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Paper No. 10
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WATSON LABORATORIES, INC.
Petitioner,

v.

UNITED THERAPEUTICS CORP.[1]
Patent Owner.

Case IPR2017-01621
Patent 9,358,240 B2

Before LORA M. GREEN, ERICA A. FRANKLIN, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
37 C.F.R. § 42.108

[1] Further to Patent Owner's request, we have changed the case caption in order to reflect that United Therapeutics Corporation is the assignee of record with respect to US Patent No. 9,399,507 B2. Prelim Resp. 1 n.1.

I. INTRODUCTION

Watson Laboratories, Inc. ("Petitioner" or "Watson") filed a Petition requesting an *inter partes* review of claims 1–9 of U.S. Patent No. 9,358,240 B2 (Ex. 1001, "the '240 patent"). Paper 2 ("Pet."). United Therapeutics Corp. ("Patent Owner" or "UTC") filed a Preliminary Response to the Petition. Paper 5 (Prelim. Resp.).

Institution of an *inter partes* review is authorized by statute only when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition, the Preliminary Response, and the cited evidence, we conclude that Petitioner has satisfied the burden under 35 U.S.C. § 314(a) to show that there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims.

A. Related Proceedings

Petitioner and Patent Owner identify the following proceedings as relating to the '240 patent: *United Therapeutics Corp. v. Watson Laboratories, Inc.* Case No. 15-cv-05723 (D.N.J.) and IPR2017-01622, which challenges the patentability of U.S. Patent No. 9,339,507 ("the '507 patent"). *Id*. The '240 patent and the '507 patent share a common parent and provisional application. *Id*. Patent Owner also identifies US Patent Application No. 15/011,999, a pending continuation application with common priority to the '240 and '507 patents, as related to this proceeding. Paper 3, 2.

B. The '240 Patent (Ex. 1001)

The '240 patent issued June 7, 2016, identifying Horst Olschewski, Robert Roscigno, Lewis J. Rubin, Thomas Schmehl, Werner Seeger, Carl Sterritt, and Robert Voswinckel as co-inventors. Ex. 1001. The patent discloses "methods and kits for therapeutic treatment . . . involving administering treprostinil using a metered dose inhaler and related kits." *Id.* at 1:15–19.

The '240 patent teaches that pulmonary hypertension is "a condition associated with an elevation of pulmonary arterial pressure (PAP) over normal levels." *Id.* at 2:6–8. "Pulmonary hypertension has been implicated in several life-threatening clinical conditions, such as adult respiratory distress syndrome ('ARDS') and persistent pulmonary hypertension of the newborn ('PPHN')." *Id.* at 2:37–40. "Pulmonary hypertension may also ultimately result in a potentially fatal heart condition known as 'cor pulmonale,' or pulmonary heart disease." *Id.* at 2:48–51. According to the '240 patent, "currently there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device, such as a metered dose inhaler." *Id.* at 2:53–55.

The '240 patent discloses that "[t]he inventors discovered that a therapeutically effective dose of treprostinil can be administered in a few single inhalations using a compact inhalation device, such as a metered dose inhaler." *Id.* at 5:8–11. The '240 patent further discloses that "such administering does not cause significant side effects." *Id.* at 5:12–13.

C. Challenged Claims

Petitioner challenges claims 1–9 of the '240 patent. Claim 1, the only independent claim, is reproduced below:

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 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 effective 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 dose event comprising from 15 μg to 90 μg treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths.

Ex. 1001, 18:2–17.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–9 of the '240 patent on the following grounds (Pet. 6):

References	Basis	Claims Challenged
Voswinckel,[2] Patton,[3] and Ghofrani[4]	§ 103(a)	1–9

[2] Robert Voswinckel, et al., *Inhaled Treprostinil Sodium (TRE) for the Treatment of Pulmonary Hypertension,* Abstract #1414, CIRCULATION, 110, 17, Supplement (Oct. 2004): III–295 (Ex. 1003, "Voswinckel").
[3] Patton et al., WO 93/00951, published Jan. 21, 1993 (Ex. 1012, "Patton").
[4] Hossein Ardeschi Ghofrani, Robert Voswinckel, et al., *Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie*, 30(4) HERTZ 296–302 (2005) (Ex. 1005, "Ghofrani"). Ghofrani was originally published in German. All citations herein are to the English translation of Ghofrani provided by Petitioner (Ex. 1005).

References	Basis	Claims Challenged
Voswinckel, Patton, and the OptiNeb User Manual[5]	§ 103(a)	1–9
Voswinckel, Ghofrani and the EU Community Register[6]	§ 103(a)	1–9

Petitioner submits the Declaration of Dr. Maureen D. Donovan (Ex. 1002), the Declaration of Dr. Scott Bennett (Ex. 1013), two Affidavits of Christopher Butler (Ex. 1014 and 1015), and the Declaration of Dr. DeForest McDuff (Ex. 1055) in support of institution of *inter partes* review. Patent Owner submits the Declaration of Dr. Richard Dalby (Ex. 2001), the Declaration of Dr. Werner Seeger (Ex. 2020), the Declaration of Dr. Hossein A. Ghofrani (Ex. 2026), the Declaration of Dr. Frank Reichenberger (Ex. 2027), and the Declaration of Dr. Friedrich Grimminger (Ex. 2028) to support their arguments in opposition to institution.

II. ANALYSIS

A. 35 U.S.C. § 315(b)

We first consider arguments raised in Patent Owner's Preliminary Response challenging whether Petitioner timely filed the Petition. Prelim. Resp. 13–20. Patent Owner initially filed a complaint against Petitioner alleging infringement of patents other than the '240 patent in the United States District Court for the District of New Jersey on July 22, 2015.

[5] Opti-Neb-ir® Operating Instructions, Model ON-100/2-2.4 MHz (2005) (Ex. 1006, "OptiNeb"). OptiNeb was originally published in German. Pet. 17, n. 6. All citations herein are to the English translation of OptiNeb provided by the Petitioner (Ex. 1006).

[6] Annexes to Commission Decision C(2005)3436 of 05 September 2005, http://ec.europa.eu/health/documents/communityregister/2005/2005090510259/anx_10259_en.pdf (Annex III–Ventavis Labelling and Package Leaflet) (Ex. 1009, "EU Community Register" or "Annex III").

Ex. 2009, 3. On June 17, 2016, Patent Owner served Petitioner with a Motion for Leave to Amend that complaint to assert infringement of the newly issued '240 patent.[7] *Id.* at 4, 11; Ex. 2010. The Motion for Leave to Amend attached as Exhibit A, a copy of a Patent Owner's proposed First Amended Complaint and Jury Demand, which added the '240 patent to Patent Owner's allegations of infringement in the original complaint. Ex. 2009, 15. Petitioner did not oppose Patent Owner's motion. *Id.* at 4. On June 21, 2016, the District Court granted the motion and Patent Owner filed the Amended Complaint. Ex. 2011; Pet. 5; Prelim. Resp. 14. Petitioner filed the Petition requesting *inter partes* review of the '240 patent on June 21, 2017.

The issue before us is whether Petitioner was "served with a complaint" alleging infringement of the '240 patent prior to June 21, 2016, which would bar institution of *inter partes* review under 35 U.S.C. § 315(b). More specifically, the issue is whether service of the "First Amended Complaint and Jury Demand" as an exhibit attached to Patent Owner's Motion for Leave to Amend constituted service of a "complaint," thereby triggering the one-year time bar under § 315(b).

