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June 12, 2015

Via FedEx®

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1735 Connecticut Ave, N.W., #2
Washington, DC 20009

General Counsel
United Therapeutics Corporation
1104 Spring Street
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Foley& Lardner
Stephen B. Meabius
300 K Street, N.W., Suite 600
Washington, DC 20007-5109

HIGHLY CONFIDENTIAL

Re: Notification of Certification for U.S. Patent Nos. 6,521,212; 6,756,033; and 8,497,393 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® 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. 6,521,212 ("the '212 patent"); 6,756,033 ("the '033 patent"); and 8,497,393 ("the '393 patent) according to the records of the U.S. Patent and Trademark Office ("PTO") and/or 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. Meabius, as the correspondent for the '212, '033, and '393 patents according to the records of the PTO and/or as indicated on the face of the patents.

Pursuant to 21 C.F.R. § 314.95(e), Watson requested and received 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. Consequently, the operative date for determining the start of the 45-day clock under 21 U.S.C. § 355(j)(5)(B)(iii) began from the receipt of this notice, as sent via FedEx®.

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 an 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 ANDA 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. 6,521,212; 6,756,033; and 8,497,393 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. 6,521,212; 6,756,033; and 8,497,393 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
6,521,212	November 13, 2018
6,756,033	November 13, 2018
8,497,393	December 15, 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. 6,521,212; 6,756,033; and 8,497,393 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 ANDA 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.

Section 355(j)(5)(C)(i)(III) allows Watson to impose restrictions "as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." That provision also grants Watson the right to redact its ANDA in response to a request for Confidential Access under this offer.

As permitted by statute, Watson imposes the following terms and restrictions on its Offer of Confidential Access:

(1) Watson will permit confidential access to certain information from its proprietary ANDA No. 208172 to attorneys from one outside law firm representing United Therapeutics, provided however that such attorneys do not engage, formally or informally, in any patent prosecution for United Therapeutics or any FDA counseling, litigation or other work before or involving FDA. Such information (hereinafter, "Confidential Watson Information") shall be marked with the legend "CONFIDENTIAL."

(2) The attorneys from the outside law firm representing United Therapeutics shall not disclose any Confidential Watson Information to any other person or entity, including employees of United Therapeutics, outside scientific consultants, and/or other outside counsel retained by United Therapeutics, without the prior written consent of Watson.

(3) As provided by § 355(j)(5)(C)(i)(III), the outside law firm representing United Therapeutics shall make use of the Confidential Watson Information for the sole and exclusive purpose of determining whether an action referred to in § 355(j)(5)(B)(iii) can be brought — and for no other purpose. By way of example only, the Confidential Watson Information shall not be used to prepare or prosecute any future or pending patent application by United Therapeutics; in connection with any filing to, or communication with, FDA relating to Watson's ANDA No. 208172; or in connection with any submission to, or communication with, the United States Pharmacopeia or any similar organization. The outside law firm representing United Therapeutics agrees to take all measures necessary

to prevent unauthorized disclosure or use of the Confidential Watson Information, and that all Confidential Watson Information shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(4) The Confidential Watson Information disclosed is, and remains, the property of Watson. By providing the Confidential Watson Information, Watson does not grant United Therapeutics and/or their outside law firm any interest in or license for the Confidential Watson Information.

(5) The outside law firm representing United Therapeutics shall, within thirty-five (35) days from the date that it first receives the Confidential Watson Information, return to Watson all Confidential Watson Information and any copies thereof. Said outside law firm shall return all Confidential Watson Information before any infringement suit is filed by United Therapeutics, if suit is commenced before this 35-day period expires. In the event that United Therapeutics opts to file suit, none of the information contained in or obtained from any Confidential Watson Information that Watson provides shall be included in any publicly-available complaint or other pleading.

(6) Nothing in this Offer of Confidential Access shall be construed as an admission by Watson regarding the validity, enforceability, and/or infringement of any U.S. patent. Further, nothing herein shall be construed as an agreement or admission by Watson with respect to the competency, relevance, or materiality of any such Confidential Watson Information, document, or thing. The fact that Watson provides Confidential Watson Information upon request of United Therapeutics shall not be construed as an admission by Watson that such Confidential Watson Information is relevant to the disposition of any issue relating to any alleged infringement of or to the validity or enforceability of U.S. Patent Nos. 6,521,212; 6,756,033; and 8,497,393.

(7) The attorneys from the outside law firm representing United Therapeutics shall acknowledge in writing their receipt of a copy of these terms and restrictions prior to production of any Confidential Watson Information. Such written acknowledgement shall be provided to Watson.

