebulizers.

A person skilled in the art would look to improve upon the aerosol administration taught by Cloutier because a person skilled in the art would seek to shorten the administration time taught by Cloutier in order to improve patient convenience and compliance.[8] A person skilled in the art would know that ultrasonic nebulizers, such as the Nebu-Tec OPTINEB®, were more efficient than the jet nebulizers proposed by Cloutier, and that ultrasonic nebulizers could deliver more drug in a shorter amount of time. *See, e.g.,* Gessler at pp. 17, 19. Therefore, the skilled artisan would look to Mueller, Chaudry, Gessler, or the OPTINEB® website to select an ultrasonic nebulizer, and could easily optimize the dose, *i.e.*, the therapeutic amount to be delivered over the shorter time period, with a reasonable expectation of success. Upon using the more efficient ultrasonic nebulizer instead of a jet nebulizer, a person skilled in the art could optimize the administration time down to 1 to 18 breaths based on the parameters of the selected ultrasonic nebulizer and concentration of drug composition to be nebulized with a reasonable expectation of success. Support for this position can be found in Labiris et al., *Pulmonary Drug Delivery. Part II: The Role of Inhalant Delivery Devices and Drug Formulations in Therapeutic Effectiveness of Aerosolized Medications*, Br. J. Clin. Pharmacol., 56(6):600-612 (2003) ("Labiris"), which teaches that there can be considerable variation in the performance of various nebulizers and brands and states:

> Physicians may need to adapt a prescription to the performance of the nebulizer available to their patient or determine the most efficient nebulizer/compressor system to ensure optimal therapeutic effectiveness of nebulized medications.

Labiris at p. 604.

In addition, a person skilled in the art would be motivated to combine Chaudry and Cloutier with a reasonable expectation of success because both references relates to the aerosolized administration of treprostinil by nebulization. Furthermore, a person skilled in the art would be motivated to combine Mueller or Gessler, which relate to iloprost, with Cloutier with a reasonable expectation of success because these references relate to the inhaled administration of known, safe and effective prostaglandins, either iloprost or treprostinil, to treat pulmonary hypertension. Additional support for the position that a skilled artisan would look to art relating to iloprost when considering treprostinil teachings can be found throughout the prosecution of the patents at issue wherein Applicants relied upon iloprost art, including Gessler, as providing guidance to a skilled artisan seeking to prepare and administer aerosolized treprostinil. A person skilled in the art would be motivated to combine the OPTINEB® website and Cloutier with a reasonable expectation of success because the OPTINEB® website indicates that the OPTINEB® nebulizer can be used with all non-oily medications to treat pulmonary hypertension. Thus, a skilled artisan searching for nebulizers that are useful in treating pulmonary hypertension as taught by Cloutier, would be led to the OPTINEB® website.

[8] Long administration times associated with aerosolized administration of prostaglandins were well known. *See generally* Chaudry at [0063]; Gessler at pp. 14-15.

Alternatively, a skilled artisan would be led to the OPTINEB® website based upon the teachings of Mueller, which identify the OPTINEB® nebulizer as useful in administering aerosolized prostaglandins for treating pulmonary hypertension.

Regarding the claimed instructions, instructions for using the pulsed ultrasonic nebulizer do not distinguish the claims from the prior art. *See In re Ngai*, 367 F.3d 1336, 1339 (Fed. Cir. 2004); *In re Gulack*, 703 F.2d 1381, 1385-86 (Fed. Cir. 1983). Moreover, the ultrasonic nebulizers of the prior art were sold with instructions. *See generally* OPTINEB® website.