The relevant portion of § 315(b) provides:

> (b) PATENT OWNER'S ACTION.--An *inter partes* review may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner, real party in interest, or privy of the petitioner is served with a complaint alleging infringement of the patent.

35 U.S.C. § 315(b).

Patent Owner urges us to deny the Petition, arguing that Petitioner is

[7] Patent Owner also sought to add the newly issued '507 patent, which is at issue in IPR2017-01622.

time-barred from seeking *inter partes* review of the '240 patent under § 315(b) because Petitioner was served with a complaint on June 17, 2016, i.e., more than one year before the June 21, 2017 filing date of the Petitions in this proceeding. Prelim. Resp. 13–20.

The Board has previously addressed the issue of when an amended complaint is considered to be served in *TRW Automotive US LLC v. Magna Electronics, Inc.*, IPR2014-00293, Paper 18 (June 27, 2014) (informative) and in *Amneal Pharmaceuticals, LLC v. Endo Pharmaceuticals Inc.*, IPR2014-00360 Paper 15, (June 27, 2014). In both cases, leave of court was required in order for the patent owners to amend their complaints to include additional newly issued patents. In both cases, the Board concluded that serving an amended complaint as an attachment to a motion seeking leave from the District Court to amend the patent owners' complaints did not constitute service of the amended complaint under 35 U.S.C. § 315(b). The rationale, as articulated in *TRW,* was that the patent owner had "requested, but had not obtained yet, permission to file a Second Amended Complaint" and, thus, "[a]t the point of filing the Motion for Leave to file its Second Amended Complaint, the attachment to the Motion for Leave was merely a proposed complaint, and Petitioner was not yet a defendant in a lawsuit with respect to the [patent at issue]." *TRW*, IPR2014-00293, Paper 18 at 10; *see also, Amneal,* IPR2014-00360 Paper 15 at 7–8. The Board further reasoned: "We do not believe that Congress intended to have the [one-year] time period start before a petitioner is officially a defendant in a lawsuit." *TRW*, IPR2014-00293, Paper 18 at 10 (citing *Motorola Mobility LLC v. Arnouse,* IPR2013-00010, paper 20, 5 (Jan. 30, 2013).

Patent Owner argues that this case is distinguishable over *TRW* because Petitioner "conceded its status as a defendant." Prelim. Resp. 15. Patent Owner notes that the parties agreed upon a "proposed schedule to account for the inclusion of the new patents in the Civil Action while maintaining the original trial schedule" and that Petitioner informed Patent Owner that it did not oppose the Motion for Leave. *Id.* at 16–17. Patent Owner further notes that Petitioner sent a Paragraph IV Certification alleging invalidity of the '240 patent (which constitutes an act of infringement). *Id.* at 18. Finally, Patent Owner argues that the magistrate judge ruling on the Motion for Leave to Amend has a 100% allowance rate and there was, thus, "no doubt Petitioner was a defendant as to those patents." *Id.*

The distinctions advanced by Patent Owner do not compel a different result than was reached in *TRW* and *Amneal*. Here, as in *TRW* and *Amneal*, Patent Owner did not have the authority to amend its complaint until granted permission by the District Court. It is undisputed in this case that Patent Owner sought leave from the District Court to file an amended complaint and that such leave was not granted until June 21, 2016. Ex. 2009; Ex. 2011. Thus, regardless of whether Petitioner "conceded its status as a defendant," Patent Owner requested leave to amend its pleading and make Petitioner a defendant with respect to '240 patent, which left the matter in the Court's hands to decide. The attachment to the Motion for Leave was thus merely a proposed complaint, not an actual "complaint" within the meaning of § 315(b).

In view of the record before us at this time, we conclude Petitioner was not "served with a complaint" alleging infringement of the '240 patent

for the purposes of § 315(b) until June 21, 2016 and, therefore, that 35 U.S.C. § 315(b) does not bar institution of this Petition.

B. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include "the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field." *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co., v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros*.).

Petitioner and Patent Owner offer different descriptions of the person of ordinary skill in the art, but appear generally to agree that the person of ordinary skill would have had a post-graduate degree in a field related to drug development and at least two years of practical experience. Pet. 8–9; Prelim. Resp. 7. Petitioner formulates its definition as "a person having . . . a Ph.D. degree in pharmaceutical science or a related discipline like chemistry or medicinal chemistry, as well as at least two years of practical experience in the development of potential drug candidates, specifically in the delivery of drug by inhalation." Pet. 8–9. Patent Owner formulates its definition as "a person with a post-graduate degree in medicine or drug development (such as the pharmaceutical sciences) with at least two years of experience in the investigation or treatment of pulmonary hypertension." Prelim. Resp. 8.

Petitioner's description of the level of ordinary skill in the art is supported by the current record. In addition, both parties' experts applied Petitioner's definition of the person of ordinary skill in the art. *See* Prelim.

Resp. 8 (noting that Patent Owner's Expert, Dr. Richard Dalby, applied the Petitioner's definition of the person of ordinary skill in the art). Accordingly, for purposes of this Decision, we adopt Petitioner's description.

Moreover, we have reviewed Dr. Donovan's credentials (Ex. 1002 ¶¶ 5–9) and, at this stage in the proceeding, we consider Dr. Donovan to be qualified to provide an opinion on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. Additionally, we have reviewed Dr. Dalby's credentials (Ex. 2022) and, at this stage in the proceeding, we consider Dr. Dalby to be qualified to provide an opinion on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. [8]

C. Claim Construction

We interpret claims of an unexpired patent using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim terms are generally given their ordinary and customary meaning as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

[8] These determinations would be the same if Patent Owner's description of the person of ordinary skill in the art were applied.

Although Patent Owner offers constructions for several claim terms (Prelim. Resp. 9–13), at this stage of the proceeding, we determine that no explicit construction of any claim term is necessary to determine whether to institute a trial in this case. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))); *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy'").

D. Availability of Ghofrani and the EU Community Register as Prior Art Printed Publications

Patent Owner argues that Ghofrani and the EU Community Register do not qualify as prior art printed publications.[9] For the reasons explained below, we determine that Petitioner has made a sufficient threshold showing that Ghofrani qualifies as a prior art printed publication for purposes of institution. To be clear, we have not yet made a determination that Petitioner has established by a preponderance of the evidence that Ghofrani is a prior art printed publication. Rather, at this preliminary stage, resolving factual disputes involving a genuine issue of material fact in favor of Petitioner, we have determined only that Petitioner's evidence is sufficient for institution. For the reasons explained below, we determine that the

[9] Patent Owner also argues that Petitioner has not established that OptiNeb qualifies as a prior art printed publication. We do not address this argument because, even assuming OptiNeb qualifies as a printed publication, we determine that Petitioner has not shown a reasonable likelihood of prevailing on Ground 2, as explained below in section II. F.

Petitioner has not provided sufficient threshold evidence demonstrating that the EU Community Register qualifies as a prior art printed publication.

i. Availability of Ghofrani

Ghofrani is a journal article published in the June 2005 issue of *Herz.* Ex. 2005. Petitioner asserts that Ghofrani is a prior art printed publication under 35 U.S.C. § 102(a). Pet. 15. Patent Owner contends that Ghofrani does not qualify as prior art because it is not the work of "another." Prelim. Resp. 21–24.