(8) This Offer of Confidential Access shall be governed by the laws of the State of New Jersey.

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. Written notice requesting access under this Offer of Confidential Access should be made to:

Brian Anderson, Esq.
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054
(862) 261-8406
brian.anderson@actavis.com

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: _____
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. 6,521,212; 6,756,033; and 8,497,393 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. 6,521,212; 6,756,033; and 8,497,393 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. 6,521,212 ("the '212 patent"); 6,756,033 ("the '033 patent"); and 8,497,393 ("the '393 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
6,521,212	November 13, 2018
6,756,033	November 13, 2018
8,497,393	December 15, 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 in 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)).

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[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.

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 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. 6,521,212; Method for Treating Peripheral Vascular Disease by Administering Benzindene Prostaglandins by Inhalation

U.S. Patent No. 6,521,212 ("the '212 patent") to Cloutier et al. issued February 18, 2003. The '212 patent is entitled "Method for Treating Peripheral Vascular Disease by Administering Benzindene Prostaglandins by Inhalation," and is assigned on its face and according to the PTO Assignment database to United Therapeutics Corporation. The application which became the '212 patent was filed with the USPTO on March 15, 2000 and assigned U.S. Patent Application No. 09/525,471 ("the '212 patent application"). The '212 patent application claimed priority to U.S. Provisional Patent Application No. 60/124,999, filed on March 18, 1999.

1. The Claims of the '212 Patent

The claims of the '212 patent, as amended by the Certificate of Correction, read as follows:

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.

2. The method of claim 1, wherein said benzindene prostaglandin is inhaled in an aerosolized form.

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.

6. A method for treating pulmonary hypertension in a mammal comprising delivering to said mammal an effective amount of UT-15 or its pharmaceutically acceptable salt or ester by inhalation.

7. The method of claim 6, wherein said UT-15 is inhaled in an aerosolized form.

8. The method of claim 7, wherein said aerosolized form comprises droplets less than 10 micrometers in diameter, said droplets comprising UT-15 in a suitable pharmacologically-acceptable liquid carrier.

9. The method of claim 6, wherein said UT-15 is inhaled in powder form comprising particles less than 10 micrometers in diameter.

10. The method of claim 1, wherein the formulation comprises a sustained release form of a benzindene prostaglandin [sic].

11. The method of claim 6, wherein said UT-15 is a sustained release form.

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

('212 patent at col. 13, l. 26, to col. 14, l. 29.)

B. U.S. Patent No. 6,756,033; Method for Delivering Benzindene Prostaglandins by Inhalation

U.S. Patent No. 6,756,033 ("the '033 patent") to Cloutier et al. issued June 29, 2004. The '033 patent is entitled "Method for Delivering Benzindene Prostaglandins by Inhalation," and is assigned on its face to United Therapeutics Corporation. The application which became the '033 patent was filed with the USPTO on August 6, 2002 as a continuation of the '212 patent application and assigned U.S. Patent Application No. 10/212,144 ("the '033 patent application").

1. The Claims of the '033 Patent

The claims of the '033 patent, as amended by the Certificate of Correction, read as follows:

1. A method of delivering to a mammal in need thereof a therapeutically effective amount of a benzindene prostaglandin comprising administering to the mammal by inhalation a formulation comprising droplets measuring less than 10 micrometers in diameter, wherein said droplets comprise a therapeutically effective amount of the benzindene prostaglandin.

2. The method of claim 1, wherein said formulation comprises droplets less than 10 micrometers in diameter, said droplets comprising said benzindene prostaglandin is 9-deoxy-2′,9-alpha-methano-3-oxa-4,5,6-trinor3,7-(1′3′-interphenylene)-13,14-dihydro-prostaglandin F_1 in a suitable pharmacologically-acceptable liquid carrier.

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

4. The method of claim 1, wherein the formulation comprises a sustained release form of the benzindene prostaglandin.

5. The method of claim 1, wherein the administering of benzindene prostaglandin has no effect on heart rate.

6. A method of delivering to a mammal in need thereof a therapeutically effective amount of a benzindene prostaglandin comprising administering to the mammal by inhalation a powder formulation comprising particles measuring less than 10 micrometers in diameter, wherein said particles comprise a therapeutically effective amount of the benzindene prostaglandin.

7. The method of claim 6, wherein the benzindene prostaglandin is UT-15

8. The method of claim 6, wherein the mammal is a human.

9. The method of claim 6, wherein the formulation comprises a sustained release form of the benzindene prostaglandin.

10. The method of claim 6, wherein the administering of the benzindene prostaglandin has no effect on heart rate.

('033 patent at col. 13, l. 25 to col. 14, l. 29.)

