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Paper No. 82
Entered: March 31, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

Case IPR2016-00006
Patent 8,497,393 B2

Before LORA M. GREEN, JONI Y. CHANG, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Petitioner, SteadyMed LTD ("SteadyMed"), filed a Petition on October 2, 2015, requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,497,393 B2 (Ex. 1001, "the '393 patent"). Paper 1 ("Pet."). Patent Owner, United Therapeutics Corporation ("UTC"), filed a Preliminary Response on January 14, 2016. Paper 10 ("Prelim. Resp.").[1] We determined that the information presented in the Petition demonstrated that there was a reasonable likelihood that SteadyMed would prevail with respect to at least one challenged claim. Pursuant to 35 U.S.C. § 314, we instituted trial on April 8, 2016, as to claims 1–22 of the '393 patent. Paper 12 ("Dec.").[2]

After institution, UTC filed a Patent Owner Response. Paper 31 ("PO Resp.").[3] SteadyMed filed a Reply to the Patent Owner Response. Paper 51 ("Pet. Reply").[4]

In addition, SteadyMed filed a Motion to Exclude Evidence (Paper 63, "Pet. Mot. Exclude").[5] UTC filed an Opposition (Paper 66, "PO Opp. Exclude"), and SteadyMed filed a Reply (Paper 72, "Pet. Reply Exclude"). UTC likewise filed a Motion to Exclude Evidence (Paper 65, "PO Mot.

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[1] Paper 8 is a redacted version of the Patent Owner Preliminary Response.
[2] Paper 78 is a redacted version of the Decision on Institution.
[3] Paper 76 is a redacted version of the Patent Owner Response to Petition.
[4] Paper 52 is a redacted version of the Reply to Patent Owner's Response.
[5] Paper 62 is a redacted version of Petitioner's Motion to Exclude Evidence.

Exclude"). SteadyMed filed an Opposition (Paper 68, "Pet. Opp. Exclude"),[6] and UTC filed a Reply (Paper 71, "PO Reply Exclude").

Oral hearing was held November 29, 2016.

This final written decision is entered pursuant to 35 U.S.C. § 318(a). We have jurisdiction under 35 U.S.C. § 6.

We hold that SteadyMed has demonstrated by a preponderance of the evidence that claims 1–22 are unpatentable under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a). SteadyMed's Motion to Exclude is *dismissed*. UTC's Motion to Exclude is *denied*.

A. Related Matters

The '393 patent is asserted in several cases in the District of New Jersey. Pet. 1; Paper 4; Paper 15; Paper 21.

B. The '393 Patent

The '393 patent, titled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin®," issued July 30, 2013, from U.S. Patent Application No. 13/548,446 ("the '446 application") (Ex. 1002), filed July 13, 2012. Ex. 1001, [54], [45], [21], [22]. The '446 application is a continuation of U.S. Patent Application No. 12/334,731 ("the '731 application") (Ex. 1002), filed on December 15, 2008, now issued as U.S. Patent No. 8,242,305 ("the '305 patent"). Ex. 1001, [63]. The

[6] Paper 67 is a redacted version of Petitioner's Opposition to Patent Owner's Motion to Exclude Evidence.

'393 patent claims priority to U.S. Provisional Patent Application No. 61/014,232 (Ex. 2008), filed December 17, 2007. Ex. 1001, [60].

The '393 patent recites 22 product-by-process claims for prostacyclin derivatives, including treprostinil.[7] *Id*. at 17:51–21:16; Pet. 5; Prelim. Resp. 3. The process disclosed by the '393 patent takes advantage of carbon treatment and salt formation steps to remove impurities, eliminating the need for purification by column chromatography. *Id*. at 17:29–32; *see also id*. at 5:41–45 ("[P]urification by column chromatography is eliminated . . . . [T]he salt formation is a much easier operation than column chromatography.").

The process for forming prostacyclin derivatives described in the '393 patent includes four steps: (a) alkylating a prostacyclin derivative to form an alkylated prostacyclin derivative; (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid; (c) contacting the prostacyclin acid with a base to form a prostacyclin carboxylate salt; and (d) optionally reacting the prostacyclin carboxylate salt formed in (c) with an acid to form the desired compound, or pharmaceutically acceptable salt thereof. *Id*. at 1:65–3:19.

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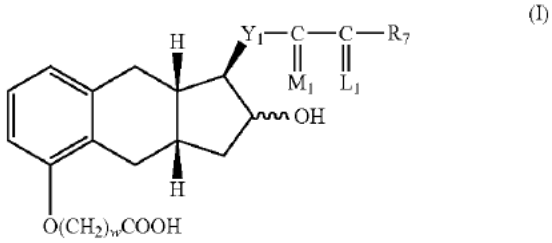
[7] The '305 patent, which issued from the parent to the application for the '393 patent, recites claims to a process for the preparation of prostacyclin derivatives comprising steps similar to those set forth in the product-by-process claims of the '393 patent. *Compare* Ex. 1001, 17:51–21:16, *with* Ex. 2007, 17:39–24:3.

C. Illustrative Claim

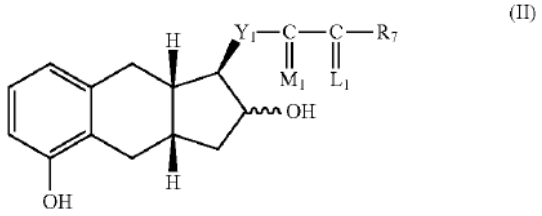
Each of the challenged claims is a product-by-process claim. Of the challenged claims, claims 1 and 9 are independent. Claim 1, reproduced below, is illustrative of the claimed subject matter.

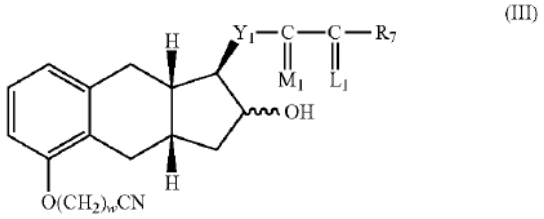
1. A product comprising a compound of formula I



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,

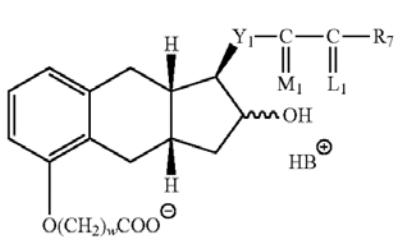




wherein [recitation of Markush groups for the specified structures],

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

c) contacting the product of step (h)[8] with a base B to form a salt of formula I_s.



and

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

Ex. 1001, 17:51–19:29. Claim 9 is drawn to a product comprising a specific treprostinil compound within the genus set forth in claim 1, and made by the process recited in claim 1. *Id*. at 19:48–20:46.

D. Prior Art Relied Upon

In its Petition, SteadyMed relies upon the following prior art references (Pet. 4–6):

Phares	WO 2005/007081 A2	Jan. 27, 2005	(Ex. 1005)
Kawakami	JP 56-122328A	Sept. 25, 1981	(Ex. 1006)[9]

Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins:*

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[8] We note that the reference to "step (h)," rather than "step (b)," in claim 1 is an apparent typographical error. *See* Ex. 1001, 3:66–67 ("(c) contacting the product of step (b) with a base B to for a salt of formula IV_s"); *see also* Pet. 25; Ex. 1009 ¶ 51.

[9] SteadyMed submitted a certified English translation of Kawakami as Ex. 1007. Exhibits 1011, 1019, and 1020 are translator declarations attesting to the accuracy of that translation.

Synthesis of UT-15 (Treprostinil), 69 J. Org. Chem. 1890–1902 (2004) ("Moriarty") (Ex. 1004); and

Seyhan N. Eğe, ORGANIC CHEMISTRY 543–547 (2d ed. 1989) ("Eğe") (Ex. 1008).

E. Instituted Grounds of Unpatentability

We instituted the instant trial based on the following grounds of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Eğe

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under the broadest reasonable interpretation standard, claim terms are generally given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under this standard, we may take into account definitions or other explanations provided in the written description of the specification. *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Any special definition for a claim term must be set forth in the

specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

1. "A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" / "product"

Independent claims 1 and 9 recite the phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof . . . ." In addition, each challenged dependent claim recites the term "product." In the Decision on Institution, we construed "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" to mean "a product including, but not limited to, a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof." We additionally determined that the claim term "product," as it is used in the '393 patent, does not require interpretation because the claimed "product" is defined by the limitations recited in the challenged claims.

In its Patent Owner Response, UTC contends that our constructions of the above terms, as set forth in the Decision on Institution, are unreasonably broad. PO Resp. 13. In particular, UTC argues that we erred in interpreting the subsidiary term "comprising," as recited in the larger phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" to mean "including, but not limited to." *Id*. at 13–16. UTC also asserts that we erred in declining to construe "product" as "a

substance resulting from a chemical reaction," and having the impurity profile conferred by the recited process steps. *Id*. at 16–18.

a. "Comprising"

UTC contends that the intrinsic evidence overrides the presumption that the transition phrase "comprising," as recited in the challenged claims, is an "open" phrase. *Id*. at 13. Although UTC does not identify which portions of the prosecution history or specification of the '393 patent support deviating from the well-established meaning of "comprising" in patent law, UTC nevertheless urges that review of the intrinsic record demonstrates disclaimer or disavowal of an open-ended interpretation of "comprising." *Id*. at 13–16.

SteadyMed agrees with the construction of "comprising" set forth in the Decision on Institution, and contends that "comprising" is a term of art in patent law, and not susceptible to the narrow construction proffered by UTC. Pet. Reply 21. SteadyMed also observes (*id.*) that UTC argued in its Preliminary Response for broadly construing that term to mean "including but not limited to" (Prelim. Resp. 23). SteadyMed further asserts that UTC fails to identify any statements in the prosecution history regarding the meaning of "comprising," and improperly conflates the examiner's allowance of the challenged claims with a disavowal of claim scope. Pet. Reply 21.

SteadyMed additionally argues that the interpretation of "comprising" proffered by UTC cannot effect UTC's desired result of limiting the challenged claims to require a particular impurity profile. SteadyMed

asserts that the record is devoid of support for the conclusion that the claimed products and recited processes have unique impurity profiles. *Id*. at 22. In this regard, SteadyMed contends that the observed impurity profiles are not unique to the challenged claims, but rather, depend on unclaimed elements like what solvents were used, whether intermediate products were purified, and what bases, acids, or other reactants were used (*id*. at 23).

"In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'" *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007); *see also Genentech, Inc. v. Chiron Corp*., 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."). Moreover, the specification of the '393 patent itself adopts this art-established definition of "comprising," stating "[t]he expression 'comprising' means 'including but not limited to.' Thus, other non-mentioned substances, additives, carriers, or steps may be present." Ex. 1001, 4:23–25.

Indeed, in its Preliminary Response, UTC noted both that "comprising" is a term of art in patent law, and that the specification of the '393 patent defines "comprising" consistently with its well-understood meaning in arguing that the claim term "[a/the] process comprising" should be construed to mean "a/the process including but not limited to." Prelim. Resp. 23–24. In contrast, UTC does not identify, and we do not discern support in either the specification or the prosecution history for the

proposition that the Applicant disclaimed or disavowed the full scope of "comprising."

Accordingly, upon review of the parties' arguments and the evidence before us, including the claims, specification, and prosecution history of the '393 patent, we conclude that the broadest reasonable interpretation of the term "comprising," as it is used in the '393 patent, is "including, but not limited to."

b. "Product"

UTC asserts that both the specification and prosecution history of the '393 patent demonstrate that the product of the challenged claims must have the particular impurity profile that is conferred by the recited process steps (PO Resp. 17), and, thus, the challenged claims exclude products made using different processes, such as the process taught by Moriarty (*id*. at 16). UTC further argues that "product" should be construed as "a substance resulting from a chemical reaction." *Id*. at 17.

SteadyMed agrees with our determination in the Decision on Institution that the term "product," as it is used in the '393 patent, does not require interpretation because the claimed "product" is defined by the limitations recited in the challenged claims. Pet. Reply 21. In this regard, SteadyMed points out that UTC's expert, Dr. Williams, contemplates four different meanings for that term, only one of which conforms to the narrow interpretation advanced by UTC. *Id*. at 21–22.

SteadyMed additionally asserts that UTC's proffered interpretation of "product" cannot effect the desired result of limiting the challenged claims

to require a particular impurity profile. SteadyMed argues that the record is devoid of support for the conclusion that that claimed processes and their products have unique impurity profiles. *Id*. at 22. In this regard, SteadyMed contends that the observed impurity profiles are not unique to the challenged claims, but rather, depend on unclaimed elements like what solvents were used, whether intermediate products were purified, and what bases, acids, or other reactants were used. *Id*. at 23.