Claim 2 limits the kit of claim 1 to one wherein the formulation comprises 600 μg/ml of the treprostinil or its pharmaceutically acceptable salt. A person skilled in the art could easily and routinely optimize the 500 μg/ml treprostinil solution taught in Cloutier to achieve a 600 μg/ml treprostinil solution. Accordingly, claim 2 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 3 limits the kit of claim 1 to one further comprising instructions for the human not to repeat the single event dose for a period of at least 3 hours. A person skilled in the art could easily and routinely arrive at the recited dosing regimen after determining the duration of therapeutic effect for 15 μg to 90 μg of treprostinil administered by a pulsed ultrasonic nebulizer, especially in view of the general knowledge in the art that the half-life of treprostinil was about 3 hours. *See* Badesh at 58S-59S. Accordingly, claim 3 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 4 limits the kit of claim 1 to one where the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose. This claim recites an inherent property of the claimed kit/formulation/method. Accordingly, claim 4 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 5 limits the kit of claim 1 to one where the fixed amount of treprostinil or its pharmaceutically acceptable salt for each breath inhaled by the human comprises at least 5 ng of treprostinil or its pharmaceutically acceptable salt.[9] A person skilled in the art could easily and routinely optimize the known dosage range of treprostinil to achieve the recited per-breath dosage. Moreover, the use of the composition taught by Cloutier in the OPTINEB® ultrasonic device, which could deliver 173 μL/min, would necessarily result in the recited amount per breath on the assumption that the patient takes about 10-30 breaths per minute. *See* Elder Declaration at ¶ 23. Accordingly, claim 5 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 6 limits the kit of claim 2 to one where the fixed amount of treprostinil or its pharmaceutically acceptable salt for each breath inhaled by the human comprises at least 5 ng of

[9] Prior to the printing of the issued patent, the previous version of this claim pending in the '507 patent application recited "5 μg" rather than "5 ng" of treprostinil. Although no certificate of correction has yet issued for the '507 patent, Watson assumes the claimed value should be "5 ug".

treprostinil or its pharmaceutically acceptable salt.[10] A person skilled in the art could easily and routinely optimize the known dosage range of treprostinil to achieve the recited per-breath dosage. Moreover, the use of the composition taught by Cloutier in the OPTINEB® ultrasonic device, which could deliver 173 µL/min, would necessarily result in the recited amount per breath on the assumption that the patient takes about 10-30 breaths per minute. *See* Elder Declaration at ¶ 23. Accordingly, claim 6 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 7 limits the kit of claim 1 to one where the single event dose is inhaled in 3 to 18 breaths by the human. This claim recites a feature that is the inherent result of the use of a pulsed ultrasonic nebulizer, the recited dosage range of treprostinil, and the lung capacity and absorption of treprostinil in the lungs of a human. Accordingly, claim 7 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 8 limits the kit of claim 6 to one where the single event dose is inhaled in 3 to 18 breaths by the human. This claim recites a feature that is the inherent result of the use of a pulsed ultrasonic nebulizer, the recited dosage range of treprostinil, and the lung capacity and absorption of treprostinil in the lungs of a human. Accordingly, claim 8 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 9 limits the kit of claim 6 to one further comprising instructions for the human not to repeat the single event dose for a period of at least 3 hours. A person skilled in the art could easily and routinely arrive at the recited dosing regimen after determining the duration of therapeutic effect for 15 µg to 90 µg of treprostinil administered by a pulsed ultrasonic nebulizer, especially in view of the general knowledge in the art that the half-life of treprostinil was about 3 hours. *See* Badesh at 58S-59S. Accordingly, claim 9 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

(a) Secondary Considerations

Watson is unaware of any probative evidence of secondary considerations of non-obviousness that exists to rebut the prima facie case of invalidity set forth above.

4. The '240 Patent

Claims 1-9 of the '240 patent are invalid under 35 U.S.C. § 103(a) as obvious over Cloutier et al., U.S. Patent No. 6,521,212 ("Cloutier") combined with (i) Mueller et al., *Inhaled Iloprost in the Management of Pulmonary Hypertension in Infants Undergoing Congenital Heart Surgery*, European Journal of Anesthesiology, 21(suppl. 33):3, Abstract No. 084 (June 2004) ("Mueller"); (ii) Chaudry, U.S. Patent Application Publication No. 2004/0265238 ("Chaudry");

[10] Prior to the printing of the issued patent, the previous version of this claim pending in the '507 patent application recited "5 µg" rather than "5 ng" of treprostinil. Although no certificate of correction has yet issued for the '507 patent, Watson assumes the claimed value should be "5 ug".

(iii) Gessler et al., *Ultrasonic versus Jet Nebulization of Iloprost in Severe Pulmonary Hypertension*, European Respiratory Journal, 17:14-19 (2001) ("Gessler"); and/or (iv) the Nebu-Tec, OPTINEB® website ("OPTINEB® website"). Any differences between the claims of the '240 patent and the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website are mere process optimizations that a skilled artisan could easily undertake based upon the general knowledge in the art regarding aerosolized administration of treprostinil.