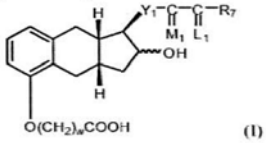
C. U.S. Patent No. 8,497,393; Process to Prepare Treprostinil, the Active Ingredient in Remodulin®

U.S. Patent No. 8,497,393 ("the '393 patent") to Batra et al. issued July 30, 2013. The '393 patent is entitled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin," and is assigned on its face to United Therapeutics Corporation. The '393 patent application was filed on July 13, 2012 as a continuation of U.S. Patent Application No. 12/334,731, filed on December 15, 2008, now U.S. Patent No. 8,242,305. The '393 patent further claims priority to Provisional Application No. 61/014,232, filed on December 17, 2007.

1. The Claims of the '393 Patent

The '393 patent issued on July 20, 2013 with the following twenty-two claims:

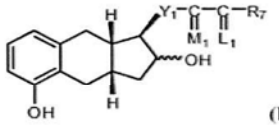
1. A product comprising a compound of formula I



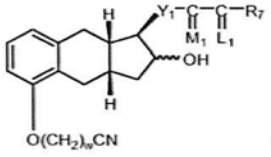
(I)

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

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)



(III)

wherein

w = 1, 2 or 3:
Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)m-$, or C≡C-; m is

1, 2, or 3;
R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,
(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-$CH=CH-CH_2-CH_3$,
(5) $-(CH_2)_2-CH(OH)-CH_3$, or
(6) $-(CH_2)_3-CH=C(CH_3)_2$;

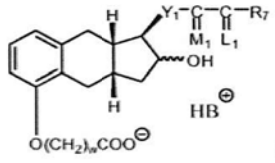
$-C(L_1)-R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl;
(2) 2-(2-furyl)ethyl,
(3) 2-(3-thienyl)ethoxy, or
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or αR_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group , and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,

(b) hydrolyzing the product of formula III of step (a) with a base,
(c) contacting the product of step (b) with base B to form a salt of formula Is,



(Is)

(d) optionally reacting the salt formed in step (c) with an

acid to form the compound of formula I.

2. The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.

3. The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.

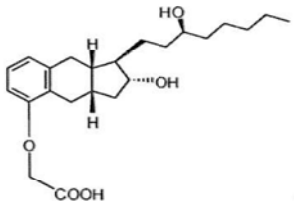
5. The product of claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine [sic], magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

6. The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. The product of claim 1, wherein Y_1 is $--CH_2CH_2--$; M_1 is α.-OH: β-H or α-H:β-OH; $--C(L_1)-R_7$ taken together is $--(CH_2)_4CH_3$; and w is 1.

8. The product of claim 1, wherein the process does not include purifying the compound of formula (III) produced in step (a).

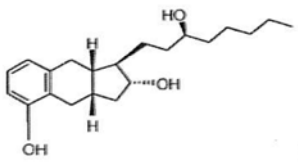
9. A product comprising a compound having a formula IV



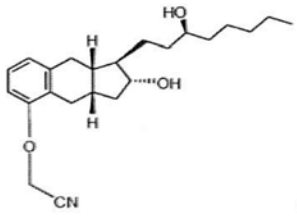
(IV)

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

(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,



(V)

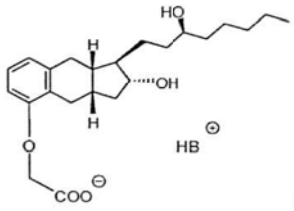


(VI)

(b) hydrolyzing the product of formula VI of step (a) with a base,

(c) contacting the product of step (b) with a base B to form a salt of formula IVs,

and



(IV_s)

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

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

11. The product of claim 9, wherein the alkylating agent is $ClCH_2CN$.

12. The product of claim 9, wherein the base in step (b) is KOH.

13. The product of claim 9, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine [sic], magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

14. The product of claim 9, wherein the base B is diethanolamine.

15. The product of claim 9, wherein the acid in step (d) is HCl.

16. The product of claim 9, wherein the process does not include purifying the compound of formula (VI) produced in step (a).

17. The product of claim 16, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine [sic], magnesium, L-lysine, L-arginine, tricthanolamine, and diethanolamine.

18. The product of claim 17, wherein the base B is diethanolamine.

19. The product of claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base 13 in step (c) is selected from the group consisting of ammonia. N-methyl glucamine, procaine, tromethanine [sic], magnesium, L-lysine, L-arginine,

triethanolamine, and diethanolamine.