In patent parlance, "product" claims relate to structural entities, i.e., compositions of matter, machines, and manufactures. 1 DONALD S. CHISUM, CHISUM ON PATENTS, § 1.02 (Matthew Bender, 2017) ("Three of the four classes of statutory subject matter of utility patents (machines, manufactures, and compositions of matter) relate to structural entities and can be grouped as 'product' claims in order to contrast them with process claims."); *see also* MPEP § 2103 (9th ed., Rev. 07.2015, November 2015) ("Product claims are claims that are directed to either machines, manufactures or compositions of matter."). Accordingly, "[f]or products, the claim limitations will define discrete physical structures or materials." MPEP § 2103.

That a product is claimed in product-by-process format does not support deviation from this rule. Indeed, to subsume evaluation of whether the process steps recited in the challenged claims distinguish the claimed product from the prior art into the claim construction analysis, as UTC suggests, would be to improperly conflate the claim construction determination and patentability analysis, and would require importing unrecited limitations into the claims. As our reviewing court has explained:

> "In determining validity of a product-by-process claim, the focus is on the product and not the process of making it." *Amgen Inc. v. F. Hoffman–La Roche Ltd*., 580 F.3d 1340, 1369 (Fed.Cir.2009). . . . However, there is an exception to this general rule that the process by which the product is made is irrelevant. As we recognized in *Amgen*, if the process by which a product is made imparts "structural and functional differences" distinguishing the claimed product from the prior art, then those differences "are relevant as evidence of no anticipation" although they "are not explicitly part of the claim."

Greenliant Sys., Inc. v. Xicor LLC, 692 F.3d 1261, 1268 (Fed. Cir. 2012).

Even setting aside the art-established meaning of "product," UTC's proposed construction of that term as "a substance resulting from a chemical reaction," having the impurity profile conferred by performance of the recited process steps is unsupported by either the intrinsic or extrinsic evidence of record. Neither the specification nor the prosecution history of the '393 patent defines the term "product." In addition, the portions of the specification to which UTC points comport with an understanding of "product" as being defined only by the recited claim elements. For example, the bulk of the specification excerpts identified by UTC in its Patent Owner Response (PO Resp. 17) as supporting an interpretation of "product" as "a substance resulting from a chemical reaction" simply mirror the language of the process steps recited in the challenged claims, and do not further characterize the claim term "product." Ex. 1001, 3:3–4, 3:65–66, 6:65–66. Reference in the '393 patent specification to preparing the compound of formula II "from a compound of formula XI, which is a cyclization product of a compound of formula X" (*id*. at 7:17) likewise does not support UTC's

proposed construction (PO Resp. 17). Indeed, if any conclusion can be drawn from the specification excerpts highlighted by UTC, it is that the claim term "product" is defined solely by the recited claim limitations. *See* Ex. 1001, 5:45–46 (referring to the purportedly improved impurity of the "product of the process according to the present invention.").

Moreover, as UTC's expert, Dr. Williams explains, "chemists use the word 'product' in two different contexts, routinely." Ex. 2059, 248:4–5. "[T]here's the molecular structural context, and then there's the real-world substance context of the word 'product.'" *Id*. at 248:19–21. Indeed, Dr. Williams' own writings indicate that the term "product" does not necessarily refer to the result of a chemical reaction. Ex. 2020 ¶ 63 ("The scarcity of the natural product from marine sources renders Et-743 an important target for synthesis."). Accordingly, we do not agree with UTC that the broadest reasonable interpretation of "product" as used in the '393 patent includes a requirement that the claimed "product" be "a substance resulting from a chemical reaction."

Nor do we agree with UTC (PO Resp. 17) that the specification or prosecution history of the '393 patent disclaims or disavows from the scope of the term "product" substances having a different overall purity, or different impurity profile than is purportedly conferred by the recited process steps. "While a court may look to the specification and prosecution history to interpret what a patentee meant by a word or phrase in a claim, extraneous limitations cannot be read into the claims from the specification

or prosecution history." *Bayer AG. v. Biovail Corp.*, 279 F.3d 1340, 1348 (Fed. Cir. 2002).

During prosecution of the '393 patent, relying on the Declaration of Dr. David Walsh ("Walsh Declaration"), the applicants argued that "the product of present claims is physically differen[t] than treprostinil produced according to the process of Moriarty," and, therefore, "Moriarty cannot anticipate the present claims." Ex. 1002, 344. In his declaration, Dr. Walsh presented a comparison of three certificates of analysis, one for each of treprostinil free acid prepared according to Moriarty, treprostinil diethanolamine prepared according to challenged claims 1 or 9, and treprostinil free acid prepared according to challenged claims 1 or 9.[10] *Id*. at 347–349. Dr. Walsh went on to testify that the treprostinil of Moriarty was physically different from treprostinil prepared according to challenged claims 1 or 9 because the former included detectable amounts of certain impurities not observed in the latter. *Id*. at 349. The examiner subsequently issued a Notice of Allowance. *Id*. at 354–360.

The applicants' arguments during prosecution concerning the alleged physical differences between treprostinil prepared according to Moriarty and treprostinil prepared according to the process steps recited in the challenged claims are not tantamount to a clear disclaimer or disavowal of the full scope of the claim term "product." As an initial matter, the applicants did not

[10] Issued claim 9 of the '393 patent is identified as claim 10 in the Walsh Declaration, and other documents in the prosecution history in the '393 patent.

identify a specific impurity profile associated with treprostinil produced according to the recited process steps that could serve as a definite limitation on claim scope; rather, the applicants simply asserted that the Moriarty treprostinil was physically different from that made according to the '393 patent (Ex. 1002, 344). Moreover, the certificates of analysis for treprostinil diethanolamine and treprostinil free acid presented in the Walsh Declaration indicate that treprostinil compounds produced according to the challenged claims can have different impurity profiles and purity levels, suggesting that an attempt to define such parameters would prove elusive. Ex. 1002, 348. Indeed, as discussed in greater detail in Parts II.C.2.b, II.D.2.e, and II.E.3.d., below, the evidence of record establishes that the variability in the impurity profile and overall purity level between individual batches of treprostinil produced according to the process steps recited in the challenged claims renders the claimed treprostinil structurally and functionally the same as treprostinil produced according to Moriarty. In addition, even assuming Dr. Walsh's analysis of the impurity profiles for treprostinil produced according to Moriarty and the '393 patent is correct, the prosecution history is devoid of evidence to support the conclusion that those differences are due to the recited process steps themselves, and not the use of unclaimed reagents and reaction conditions, or that any differences in impurity profile extend to the thousands of additional compounds covered by the challenged claims.

The specification of the '393 patent likewise does not disclaim or disavow the full scope of the term "product." Akin to its arguments

concerning the prosecution history of the ’393 patent, UTC does not specifically identify the contours of the subject matter purportedly disavowed or disclaimed by the specification. In addition, although UTC points to Example 6 of the ’393 patent specification, and the related discussion, as supporting the conclusion that “the claimed ‘product’ must have an impurity profile conferred by its process steps” (PO Resp. 17), UTC does not identify, and we do not discern discussion in the specification of the impurity profile for treprostinil prepared either by the recited process, or as described by Moriarty.

Example 6 of the specification presents a comparison of processes for preparing treprostinil according to Moriarty and a working example of the process disclosed in the ’393 patent. Ex. 1001, 15:1–17:26. Example 6 reports an overall purity of ~99.0% for Moriarty treprostinil, and one of 99.9% for treprostinil prepared in accordance with the claimed invention. Example 6 does not disclose the impurity profile for treprostinil made by either process.

In describing Example 6, the specification states:

> The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the

> solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

Id. at 17:27–40.

Neither the purported difference in overall purity of treprostinil produced according to Moriarty versus that produced according to the process of the ’393 patent, nor stated advantages of the ’393 patent process as compared to the Moriarty process constitutes a disavowal or disclaimer of the full scope of the term “product.” Example 6 includes numerous process steps in addition to those recited in the challenged claims, and it is not apparent from the specification that the reported purity improvement over Moriarty treprostinil is due to the recited process steps, rather than the unclaimed steps. Furthermore, as Dr. Williams testifies, “there is the possibility for significant batch-to-batch variations in the impurity profile of each batch of treprostinil.” Ex. 2020 ¶ 93 (internal quotation omitted). In addition, as discussed in greater detail in Parts II.C.2.b., II.D.2.e., and II.E.3.d., below, the overall purity for Moriarty treprostinil set forth in the ’393 patent specification is inconsistent with that reported by Moriarty (99.7%) (Ex. 1004, 13), as well as the average purity of 46 commercial Moriarty batches (99.7%) (Ex. 1021; Ex. 2059, 218:3–219:20). Lastly, we observe that the challenged claims contain no limitations relating to the impurity profile of the recited product, “and it is the claims ultimately that define the invention.” *Purdue Pharma L.P. v. Endo Pharm. Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006).

Accordingly, upon review of the parties' arguments and the evidence before us, including the claims, specification, and prosecution history of the '393 patent, we conclude that the term "product," as it is used in that patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. We additionally conclude that the broadest reasonable construction of the larger phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" is "a product including, but not limited to, a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof."

2. "[A/the] process comprising"

Claims 1 and 9 recite "[a/the] process comprising." In the Decision on Institution, we construed this term to mean "a/the process including, but not limited to." Dec. 13. Neither SteadyMed nor UTC challenges the interpretation set forth in the Decision on Institution. *See* PO Resp. 13–18; Pet. Reply 21–23. Accordingly, for the reasons set forth in the Decision on Institution (Dec. 13), we broadly, but reasonably, construe "[a/the] process comprising" to mean "a/the process including, but not limited to."

B. Principles of Law

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). "A reference anticipates a claim 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 (Fed. Cir. 1995) (emphasis omitted) (quoting *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* [*v. Ag Pro, Inc*., 425 U.S. 273 (1976)] and *Anderson's–Black Rock* [*v. Pavement Salvage Co.*, 396 U.S. 57 (1969)] are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR, 550 U.S. at 417.

The level of ordinary skill in the art may be reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

"The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Indeed, "evidence of secondary considerations may often be the most probative and cogent evidence [of nonobviousness] in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

C. Anticipation Grounds of Unpatentability Based on Phares

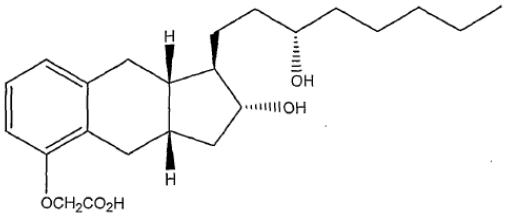
SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 102(b) as anticipated by Phares. Pet. 22–37. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) and the Rogers Declaration (Ex. 1022) to support its positions.

Upon review of SteadyMed's contentions and supporting evidence, as well as UTC's Patent Owner Response and supporting evidence, we determine that SteadyMed has demonstrated, by a preponderance of the

evidence, that claims 1–5, 7–9, 11–14, and 16–20 of the ’393 patent are unpatentable over Phares.

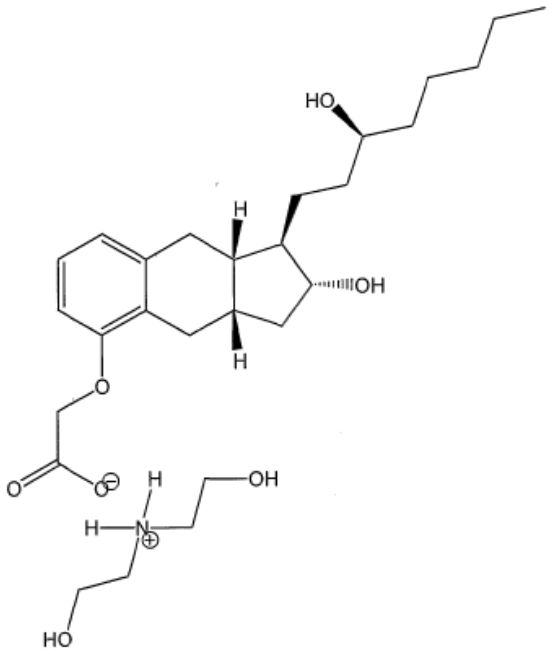
1. Phares

Phares describes “compounds and methods for inducing prostacyclin-like effects in a subject or patient,” including treprostinil and derivatives thereof. Ex. 1005, 10. The chemical structure of treprostinil disclosed by Phares, on page 10 of Exhibit 1005, is reproduced below:



Id. Phares explains that “[t]reprostinil is a chemically stable analog of prostacyclin, and as such is a potent vasodilator and inhibitor of platelet aggregation.” *Id*.