Claim 1 of the '240 patent reads:

> 1. A method of treating pulmonary hypertension comprising:
> administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising from 200 to 1000 μg/ml of treprostinil or a pharmaceutically acceptable salt thereof with a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse,
> said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse,
> said therapeutically effective single event dose comprising from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths.

Cloutier claims methods for treating pulmonary hypertension comprising the aerosolized administration of treprostinil to humans.

Cloutier describes the aerosol administration of a treprostinil formulation comprising 500 μg/mL of treprostinil to treat pulmonary hypertension. Cloutier teaches a wide range of doses to obtain a therapeutic effect and exemplifies the administration of 262.5 μg, 525 μg, and 1050 μg of treprostinil to sheep over a 30 minute interval using a jet nebulizer.[11] Cloutier at 9:4-12. Figure 16 of Cloutier shows that these doses are effective and that the decrease in pulmonary vascular resistance with increasing dose is relatively minor. More importantly, Cloutier teaches that "the time at which intravenous and aerosol UT-15 [treprostinil] began to attenuate the increase in PVR were very similarly (4-5 minutes), whereas the off response for aerosolized UT-15 was much longer than intravenous UT-15." Cloutier at 13:7-10.

Cloutier further teaches high doses of treprostinil can be administered via inhalation without significantly effecting non-lung parameters such as heart rate and cardiac output. *See id.* at 10:50-57.

---

[11] Although the specific nebulizer is not mentioned in the examples of Cloutier, Watson believes that the data generated in Examples III-V of Cloutier was obtained by using a jet nebulizer, specifically AM-601 Medicator Aerosol Delivery System, manufactured by Healthline Medical of Baldwin Park, Ca. (*see* U.S. 2008/0095711 at [0058] (stating that the AM-601 is a jet nebulizer)). This belief is based on the fact that the foregoing nebulizer is the only nebulizer mentioned in Cloutier (5:30-36); Example 1 states that the test solutions were prepared in larger volumes to account for "void" volume or the amount typically left in a jet nebulizer (9:7-12) and Sandifer which reports the results of the same experiments as Cloutier and states the treprostinil solution was administered with a "Healthline Medical AM-601 Medicator Aerosol Delivery System" (Sandifer at p. 2364).

Cloutier teaches that formulations containing a dose of treprostinil of 250 ng/kg/minute, 500 ng/kg/minute, and 1,000 ng/kg/minute were administered to sheep (weighing 35 kg) at a nebulization rate of 0.28 mL per minute via tracheostromy. *See id.* at 9:4-12, 11:7-14. Thus, in view of Cloutier's teaching that aerosol treprostinil began to attenuate the increase in pulmonary vascular resistance after 4-5 minutes, Cloutier demonstrates that therapeutic effects for an administration of 250 ng/kg/minute were present after 35-43.75 μg of treprostinil was administered; therapeutic effects for an administration of 500 ng/kg/minute were present after 70-87.5 μg of treprostinil was administered; and therapeutic effects for an administration of 1,000 ng/kg/minute were present after 140-175 μg of treprostinil was administered disclosing a range overlapping with the claimed single event dose.[12]

Accordingly, Cloutier teaches all the essential elements of the claims of the '240 patent except for the use of a pulsed ultrasonic nebulizer with an opto-acoustical trigger or the administration of a therapeutically effective dose of treprostinil in 1-18 breaths. These features are taught by the secondary references. Specifically, ultrasonic nebulizers are taught by Mueller, Chaudry, Gessler, and the OPTINEB® website. Moreover, Mueller and the OPTINEB® website specifically identify the exact ultrasonic nebulizer employed in the examples of the '240 patent patent.[13] In addition, the recitation of 1-18 breaths is nothing more than an inherent/optimized feature that occurs from using the specific treprostinil compositions of Cloutier in the known ultrasonic nebulizers.