20. The product of claim 9, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine [sic], magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

21. The product of claim 1, wherein step (d) is performed.

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

('393 patent, col. 17, l. 52 to col.21, l. 16.)

D. Claim Construction

The claims of the '212, '033, and '393 patents are to be accorded their usual and ordinary meanings as informed by the specification and file history.

E. Non-Infringement Analysis

1. The '212 Patent

(a) Watson's ANDA Product Does Not Directly Infringe Claims 1-12 Of The '212 Patent.

The manufacture and sale of the Watson ANDA product does not directly infringe claims 1-12 of the '212 patent because the manufacture and sale of the Watson ANDA product does not comprise a step of administration or delivery by inhalation.

(b) Watson's ANDA Product Does Not Indirectly Infringe Claims 1-5, 10 And 12 Of The '212 Patent Because The Watson ANDA Product Is Not Indicated For Peripheral Vascular Disease ("PVD")

Claim 1 of the '212 patent is an independent claim that reads as follows:

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.

('212 patent at col. 13, ll. 25-29.)

To be liable for indirect infringement, there must be direct infringement. *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."); *see also C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 673 (Fed. Cir. 1990).

Claim 1 of the '212 patent is not infringed by the use of the Watson ANDA Product because the Watson ANDA product will not be indicated for treating peripheral vascular disease ("PVD"). *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1334 (Fed. Cir. 2003) (holding that Allergan was precluded from suing Alcon for inducing infringement of two patents because Alcon was "not seeking FDA approval for the uses claimed in the patents."); *see also Bayer Schering Pharma AG v. Lupin Ltd.*, 676 F.3d 1316, 1319-23 (Fed. Cir. 2012) ("The [FDA labeling] regulation adds that indications or uses 'must not be implied or suggested in other sections of the labeling if not included in [the Indications and Usage] section.'").

Further, claim 1 of the '212 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA Product based on prosecution history estoppel. Claim 1 of the '212 patent as originally filed did not recite the treatment of a particular disease. However, in response to the Examiner's rejection of the claim over the Aristoff reference, Applicants amended claim 1 to recite a method of treating PVD. In the remarks accompanying the amendment to claim 1, Applicants asserted:

> Even though Aristoff discloses UT-15, there is no teaching or suggestion that the substance is incorporated into an inhalation formulation and the use of it in a method of treating peripheral vascular disease.

('212 patent prosecution history, Response dated September 20, 2001 at p. 3.) Based on Applicants' amendments and arguments during prosecution of the '212 patent, the patent owner is estopped from expanding claim 1 of the '212 patent under the doctrine of equivalents to encompass the use of the Watson ANDA product as indicated in its prescribing information.

Claims 2-5, 10 and 12 of the '212 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."). Therefore, the Watson ANDA Product does not infringe claims 2-5, 10 and 12 of the '212 patent either literally or under the doctrine of equivalents for the reasons discussed above regarding claim 1 of the '212 patent. *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)).

Additionally, claim 10 is not infringed by the use of the Watson ANDA Product because the Watson ANDA Product does not contain a sustained release form of a benzindene prostaglandin product as required by claim 10 of the '212 patent.

Further, claim 10 of the '212 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA Product based on claim vitiation. That is, if claim 10 was expanded under the doctrine of equivalents to include the Watson ANDA Product, then the claim element requiring "a sustained release form" would be vitiated. Such an interpretation under the

doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

(c) Watson's ANDA Product Does Not Indirectly Infringe Claims 9 And 11 Of The '212 Patent Because The Watson ANDA Product Will Not Be Inhaled In A Powder Form

Claims 9 and 11 of the '212 patent depend from independent claim 6. Claims 6, 9 and 11 of the '212 patent read as follows:

> 6. A method for treating pulmonary hypertension in a mammal comprising delivering to said mammal an effective amount of UT-15 or its pharmaceutically acceptable salt or ester by inhalation.
>
> 9. The method of claim 6, wherein said UT-15 is inhaled in powder form comprising particles less than 10 micrometers in diameter.
>
> 11. The method of claim 6, wherein said UT-15 is a sustained release form.

('212 patent at col.14 ll.9-21.)

To be liable for indirect infringement, there must be direct infringement. *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."); *see also C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 673 (Fed. Cir. 1990).

Claim 9 of the '212 patent is not infringed by the Watson ANDA Product because the Watson ANDA Product will not be inhaled in powder form.

Further, claim 9 of the '212 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA Product based on claim vitiation. That is, if claim 9 was expanded under the doctrine of equivalents to include the Watson ANDA Product, then the claim element requiring "in powder form" would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

Claim 11 is not infringed by the use of the Watson ANDA Product because the Watson ANDA Product does not contain a sustained release form of a benzindene prostaglandin product as required by claim 10 of the '212 patent.