In order to determine whether Ghofrani qualifies as prior art under 35 U.S.C. § 102(a), we must consider whether Ghofrani is the work of another. *In re Katz*, 687 F.2d 450, 454 (CCPA 1982) ("A printed publication cannot stand as a reference under § 102(a) unless it is describing the work of another.") "A [reference] is considered 'to another' when the 'inventive entities' are different." *In re Fong*, 378 F.2d 977, 980 (CCPA 1967). The determination of whether the disclosure in a reference is the work of another focuses on authorship of the portions of the reference relied upon as prior art. *Riverwood Int'l Corp. v. R.A. Jones &Co., Inc.*, 324 F.3d 1346, 1356 (Fed. Cir. 2003) ("What is significant is not merely the differences in the listed inventors, but whether the portions of the reference relied on as prior art, and the subject matter of the claims in question, represent the work of a common inventive entity.").

Here, Ghofrani lists as authors two persons identified on the face of the '240 patent as inventors (Robert Voswinckel and Werner Seeger) as well as three non-inventors (Hossein Ardeschir Ghofrani, Frank Reichenberger, and Friedrich Grimminger). Exs. 1001 & 1005. Patent Owner asserts that the "non-inventor co-authors made specific and limited contributions to the

reference, none of which were pertinent to the section (Ex. 1005, 298) relied upon by Petitioner." Prelim. Resp. 22. To support this assertion, Patent Owner provides the Declaration of Dr. Seeger, who quotes the passage of Ghofrani relied upon by Petitioner and then states:

> The information in this excerpt was compiled and composed by Dr. Voswinckel and myself. The idea to perform the underlying work described in this section originated with Dr. Voswinckel and myself, in view of our work with the other inventors listed on the '240 patent. The other authors listed in the Ghofrani article – Drs. Ghofrani, Reichenberger and Grimminger – did not contribute to this excerpt or the underlying work.

Ex. 2020 ¶ 7. In addition, Patent Owner provides Declarations from Drs. Ghofrani, Reichenberger and Grimminger that describe their contributions to the Ghofrani article and, consistent with the Seeger Declaration, disclaim having made any contribution to the excerpted passage of Ghofrani relied upon by Petitioner. Ex. 2026 ¶¶ 4–6; Ex. 2027 ¶¶ 4–6; Ex. 2028 ¶¶ 4–6.

The declarations from the Ghofrani authors leave some ambiguity as to whether and to what extent the five persons who were listed as inventors of the '240 patent, but who were not listed as authors of Ghofrani, contributed to the relevant portion of Ghofrani. The contribution of these five non-author inventors is discussed in one sentence in Dr. Seeger's Declaration. Dr. Seeger states that the idea to perform the work described in the relevant portion of Ghofrani "originated with Dr. Voswinckel and myself, in view of our work with the other inventors listed on the '240 patent." Ex. 2020 ¶ 7. It is not clear whether this means that the five non-author inventors contributed to the relevant portion of Ghofrani, as would be

necessary to establish that Ghofrani is not the work of another.[10] *See In re Land*, 368 F.2d 866, 881 (CCPA 1966) (holding that individual applications to Land and to Rogers were prior art with respect to joint application to Land and Rogers). This ambiguity creates a genuine issue of material fact.

In addition, the non-inventor Ghofrani authors are identified as authors of Voswinckel, a reference with subject matter limited to inhaled treprostinil. Ex. 1004. Voswinckel references a 17 patient study that appears to be the same as the 17 patent study discussed in the relevant portions of Ghofrani. *Compare,* Ex. 1004 and Ex. 1005. The narrow focus of Voswinckel and the potential that Voswinckel involved the same study as disclosed in Ghofrani, create a genuine issue of material fact as to the contribution of these non-inventors to Voswinckel and, by extension, to the relevant portions of Ghofrani.

At this stage of this proceeding, we are required to resolve any genuine issue of material fact in the light most favorable to Petitioner. 37 C.F.R. § 42.108(c). For purposes of the present decision only, we must resolve the disputed factual issues regarding whether Ghofrani constitutes the work of another in Petitioner's favor. Accordingly, for purposes of institution, we find that Petitioner has provided a sufficient basis on which to conclude that Ghofrani was the work of another.

ii. Availability of the EU Community Register

The EU Community Register appears to be the third annex to a decision of the Commission of the European Communities "amending the marketing authorization for 'Ventavis® – Iloprost,' a medicinal product for

[10] Patent Owner has not asserted that fewer than all of the listed inventors contributed to any of the challenged claims.

human use, granted by Decision C(2003)3348" ("the Commission Decision"). Ex. 1042; Ex. 1009 (Annexes to the Decision). The Commission Decision is marked "NOT FOR PUBLICATION," (Ex. 1042, 1) and the penultimate page of Annex III states: "**This leaflet was last approved on** {date}." Ex. 1009, 29. Petitioner asserts that the EU Community Register is a prior art printed publication under 35 U.S.C. § 102(a). Pet. 18. Patent Owner contends that the Petitioner has not established public accessibility for the EU Community Register. Prelim. Resp. 29–33.

"In order to qualify as a printed publication within the meaning of § 102, a reference 'must have been sufficiently accessible to the public interested in the art.'" *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009). "A reference is considered publicly accessible if it was 'disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.'" *Id.* "The decision whether a particular reference is a printed publication 'must be approached on a case-by-case basis.'" *In re Cronyn,* 890 F.2d 1158, 1161 (Fed.Cir.1989) (quoting *In re Hall*, 781 F.2d 897, 899 (Fed.Cir.1986)).

Petitioner, relying on the testimony of Dr. Donovan, asserts that a person of ordinary skill in the art would have been aware that Ventavis, like treprostinil, is a stable postcyclin analogue and would have "investigated the capabilities of the nebulizers used to deliver Ventavis®" including by accessing "regulatory filings in United States and Europe." Pet. 19. Petitioner then offers two alternate arguments for why Annex III to the Commission Decision was publically available.

First, Petitioner contends that Annex III to the Commission Decision was available to the public through the EU Community Register of Medicinal Products. Pet. 19. The Community Register page for Ventavis is reproduced in relevant part below.