A person skilled in the art would look to improve upon the aerosol administration taught by Cloutier because a person skilled in the art would seek to shorten the administration time taught by Cloutier in order to improve patient convenience and compliance.[14] A person skilled in the art would know that ultrasonic nebulizers, such as the Nebu-Tec OPTINEB®, were more efficient than the jet nebulizers proposed by Cloutier, and that ultrasonic nebulizers could deliver more drug in a shorter amount of time. *See, e.g.,* Gessler at pp. 17, 19. Therefore, the skilled artisan would look to Mueller, Chaudry, Gessler, or the OPTINEB® website to select an ultrasonic nebulizer, and could easily optimize the dose, *i.e.*, the therapeutic amount to be delivered over the shorter time period, with a reasonable expectation of success. Upon using the more efficient ultrasonic nebulizer instead of a jet nebulizer, a person skilled in the art could optimize the administration time down to 1 to 18 breaths based on the parameters of the selected ultrasonic nebulizer and concentration of drug composition to be nebulized with a reasonable expectation of success. Support for this position can be found in Labiris et al., *Pulmonary Drug Delivery. Part II: The Role of Inhalant Delivery Devices and Drug Formulations in Therapeutic Effectiveness of Aerosolized Medications*, Br. J. Clin. Pharmacol., 56(6):600-612 (2003) ("Labiris"), which teaches that there can be considerable variation in the performance of various nebulizers and brands and states:

---

[12] A skilled artisan would understand that these values are not absolute because the aerosolize delivery only delivers about 1—50% of the expected value. Cloutier at 8:10-12 ("the actual amount of UT-15 delivered via aerosolization is only a fraction (10-50%) of the dosage delivered intravascularly"). *See also* Gessler at p. 15 ("limited efficiency of the jet nebulizer system causes a notable waste of drug.")

[13] The same device employed in the examples of the '240 patent, which is reported to have an "opto-acoustical trigger," is employed in Mueller and the OPTINEB® website.

[14] Long administration times associated with aerosolized administration of prostaglandins were well known. *See generally* Chaudry at [0063]; Gessler at pp. 14-15.

> Physicians may need to adapt a prescription to the performance of the nebulizer available to their patient or determine the most efficient nebulizer/compressor system to ensure optimal therapeutic effectiveness of nebulized medications.

Labiris at p. 604.

In addition, a person skilled in the art would be motivated to combine Chaudry and Cloutier with a reasonable expectation of success because both references relates to the aerosolized administration of treprostinil by nebulization. Furthermore, a person skilled in the art would be motivated to combine Mueller or Gessler, which relate to iloprost, with Cloutier with a reasonable expectation of success because these references relate to the inhaled administration of known, safe and effective prostaglandins, either iloprost or treprostinil, to treat pulmonary hypertension. Additional support for the position that a skilled artisan would look to art relating to iloprost when considering treprostinil teachings can be found throughout the prosecution of the '240 patent application wherein Applicants relied upon iloprost art, including Gessler, as providing guidance to a skilled artisan seeking to prepare and administer aerosolized treprostinil. A person skilled in the art would be motivated to combine the OPTINEB® website and Cloutier with a reasonable expectation of success because the OPTINEB® website indicates that the OPTINEB® nebulizer can be used with all non-oily medications to treat pulmonary hypertension. Thus, a skilled artisan searching for nebulizers that are useful in treating pulmonary hypertension as taught by Cloutier, would be led to the OPTINEB® website. Alternatively, a skilled artisan would be led to the OPTINEB® website based upon the teachings of Mueller, which identify the OPTINEB® nebulizer as useful in administering aerosolized prostaglandins for treating pulmonary hypertension.

Claim 2 limits the method of claim 1 to one wherein the formulation comprises 600 µg/ml of the treprostinil or its pharmaceutically acceptable salt. A person skilled in the art could easily and routinely optimize the 500 µg/ml treprostinil solution taught in Cloutier to achieve a 600 µg/ml treprostinil solution. Accordingly, claim 2 of the '240 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 3 limits the method of claim 1 to one where the single event dose is not repeated for a period of at least 3 hours. A person skilled in the art could easily and routinely arrive at the recited dosing regimen after determining the duration of therapeutic effect for 15 µg to 90 µg of treprostinil administered by a pulsed ultrasonic nebulizer, especially in view of the general knowledge in the art that the half-life of treprostinil was about 3 hours. *See* Badesh at 58S-59S. Accordingly, claim 3 of the '240 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 4 limits the method of claim 1 to one where the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose. This claim recites an inherent property of the claimed kit/formulation/method. Accordingly, claim 4 of the