Further, claim 11 of the '212 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA Product based on claim vitiation. That is, if claim 10 was expanded under the doctrine of equivalents to include the Watson ANDA Product, then the claim element requiring "a sustained release form" would be vitiated. Such an interpretation under the

doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

(d) Watson's ANDA Product Does Not Indirectly Infringe Claims 6-8 Of The '212 Patent

Claims 6-8 of the '212 patent are not infringed by the Watson ANDA Product because claims 6-8 of the '212 patent are invalid. "It is axiomatic that one cannot infringe an invalid patent." *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983).

2. The '033 Patent

(a) Watson's ANDA Product Does Not Directly Infringe Claims 1-10 Of The '033 Patent.

The manufacture and sale of the Watson ANDA Product are not acts of direct infringement because manufacture and sale are not acts of "administering . . . by inhalation," which is required by the claims of the '033 patent.

(b) Watson's ANDA Product Does Not Indirectly Infringe Claims 6-10 Of The '033 Patent Because The Watson ANDA Product Is Not A Powder Formulation Administered By Inhalation

Claim 6 is an independent claim of the '033 patent that reads as follows:

> 6. A method of delivering to a mammal in need thereof a therapeutically effective amount of a benzindene prostaglandin comprising administering to the mammal by inhalation a powder formulation comprising particles measuring less than 10 micrometers in diameter, wherein said particles comprise a therapeutically effective amount of the benzindene prostaglandin.

('033 patent at col.14 ll.14-20.)

To be liable for indirect infringement, there must be direct infringement. *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.").

Claim 6 of the '033 patent is not infringed by the Watson ANDA Product because the Watson ANDA Product will not be a powder formulation administered by inhalation.

Claim 6 of the '033 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA Product based on claim vitiation. That is, if claim 6 was expanded under the doctrine of equivalents to include the Watson ANDA Product, then the entire claim element of "administering to the mammal by inhalation a powder formulation" would be

vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

Claims 7-10 of the '033 patent depend directly from claim 6 and thereby incorporate all the limitations of claim 6. *See* 35 U.S.C. § 112, ¶ 4. Therefore, the Watson ANDA Product does not infringe claims 7-10 of the '033 patent either literally or under the doctrine of equivalents for the reasons discussed above regarding claim 6 of the '033 patent. *Wolverine World Wide, Inc.*, 38 F.3d at 1199.

Claim 9 is not infringed by the use of the Watson ANDA product because the Watson ANDA Product does not contain a sustained release form of the benzindene prostaglandin as required by claim 9 of the '033 patent.

Claim 9 of the '033 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based on claim vitiation. That is, if claim 9 was expanded under the doctrine of equivalents to include the Watson ANDA product, then the entire claim element requiring "a sustained release form" would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

(c) Watson's ANDA Product Does Not Indirectly Infringe Claims 4 Of The '033 Patent Because The Watson ANDA Product Does Not Contain A Sustained Release Form Of The Benzindene Prostaglandin

Claim 4 of the '033 patent depends from claim 1. Claims 1 and 4 of the '033 patent read as follows:

> 1. A method of delivering to a mammal in need thereof a therapeutically effective amount of a benzindene prostaglandin comprising administering to the mammal by inhalation a formulation comprising droplets measuring less than 10 micrometers in diameter, wherein said droplets comprise a therapeutically effective amount of the benzindene prostaglandin.
>
> 4. The method of claim 1, wherein the formulation comprises a sustained release form of the benzindene prostaglandin.

('033 patent at col. 13, l. 26 to col. 14, l. 11.)

To be liable for indirect infringement, there must be direct infringement. *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.").

Claim 4 of the '033 patent is not infringed by the Watson ANDA Product because the Watson ANDA Product will not contain a sustained release form of the benzindene prostaglandin.

Claim 4 of the '033 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based on claim vitiation. That is, if claim 4 was expanded under the doctrine of equivalents to include the Watson ANDA Product, then the claim element requiring "a sustained release form" would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

(d) Watson's ANDA Product Does Not Indirectly Infringe Claims 1-3 And 5 Of The '033 Patent

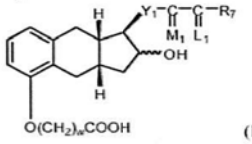
Claims 1-3 and 5 of the '033 patent are not infringed by the Watson ANDA Product because claims 1-3 and 5 of the '033 patent are invalid. "It is axiomatic that one cannot infringe an invalid patent." *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983).