Phares further discloses that “[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil . . . . A particularly preferred embodiment of the present invention is form B of treprostinil diethanolamine.” *Id*. at 11. The structure of the diethanolamine salt of treprostinil described by Phares, on page 99 of Exhibit 1005, is reproduced below:

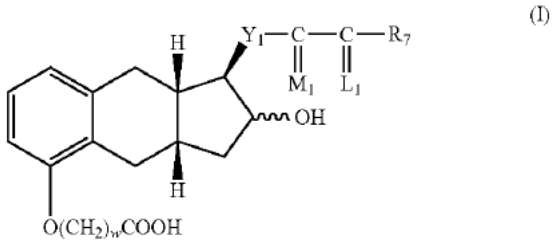


Id. at 99 (claim 49). Phares reports that form B of the diethanolamine salt of treprostinil "appears to be a crystalline material which melts at 107°C." *Id*. at 91.

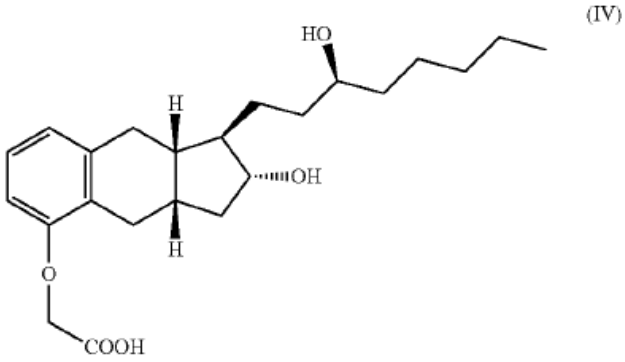
Phares describes the synthesis of (-)-treprostinil, the enantiomer of treprostinil. Ex. 1005, 41–42. Phares explains that "[e]nantiomers of these compounds . . . can be synthesized using reagents and synthons of enantiomeric chirality of the above reagents." *Id*. at 41. In particular, Phares teaches that "the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group." *Id*. at 42. Phares discloses the following reaction procedure: "i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps)." *Id*.

2. Discussion

Each of the challenged claims, including independent claims 1 and 9, is a product-by-process claim. Claim 1 of the '393 patent recites "[a] product comprising a compound of formula I



or a pharmaceutically acceptable salt thereof," and sets forth a series of process steps for obtaining the claimed product. Claim 9 recites "[a] product comprising a compound having formula IV



or a pharmaceutically acceptable salt thereof," and includes the same process steps for obtaining the claimed product as recited in claim 1.

Claim 9 is identical to claim 1, except that it is drawn to a product comprising the specific treprostinil compound, a species of the genus of claim 1. Accordingly, we address claims 1 and 9 together. Dependent claim 2 further limits claim 1, additionally requiring that "the purity of compound of formula I in said product is at least 99.5%."

SteadyMed contends that "Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt" claimed in the '393 patent. Pet. 26. SteadyMed further asserts that the process steps recited in the challenged claims of the '393 patent do not result in a treprostinil product that is physically different or unique from treprostinil produced by prior art methods. *Id*. at 19–22. In support of its position, SteadyMed argues that because the melting point for treprostinil diethanolamine salt reported by Phares is higher and exhibits a narrow range than that reported in the '393 patent, the treprostinil diethanolamine salt of Phares is at least as pure as that generated according to the process of the '393 patent. *Id*. at 27–28. SteadyMed also asserts that Phares inherently anticipates the process steps recited in the challenged claims. *Id*. at 24–28.

We have reviewed the Petition and the supporting evidence to which we are directed as to how Phares teaches each limitation of the challenged claims. We are persuaded by SteadyMed's showing that Phares discloses the identical, pharmaceutically acceptable treprostinil diethanolamine salt claimed in the '393 patent. Ex. 1005, 99 (claim 49); *see also* Ex. 1009 ¶¶ 52–53.

Notwithstanding UTC's arguments to the contrary, which we address below, we are also persuaded by SteadyMed's showing that the process steps recited in the challenged claims of the '393 patent are not entitled to patentable weight because they do not result in a treprostinil product that is structurally or functionally different from treprostinil produced by prior art methods. In this regard, we note, as SteadyMed points out, that the 99.7%

treprostinil purity reported by Moriarty (Ex. 1004, 13) exceeds each of the purity levels exemplified in the specification of the '393 patent (Ex. 1001, 8:66–67), as well as the 99.5% purity recited in dependent claims 2 and 10 of the '393 patent, the only challenged claims that recite a purity level (*id*. at 19:30–31, 20:47–48). Pet. 20–21. Moreover, as discussed in greater detail below, we are persuaded by SteadyMed's showing that any purported differences in the overall purity or impurity profile observed for treprostinil produced according to the '393 patent as compared to prior art methods are attributable to inter-batch variability in purity levels and impurity profiles, as well as variations in reagents, solvents, and reaction conditions, rather than structural and functional differences arising from performance of the process steps recited in the challenged claims. *Id*. at 21.

UTC does not dispute that Phares discloses the identical chemical structure for the treprostinil diethanolamine product claimed in the '393 patent. UTC asserts, however, that SteadyMed improperly combines disparate disclosures of Phares in arguing that Phares teaches the same process for manufacturing treprostinil as recited in claims 1 and 9. PO Resp. 19–20, 24–26.

Corollary to its contentions concerning how Phares treprostinil is made, UTC additionally argues that treprostinil produced according to Phares exhibits differences in overall purity and impurity profile compared to treprostinil produced according to the challenged claims, and, thus, cannot anticipate the claimed product. *Id*. at 20–26. In this regard, UTC argues that "SteadyMed must show that the Phares' diethanolamine salt necessarily

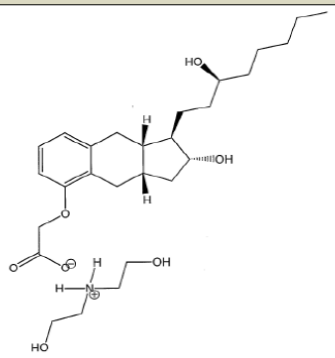
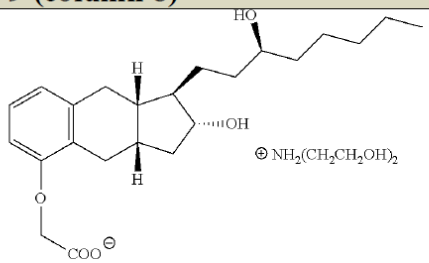
possesses an impurity profile that is distinct from that of the Moriarty product and with higher purity." *Id*. at 21. UTC further asserts that the melting point data on which SteadyMed relies as establishing that Phares treprostinil is of at least equal purity to treprostinil produced according to the recited process is "not necessarily a reliable metric of purity" (*id*. at 22), and that SteadyMed's analysis of Phares' purity level is unsound (*id*. at 23–24). With regard to dependent claim 2, UTC argues that "nothing in Phares discloses a purity of at least 99.5%." *Id*. at 24.

Lastly, UTC asserts that "[b]ecause Phares does not disclose the process of preparing the starting treprostinil acid for the diethanolamine salt, the impurity profile of the diethanolamine salt cannot be established" and, thus, SteadyMed "cannot show that it is necessarily identical to the claimed product or has equal purity to the claimed product." *Id*. at 26. We address UTC's arguments below.

a. "A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof"

It is undisputed that Phares and the '393 patent disclose identical chemical structures for treprostinil diethanolamine salt. This structural identity is illustrated in the side-by-side comparison of the compounds disclosed in claim 49 of Phares, and column 8, lines 50–63 of the '393

patent set forth in paragraph 52 of the Winkler Declaration, and reproduced below:

Phares (Ex. 1005), Claim 49	'393 Patent (Ex. 1001), Claims 1 & 9 (column 8)
	

Ex 1009 ¶ 52. As shown in the figure from paragraph 52 of the Winkler Declaration, the treprostinil diethanolamine salt disclosed by Phares is structurally identical to that disclosed in the '393 patent.

b. Recited Process Steps

In order to determine whether Phares anticipates the challenged claims, we must determine whether the process steps recited in the challenged product-by-process claims are entitled to patentable weight. The general rule when determining patentability of a product-by-process claim is to "focus . . . on the product and not on the process of making it." *Amgen, Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). This rule embodies the long-standing principle that "an old product is not patentable even if it is made by a new process." *Id.* at 1370. Thus, although a party may be entitled to a patent on a method for purifying a known substance, it is "not entitled to a patent on the article which after being

produced has a greater degree of purity than the product produced by former methods." *In re Merz*, 97 F.2d 599, 601 (CCPA 1938).

An exception to the general rule applies, however, when process steps recited in the claim impart "structural and functional differences" to the claimed product. *Greenliant Sys.*, 692 F.3d at 1267–1268. If the exception applies, the structural and functional differences conveyed by the recited process steps "'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'" *Id*. at 1268 (citing *Amgen*, 580 F.3d at 1370); *Merz*, 97 F.2d at 601 ("[I]f the process produces an article of such purity that it differs not only in degree but in kind it may be patentable.").

Based on the entire record before us, we find that the process steps recited in the challenged claims do not impart structural or functional differences to the claimed product, and, therefore, conclude that those process steps are not entitled to patentable weight. Instead, we find that the evidence of record supports a finding that treprostinil produced according to Phares has the same, or better, overall purity and purity profile than treprostinil produced according to the process recited in the '393 patent. We further find that, to the extent they exist at all, any purity differences between treprostinil produced by prior art methods and that produced according to the process recited in the '393 patent are attributable to inter-batch variability in impurity profiles, as well as variations in reagents, solvents, and reaction conditions, and are not indicative of structural or functional differences imparted by performing the steps recited in the challenged claims of the '393 patent. Moreover, even assuming the

existence of impurity differences between prior art treprostinil and '393 patent treprostinil, we find that the evidence of record does not support a determination that those impurity differences render prior art treprostinil functionally different from '393 patent treprostinil.[11]

As an initial matter, we observe that UTC does not identify, and we do not discern, evidence of record to suggest that treprostinil produced according to the process steps recited in claims 1 and 9 has a higher overall purity or different impurity profile than treprostinil diethanolamine salt produced according to Phares. Although UTC attempts to discredit evidence proffered by SteadyMed to demonstrate that Phares treprostinil is of equivalent purity to that produced according to the '393 patent (which arguments we address below), it is nevertheless the case that the record is devoid of evidence affirmatively suggesting the existence of any structural or functional difference between treprostinil made according to Phares and that made according to the '393 patent.

Moreover, we find that the 107°C melting point for treprostinil diethanolamine salt Form B reported by Phares (Ex. 1005, 91) indicates that the treprostinil product produced by to Phares is at least as pure as that made according to the steps recited in the '393 patent. Phares and the '393 patent each report melting point data for treprostinil diethanolamine salt Form B. Ex. 1005, 91; Ex. 1001, 12:52–13:20, 13:50–65. In particular, Phares

[11] Because we determine that the recited process steps are not entitled to patentable weight, we do not address the parties' contentions concerning Phares' anticipation of the recited process steps.

reports a melting point of 107°C (Ex. 1005, 91), and the ’393 patent reports melting point ranges of 104.3°C–106.3°C, 105.5°C–107.2°C, 104.7°C–106.6°C, 105°C–108°C, 105.0°C–106.5°C, and 104.5°C–105.5°C (Ex. 1001, 12:52–13:20, 13:50–65). Because the melting point for treprostinil diethanolamine salt Form B produced according to Phares exceeds the melting point ranges reported for four batches produced according to the challenged claims, and falls within the ranges of the remaining two batches, we find that the treprostinil diethanolamine salt produced according to Phares is of at least equal purity to that produced by the recited process steps, and thus, is not structurally or functionally different from ’393 patent treprostinil. We also find that the 2°C width of the melting peak for treprostinil diethanolamine salt Form B reported by Phares further indicates a high purity for Phares treprostinil, although we note that this additional finding is not essential to our determination that Phares treprostinil is not structurally or functionally different from treprostinil produced according to the ’393 patent. Ex. 1005, Fig. 21.