'240 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 5 limits the method of claim 1 to one where the fixed amount of treprostinil or its pharmaceuticallyacceptable salt for each breath inhaled by the human comprises at least 5 ug of treprostinil or its pharmaceutically acceptable salt. A person skilled in the art could easily and routinely optimize the known dosage range of treprostinil to achieve the recited per-breath dosage. Moreover, the use of the composition taught by Cloutier in the OPTINEB® ultrasonic device, which could deliver 173 μL/min, would necessarily result in the recited amount per breath on the assumption that the patient takes about 10-30 breaths per minute. *See* Elder Declaration at ¶ 23. Accordingly, claim 5 of the '240 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 6 limits the method of claim 2 to one where the fixed amount of treprostinil or its pharmaceutically acceptable salt for each breath inhaled by the human comprises at least 5 ug of treprostinil or its pharmaceutically acceptable salt. A person skilled in the art could easily and routinely optimize the known dosage range of treprostinil to achieve the recited per-breath dosage. Moreover, the use of the composition taught by Cloutier in the OPTINEB® ultrasonic device, which could deliver 173 μL/min, would necessarily result in the recited amount per breath on the assumption that the patient takes about 10-30 breaths per minute. *See* Elder Declaration at ¶ 23. Accordingly, claim 6 of the '507 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 7 limits the method of claim 1 to one where the single event dose is inhaled in 3 to 18 breaths by the human. This claim recites a feature that is the inherent result of the use of a pulsed ultrasonic nebulizer, the recited dosage range of treprostinil, and the lung capacity and absorption of treprostinil in the lungs of a human. Accordingly, claim 7 of the '240 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 8 limits the method of claim 6 to one where the single event dose is inhaled in 3 to 18 breaths by the human. This claim recites a feature that is the inherent result of the use of a pulsed ultrasonic nebulizer, the recited dosage range of treprostinil, and the lung capacity and absorption of treprostinil in the lungs of a human. Accordingly, claim 8 of the '240 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

Claim 9 limits the method of claim 6 to one where the single event dose is not repeated for a period of at least 3 hours. A person skilled in the art could easily and routinely arrive at the recited dosing regimen after determining the duration of therapeutic effect for 15 μg to 90 μg of treprostinil administered by a pulsed ultrasonic nebulizer, especially in view of the general knowledge in the art that the half-life of treprostinil was about 3 hours. *See* Badesh at 58S-59S. Accordingly, claim 9 of the '240 patent is invalid as obvious over the teachings of Cloutier combined with Mueller, Chaudry, Gessler, and/or the OPTINEB® website.

(a) Secondary Considerations

Watson is not aware of any probative evidence of secondary considerations of non-obviousness that exists to rebut the prima facie case of invalidity set forth above.

VI. Conclusion

For the reasons discussed herein, each and every claim of U.S. Patent Nos. 9,339,507 and 9,358,240 are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the drug product described in Watson's ANDA.

As such, there is no reasonable basis upon which United Therapeutics Corporation, as the apparent holder of approved New Drug Application ("NDA") No. 022387 for Tyvaso® (treprostinil) Inhalation Solution, 0.6 mg/ml and as record owner of U.S. Patent Nos. 9,339,507 and 9,358,240 can institute suit against Watson for filing of its ANDA No. 208172, as the information provided here makes clear.

Watson expressly reserves the right to develop and make other arguments and assert any defenses relating to non-infringement, invalidity and/or unenforceability of any or all of the claims of U.S. Patent Nos. 9,339,507 and 9,358,240.

Extremely Urgent

ORIGIN ID:ANNA (908) 859-2527
CARLA HEDRICK
ACTAVIS
200 ELMORA AVENUE

ELIZABETH, NJ 07207
UNITED STATES US

SHIP DATE: 27JUN16
ACTWGT: 0.50 LB
CAD: 105112382/INET3730

BILL SENDER

TO GENERAL COUNSEL
UNITED THERAPEUTICS CORPORATION
55 TW ALEXANDER DRIVE

RESEARCH TRIANGLE PA NC 27709
(919) 485-8350 REF:
INV:
PO: DEPT:

540J15C8D/727F

FedEx Express

TUE - 28 JUN

FedEx
TRK# 0201 7766 1513 7996

THU - 30 JUN AA
STANDARD OVERNIGHT

NL MXEA

27709
NC-US
RDU

FID 285913 29JUN16 MMUA 539C1/5C8D/6A88

FedEx

RT 573 8 D
FZ B50 15:00 7996
06.30