3. The '393 Patent

(a) Watson's ANDA Product Does Not Infringe Claims 1-8, 19, 21 And 22 Because Watson's API Is Not Prepared By A Process That Creates A Salt Of Formula I_s

Claim 1 of the '393 patent is an independent claim that reads as follows:

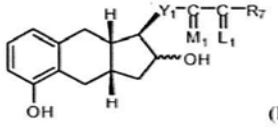
1. A product comprising a compound of formula I



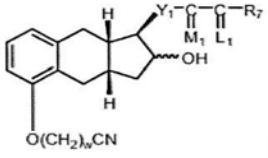
(I)

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

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)



(III)

wherein

w = 1, 2 or 3:
Y_1 is trans-CH=CH-, cis-CH=CH-, -$CH_2(CH_2)$m-, or C≡C-; m is 1, 2, or 3;
R_7 is

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

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl, with proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3) alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) –(CH_2)$_2$-CH(OH)-CH_3, or

(6) –(CH_2)$_3$-CH=C(CH_3)$_2$;

-C(L_1)-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5) alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

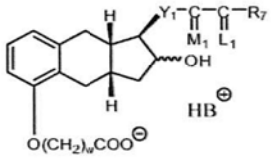
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or αR_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group , and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro,

(b) hydrolyzing the product of formula III of step (a) with a base,

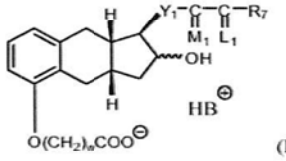
(c) contacting the product of step (b) with base B to form a salt of formula Is,



(Is)

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

Claim 1 of the '393 patent recites a process that requires the formation of a salt of formula I_s:



(Is)

The Watson ANDA Product does not literally infringe claim 1 because the Watson API is not prepared by a process that creates a salt of formula I_s.

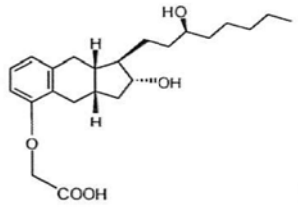
Further, the '393 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 1 was expanded under the doctrine of equivalents to include the Watson ANDA Product, then the entire claim element of requiring a salt of formula I_s would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs*, 402 F.3d at 1195; *Freedman Seating*, 420 F.3d at 1358.

Claims 2-8, 19, 21 and 22 depend, either directly or indirectly, from claim 1 of the '393 patent and thereby incorporate all the limitations of claim 1. *See* 35 U.S.C. § 112, ¶ 4. Therefore, the Watson ANDA Product does not infringe claims 2-8, 19, 21 and 22 of the '393 patent either literally or under the doctrine of equivalents for the reasons discussed above regarding claim 1 of the '393 patent. *Wolverine World Wide, Inc.*, 38 F.3d at 1199.

(b) Watson's ANDA Product Does Not Infringe Claims 9-18 And 20 Because Watson's API Is Not Prepared By A Process That Creates A Salt of Formula IV_s

Claim 9 of the '393 patent is an independent claim that reads as follows:

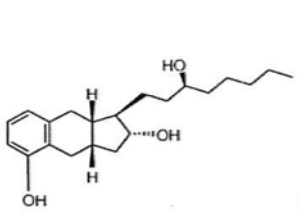
9. A product comprising a compound having a formula IV



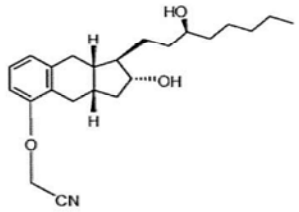
(IV)

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

(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI,



(V)

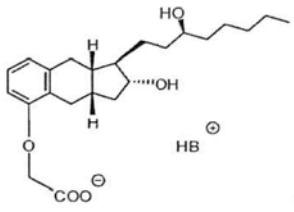


(VI)

(b) hydrolyzing the product of formula VI of step (a) with a base,

(c) contacting the product of step (b) with a base B to form a salt of formula IVs,

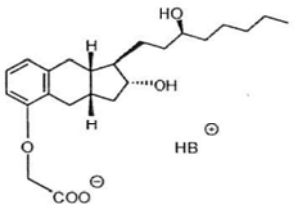
and



(IV_s)

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

Claim 9 of the '393 patent recites a process that requires the formation of a salt of formula IV_s:



(IV_s)

The Watson ANDA Product does not literally infringe claim 9 because the Watson API is not prepared by a process that creates a salt of formula IV_s.