European Commission procedures

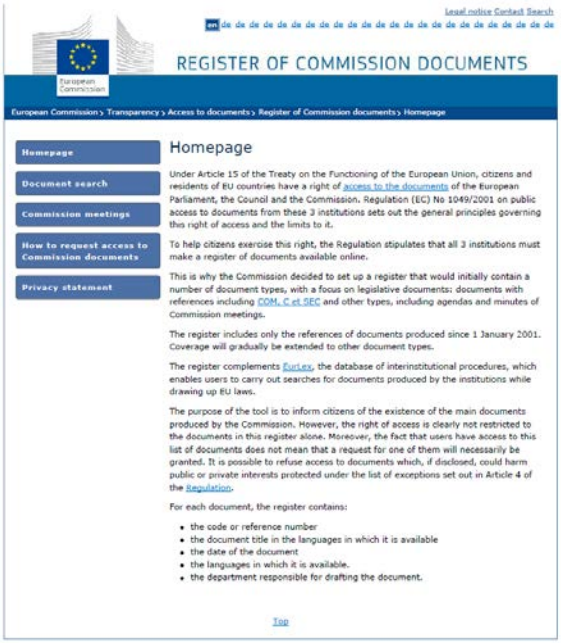
Close date procedure	Procedure type	EMEA number	Decision	summary publ	decision docs	annex
18/09/2003	Centralised - Authorisation	EMEA/H/C/474	(2003)3348 of 16/09/2003	sum	dec	anx
16/04/2004	Centralised - Notification	EMEA/H/C/474/N/1	(2004)1486 of 13/04/2004	sum	dec	anx
14/10/2004	Centralised - Notification Updated with Decision(2005)660 of 07/03/2005	EMEA/H/C/474/N/2				
25/11/2004	Centralised - Notification Updated with Decision(2005)3436 of 05/09/2005	EMEA/H/C/474/N/4				
09/03/2005	Centralised - Annual reassessment	EMEA/H/C/474/S/3	(2005)660 of 07/03/2005	sum	dec	anx
08/09/2005	Centralised - Variation	EMEA/H/C/474/II/5	(2005)3436 of 05/09/2005	sum	dec	anx
04/05/2006	Centralised - Variation	EMEA/H/C/474/II/6	(2006)1884 of 02/05/2006	sum	dec	anx
01/06/2006	Centralised - Annual reassessment	EMEA/H/C/474/S/7				
12/06/2006	Centralised - Variation	EMEA/H/C/474/II/8	(2006)2303 of 08/06/2006	sum	dec	anx
27/09/2006	Centralised - Variation (no change in Commission Decision)	EMEA/H/C/474/II/9				
29/01/2007	Centralised - Annual reassessment	EMEA/H/C/474/S/10				
10/04/2007	Centralised - Variation Updated with Decision(2007)2347 of 30/05/2007	EMEA/H/C/474/IA/12				
01/06/2007	Centralised - Variation	EMEA/H/C/474/II/11	(2007)2347 of 30/05/2007	sum	dec	anx
04/10/2007	Centralised - Notification Updated with Decision(2008)4111 of 28/07/2008	EMEA/H/C/474/N/13				
16/01/2008	Centralised - Variation Updated with Decision(2008)4111 of 28/07/2008	EMEA/H/C/474/IA/16				
24/01/2008	Centralised - Annual reassessment	EMEA/H/C/474/S/15				
31/03/2008	Centralised - Variation (no change in Commission Decision)	EMEA/H/C/474/II/17				
20/06/2008	Centralised - Variation Updated with Decision(2008)4111 of 28/07/2008	EMEA/H/C/474/IA/21				
30/07/2008	Centralised - Variation	EMEA/H/C/474/II/19, 20	(2008)4111 of 28/07/2008	sum	dec	anx
04/09/2008	Centralised - Renewal	EMEA/H/C/474/R/18	(2008)4951 of 02/09/2008	sum	dec	anx
31/10/2008	Centralised - Variation Updated with Decision(2009)4240 of	EMEA/H/C/474/IA/24				

Ex. 1043, 1–4 (annotation added). The above table is a portion of a three-page table entitle "EU Commission procedures" reproduced from a webpage identified by Petitioner as the EU Community Register page for Ventavis (Ex. 1043). Dr. Donovan testifies that by using the "decision docs"

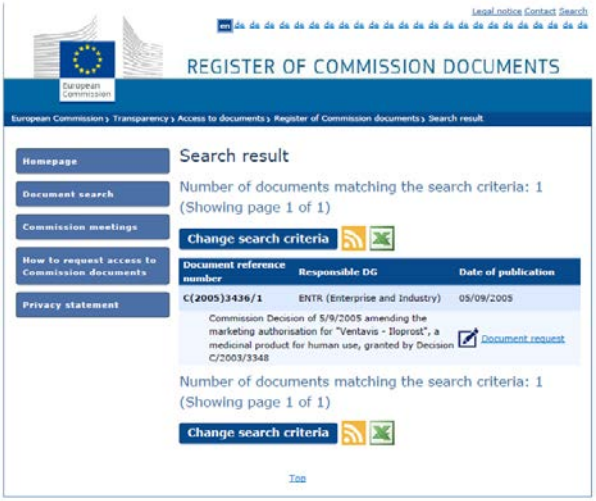
dropdown for the encircled entry she was able to access the Commission Decision and by using the "annex" dropdown, she was able to access the Annexes to that decision. Ex. 1002, ¶ 99.[11]

Second, Petitioner argues that the Commission Decision and its Annexes were "available to the public through the European Commission's Register of Commission Documents ('European Register'), which provides public access to the documents of the European Parliament, the Council and the Commission pursuant to Regulation (EC) No 1049/2001." Pet. 19–20. Dr. Donovan testifies that she used the "Document search" feature on the webpage (reproduced below) for the Register of Commission documents.

[11] Dr. Donovan references the Exhibits she accessed by name and by Exhibit number; however, the names do not match the exhibit numbers. For purposes of this decision, we assume that this was a typographical error and that the Annexes Dr. Donovan accessed were Exhibit 1009 (not Exhibit 1043 as recited in her Declaration). *See*, Ex. 1002, ¶ 99. Similarly, it appears that the Commission Decision she accessed was Exhibit 1042 (not Exhibit 1043 as recited in her Declaration). *Id.*



Ex. 1002, ¶ 100. The image reproduced above is the webpage that Dr. Donovan testified was reached at http://ec.europa.eu/health/documents/community-register/. *Id.*; Ex. 1051. By using "Document search" feature on the above webpage and searching using the keyword "Ventavis" she reached a page (reproduced below) including a "Document request" link. Ex. 1002 ¶ 100.



Id. The above image is a reproduction of Exhibit 1053, the web page that Dr. Donovan testified was reached by searching the Community Register for the keyword "Ventavis." *Id.* Dr. Donovan explains that keyword searching

for "Ventavis" does not pull up the Commission Decision when searching "final versions only," which she suggests means the "Commission Decision was not a final version" and explains "why it includes the notation 'Not for Publication' on its face." *Id.*

Patent Owner argues that Petitioner has not sufficiently demonstrated public accessibility of Annex III. Prelim. Resp. 29–33. We agree.

Annex III is identified as a "Labeling and Package Leaflet" for the drug Ventavis. As an initial matter, Petitioner does not contend, and does not provide evidence supporting, that Annex III was ever actually included as product literature with the drug Ventavis. Given that Annex III was appended to a Commission Decision marked "Not for Publication," includes an empty place holder for the date on which "this leaflet was last approved," and cannot be retrieved when searching for "final versions only," we do not consider Annex III to be representative of an actual product label disseminated for Ventavis. Accordingly we do not consider whether actual dissemination of Annex III as a product label for Ventavis is sufficient to establish public accessibility. Rather, we consider the public accessibility of Annex III only as an annex to a non-final regulatory document.

Regarding public accessibility of the non-final regulatory document, Patent Owner argues that Petitioner has not established that the Commission Decision "was indexed at the critical time period in a manner allowing it to be retrieved at a time that would make it prior art." Prelim. Resp. 31. Patent Owner thus asserts that the "various exhibits referenced by Dr. Donovan nowhere show that the same retrieval user interface has always been in place dating back to the earlier time alleged by Petitioner." *Id.* at 31–32. We agree.