In making these findings, we credit the testimony of SteadyMed’s polymorph expert, Dr. Rogers that “[n]o matter how Form B is made, Form B has a single, defined melting point. If impurities are present, the apparent melting point may decrease due to a phenomenon called ‘melting point depression,’ but the melting point of a pure substance never changes.” Ex. 1022 ¶ 64. In this regard, we note that reliance by Dr. Williams, UTC’s

expert, on Adhiyaman[12] as suggesting that two crystals having the same crystal form could have different pure melting point ("T_0") values if made using different solvents (*see* Ex. 2022 ¶ 75) is misplaced. As explained by Dr. Rogers (Ex. 1022 ¶¶ 78–80), in Adhiyaman, different crystal forms of the same drug were made using different solvents, and thus, the different crystal forms exhibited different pure melting points. Ex. 2030, 4–5; *see also* Ex. 2059, 180:9–25. In contrast, Phares and the '393 patent discuss the same crystal form—treprostinil diethanolamine salt Form B—and, accordingly, "the crystals being compared in the '393 Patent and Phares Reference are the same crystal form, and thus have the same T_0 pure melting point value. Any difference in their measured melting point, T_s, is due to differing levels of impurities." Ex. 1022 ¶ 82. Because it is consistent with the disclosures of Phares, we also credit Dr. Roger's testimony that the onset temperature for Phares' treprostinil diethanolamine salt Form B is 105.00°C, and, therefore, the width of the melting peak reported by Phares is 2°C, suggesting a high overall purity level. Ex. 1022 ¶ 87; *see also* Ex. 1005, Fig. 21.

We also find unpersuasive UTC's contention that the melting point data provided in Phares is insufficient to support a determination that treprostinil produced according to Phares is of equivalent purity to that produced according to the '393 patent. PO Resp. 22, 25–26. In this regard,

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[12] R. Adhiyaman and Sanat Kumar Basu, *Crystal Modification of Dipyridamole Using Different Solvents and Crystallization Conditions*, Int'l J. Pharmaceutics 321:27-34 (2006) ("Adhiyaman") (Ex. 2030).

we note that neither UTC nor Dr. Williams identifies support for Dr. Williams' opinion that an ordinarily skilled artisan "would not have concluded based on a single melting point example of polymorph B prepared under unknown conditions (e.g., recrystallization solvent and recrystallization conditions are not identified) would be of a higher purity than the known purity of the '393 patent" (Ex. 2020 ¶ 76; *see also id*. ¶¶ 77–78). We are similarly unpersuaded by Dr. Williams' conclusory testimony that the purity values reported in Phares and the '393 patent cannot be compared because "[i]t is known in the art that sample size, rate of heating, the recrystallization solvent(s) used, and the conditions under which the crystalline sample was obtained can significantly affect the DSC data" (*id*. ¶ 76; *see also id*. ¶¶ 77–78), as well as his generic assertion, unsupported by reference to scientific literature, that in his experience, crystals having the same crystal form but made with different solvents can exhibit different pure melt points (*see* Ex. 2059, 184:22–185:2). We give such testimony little or no weight. 37 C.F.R. § 42.65(a).

Furthermore, as Dr. Williams' acknowledges, he is "not a polymorph expert." Ex. 2059, 158:17–18; *see also id*. at 156:25–157:2. In addition, the record nowhere indicates that Dr. Williams' experience with identical crystal forms made using different solvents exhibiting different pure melting points extends to treprostinil or related compounds. We are also unpersuaded by Dr. Williams' opinion that Phares' treprostinil diethanolamine salt exhibits a "broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance" (Ex. 2020 ¶ 76). In particular, we note that

Dr. Williams does not explain how he determined the width of that peak, or how the peak width he identified relates to the onset of the melting event. *See id*.

Neither do we agree with UTC's contention that "SteadyMed must show that the Phares' diethanolamine salt necessarily possesses an impurity profile that is distinct from that of the Moriarty product and with higher purity." PO Resp. 21. In order for process steps recited in a product-by-process claim to be entitled to patentable weight, they must impart structural and functional differences onto the product claimed. *See Greenliant*, 692 F.3d at 1267–1268. Accordingly, the relevant comparison is between Phares treprostinil and '393 patent treprostinil, irrespective of what starting materials were used by Phares. As explained above, the evidence of record shows that Phares treprostinil is of at least equal purity to '393 patent treprostinil, and, therefore, treprostinil produced according to the process steps recited in the challenged claims cannot be said to differ structurally or functionally from treprostinil produced according to Phares.

Although UTC does not endeavor to compare the purity of Phares' treprostinil to that produced according to the '393 patent, it does present purity data for developmental and commercial batches of '393 patent treprostinil, as well as for treprostinil purportedly made according to the process described by Moriarty (Ex. 2020, Appx. A–B (compiling purity data); Ex. 2059, 79:11–16, 81:14–22 (identifying first ten batches of Appendix A as development batches); *id*. at 272:15–273:16 (identifying first five batches of Appendix B as development batches)), which SteadyMed

contends would have been the starting material used by Phares (Pet. 25–26). The average overall purity as measured by HPLC for the commercial batches of '393 patent treprostinil and for the commercial batches of Moriarty treprostinil is the same: 99.7%. Ex. 2059, 218:25–219:20; *see also id*. at 93:11–25; Ex. 1021. Notably, this is the same HPLC purity assay value as reported by Moriarty. Ex. 1004, 13 (reporting an HPLC-determined "purity [of] 99.7%", and noting that the compound tested "was identical in all respects to an authentic sample of UT-15 [treprostinil]").[13]

Because UTC's expert, Dr. Williams, included a disproportionate number of development batches relative to commercial batches in its overall purity calculation for Moriarty treprostinil (10 development batches out of a total of 56 batches) (*see* Ex. 2059, 79:11–16, 81:14–22) as compared to '393 patent treprostinil (5 development batches out of a total of 121) (*see id*. at 272:15–273:16), and did not account for this disparity in the purity calculation, we find that the comparison of like to like, as represented by the average overall purity of the commercial batches only, provides the most reliable evidence of treprostinil purity. We also find that the development

[13] UTC urges us to ignore the purity reported by Moriarty because "it is not clear what method was used to determine the purity in Moriarty." PO Resp. 29. We observe, however, that Moriarty, like the '393 patent specification itself, discloses that an HPLC purity assay was used without identifying the particular reference standard employed. We further note that because reference standards are just that, the absence of information concerning the precise reference standard used does not call into question the validity of the purity reported in Moriarty.

batches are a less reliable indicator of product purity, as they are not necessarily representative of the final, fully optimized production processes. *See e.g.*, Ex. 2059 102:9–12 ("So the development batches for the '393 are also poorer than the later commercial batches. And so by the same token, those numbers bring down the average purity of the '393 process."), 102:20–22 ("But if you did eliminate the development batches, it would certainly improve the overall purity of the '393 batches."), 105:11–16 ("[W]ith the — the Moriarty process, you're starting with an inferior process. So the development batches were not as nice as the development batches that you started with the '393. . . .").

As further support for these findings, we observe that Dr. Williams neither asserts that exclusion of the development batches from the purity analysis would be improper (*see, e.g.*, Ex. 2059, 91:12–20, 115:7–18), nor articulates any reason the development batches should be included in the purity analysis, beyond stating that he included development batches for both processes and factored all of the data that was presented to him into his calculation (*id*. at 271:25–272:5, 273:13–24). In addition, although it is not necessary to our findings, we note that Dr. Williams' uncertainty regarding whether the purported Moriarty development batches were in fact produced according to the Moriarty process provides an additional reason to exclude the alleged Moriarty development batches from the overall purity calculation. *See, e.g.*, Ex. 2059, 270:23–271:2. Accordingly, we find that there is no difference in the overall purity for treprostinil produced according to Moriarty and that produced according to the '393 patent.

UTC additionally argues that treprostinil produced according to the '393 patent has a different impurity profile than that produced by Moriarty. In particular, UTC contends that comparison of the average impurity profiles for treprostinil produced by each of these methods reveals that certain specific impurities found in Moriarty treprostinil are essentially eliminated from treprostinil made according to the '393 patent. For example, UTC identifies three impurities as being eliminated from commercial batches of '393 patent treprostinil: 97W86, 1AU90, and 2AU90, and asserts that four more impurities are, on average, greatly reduced: methyl ester, 751W93, 750W93, and 3AU90. PO Resp. 10. UTC additionally states that ethyl ester is slightly increased in '393 patent treprostinil. *Id*. UTC then concludes that these impurity differences constitute structural differences between Moriarty and the claimed product.

But we find that UTC's reliance on average impurity profiles for treprostinil produced by different methods is misplaced, as UTC's averages do not account for the significant inter-batch variation in both the types and amounts of impurities present in batches of treprostinil made by either the Moriarty or the '393 patent process. *See, e.g.*, Ex. 2020, Appx. A–B (compiling impurity data from individual treprostinil batches); PO Resp. 11 ("Moriarty treprostinil may show inter-batch variation in overall purity and impurity profiles"); Ex. 2020 ¶ 93 ("Third, as Dr. Winkler himself points out, there is the possibility for 'significant batch-to-batch variations in the impurity profile of each batch of treprostinil.'"). We also find that the impurity profile averages on which Dr. Williams relies in asserting the

existence of impurity differences between ’393 patent treprostinil and Moriarty treprostinil are unpersuasive, because those averages obfuscate, and make no attempt to account for, the extent of inter-batch variation for treprostinil produced by any method.

The extent of the inter-batch variation for both Moriarty and ’393 patent treprostinil batches is illustrated by the fact that, irrespective of the averages calculated by Dr. Williams, individual commercial batches of Moriarty treprostinil exhibit impurity profiles nearly identical, if not superior, to those seen in individual commercial batches of ’393 patent treprostinil. For example, the table below compares the types and amounts of impurities detected in one commercial batch of Moriarty treprostinil (Lot. No. UT15-031202, Ex. 2036, 5) to those detected in one commercial batch of ’393 patent treprostinil (Lot. No. 01F08017, Ex. 2037, 58–59).

Compound	**Moriarty UT15-031202 (Ex. 2036, 5)**	**’393 Patent 01F08017 (Ex. 2037, 58–59)**
1AU90	Not detected	Not detected
2AU90	Not detected	Not detected
97W86	Not detected	Not detected
3AU90	0.2%	0.09%
treprostinil methyl ester	<0.05%	<0.05%
treprostinil ethyl ester	0.2%	0.5%
750W93	0.07%	0.09%
751W93	<0.05%	<0.05%
unidentified impurities	Not detected	0.08%
total related substances	0.5%	0.8%
assay purity	99.7%	99.5%

As revealed by the above comparison, the Moriarty batch has a higher overall purity, and the same or lower amounts of all but one impurity, 3AU90, than the '393 patent batch. *Compare* Ex. 2036, 5, *with* Ex. 2037, 58–59. In addition, we observe that both the Moriarty batch and the '393 patent batch satisfy the treprostinil drug specification requirements concerning the types and amounts of impurities that may be present in a batch of treprostinil—which requirements notably did not change when UTC switched over from producing treprostinil according to Moriarty to producing it using the process disclosed in the '393 patent. Ex. 2036, 5; Ex. 2037, 58–59; Ex. 2006, 5–6; Ex. 2003. We further note that both batches also satisfy the overall purity requirements under the revised treprostinil drug specification (Ex. 2006, 3–4; Ex. 2003).

As explained above in Part II.A.1.b., the comparisons of purity data for Moriarty and '393 patent treprostinil set forth in the Walsh Declaration and in the specification of the '393 patent itself similarly indicate that batch-to-batch variation, rather than any structural or functional difference between treprostinil products, accounts for the reported differences in overall purity and impurity profile.

UTC additionally contends that whether individual batches of Moriarty treprostinil satisfy the current FDA purity specification is not relevant to patentability. Rather, UTC asserts that "[t]he question for patentability is whether or not a given batch of *starting* Moriarty treprostinil (steps a and b of the '393 independent claims) will be physically changed when step (c) is performed *on that batch*." PO Resp. 11. But whether an

intermediate, or even the final product of the Moriarty process might be further purified when subject to step (c) of the challenged claims is not the test for determining whether the process steps recited in the challenged product-by-process claims are entitled to patentable weight. Instead, the question before us is whether the process for making treprostinil set forth in the challenged claims imparts structural or functional differences to the product claimed as compared to prior art processes for making the claimed product. *See Greenliant*, 692 F.3d at 1267–1268. For the reasons set forth above, and as exemplified by comparison of individual batches of Moriarty and '393 patent treprostinil, we determine that the process steps set recited in the challenged claims do not impart structural or functional differences on the product claimed. Moreover, we observe that none of the asserted grounds of unpatentability depends on Moriarty alone; rather, each asserted ground of unpatentability is based, in whole or in part, on Phares, which expressly discloses step (c) of the asserted claims, and yields a treprostinil product that is at least as pure as '393 patent treprostinil. As evident from the discussion above, the use of Moriarty treprostinil as the starting material for the purification disclosed by Phares would result in a treprostinil diethanolamine salt at least as pure as that disclosed by the '393 patent, and thus, a product that is not structurally or functionally different from that disclosed by the '393 patent.