Claim 9 of the '393 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 9 was expanded under the doctrine of equivalents to include the Watson ANDA Product, then the claim element of requiring a salt of formula IV_s would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs*, 402 F.3d 1195; *Freedman Seating*, 420 F.3d 1358.

Claims 10-18 and 20 depend, either directly or indirectly, from claim 9 of the '393 patent and thereby incorporate all the limitations of claim 9. *See* 35 U.S.C. § 112, ¶ 4. Therefore, the Watson ANDA Product does not infringe claims 10-18 and 20 of the '393 patent either literally or under the doctrine of equivalents for the reasons discussed above regarding claim 9 of the '393 patent. *Wolverine World Wide, Inc.*, 38 F.3d at 1199.

F. Invalidity Analysis

1. Level of Ordinary Skill In The Art

The subject matter of the '212 and '033 patents falls within the medical/pharmaceutical arts. The person of ordinary skill to whom the '212 and '033 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. 5,234,953, Treatment of Congestive Heart Failure, Crow et. al.

U.S. Patent No. 5,234,953 to Crow et al. (hereinafter "Crow") titled "Treatment of Congestive Heart Failure," was filed May 3, 1991, and issued August 10, 1993.

Crow describes compounds for use "in the treatment of CHF [congestive heart failure] which is accompanied by pulmonary hypertension." (Crow at col. 2, ll. 8-11.) In particular, Crow states:

> [p]referred compounds of formula (I) having particularly advantageous properties in respect of the treatment of CHF are (1R,2R,3aS,9aS)-([2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-((S)-3-hydroxyoctyl)-1H-benz[f]inden-5-yl]oxy)acetic acid (which is also known as [1R-(1α(S*),2α,3aα,9aα)]-([2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-(3-hydroxyoctyl)-1H-benz-[f]inden-5-yl]oxy)acetic acid or 9-deoxy-2',9-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F_1) having formula (A),

(Crow at col. 2, ll. 53-65.) The compound referred to in Crow is treprostinil, *i.e.*, UT-15.[2]

In addition, Crow notes:

> [c]ompound (A) was found to a potent pulmonary vasodilator in this model and markedly attenuated the pulmonary vasoconstriction induced by hypoxia. The overall acute beneficial hemodynamic effects observed were substantial reductions in pulmonary vascular resistance, pulmonary arterial pressure, systemic vascular resistance and mean arterial blood pressure and increases in cardiac output and stroke volume.

(Crow at col. 7, ll. 19-27.)

Crow also teaches that "[t]he compositions of the invention include those suitable for . . . nasal and pulmonary administration . . . ." (Crow at col. 4, ll. 32-36.) Crow elaborates:

> [f]or nasal administration, a particle size in the range 10-500 um is preferred to ensure retention in the nasal cavity. For pulmonary administration via the mouth, the particle size of the powder or droplets is typically in the range 0.5-10 um, preferably 1-5 um, to ensure delivery into the bronchial tree.

[2] It is noted that Crow reports to show the molecular structure of formula A at column 3, lines 1-10. Watson believes the depicted structure is inaccurate because it does not reflect the intermediate six member ring configuration in the three ring base.

> Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution composition of the active ingredient in a liquefied propellant. During use these devices discharge the composition through a valve adapted to deliver a metered volume, typically from 10 to 150 ul, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The composition may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate or EXOSURF Neonatal®, antioxidants and suitable flavoring agents.
>
> . . . .
>
> Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas through a narrow venturi orifice, typically air or oxygen, or by mean of ultrasonic agitation. Suitable compositions for use in nebulizers consist of the active ingredient in a liquid carrier, the active ingredient comprising up to 40% w/w of the composition, but preferably less than 20% w/w. The carrier is typically water or a dilute aqueous alcoholic solution . . . .
>
> Suitable compositions for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. . . . The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient . . . .

(Crow at col. 5, l. 48 to col. 6, l. 36.)

Crow also teaches that the compounds of the invention are suitable for administration to a mammal, such as a human:

> [a]ccording to a further aspect of the invention, therefore, there is also provided a method for the treatment of CHF in a mammal, such as a human, which comprises the administration of a therapeutically effective amount of a compound of formula (I).

(Crow at col. 2, ll. 48-52.)

3. The '212 Patent

(a) Claims 6-8 Are Invalid As Anticipated Over Crow

Claims 6-8 of the '212 patent are invalid as anticipated under 35 U.S.C. §102(b)[3] over Crow.

Claim 6 is an independent claim of the '212 patent that reads as follows:

> 6. A method for treating pulmonary hypertension in a mammal comprising delivering to said mammal an effective amount of UT-15 or its pharmaceutically acceptable salt or ester by inhalation.