With respect to Petitioner's first argument for public accessibility – that based on availability through the EU Community Register of Medicinal Products (Ex. 1043) – Petitioner provides no evidence that the webpage it relies upon as providing access to Annex III existed during the critical time period. *See* Pet. 18–21.

In addition, to the extent the webpage did exist during the critical time period, it would have provided little guidance to direct the skilled artisan to the subject matter of interest – nebulizer capabilities. Although the evidence indicates that Dr. Donovan was, at some unspecified point in time, able to access Annex III through the EU Community Register of Medicinal Products, Petitioner does not provide persuasive evidence indicating that "persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence" could have located it. Pet. Reply 22–25; *see SRI Int'l, Inc. v. Internet Security Sys., Inc.*, 511 F.3d 1186, 1194, 1196–97 (Fed. Cir. 2008). In this regard, the facts here are similar to those in *In re Cronyn*, in which the Federal Circuit found that theses documents indexed alphabetically by author name were not publicly accessible because "the only research aid [in finding the theses] was the student's name, which, of course, bears no relationship to the subject of the student's thesis" and, thus, they were not "cataloged or indexed in a meaningful way" so as to be accessible to the public. 890 F.2d at 1161. Here, the only information identified by Petitioner that would have suggested that the "08/09/2005 Centralized – Variation" entry in Exhibit 1043 would contain relevant information on nebulizer capabilities was the general knowledge that Ventavis was related to treprostinil and was used with a nebulizer. We are not persuaded that a skilled artisan exercising reasonable diligence and

interested in nebulizer capabilities could have found Annex III, an annex to a non-final regulatory filing for a drug, based on the general knowledge that the drug could be administered using a nebulizer. *Cf. Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374 (Fed. Cit. 2006) (finding that published patent application provided "a roadmap to the application file").

With respect to Petitioner's second argument for public accessibility – availability through the European Commission's Register of Commission Documents (Ex. 1051) – Petitioner does not provide persuasive evidence that the webpage it relies upon as providing access to Annex III, and the search functionality it provides, existed during the critical time period. *See* Pet. 18–21. Petitioner does point to regulations requiring various European Union institutions to make a register of documents available online by June of 2002. Ex. 1052. However, a mere possibility that a document might be accessed over the internet is not sufficient to establish "public availability." *See SRI Int'l, Inc. v. Internet Security Sys., Inc.*, 511 F.3d at 1196 (finding document posted to FTP server unavailable where the "FTP server did not contain an index or catalogue or other tools for customary and meaningful research"). In this regard, the ability to search for and thus locate the document online is key, and Petitioner does not provide persuasive evidence establishing that the user interface and search function relied upon by Dr. Donovan was in place at the relevant time period.

In addition, Petitioner has not presented evidence that using the "document request" link in Exhibit 1053 would have caused the entity maintaining the website to provide a copy of Annex III. Dr. Donovan is silent as to what happens when the "document request" link is used. *See* Ex. 1002 ¶ 100. Moreover, we understand Dr. Donovan's testimony with

respect to the Community Register (Ex. 1043) to be that the Commission Decision and Annex III were obtained separately using one dropdown link to obtain the Commission Decision and a different dropdown link to obtain Annex III. Ex. 1002 ¶ 99. On the record before us, we are left to speculate as to whether the "document request" link in Exhibit 1053 would have allowed the skilled artisan to access both the Commission Decision and Annex III.

Further, even assuming the search functionality relied upon by Dr. Donovan was available during the relevant time period, and that the "document request" link in Exhibit 1053 would have allowed the skilled artisan to access Annex III, we are not persuaded that the evidence of record sufficiently establishes a person "interested and ordinarily skilled in the subject matter or art exercising reasonable diligence" could have located Annex III. *Lister*, 583 F.3d at 1311. In particular, Dr. Donovan testified that the keyword search called up the "document request" link for the Commission Decision only when the search parameters were toggled to include non-final versions. We are not persuaded that "reasonable diligence" to locate documents relating to nebulizers encompasses a keyword search of non-final regulatory documents for a drug known to be administered using a nebulizer.

For the reasons discussed, on the record before us, Petitioner did not establish a reasonable likelihood that it would prevail in proving that the EU Community Register is a prior art printed publication available as prior art under 35 U.S.C. § 102(a) with respect to the '507 patent.

E. Ground 1: Obviousness over the combination of Voswinckel, Patton, and Ghofrani

Petitioner asserts that claims 1–9 are rendered obvious by the combination of Voswinckel, Patton and Ghofrani. Pet. 21–35. We have reviewed Petitioner's assertions and supporting evidence, and, for the reasons discussed below, we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing in showing that claims 1–9 would have been obvious over the combination of Voswinckel, Patton and Ghofrani.

i. Disclosures of the Asserted Prior Art

Voswinckel

Voswinckel discloses an open label study in which 17 patients with severe pulmonary hypertension "received a TRE [treprostinil sodium] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 μg/ml)." Ex. 1003. Voswinckel concluded that "[i]nhaled TRE shows strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing." *Id.* Voswinckel further concluded that tolerability was "excellent even at high drug concentrations," and that "[l]ong term treatment effects are very promising." *Id.*

Patton

Patton discloses "methods and apparatus for producing an aerosolized dose of a medicament for subsequent inhalation by a patient." Ex. 1012, 4:28–30. The apparatus may be "a conventional jet nebulizer" (*id.* at 10:7) and "is of a type that will nebulize or mix a defined amount of medicant [referred to as a dosage or bolus] with the preselected amount of compressed air received from compressor." *Id.*, 13:3–5. The apparatus further includes a "light 50 and/or an audible signal 52" that "will alert the user that a puff is

ready to be withdrawn from chamber 42 when the compressor 22 shuts down." *Id.*, 14:3-5. These two signals (50, 52) "are set to begin immediately after operation of the compressor 22 ceases," and indicate that "bolus formation is complete." *Id.*, 14:3–20.

Ghofrani

Ghofrani is a review article addressing "[n]ew therapies in the treatment of pulmonary hypertension." Ex. 1005, title. Ghofrani discloses that a study of 17 patients with severe pre-capillary pulmonary hypertension showed "proof of efficacy of inhaled treprostinil." *Id.* at 298.[12] The patients were administered "inhaled treprostinil (15 mcg/inhalation)" which led to "a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min." *Id.* Ghofrani further discloses that "it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring." *Id*.

ii. Analysis

Petitioner contends that Voswinckel discloses the following elements of claim 1: "a method of treating pulmonary hypertension," "administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising 200 to 1000 μg/ml of treprostinil or a pharmaceutically acceptable salt thereof," and a "pulsed ultrasonic nebulizer" that provides a "single dose event

[12] The 17 patient study disclosed in Ghofrani appears to be the same study as is disclosed in Voswinckel, as reflected by the number of patients, overlapping authors, similarity of results, and the fact that the study in Ghofrani occurred in Gissen while Voswinckel acknowledges "Univ Hosp Gissen, Gissen, Germany" among the authors. Ex. 1003; Ex. 1005, 298.

comprising . . . treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths." Pet. 21–24, 28–29.