Furthermore, even if it had been shown that treprostinil produced according to the '393 patent differed in overall purity and/or impurity profile from treprostinil produced according to prior art methods, the record

nevertheless fails to support a determination that those differences confer patentable weight to the process steps recited in the challenged claims. *See Merz*, 97 F.2d at 601 ("No new use is claimed for appellant's purified ultramarine. It is the same old ultramarine with the same old use though it may have brighter color and be more desirable as a pigment than formerly."). Indeed, as Dr. Williams acknowledged during deposition, with chromatography, as is used in Moriarty, it would be possible to purify treprostinil to "99.99999 percent" by purifying and re-purifying the product. Ex. 2059, 94:1–24.

UTC nevertheless contends that the FDA's approval of UTC's request for a change in the purity assay value for the treprostinil from a range of 97%–101% to a range of 98%–102% was a "major" change evidencing the functional importance of the purported difference in purity between Moriarty treprostinil and treprostinil made according to the '393 patent. PO Resp. 12. UTC argues also that FDA pharmaceutical batch testing requirements, and prohibition by the FDA of the sale for patient use of batches that fall outside of the relevant purity specification further illustrate the importance of the alleged purity improvements obtained using the process recited in the '393 patent. *Id*.

Absent from the record, however, is evidence to suggest that the 1% increase in the purity assay value for treprostinil produced according to the '393 patent, or the FDA's general requirements for pharmaceutical purity, demonstrates a functional difference between Moriarty treprostinil and '393 patent treprostinil. Instead, the record indicates that batches of

Moriarty treprostinil satisfy the 98% minimum purity requirement for treprostinil approved by the FDA, and could be sold to the public (Ex. 2058, 179:23–180:17). This is true irrespective of whether the overall purity level of 99.7% reported by Moriarty (Ex. 1004, 13), 99.05% reported by Dr. Williams (Ex. 2020 ¶ 98), or 99.7% as obtained when development batches are excluded from Dr. Williams' analysis (Ex. 1021; Ex. 2059, 218:3–20) is accepted, as each of these reported purity levels exceeds the 98% purity required by the FDA. In addition, we note that UTC's expert, Dr. Ruffolo confirmed during deposition that the 1% purity change sought by UTC and approved by the FDA did not itself constitute a "major" change to the treprostinil drug specification. Ex. 2058, 310:5–18. Finally, we observe that the record does not include evidence to suggest the existence of any clinical or safety differences between Moriarty treprostinil and treprostinil produced according to the '393 patent. *See, e.g.*, Ex. 2058, 257:22–258:9, 315:15–23; Ex. 2059, 47:3–13.

With regard to the purported differences in the impurity profiles for Moriarty treprostinil and '393 patent treprostinil, we additionally note that UTC did not seek, and the FDA did not impose, any changes to the types or amounts of impurities that may be present in treprostinil manufactured according to the '393 patent versus that made by the Moriarty process. Ex. 2006, 5–6; Ex. 2003. We observe also that the '393 patent itself does not discuss any of the individual impurities, or attribute any clinical relevance to the purported differences between Moriarty treprostinil and that made according to the '393 patent process.

Accordingly, on the record before us, we determine that the process steps recited in the challenged claims of '393 patent do not impart structural or functional differences to the claimed product, and thus, do not patentably limit the claimed product.

c. Claim 2

Claim 2 depends from claim 1 and further requires that "the purity of compound of formula I in said product is at least 99.5%."

UTC asserts that Phares does not anticipate claim 2, because "nothing in Phares discloses a purity of at least 99.5%." PO Resp. 24.

We do not agree. For the reasons set forth above, we find that Phares treprostinil is at least as pure as treprostinil produced according to the process disclosed in the '393 patent, and therefore, Phares necessarily discloses treprostinil having a purity of 99.5% or higher. Ex. 1009 ¶ 62. Furthermore, a claim to a degree of purity in and of itself does not render the claim patentable over the prior art. *In re Fink*, 62 F.2d 103, 104 (CCPA 1932) (affirming decision where purity of claimed product was merely a matter of degree and there was no reason to believe that prior art product would not be as pure).

3. Conclusion

UTC does not separately argue claims 3–5, 7, 8, 11–14, and 16–20. *See* PO Resp. 18–26. We have reviewed Petitioner's evidence and argument as to those claims, and, based on the evidence, find that Petitioner has

established by a preponderance of the evidence that those claims are anticipated by Phares. Pet. 30–32, 34–37.

For the foregoing reasons, therefore, we determine SteadyMed has demonstrated, by a preponderance of the evidence, that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 102(b) as anticipated by Phares.

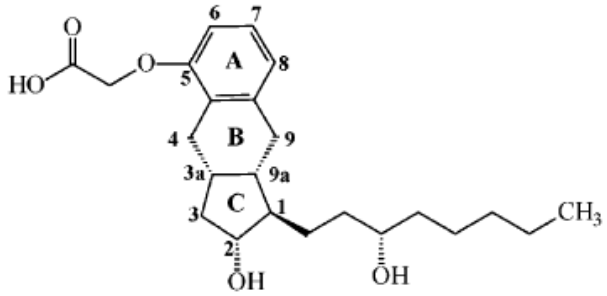
D. Obviousness Grounds of Unpatentability Based on Moriarty and Phares

SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 103(a) as obvious in view of Moriarty and Phares. Pet. 37–52. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty and Phares discloses each claim limitation (*id*.), and relies upon the Winkler Declaration (Ex. 1009) and the Rogers Declaration (Ex. 1022) to support its positions.

Upon review of SteadyMed's contentions and supporting evidence, as well as UTC's Patent Owner Response and supporting evidence, we determine that SteadyMed has demonstrated, by a preponderance of the evidence, that claims 1–5, 7–9, 11–14, and 16–20 of the '393 patent are unpatentable over the combination of Moriarty and Phares.

1. Moriarty

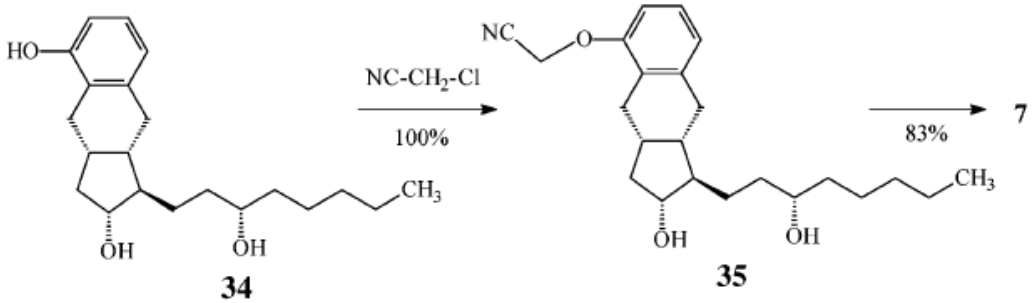
Moriarty describes the synthesis of treprostinil "via the stereoselective intramolecular Pauson-Khand cyclization." Ex. 1004, 1. Formula 7 of Moriarty is reproduced below:



7

Id. at 3. Formula 7 of Moriarty depicts the chemical structure of treprostinil. *Id*.

An excerpt of Scheme 4 of Moriarty is reproduced below:



34 **35**

Id. at 6. The excerpted portion of Scheme 4 of Moriarty illustrates the alkylation of Formula 34 to yield Formula 35, and subsequent hydrolysis of Formula 35 with a base (followed by acidification) to yield Formula 7, treprostinil. Ex. 1004, 6, 13.

2. Discussion

SteadyMed contends that Moriarty and Phares respectively disclose treprostinil acid and treprostinil diethanolamine salt, as recited in that challenged claims of the '393 patent. Pet. 22–23, 24, 33, 39, 48. SteadyMed further asserts that Moriarty discloses steps (a) and (b), and Phares discloses step (c) of the process recited in independent claims 1 and 9 of the '393 patent. Pet. 43, 48–49.

We have reviewed the Petition and the supporting evidence to which we are directed as to how the combination of Moriarty and Phares discloses each limitation of the challenged claimed. We are persuaded by SteadyMed's showing that the combination of Moriarty and Phares discloses both the treprostinil products claims, as well as the production of those treprostinil products through the performance of steps (a)–(c) recited in claims 1 and 9 of the '393 patent.

Relying on its expert, Dr. Winkler, SteadyMed asserts that an ordinarily skilled artisan, at the time of invention of the '393 patent, would have had reason to combine, and a reasonable expectation of success in combining, Moriarty and Phares. Pet. 43. Dr. Winkler testifies that an ordinarily skilled artisan would have sought to combine Moriarty and Phares in order to eliminate the intermediate purification step taught by Moriarty, thereby increasing synthetic efficiency and lowering production costs for treprostinil diethanolamine salt. Ex. 1009 ¶¶ 77–78. Dr. Winkler additionally testifies that an ordinarily skilled artisan would have had a reasonable expectation of success in reacting treprostinil with

diethanolamine because Phares successfully performed precisely that reaction. *Id*. ¶ 80.

Notwithstanding UTC's arguments to the contrary, which we address below, we are persuaded by SteadyMed's showing that an ordinarily skilled artisan, at the time of invention of the '393 patent, would have had reason to combine, and a reasonable expectation of success in combining, Moriarty and Phares. "[T]he skilled artisan need not be motivated to combine [the prior art] for the same reason contemplated by [the inventor]." *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006). In this regard, we note that in addition to teaching that intermediate purification is unnecessary to the production of treprostinil diethanolamine salt by the disclosed process (Ex. 1005, 40–42), Phares explicitly describes the Moriarty process in disclosing the production of (-)-treprostinil, the enantiomer of (+)-treprostinil (*id*. at 42). Ex. 1009 ¶¶ 50, 77–78. Accordingly, we are persuaded that an ordinarily skilled artisan would have modified the process of Moriarty to incorporate the step of adding and dissolving diethanolamine to treprostinil as taught by Phares (Ex. 1005, 24) to eliminate the requirement for intermediate purification, thus, improving synthetic efficiency and reducing cost.

UTC does not dispute either that the combination of Moriarty and Phares discloses treprostinil and treprostinil diethanolamine salt, or that the cited combination discloses steps (a)–(c) of claims 1 and 9. UTC contends, however, that an ordinarily skilled artisan would have had neither reason to combine, nor a reasonable expectation of success in combining Moriarty and Phares. PO Resp. 27–32. UTC additionally asserts that the salt formation

recited in step (c) of the challenged claims yields unexpected improvements in both the overall purity and impurity profile of the treprostinil product. *Id*. UTC also argues that treprostinil diethanolamine salt produced according to the cited combination is physically different from treprostinil produced according to the '393 patent process. *Id*. at 28–30. Lastly, UTC asserts that evidence of objective indicia of nonobviousness, including long-felt but unmet need and unexpected results, establish the nonobviousness of the challenged claims. *Id*. at 47–49. We address UTC's arguments below.

a. Level of Ordinary Skill in the Art

SteadyMed contends that a relevant skilled artisan would have had, at the time of invention of the '393 patent, "a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. (Ex. 1009, Winkler Decl., ¶ 14). Alternatively, a person of ordinary skill would include an individual with a bachelor's degree and at least five years of practical experience in medicinal or organic chemistry." Pet. 4.

UTC does not, in its Patent Owner Response, directly dispute SteadyMed's assertions with regard to the level of ordinary skill in the art, or argue that any differences in the skill levels advanced by the parties are relevant to the nonobviousness analysis. UTC's expert, Dr. Williams, however, advocates for a similar, albeit somewhat higher level of skill than is advanced by SteadyMed. In particular, Dr. Williams testifies that an ordinarily skilled artisan at the time of invention of the '393 patent would have had "a doctorate degree in chemistry, pharmaceutics, pharmaceutical sciences, medicine, or a related discipline. Alternatively, the POSA may

have had a lesser degree in one of those fields, with correspondingly more experience." Ex. 2020 ¶ 33. Dr. Williams additionally testifies that "[t]o the extent necessary, a POSA may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds." *Id*. Dr. Ruffolo, UTC's second expert, agrees with Dr. Williams' opinions concerning the ordinarily level of skill in the art. Ex. 2022 ¶ 23.