As discussed above, Crow discloses the use of UT-15 in the treatment of pulmonary hypertension. (Crow at col. 2, ll. 53-65; col 2, ll. 9-11.) Crow also discloses the delivery of an effective amount of UT-15 by inhalation. Specifically, Crow discloses "the compositions of the invention include those suitable for . . . nasal and pulmonary administration . . . ." (Crow at col. 4, ll. 32-36.) Crow further states:

> [a]ccording to a further aspect of the invention, therefore, there is also provided a method for the treatment of CHF in a mammal, such as a human, which comprises the administration of a therapeutically effective amount of a compound of formula (I).

(Crow at col. 2, ll. 48-52.)

Claim 7 limits the method of claim 6 to one where the active ingredient (UT-15) is inhaled in an aerosolized form. Crow discloses inhalation of UT-15 in an aerosolized form. Crow discloses metered dose inhalers which are pressurized aerosol dispensers, typically containing a suspension or solution composition of the active ingredient in a liquefied propellant. (Crow at col. 5, ll. 54-57.) Crow further teaches:

> [n]ebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas through a narrow venturi orifice, typically air or oxygen, or by mean of ultrasonic agitation. Suitable compositions for use in nebulizers consist of the active ingredient in a liquid carrier, the active ingredient comprising up to 40% w/w of the composition, but preferably less than 20% w/w. The carrier is typically water or a dilute aqueous alcoholic solution . . . .

(Crow at col. 6, ll. 18.)

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[3] 35 U.S.C. 102(b) 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 falls before March 16, 2013.

Claim 8 limits the method of claim 7 to one where the aerosolized form comprises droplets less than 10 micrometers in diameter. Crow discloses droplets of less than 10 micrometers in diameter. Specifically, Crow discloses:

> [f]or pulmonary administration via the mouth, the particle size of the powder or droplets is typically in the range 0.5-10 um, preferably 1-5 um, to ensure delivery into the bronchial tree.

(Crow at col. 5, ll. 50-53.)

(b) 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 '033 Patent

(a) Claims 1-3 and 5 are Invalid as Anticipated Over Crow

Claims 1-3 and 5 of the '033 patent are invalid as anticipated under 35 U.S.C. §102(b) over Crow.

Claim 1 is an independent claim of the '033 patent that reads as follows:

> 1. A method of delivering to a mammal in need thereof a therapeutically effective amount of a benzindene prostaglandin comprising administering to the mammal by inhalation a formulation comprising droplets measuring less than 10 micrometers in diameter, wherein said droplets comprise a therapeutically effective amount of the benzindene prostaglandin.

As discussed above, Crow discloses the use of a benzindene prostaglandin in the treatment of CHF [congestive heart failure] which is accompanied by pulmonary hypertension. (Crow at col 2, ll. 8-11.) Crow also discloses the delivery of an effective amount of benzindene prostaglandin by inhalation. Specifically, Crow discloses "the compositions of the invention include those suitable for . . . nasal and pulmonary administration . . . ." (Crow at col. 4, ll. 32-36.) Crow further states:

> [a]ccording to a further aspect of the invention, therefore, there is also provided a method for the treatment of CHF in a mammal, such as a human, which comprises the administration of a therapeutically effective amount of a compound of formula (I).

(Crow at col. 2, ll. 48-52.)

Crow further discloses droplets of less than 10 micrometers in diameter. Specifically, Crow discloses:

> [f]or pulmonary administration via the mouth, the particle size of the powder or droplets is typically in the range 0.5-10 um, preferably 1-5 um, to ensure delivery into the bronchial tree.

(Crow at col. 5, ll. 50-53.)

Claim 2 limits the method of claim 1 to one where the benzindene prostaglandin is treprostinil in a suitable pharmacologically-acceptable liquid carrier. As discussed above, Crow discloses treprostinil in a suitable pharmacologically-acceptable liquid carrier. (Crow at col. 2, ll. 53-65; col. 5, ll. 54-57; col. 6, ll. 18.)

Claim 3 limits the method of claim 1 to where the mammal is a human. Crow discloses this limitation. (Crow at col. 2, ll. 48-52.)

Claim 5 limits the method of claim 1 to one where the administering of benzindene prostaglandin has no effect on heart rate. The claimed limitation of no effect on heart rate is merely an inherent property of the method disclosed in Crow. Therefore, Crow anticipates claim 5 of the '033 patent.

(b) 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. 6,521,212; 6,756,033; and 8,497,393 are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the drug products 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. 6,521,212; 6,756,033; and 8,497,393 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. 6,521,212; 6,756,033; and 8,497,393.