Voswinckel discloses that patients received "3 single breaths, TRE solution 600 μg/ml," but does not expressly state that the nebulizer aerosolized "a fixed amount" of the formulation "per pulse." Ex. 1003. Petitioner contends that Patton teaches that its nebulizer "is of a type that will nebulize or mix a defined amount of medicant with the preselected amount of compressed air from [the] compressor." Pet. 25. Petitioner asserts that it would have been obvious to aerosolize a fixed amount of treprostinil per pulse because this provides a simple, efficient, and precise way to deliver the drug. Pet. 25–26; Ex. 1002 ¶¶ 121–125.

Voswinckel discloses that an "OptiNeb® pulsed ultrasonic nebulizer" was used to administer treprostinil, but does not disclose that the OptiNeb® nebulizer included an "opto-acoustical trigger which allows [a] human to synchronize each breath to each pulse." Ex. 1003. Petitioner contends that Patton discloses an "opto-acoustical trigger" as recited in claim 1, in the form of "light 50 and/or audible signal 52" on a nebulizer that "alert[s] the user that a puff is ready to be withdrawn from chamber 42 when the compressor 22 shuts down." Pet. 26–27. The light and sound signals "are set to begin immediately after operation of the compressor 22 ceases,' and indicate that the formation of the bolus is complete."' *Id.* at 27.

Petitioner asserts that it would have been obvious to include an opto-acoustical trigger, like that disclosed in Patton, with the pulsed nebulizer disclosed in Voswinckel. As support, Petitioner provides the testimony of Dr. Donovan, who states:

> A POSA would . . . appreciate that when using a pulsed nebulizer, the patient needs to know when the drug is ready to

> be inhaled, otherwise the efficiency gains from the pulsed nebulizer would be lost. Thus, by necessity, a POSA would implement some sort of signal to demonstrate to the patient that the device is generating aerosol and is ready for the patient to inhale. Without this sort of trigger, the patient would be unable to synchronize their breathing to the distribution of drug, and the pulsed nebulizer would not function as intended.
>
> * * *
>
> A POSA would be motivated to combine Patton and Voswinckel because Patton teaches the parameters and configurations that can be implemented in a nebulizer, specifically ways in which a nebulizer can accurately and efficiently deliver a target dose. In particular, a POSA with the knowledge of Voswinckel's finding of therapeutic efficacy with inhaled treprostinil would be motivated to find ways to ensure the drug is delivered efficiently to keep costs down and delivered precisely to ensure the reliability of the future studies that Voswinckel recommends.

Ex. 1002 ¶¶ 128–132.

Voswinckel discloses the concentration of the treprostinil sodium formulation used, and the number of breaths patients took ("3 single breaths, TRE solution 600 μg/ml"), but does not disclose the total dose of treprostinil administered. Ex. 1003. Petitioner contends that Ghofrani discloses a dose of 15–90 μg of inhaled treprostinil. *Id*. at 29. Petitioner asserts that it would have been obvious to a person of ordinary skill in the art "administering treprostinil in accordance with the teachings of Voswinckel . . . to use the range of doses disclosed by Ghofrani because such doses 'led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min.'" *Id.* at 30 (quoting Ex. 1005, 298); *see also* Ex. 1002 ¶ 136.

Based upon our review of the current record, we discern no deficiency in Petitioner's characterization of the cited references and the knowledge in the art, or in Petitioner's assertions as to the reasonable inferences an ordinary artisan would make from those references. Thus, based on the information presented at this stage of the proceeding, Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of independent claim 1 over the combined references. Further, at this stage in the proceeding, for reasons discussed by Petitioner (*see* Pet. 21–35), we are satisfied that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of dependent claims 2–9. Our remaining analysis with respect to Ground 1 focuses on the deficiencies in Patent Owner's arguments in its Preliminary Response as to the challenged claims.

Patent Owner argues that Patton does not disclose an opto-acoustical trigger as recited in claim 1. This argument is based on a claim construction that construes the term "trigger" in "opto-acoustical trigger" to refer to optical and acoustical elements that are "designed to cause a human to immediately inhale each aerosol pulse from the pulsed ultrasonic nebulizer." Prelim. Resp. 12.[13] Based on this claim construction, Patent Owner seeks to distinguish "signals and alerts" which Patent Owner contends are "merely informative," from a "trigger" which is "designed to cause an event."

[13] United Therapeutics and Watson reached an agreement in Civil Action No: 3:15-cv-05723 PGS-LHG in the U.S. District Court for the District of New Jersey ("the civil action") that the phrase "an opto-acoustical trigger" in claim 1 means "a trigger with an optical element (e.g., light) and an acoustical element (e.g., sound)." Pet. 7; Prelim. Resp. 10. Patent Owner contends that this agreed definition does not address the term "trigger." Prelim Resp. 10.

Prelim. Resp. 46. According to Patent Owner, the "light 50 and/or audible signal 52" disclosed in Patton are mere "signal[s] to inform a patient that a bolus of medication has been delivered" and "Patton is ambivalent on when the patient actually withdraws the bolus other than that it should occur sometime after aerosol generation." *Id.* We are not persuaded.

As an initial matter, we decline to construe the term "opto-acoustical trigger" at this stage in the proceeding, because we fail to see how a light or sound that "informs" a patient that a medication is ready to be inhaled differs from a light or sound that is "designed to cause a human to immediately inhale." *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy. . . .'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))). Patent Owner does not identify, and we do not find, any structural difference between an informative light or signal and a light signal that is designed to cause immediate inhalation. Nor, on the record before us, do we see any other basis for distinguishing the "light 50 and/or audible signal 52" disclosed in Patton from the claimed "opto-acoustical trigger." Accordingly, we agree with the Petitioner that Patton discloses an opto-acoustical trigger as recited in claim 1.

Patent Owner argues that Patton provides "no motivation to adapt the signal into a trigger because the device in Patton does not require synchronizing a breath with a pulse." Prelim. Resp. 46. Patent Owner contends that Patton "criticizes metered dose inhalers for requiring such coordination between activation and inhalation to deliver a precise amount of medication and proposes an alternate solution this problem." *Id*. at 47.

Patent Owner concludes that "the timing and duration of a single breath is not critical" in Patton because Patton teaches maintaining a stable aerosol concentration such that "at least 40% by weight of the aerosolized material entering the chamber will remain aerosolized and suspended within the chamber" and because Patton "includes structures to 'block aerosol outflow.'" *Id.* at 47. We are not persuaded.

Patent Owner's argument misses the point. The relevant question is not whether Patton employs a nebulizer that requires breath synchronization – i.e. a pulsed nebulizer. Voswinckel expressly discloses a pulsed nebulizer. Ex. 1003. Rather, the relevant question is whether it would have been obvious to use a light and sound signal, like that taught in Patton, in Voswinckel's pulsed nebulizer. Based on the current record, we agree with the Petitioner and Dr. Donovan that Patton's disclosure of light and sound signals that "are set to begin immediately after operation of the compressor 22 ceases" in order to "alert the user that a puff is ready to be withdrawn" would have motivated the person of ordinary skill in the art to incorporate a light and sound signal in Voswinckel's pulsed nebulizer. Ex. 1012, 14:3–12.