We find that the level of ordinary skill in the art is reflected by the prior art of record. *See Okajima*, 261 F.3d at 1355. With respect to the slight variance in the educational attainment of a relevant artisan advanced by the parties, we agree with Drs. Williams and Ruffolo that an ordinarily skilled artisan at the time of invention of the '393 patent would have had a doctorate in chemistry, pharmaceutics, pharmaceutical sciences, medicine, or a related discipline, or a lesser degree in one of those fields, with correspondingly more experience. We also agree that the relevant skilled artisan may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds. We observe, however, that our findings and legal conclusions apply with equal force whether the level of ordinary skill in the art advanced by SteadyMed or by UTC is adopted.

b. Rationale to Combine

UTC asserts that an ordinarily skilled artisan would not have had reason to combine Moriarty and Phares because Moriarty discloses the use

of column chromatography for purification, and "Phares does not disclose any benefit or increased purity as a result of using the diethanolamine salt." PO Resp. 31. UTC additionally contends that Moriarty teaches three different ways to make treprostinil, and thus, an ordinarily skilled artisan would not have had reason to select the method that uses steps (a) and (b) recited in the challenged claims over the remaining two options. *Id*. at 27.

We do not agree. "[T]he problem motivating the patentee may be only one of many addressed by the patent's subject matter. . . . [A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *KSR*, 550 U.S. at 420; *see also Kahn*, 441 F.3d at 990 ("[T]he skilled artisan need not be motivated to combine [the prior art] for the same reason contemplated by [the inventor]."). Irrespective of whether Phares suggests any purity benefits over Moriarty, the proposed combination of Moriarty and Phares would eliminate the need for intermediate purification as required by Moriarty alone, and thereby confer efficiency and cost benefits. Ex. 1009 ¶¶ 77–78. We determine that an ordinarily skilled artisan would have sought to combine Moriarty and Phares in order to reap these efficiency and cost benefits.

We additionally find that an ordinarily skilled artisan would have sought to make the proposed combination for the independent reason that Phares is directed to improving treprostinil, and the Moriarty process, including the performance of steps (a) and (b) of the challenged claims, was a well-known way to make treprostinil. *See* Ex. 2059, 240:2–7, 244:10–21.

"[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. For the same reason, we also find that an ordinarily skilled artisan would have had reason to combine the Moriarty process, including steps (a) and (b) of the challenged claims, with Phares. Indeed, Phares itself describes the Moriarty process, including recited steps (a) and (b), with respect to producing the enantiomer of treprostinil. Ex. 1005, 42.

c. Reasonable Expectation of Success

Akin to its arguments concerning the rationale for combining Moriarty and Phares, UTC asserts that an ordinarily skilled artisan would not have had "a reasonable expectation of success by using salt formation as a purification step separate from or in addition to the column chromatography of Moriarty." PO Resp. 31. In particular, UTC contends that "Phares does not disclose any alleged benefit to forming the salt and a POSA would have no expectation that only certain acidic and neutral impurities would be reduced or completely eliminated while others remained." *Id*. at 31–32

But whether or not an ordinarily skilled artisan would have had an expectation that salt formation would improve the purity of Moriarty treprostinil is not the relevant inquiry. "The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

It is undisputed that the proposed combination of Moriarty and Phares yields treprostinil diethanolamine salt, i.e., the product claimed in independent claims 1 and 9. Furthermore, as detailed in Part II.C.2.b above, both Moriarty treprostinil and Phares treprostinil diethanolamine salt are highly pure. Indeed, Phares treprostinil diethanolamine salt is at least as pure as that claimed in the '393 patent. Accordingly, we find that an ordinarily skilled artisan would have a reasonable expectation of success in combining Moriarty and Phares.

d. A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

The present record supports SteadyMed's contention that the treprostinil diethanolamine salt disclosed by the combination of Moriarty and Phares is structurally identical to the pharmaceutically acceptable treprostinil diethanolamine salt recited in the challenged claims. Pet. 41–42; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶ 76. As explained in Part II.C.2.a., above, it is undisputed that the treprostinil diethanolamine salt disclosed by Phares, which is the product that would result from the proposed combination, has the same chemical structure as the treprostinil diethanolamine salt claimed in the '393 patent.

e. Recited Process Steps

UTC does not dispute that the proposed combination of Moriarty and Phares discloses the process steps recited in the challenged product-by-process claims. Nevertheless, UTC contends that the claimed product is structurally different from prior art treprostinil products, and

therefore, nonobvious. In addition to reiterating many of the arguments addressed in Part II.C.2.b., above, concerning the purported differences in the overall purity and impurity profile for treprostinil prepared according to the process described in the '393 patent versus that made according to prior art processes, UTC asserts that there is no basis for comparing the purity reported in Moriarty to that reported in the Walsh Declaration submitted during prosecution of the '393 patent. PO Resp. 29. UTC also argues that Dr. Winkler's opinions concerning error in purity measurements are themselves erroneous, and should be disregarded.

First, we note that the absence of dispute concerning the disclosure of the recited process steps by the cited combination renders moot the question of whether the process steps recited in the challenged claims impart structural or functional differences to treprostinil so produced as compared to prior art treprostinil products. Because the combination of Moriarty and Phares discloses both the product claimed and the process recited in the challenged product-by-process claims, it renders those claims obvious.

Furthermore, as explained in Part II.C.2.b., above, we find that the evidence of record does not support the existence of any structural or functional differences between prior art treprostinil and that produced according to the '393 patent. Notably, our findings in this regard depend neither on comparison of the purity reported by Moriarty to that reported in the Walsh Declaration, nor on Dr. Winkler's opinions concerning error in purity measurements. Nevertheless, for completeness, we note that the 99.7% purity reported by Moriarty is the same as that derived from analysis

of the purity of the commercial batch data for Moriarty treprostinil produced by UTC. We also observe, as explained in footnote 13, above, that the 99.7% HPLC purity assay value reported by Moriarty is reliable.

f. Claim 2

UTC asserts that the requirement for a product having a purity of at least 99.5% set forth in claim 2 is not rendered obvious by the combination of Phares and Moriarty because "there is no basis to compare the purity disclosed in Moriarty to the measurements obtained in the '393 patent or those obtained by Dr. Walsh in his declaration." PO Resp. 32.

We do not agree. The combination of Moriarty and Phares necessarily discloses treprostinil diethanolamine salt having a purity of at least 99.5%. First, as set forth above in Part II.C.2.c, Phares necessarily discloses treprostinil diethanolamine salt having a purity of 99.5% or higher. Second, as detailed in Part II.C.2.b., above, Moriarty treprostinil has an overall purity of 99.7%, thus, performing the purification disclosed by Phares on Moriarty would yield a product having at least as high a purity as the starting Moriarty treprostinil.

Furthermore, we find that the 99.7% purity reported in Moriarty is reliable and can be compared to the purity values reported in the '393 patent specification and Walsh Declaration. Moriarty discloses both that the purity of the disclosed treprostinil product was determined via an HPLC purity assay, and that Moriarty treprostinil "was identical in all respects to an authentic sample of UT-15 [treprostinil]". Ex. 1004, 13. The fact that Moriarty does not explicitly identify the reference standard used in the

HPLC purity assay does not call into question the veracity of the purity reported. In this regard, we note that, like Moriarty, the '393 patent does not expressly identify the reference standard used for purity measurements. *See* Paper 81, 18:1–3 ("The specification of the '393 patent does not identify the reference and neither does the Moriarty reference."). We also observe that reference standards are, just that—standards, and as such, the absence of information concerning the precise reference standard used does not call into question the validity of the purity reported in Moriarty.

g. Claims 8 and 16

Claims 8 and 16 depend from claims 1 and 9, respectively, and further recite "wherein the process does not include purifying the compound of formula [(III)/(IV)] produced in step (a)."

UTC contends that Moriarty teaches purification of the compound produced in step (a), and that Phares does not disclose treprostinil synthesis, or purification details. PO Resp. 32. On this basis, UTC concludes that the cited combination fails to render obvious claims 8 and 16. *Id*.

We do not agree. Rather, as explained in Part II.D.2.b., above, we find that the intermediate purification taught by Moriarty would be eliminated in the proposed combination with Phares. *See* Ex. 1009 ¶¶ 77–78. Accordingly, we agree with SteadyMed that an ordinarily skilled artisan in possession of Phares would have recognized that the alkylation step—step (a) of the challenged claims—"could be followed by the hydrolysis with a base without purifying the product of the alkylation reaction," and, further, would have recognized the elimination of the intermediate purification step

from Moriarty as an advantage of combining Moriarty with Phares. Pet. 47–48; Ex. 1009 ¶¶ 77–78.

h. Objective Indicia of Nonobviousness

UTC contends that objective indicia of nonobviousness, including evidence of a long-felt but unmet need for treprostinil having greater overall purity and an improved impurity profile compared to treprostinil produced by known methods, as well as evidence that treprostinil produced according to the process steps of the challenged claims unexpectedly yields a product having increased purity as compared to prior art processes establishes that the challenged claims are nonobvious. PO Resp. 47–49.

Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17. Notwithstanding what the teachings of the prior art would have suggested to a person of ordinary skill in the art at the time of the claimed invention, the totality of evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Indeed, when present, evidence of objective indicia of nonobviousness, such as evidence of a long-felt but unmet need or unexpected results "may often be the most probative and cogent evidence [of nonobviousness] in the record." *Stratoflex*, 713 F.2d at 1538.

As explained below, however, upon full consideration of the evidence of record respecting the objective indicia of nonobviousness in this case, we are persuaded that nonobvious is not established by that evidence.

i. Long-Felt Need

Relying on the Ruffolo Declaration, UTC asserts that at the time of invention of the ’393 patent, there existed a long-felt but unmet need for “a more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner.” PO Resp. 47. In this regard, UTC argues that because treprostinil is a potent drug, “any diastereomeric impurities would also potentially be potent.” *Id*. at 48. UTC contends that “the FDA as a matter of course seeks to minimize all impurities in drug substances and particularly in highly potent drug substances such as treprostinil,” and concludes that “[t]he reduction and removal of several types of impurities met the long-felt need expressed by the FDA to minimize impurities as much as possible.” *Id*. UTC also asserts that its submission, and the FDA’s adoption, of a change in UTC’s drug specification for treprostinil increasing the purity from an assay range of 97.0%–101.0% to 98.0% to 102.0% for treprostinil produced according to the process disclosed in the ’393 patent demonstrates satisfaction of the long-felt need, expressed by the FDA, for drug substances having fewer, and lower amounts of, impurities. *Id*. at 48–49.

In response, SteadyMed observes that UTC’s expert, Dr. Ruffolo, does not offer any opinion concerning whether a long-felt need existed for higher purity versions of compounds other than treprostinil or treprostinil

diethanolamine salt that fall within the scope of the challenged claims, and notes that claims 10, 14, 15, and 17 of the '393 patent are the only claims limited to treprostinil or its salt. Pet. Reply 23.

With regard to treprostinil and treprostinil diethanolamine salt, SteadyMed points out that Dr. Ruffolo conceded during deposition that he was unaware if the FDA had sought a change in purity, or if any party had expressed a particular desire for improved purity. *Id*. SteadyMed also notes that Dr. Ruffolo acknowledged that drug purity can typically be improved by repeating purification procedures, and that Dr. Williams testified that the purity of treprostinil could be improved using such an approach. *Id*. SteadyMed thus contends that there was no need for the claimed invention. *Id*. at 23–24. SteadyMed additionally asserts that Dr. Ruffolo acknowledged that the change in UTC's purity specification for Treprostinil accepted by the FDA was not a major amendment. *Id*. at 24.

SteadyMed further points out that treprostinil produced by prior art methods exceeds the 98% purity level required by the FDA, and that the FDA would permit the sale of treprostinil produced according to Moriarty. *Id*. SteadyMed also asserts that UTC has not identified any clinical difference between Moriarty treprostinil and treprostinil produced according to the method of the '393 patent. *Id*. Lastly, SteadyMed argues that Dr. Ruffolo's opinion should be disregarded because it relies on Dr. Williams' assertion that Moriarty treprostinil has an overall purity level of 99.0%. *Id*.

As an initial matter, we note that UTC's contentions regarding long-felt need are predicated on UTC's claim that treprostinil made according to the process described in the '393 patent has a higher purity, and different impurity profile than treprostinil produced by other methods. However, as explained in Parts II.C.2.b. and II.D.2.e., above, the present record does not support that contention. We also observe that the purported differences between prior art treprostinil and the treprostinil claimed in the '393 patent derive solely from the process steps recited in the challenged product-by-process claims, and not the patented product itself. *See Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1355 (Fed. Cir. 2016) (finding evidence of objective indicia of nonobviousness unpersuasive where such evidence relates to process steps recited in a product-by-process claim, rather than the "patented product").

Moreover, the evidence of record does not support a determination that a long-felt need existed for treprostinil having a higher overall purity, or improved purity profile than that exhibited by prior art treprostinil. "Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004).