The passage Patent Owner relies upon as criticizing metered dose inhalers does not undercut the motivation proffered by Petitioner for incorporating an opto-acoustic trigger in the pulsed OptiNeb nebulizer disclosed in Voswinckel. *See,* Pet. at 25–26; *see also,* Ex. 1002 ¶¶ 126–131. Rather, the passage cited by Petitioner teaches that therapeutic proteins and polypeptides are expensive to produce and that it is therefore "important that loss of a protein drug within the delivery device be reduced or preferably eliminated." Ex. 1012, 3:28–35; Prelim. Resp. 47. Incorporating a light and sound signal for inhalation in Voswinckel's nebulizer is consistent with this

goal, as suggested by Patton's incorporation of such a signal in its nebulizer. Ex. 1012, abstract; *id.* at 14:3–12.

Patton's teaching of other ways to minimize loss of medicament similarly does not diminish the motivation to use an opto-acoustic trigger. Patton teaches to use "efficient displacement of the air with the aerosolized material," which means that "at least 40% by weight of the aerosolized material entering the chamber will remain aerosolized and suspended within the chamber." Ex. 1012, 5:3–8. Patton further teaches that efficient displacement can be achieved "by proper design of the chamber. *Id.* at 5:11–12. The availability of a nebulizer with a chamber that provides efficient displacement does not weaken the motivation of the skilled artisan to use light and sound signals to indicate that a bolus is ready for inhalation. Nor does Patton's teaching to provide a structure to prevent the aerosol from exiting the chamber discourage the use of light and sound signals. *See, e.g.*, *id.* at 6:12–14 and 6:28–36.

Patent Owner argues that Patton teaches away from claims 7 and 8, which require that the "single event dose is inhaled in 3 to 18 breaths," because Patton teaches that "each inhalation event should include only a single breath." Prelim. Resp. 48 (citing Ex. 1012, 7:23–25). We do not read the teachings of Patton as being so limited. Patton expressly states: "the steps of aerosolizing the medicament, filling the chamber, and inhalation of the chamber contents may be repeated as many times as necessary to provide a desired total dosage of the medicament for the patient." Ex. 1012, 5:23–26. Moreover, a teaching away requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Patent Owner does not identify any

criticism of administering a dose of medicament in multiple breaths in Patton.

Patent Owner argues that although Petitioner addressed the evidence of commercial success provided in the declaration of Dr. Lewis Rubin,[14] which was submitted during prosecution, Petitioner failed to address the two declarations of Dr. Rodham T. Zamanian, which were also submitted during prosecution. Prelim. Resp. 53. Patent Owner contends that the Zamanian declarations present "evidence of commercial success for Tyvaso® [treprostinil] and tie them to specific features of the claimed drug-device combination." *Id.*

In the First Zamanian Declaration,[15] Dr. Zamanian testifies that upon entry into the market, Tyvaso® gained market share at the expense of its competitor Ventavis. Ex. 1163 ¶ 18. Dr. Zamanian attributes this to "clinical advantages" including that Tyvaso® requires less frequent administration and that Tyvaso® is administered using a pulsed ultrasonic nebulizer as compared to an adaptive aerosol delivery nebulizer (as employed by Ventavis). *Id.* at ¶¶ 19–28.

In the Second Zamanian Declaration,[16] Dr. Zamanian again attributed the commercial success of Tyvaso® to the use of a pulsed ultrasonic nebulizer and additionally to its "unique dosing regimen," including "the single event dosing of 'from 15 μg to 90 μg of treprostinil' and the single

[14] Declaration under 37 C.F.R. § 1.132 of Dr. Lewis Rubin, signed May 18, 2012 (Ex. 1058, "Rubin Declaration").
[15] Declaration under 37 C.F.R. § 1.132 of Dr. Roham T. Zamanian, signed November 9, 2015 (Ex. 1162, "First Zamanian Declaration").
[16] Declaration under 37 C.F.R. § 1.132 of Dr. Roham T. Zamanian, signed February 1, 2016 (Ex. 1163 "Second Zamanian Declaration").

inhalation event of '18 or less breaths'" which "combine to . . . achieve the higher patient compliance." Ex. 1163 ¶¶ 14–15.

We agree with Patent Owner that evidence of secondary considerations of non-obviousness, when present, must always be considered en route to a determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075-76 (Fed. Cir. 2012); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983). Nevertheless, we disagree with Patent Owner that evidence of commercial success from prosecution of the '240 patent warrants denial of the Petition.

As Petitioner points out in addressing evidence of commercial success presented in the Ruben Declaration, commercial success must be attributed to something new, not what was known in the art. Pet. 49 (citing *Great Atl. & Pac. Tea. Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 153 (1950) ("commercial success without invention will not make patentability")); *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) ("If commercial success is due to an element in the prior art, no nexus exists.") Based on the record before us it appears that the features to which Dr. Zamanian attributes the commercial success of Tyvaso® were all known in the art.

Dr. Zamanian attributes the commercial success of Tyvaso to: 1) the use a pulsed ultrasonic nebulizer, 2) an inhalation event of less than 18 breaths, 3) the frequency with which Tyvaso must be administered, and 4) the 15 μg to 90 μg dosing of Tyvaso. Voswinckel expressly discloses the use of a pulsed ultrasonic nebulizer and an inhalation event of less than 18 breaths. Ex. 1003. The frequency with which Tyvaso must be administered

is a product of its halflife. Zamanian Decl. ¶ 21–22. The treprostinil disclosed in Voswinckel necessarily has the same half-life of Tyvaso. Voswinckel does not expressly disclose administering 15 μg to 90 μg of treprostinil. However, as discussed above, it appears that Voswinckel and Ghofrani disclose the same 17 patient study and Ghofrani teaches administering 15 μg to 90 μg of treprostinil. *See supra p.* 24, n. 12. Accordingly, all of the features to which Dr. Zamanian attributes commercial success were known in the art.

We have considered the evidence of secondary considerations submitted by the Patent Owner in connection with the Preliminary Response. Based on the record before us, when Patent Owner's evidence of secondary considerations is considered together with Petitioner's evidence of obviousness, we determine that the totality of the evidence currently of record supports institution.

For the reasons discussed above, we determine that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1–9 of the '240 patent are unpatentable over the combination of Voswinckel, Patton and Ghofrani. Accordingly, we institute an *inter partes* review of those claims over the combination of Voswinckel, Patton and Ghofrani.

F. Ground 2: Obviousness over the combination of Voswinckel, Patton, and OptiNeb

Petitioner asserts that claims 1–9 are rendered obvious by the combination of Voswinckel, Patton and OptiNeb. Pet. 38–47. We have reviewed Petitioner's assertions and supporting evidence, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated a

reasonable likelihood of prevailing in showing that claims 1–9 would have been obvious over the combination of Voswinckel, Patton and OptiNeb.

i. Disclosures of the Asserted Prior Art

Voswinckel and Patton

The disclosures of Voswinckel and Patton are discussed *supra p.* 23–24.

OptiNeb User Manual

OptiNeb is a user manual for the OptiNeb-ir Mobile Ultrasonic Nebulizer. It discloses, in relevant part, that the output for the OptiNeb-ir nebulizer is 0.6 ml/min. Ex. 1006, 28.

ii. Analysis

In connection with Ground 2, Petitioner relies upon the combination of Voswinckel and OptiNeb as rendering obvious the limitation of claim 1 requiring a "single event dose comprising from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof." Pet. 36–38. According to the Petitioner, although Voswinckel does not disclose the total dose administered in a single event dose, "those skilled in the art would have been able to derive the single event dose administered in Voswinckel by looking to the information in Voswinckel in view of the OptiNeb® User Manual." Pet. 36. More specifically, Petitioner contends that the total dose administered in Voswinckel can be derived from: 1) Voswickel's disclosure that a "TRE solution 600 μg/ml" was administered in "3 single breaths;" 2) the disclosure of a nebulization rate of 0.6 ml/min for the OptiNeb nebulizer; and 3) a typical inhalation length of 2–3 seconds for a therapeutic agent. Using this information, Petitioner calculates the dose of treprostinil administered in Voswinckel as follows:

(600 μg/ml) * (0.6 ml/min) = 360 μg/min
(360 μg/min) / (60 seconds/min) = 6 μg/second.
(6 μg/second) * (2-3 seconds/breath) = 12-18 μg/breath
(12-18 μg/breath) * (3 breaths) = 36-54 μg

Pet. 37. Petitioner thus contends that the person of ordinary skill in the art would have understood that the OptiNeb nebulizer used in Voswinckel "could produce drug at a rate of up to 36-54 μg in 3 breaths." *Id.* (citing Ex. 1002, ¶ 174).

The above calculation relies on an assumed inhalation length of 2–3 seconds. This assumption is based on the teaching of Ganong's Review of Medical Physiology that "a normal human breathes at a rate of 12–15 times per minute." Ex. 1002, ¶ 174 (citing Ex. 1060). From this, Dr. Donovan calculates that "a typical inhalation cycle (inhale and exhale) takes somewhere between 4 seconds (60 seconds / 15 breaths) and 5 seconds (60 seconds / 12 breaths)" and thus that "a patient may inhale from somewhere between 2–3 seconds." *Id.*

Patent Owner argues that the testimony of Dr. Donovan on breathing rate is unreliable. Patent Owner points out that Dr. Donovan relies upon the breathing pattern of a "normal human," when the claims are directed to a "human suffering from pulmonary hypertension." Prelim. Resp. 35. This is problematic because, according to Dr. Dalby, Patent Owner's Expert, "inhalation may occupy *significantly less* than half of the duration of the breath in patients with lung diseases." Ex. 2001, ¶ 34 (citing Newman, *Respiratory Drug Delivery: Essential Theory and Practice*, Respiratory Drug Delivery Online (Ex. 2003, 4)).

We agree with Patent Owner and Dr. Dalby that Petitioner's reliance on the breathing rate of "normal humans" calls into question the reliability

of Petitioner's calculation of the dose of treprostinil administered in Voswinckel. Dr. Dalby's testimony that patients with lung disease, like pulmonary hypertension, may have a shorter inhalation than healthy "normal" humans is supported by and consistent with the teachings of Newman (Ex. 2003). Moreover, we note that Dr. Donovan did not address the breathing rate of the relevant patient population.

Patent Owner argues that Dr. Donovan "cherry picked" the edition of Ganong's Review teaching a breathing rate of 12–15 breaths per minute, ignoring a later edition of Ganong's Review, cited during prosecution, that teaches a breathing rate of 10 to 30 breaths per minute in humans. Prelim. Resp. 35 (citing Ex. 2006, 31–34). We agree with the Patent Owner that the evidence of a broader range of breathing rate in the literature further calls into question the reliability of Petitioner's calculation.

In addition, the calculation of the dose administered in Voswinckel set forth in the Petition is based on a nebulization rate of 0.6 ml/min for the OptiNeb nebulizer. It appears this may overstate the nebulization rate. As Dr. Donovan points out, "[t]he Nebu-Tec website also reported that an earlier OptiNeb® device could nebulize at a rate of up to 0.6 mL/min, but could be configured to generate an output of 0.173 mL/min." Ex. 1002, ¶ 175 (citing Ex. 1014 at B2 at 31). While Dr. Donovan offers calculations of total dose administered based on a nebulization rate of 0.173 ml/min, the Petition does not discuss them. Ex. 1002 ¶ 174; Pet. 36–38. The potential that the OptiNeb device was nebulizing at a rate below 0.6 ml/min still further calls into question the reliability of Petitioner's calculation.

It is not clear to what extent Petitioner contends that the proffered range of 36–54 μg reflects the dose of treprostinil that was actually

administered in the Voswinckel study. On the one hand, Petitioner asserts that the person of ordinary skill in the art "would have been able to derive the single event dose administered in Voswinckel" by performing the calculation discussed above. Pet. 36. On the other hand, Petitioner later identifies the stated range as a "maximum dose." *Id.* at 38. To the extent the Petitioner contends the proffered range reflects the actual dose administered, we find that the Petitioner has not provided sufficient evidence to support this contention.

Petitioner argues that routine optimization could be used to arrive at the claimed dose, explaining that the "nebulization rate, concentration of solution or number of breaths could all be routinely optimized." *Id.* The Petition thus asserts: "At a minimum, the POSA would have known that a dose of 36-54 μg of treprostinil could be delivered using the solution and number of breaths from Voswinckel with the maximum capabilities of the OptiNeb device. That is within the claimed range." *Id.* (internal citations omitted). We are not persuaded.

Irrespective of whether a person of ordinary skill in the art ***could*** adjust various parameters to arrive at the claimed dose, in order to render the claimed dose obvious, there must be a reason why the person of ordinary skill in the art ***would*** have adjusted parameters to arrive at the claimed dose. In connection with Ground 2, the only evidence of record as to what might constitute an appropriate dose of treprostinil is the calculation discussed above. Because we have determined that this calculation is unreliable and not supported by sufficient evidence to reflect the dose actually administered in Voswinckel, it does not provide the skilled artisan reason to administer the treprostinil within the claimed range.

For the reasons discussed above, we determine that the information presented in the Petition does not establish a reasonable likelihood that Petitioner would prevail in showing that claims 1–9 of the '240 patent are unpatentable over the combination of Voswinckel, Patton and OptiNeb. Accordingly, we decline to institute an *inter partes* review of those claims over the combination of Voswinckel, Patton and OptiNeb.

G. Ground 3: Obviousness over the combination of Voswinckel, Ghofrani and the EU Community Register

Petitioner asserts that claims 1–9 are rendered obvious by the combination of Voswinckel, Ghofrani and the EU Community Register. Pet. 42–49. As Petitioner has not sufficiently demonstrated that the EU Community Register is a prior art printed publication under 35 U.S.C. § 102(a), we determine that the Petition does not demonstrate a reasonable likelihood that challenged claims 1–9 are rendered obvious by the combination of Voswinckel, Ghofrani and the EU Community Register.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1–9 of the '240 patent are unpatentable over the combination of Voswinckel, Patton and Ghofrani (Ground 1). Accordingly, we institute an *inter partes* review of those claims.

For the foregoing reasons, we do not institute trial as to the challenge over the combination of Voswinckel, Patton and OptiNeb (Ground 2) and over the combination of Voswinckel, the EU Community Register, and Ghofrani (Ground 3).

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is instituted only as to claims 1–9 of the ’240 patent under 35 U.S.C. § 103(a) as obvious over Voswinckel, Patton, and Ghofrani.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision.

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