UTC does not identify, and we do not discern evidence of record that any entity aside from UTC sought to produce treprostinil in a more pure form, via a more efficient synthesis, or in a more cost-effective manner than was possible using prior art processes. For example, even if we agree with

UTC that because treprostinil is a "very potent drug so any diastereomeric impurities would also *potentially* be potent" (PO Resp. 48 (emphasis added)), the record is nevertheless devoid of evidence that any of those diastereomeric impurities are in fact potent, clinically relevant, or otherwise of concern. *See e.g.*, Ex. 2022 ¶ 54 (noting that treprostinil "may contain trace amounts of potent structural analogs as impurities," but failing to identify what analogs are potent or to present evidence that such analogs are present in treprostinil produced according to prior art methods); Ex. 2058, 257:22–258:9, 315:15–23; Ex. 2059, 47:3–13.

Neither does the record include evidence to support UTC's assertion that "the FDA as a matter of course seeks to minimize all impurities in drug substances and particularly in highly potent drug substances such as treprostinil" (PO Resp. 48). UTC relies on Dr. Ruffolo's testimony in this regard, however, Dr. Ruffolo's opinion that "[a]s with all drug substances such as treprostinil, the FDA seeks to list, quantitate, and minimize impurities, and maximize the overall purity, of such drug substances as much as possible for the benefit of patients" (Ex. 2022 ¶ 31) is improperly conclusory. We give such testimony little or no weight. 37 C.F.R. § 42.65(a). Likewise, Dr. Ruffolo's opinion that "because some impurities are extremely toxic at very low levels of exposure, Thresholds of Toxicological Concern can, and often are, lowered, beyond the guidelines described above, in the specifications for the synthesis and manufacturing of a drug substance in order to be conservative" (Ex. 2022 ¶ 54), although supported by reference non-binding FDA industry guidance concerning

mutagenic impurities, is insufficient to support the proposition that the FDA seeks, as a matter of course, to minimize all impurities in all pharmaceuticals, or in treprostinil in particular.

Moreover, even crediting UTC's contention that the FDA seeks to minimize all impurities in all pharmaceuticals to the extent possible, such a general agency preference for improved purity is insufficient to establish a long-felt but unmet need for improved treprostinil, in particular. *See Tex. Instruments v. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem."). Indeed, adherence to UTC's position would dictate a conclusion of nonobvious for any pharmaceutical product exhibiting any improvement in purity over prior art versions of that same product.

The record simply does not support a determination that the FDA sought a treprostinil product having an improved overall purity or different impurity profile versus known treprostinil products. UTC's reliance on its own request to the FDA for a change in the purity assay value for treprostinil as evidencing a long-felt need for improved treprostinil (PO Resp. 48) is misplaced. Far from indicating the existence of a long-felt need for improved treprostinil, the revised Drug Substance Specification (Ex. 2006) submitted by UTC to the FDA demonstrates only that the FDA had reservations concerning UTC's proposed change from manufacturing treprostinil by the Moriarty process to using the process described in the '393 patent. For example, the FDA notes its concerns that "[b]enzindene

triol is not separated from the final intermediate (UT-I 5C intermediate) by several reaction steps *as is currently the case for the approved starting materials*" (Ex. 2006, 1 (emphasis added)) and that "[b]enzindene triol from several proposed suppliers *appears to result in carry over of impurities*" (*id.* at 2 (emphasis added)). The FDA also requests "a release specification for the residual diethanolamine present in treprostinil (UT-15) manufactured . . . following the new manufacturing process." *Id*. at 7.

Furthermore, the FDA's ultimate approval of UTC's request for a change in the purity assay value for treprostinil from a range of 97%–101% to a range of 98%–102% does not evidence the existence of a long-felt need for improved treprostinil. First, it must be noted that the record indicates that UTC itself, not the FDA, sought the authorized change. Ex. 2006; *see also* Ex. 2058, 45:15–22. Second, as Dr. Ruffolo explains, "increasing the stringency of a—of a specification is not a major amendment" to that specification in and of itself. Ex. 2058, 310:5–13. Rather, "[w]hat is a major amendment was the change in the process, the change in the starting material." *Id*. at 310:13–18. Third, batches of Moriarty treprostinil satisfy the 98% minimum purity requirement for treprostinil approved by the FDA—regardless of whether those batches have an overall purity level of 99.7% as reported by Moriarty (Ex. 1004, 13), 99.05% as originally reported by Dr. Williams (Ex. 2020 ¶ 98), or 99.7% as obtained when development batches are excluded from Dr. Williams' analysis (Ex. 1021; Ex. 2059, 218:3–20)—and could be sold to the public (Ex. 2058, 179:23–180:17). Fourth, UTC does not identify, and we do not discern evidence to support

the existence of any clinical or safety differences between Moriarty treprostinil, and treprostinil produced according to the '393 patent. *See, e.g.*, Ex. 2058, 257:22–258:9, 315:15–23; Ex. 2059, 47:3–13.

Lastly, we observe that to the extent UTC argues that a long-felt need existed not merely for treprostinil having an improved purity, but for "a more efficient synthesis to produce treprostinil in a more pure form and in a cost-effective manner" (PO Resp. 47), or for "a commercial scale synthesis of treprostinil that results in a treprostinil product with higher overall purity and lower levels of individual impurities" (Ex. 2022 ¶ 31), the challenged claims are not directed to an efficient, cost-effective, or commercial scale synthesis, and thus, cannot be said to satisfy such a need.

Alternatively, we determine that even if UTC had shown that the challenged claims satisfied a long-felt need for treprostinil having a purportedly improved purity, this secondary consideration does not undermine SteadyMed's proof of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Here, the record establishes such a strong case of obviousness that UTC's allegedly unexpectedly superior results would nevertheless be insufficient to establish nonobviousness. *Id*. at 769.

Accordingly, for the reasons set forth above, we find that the present record does not support a determination that the product of the challenged claims satisfied a long-felt but unmet need.

ii. Unexpected Results

UTC contends that "[t]he use of a salt form of treprostinil to further purify the treprostinil acid in a cheaper and better way than the previously used methods of purification was an unexpected result." PO Resp. 49. Relying on the Williams Declaration, UTC asserts that the salt purification step recited in the challenged claims unexpectedly reduced both diastereomeric impurities and certain non-acidic impurities. *Id*. In particular, UTC argues that Eğe predicted only the removal of basic and neutral impurities when an acid is used in salt purification, and contends that the reduction of some, but not all non-acidic impurities highlights the unpredictability of the observed results. *Id*.

As an initial matter, we note that UTC's contentions regarding unexpected results are predicated on UTC's claim that treprostinil made according to the process described in the '393 patent has fewer impurities than treprostinil produced by other methods. However, as explained in Parts II.C.2.b., II.D.2.e., and II.E.3.d., the present record does not support that contention. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("[I]t is well settled that unexpected results must be established by factual evidence."); *cf.*, *Epic Pharma*, 811 F.3d at 1355 (finding evidence of objective indicia of nonobviousness unpersuasive where such evidence relates to process steps recited in a product-by-process claim, rather than the "patented product" itself).

Furthermore, we observe that UTC does not offer evidence to support the contention that "[t]he use of a salt form of treprostinil to further purify

the treprostinil acid in a cheaper and better way than the previously used methods of purification was an unexpected result." In particular, we note that UTC does not identify evidence of record to support a determination that salt purification and free acid regeneration is a "better" way to produce treprostinil. Neither does UTC identify evidence to demonstrate the cost savings associated with salt formation purification, much less establish that cost savings as unexpected. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (explaining that unexpected results are useful to show the "improved properties provided by the claimed compositions are much greater than would have been predicted" (internal quotation omitted)).

With regard to the purportedly unexpected result that salt purification reduced some, but not all acidic impurities, including certain stereoisomers, as well as certain non-acidic impurities, we find that these results are not unexpected. For example, Kawakami, discussed in detail in Part II.E., below, expressly describes the use of salt purification to improve the purity of a methanoprostacyclin derivative (Ex. 1007, 6), which like treprostinil, is a prostacyclin compound. Notably, Kawakami teaches the reduction of stereoisomers, in addition to other impurities, through salt formation and subsequent free acid regeneration, suggesting, contrary to UTC's position, that the purported reduction in acidic stereoisomeric impurities obtained via the process steps recited in the challenged claims was not unexpected.

Finally, even crediting UTC's contention that salt purification unpredictably reduced some, but not other impurities, without more, such evidence would nevertheless be insufficient to establish unexpected results.

See Soni, 54 F.3d at 751 ("Mere improvement in properties does not always suffice to show unexpected results."). In this regard, we observe that the miniscule amounts of impurities present in both prior art and '393 patent treprostinil, combined with the significant inter-batch variation in impurity types and amounts between batches of treprostinil render the impurity differences alleged by UTC not unexpected. *See In re Eli Lilly & Co.*, 902 F.2d 943, 948 (Fed. Cir. 1990) (requiring a showing that "a significant aspect of [the] claimed invention is unexpected in light of the prior art" to establish nonobviousness).

Alternatively, we determine that even if UTC had shown that the challenged claims produce unexpectedly superior treprostinil, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Cos.*, 864 F.2d at 768. Here, the record establishes such a strong case of obviousness that UTC's allegedly unexpectedly superior results would nevertheless be insufficient to establish nonobviousness. *Id*. at 769.

Accordingly, for the reasons set forth above, we find that the present record does not support a determination that the product of the challenged claims was unexpectedly superior to the prior art.

iii. Process Advantages

With respect to claims 8 and 16, UTC states, without further explanation that "[p]rocess advantages should be considered as secondary considerations to rebut obviousness, even if the process steps or advantages

are not considered" in comparing the challenged claims to the prior art. PO Resp. 32.

Although we agree that all evidence of objective indicia must be considered in evaluating obviousness, we observe that UTC does not identify what evidence of "process advantages" should be taken into account, or how it should be evaluated. Accordingly, we determine that the present record does not support a determination that the challenged claims presented process advantages sufficient to overcome the strong showing of obviousness.

For the foregoing reasons, therefore, based on the entire record before us, we find that the evidence of objective indicia of nonobviousness does not undermine SteadyMed's proof of obviousness in this case. Alternatively, we determine that even if UTC had shown that the challenged claims satisfied a long-felt need for treprostinil of allegedly greater purity, produced unexpectedly superior treprostinil, and afforded process advantages as claimed, this evidence would not undermine SteadyMed's proof of obviousness.

3. Conclusion

UTC does not separately argue claims 3–5, 7, 8, 11–14, and 16–20. *See* PO Resp. 27–33. We have reviewed Petitioner's evidence and argument as to those claims, and conclude that Petitioner has established by a preponderance of the evidence that Moriarty and Phares would have rendered obvious to one with ordinary skill in the art the subject matter recited in those claims. Pet. 45–48, 50–52.

For the foregoing reasons, therefore, we determine SteadyMed has demonstrated, by a preponderance of the evidence, that the combination of Moriarty and Phares would have rendered obvious to one with ordinary skill in the art the subject matter recited in claims 1–5, 7–9, 11–14, and 16–20.

E. Obviousness Grounds of Unpatentability Based on Moriarty, Phares, Kawakami, and Eğe

SteadyMed asserts that claims 6, 10, 15, 21, and 22 are unpatentable under § 103(a) as obvious in view of Moriarty, Phares or Kawakami, and Eğe. Pet. 37–52. As explained in the Decision on Institution (Dec. 37), although SteadyMed nominally identifies this ground of unpatentability as being over "Moriarty (Ex. 1004) with Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and in further combination with Ege (Ex. 1008)" (Pet. 53 (emphasis omitted)), SteadyMed explicitly relies on Kawakami in arguing unpatentability in view of Moriarty, Phares, and Eğe. Accordingly, as set forth in the Decision on Institution, we understand SteadyMed's stated ground of unpatentability as relying on the combination of Moriarty, Phares, Kawakami, and Eğe. Dec. 37.

Claims 6, 21, and 22 depend, directly or indirectly, from claim 1, and claims 10 and 15 depend directly from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty, Eğe, Phares, and Kawakami discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) and the Rogers Declaration (Ex. 1022) to support its positions.

1. Kawakami

Kawakami describes "a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, a manufacturing method thereof, and a purifying method thereof." Ex. 1007, 3. Kawakami discloses obtaining a dicyclohexylamine salt by "mixing a methanoprostacyclin derivative [I] . . . with dicyclohexylamine in an appropriate solvent." Ex. 1007, 5–6. Kawakami explains that "[t]he dicyclohexylamine salt of the methanoprostacyclin derivative [I] thus obtained generally has fairly high purity, and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." *Id*. at 6.

Kawakami further teaches that "[t]he dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention." *Id*.

2. Eğe

Eğe is an organic chemistry textbook. Ex. 1008, 1. Eğe discloses:

> Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.

Id. at 8 (reference omitted).

3. Discussion

Claims 6, 10, 15, 21, and 22 each recite the product of either claim 1 or claim 9, subject to additional process steps. Notably, each of claims 6, 10, 15, 21, and 22 requires the performance of step (d) recited in claims 1 and 9, but identified as optional in the independent claims.

SteadyMed contends that the combination of Moriarty, Phares, Kawakami, and Eğe discloses the treprostinil products recited in claims 6, 10, 15, 21, and 22 of the '393 patent. Pet. 53–57. SteadyMed also asserts that the combination of Moriarty, Phares, Kawakami, and Eğe discloses steps (a)–(d) required by the challenged claims. *Id*.

We have reviewed the Petition and the supporting evidence to which we are directed as to how the combination of Moriarty, Phares, Kawakami, and Eğe discloses each limitation of the challenged claims. We are persuaded by SteadyMed's showing that the combination of Moriarty, Phares, Kawakami, and Eğe discloses both the treprostinil products claimed, as well as the production of treprostinil diethanolamine salt through the performance of steps (a)–(d) recited in the challenged claims of the '393 patent.

Relying on its expert, Dr. Winkler, SteadyMed asserts that a relevant skilled artisan would add further purification steps as taught by Kawakami and Eğe to the combination of Moriarty and Phares described in Part II.D.2., above, to further improve the treprostinil product. Pet. 53–54. In this regard, SteadyMed contends that Kawakami discloses prostacyclin compounds, of which treprostinil is one example, can be purified by using

weak bases and forming salts, which can then be converted back into free acid form. Pet. 43. In particular, SteadyMed argues that Kawakami "discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative 'can be easily reverted to the free methanoprostacyclin derivative by *conventional methods*,'" and that the "fairly high purity" of the salt obtained "can be further improved by recrystallization as needed with the use of an appropriate solvent." Pet. 53.

In addition, Dr. Winkler testifies that, as evidenced by Eğe, a relevant skilled artisan "would understand that one such conventional method for converting the dicyclohexylamine salt of a methanoprostacyclin derivative to the free methanoprostacyclin derivative, or converting the treprostinil diethanolamine salt to treprostinil (*i.e.*, the free acid) is by treating the salt with a strong acid such as HCl or H_2SO_4." Ex. 1009 ¶ 84; *see also* Pet. 53–54. Dr. Winkler elaborates on this rationale for combining the cited references, testifying that a relevant skilled artisan

> would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. And Ege (Ex. 1008, p. 8) teaches that one such method for obtaining the free form of treprostinil or any carboxylic acid would be by treatment of the carboxylate salt with a strong acid.

Ex. 1009 ¶ 88; *see also* Ex. 1008, 8; Pet. 54.

Notwithstanding UTC's arguments to the contrary, which we address below, we are persuaded by SteadyMed's showing that an ordinarily skilled artisan, at the time of invention of the '393 patent, would have had reason to combine, and a reasonable expectation of success in combining, Moriarty,

Phares, Kawakami, and Eğe. "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. We are persuaded that an ordinarily skilled artisan would have modified the above-described combination of Moriarty and Phares to further include carboxylate salt formation and neutral carboxylic acid regeneration steps, as taught by Kawakami, because Kawakami discloses that this purification and free acid regeneration procedure results in excellent crystallinity and improved purity for prostacyclin compounds. Ex. 1007, 6. We are additionally persuaded that a relevant skilled artisan would have sought to use a strong acid to regenerate treprostinil free acid, because Kawakami discloses the use of "conventional methods" to regenerate prostacyclin free acids (*id.*), and Eğe teaches that treatment of a carboxylate salt, such as treprostinil, with a strong acid will yield a free form of the carboxylic acid. Ex. 1008, 8.

UTC does not dispute either that the combination of Moriarty, Phares, Kawakami, and Eğe discloses treprostinil and treprostinil diethanolamine salt, or that the cited combination discloses steps (a)–(d) of independent claims 1 and 9, as required by the challenged claims. Akin to its arguments above concerning anticipation by Phares and obviousness in view of Moriarty and Phares, UTC asserts that the treprostinil products of the challenged claims are structurally and functionally different than those described in the prior art. PO Resp. 33–34. UTC also contends that any

"close" structural similarity between Moriarty treprostinil and the claimed invention is insufficient to support a conclusion of obviousness. *Id*. at 45. In addition, UTC argues that an ordinarily skilled artisan would not have had reason to, or a reasonable expectation of success in combining Kawakami and Eğe with Moriarty and Phares. *Id*. at 34–44. UTC further asserts that the cited combination fails to disclose certain process steps and purity requirements recited in the challenged claims. *Id*. at 45–47. Lastly, UTC contends that evidence of objective indicia of nonobviousness, including long-felt but unmet need and unexpected results, establish the nonobviousness of the challenged claims. *Id*. at 47–49. We address UTC's arguments below.

a. Level of Ordinary Skill in the Art

For the reasons set forth above, we apply in our analysis of the obviousness of the challenged claims in view of Moriarty, Phares, Kawakami, and Eğe the same level of ordinarily skill in the art at the time of invention of the '393 patent as described in Part II.D.2.a.

b. Rationale to Combine

UTC asserts that because the level of skill in the chemical arts in general, and in relation to the claimed invention in particular, is high, an ordinarily skilled artisan would not have looked to an undergraduate textbook such as Eğe to identify improved purification techniques for a complex drug such as treprostinil. PO Resp. 35–36. UTC argues also that neither Phares nor Eğe provides reason for a relevant skilled artisan to

include a carboxylate salt formation and neutral acid regeneration step in treprostinil synthesis. *Id*. at 37. In this regard, UTC states that there is no suggestion in Phares to convert treprostinil diethanolamine salt back to the free acid (*id*.), and asserts that Eğe teaches away from the use of salt formation and free acid regeneration to remove acidic compounds, such as certain acidic stereoisomers found in treprostinil (*id*. at 38). On this basis, UTC concludes that a relevant skilled artisan "would have understood Moriarty, Phares, and Eğe to suggest simply making the treprostinil free acid product of Moriarty, and not undergoing the additional time and expense of a 'carboxylate salt formation and regeneration of the neutral carboxylic acid' step." *Id*.

UTC additionally argues that Kawakami's teachings would not have provided reason to add a carboxylate salt formation and neutral acid regeneration step to the method for treprostinil synthesis disclosed by Moriarty and Phares because the prostacyclins described in Kawakami are "structurally very different" from treprostinil, and thus, the purification of treprostinil is quite different from the prostacyclin purification described by Kawakami. *Id*. at 39–41. UTC further asserts that Kawakami teaches away from the salts recited in claims 14 and 18 of the '393 patent. UTC thus concludes that an ordinarily skilled artisan would not have looked to Kawakami or Eğe to improve treprostinil purification, because neither reference discloses how to remove stereoisomeric impurities. *Id*. at 41.

We do not find UTC's arguments persuasive. As explained above, we find that a relevant skilled artisan would have had reason to add a

carboxylate salt formation and neutral acid regeneration step to the method of Moriarty and Phares described above based on Kawakami's teachings that prostacyclin compounds can be purified by using weak bases and forming salts that can subsequently be converted back into free acids of improved purity and crystallinity by conventional methods, and Eğe's teachings that strong acids are useful in such a conversion. Accordingly, it is of no moment whether Phares itself suggests the conversion of treprostinil diethanolamine salt back into free acid form. It is likewise irrelevant that Eğe is an introductory text. Kawakami encourages the use of "conventional methods" to regenerate the free acid. Ex. 1007, 6. As a basic chemistry text, there can be no dispute that Eğe teaches precisely that—namely, a conventional method for regenerating a free acid using a strong acid. Furthermore, the fact that Eğe is an introductory text does not demean its value as prior art.

Neither do we find persuasive UTC's assertion that Eğe teaches away from the claimed invention because it discloses that salt formation and free acid regeneration is only useful to remove neutral and basic impurities, not acidic impurities, such as certain acidic stereoisomers present in treprostinil. As an initial matter, we observe that the '393 patent, as well as the prior art of record, is silent as to the specific impurities present in treprostinil, as well as whether those impurities are acidic. Accordingly, we agree with SteadyMed (Pet. Reply 19) that undisclosed information about the impurities present in treprostinil cannot defeat the rationale for using crystallization discussed above. This is particularly true where, as here, the record

indicates that Kawakami teaches the use of crystallization to separate stereoisomers. Ex. 2051, 203:4–204:20.

Moreover, even crediting UTC's position, we observe that Eğe's teachings concerning the removal of neutral and basic impurities nevertheless support the proposed combination because the procedure disclosed would be effective for removing neutral and basic impurities, regardless of the impact on acidic impurities (Pet. 53–55; Ex. 1009 ¶¶ 86, 88). *See In re Kahn*, 441 F.3d at 988 ("[T]he skilled artisan need not be motivated to combine [the prior art] for the same reason contemplated by [the inventor]."). Indeed, as explained above, the evidence of record indicates that treprostinil diethanolamine salt formation followed by regeneration of treprostinil using a strong acid is an effective purification step. Pet. 53–55; *see also* Ex. 1007, 6; Ex. 1008, 8; Ex. 1009 ¶¶ 82–90. Accordingly, contrary to UTC's intimations, this is not a case where "there would have been no reason to incur additional time and expense to form a salt of the valuable, relatively pure Moriarty treprostinil free acid only to then convert it back to the free acid, even though the addition would have been technologically possible." PO Resp. 44. Rather, an ordinarily skilled artisan would have expected that salt formation and free acid regeneration would yield a highly pure, crystalline product.

With regard to the level of similarity between treprostinil and the methanoprostacyclin derivative described by Kawakami, we disagree with UTC's contention that these compounds are dissimilar, and that an ordinarily skilled artisan thus would not have turned to Kawakami for guidance

regarding the purification of treprostinil. In this regard, we note that both Kawakami's methanoprostacyclin derivative and treprostinil are prostacyclins. We also observe that their chemical structures are similar. Ex. 1028. In addition, we do not agree with UTC's assessment that Kawakami's methanoprostacyclin derivative and treprostinil are not improved in the same way by salt formation and free acid regeneration. To the contrary, both compounds exhibit higher overall purity, as well as a reduction in stereoisomer impurities subsequent to treatment.

Turning to UTC's contentions regarding differences between the salt used in Kawakami and the salts recited in claims 14 and 18, we observe that those claims are not challenged under this ground of unpatentability. We further note that Kawakami's teachings do not affect our determination, set forth above, that claims 14 and 18 are anticipated by Phares and obvious in view of Moriarty and Phares.

Accordingly, on the record before us, we find that SteadyMed has sufficiently demonstrated that one of ordinary skill in the art would have included the carboxylate salt formation and regeneration of the neutral carboxylic acid of Eğe with the syntheses of Moriarty and Phares based on Kawakami's disclosure that the conversion of salts of prostacyclin derivatives to their free forms by conventional methods increases purity and crystallinity of the final product. *See KSR*, 550 U.S. at 417.

c. Reasonable Expectation of Success

UTC recasts several of the same arguments addressed above with respect to the rationale to combine the cited references as supporting a

determination that an ordinarily skilled artisan would not have had a reasonable expectation of success in the proposed combination of Moriarty, Phares, Kawakami, and Eğe. PO Resp. 37, 42–44. In particular, UTC asserts that a relevant skilled artisan would not have had a reasonable expectation of success in further purifying the treprostinil product of Moriarty using carboxylate salt formation and neutral carboxylic acid regeneration. *Id*. at 37. UTC also argues that treprostinil purification is "quite different" from the purification of the methanoprostacyclin derivative described by Kawakami, and, thus, an ordinarily skilled artisan would have had no reasonable expectation of success in applying the methods of Kawakami to purify treprostinil. *Id*. at 42.

We do not agree. As explained in Part II.D.2.c., above, whether or not an ordinarily skilled artisan would have had an expectation that salt formation and free acid regeneration would improve the purity of Moriarty treprostinil is not the relevant inquiry. *See Intelligent Bio-Sys.*, 821 F.3d at 1367 ("The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention."). It is undisputed that the proposed combination yields treprostinil. Furthermore, as detailed in Parts II.C.2.b. and II.D.2.e., above, both Moriarty treprostinil and Phares treprostinil diethanolamine salt are highly pure, and Kawakami shows that salt formation and free acid regeneration is an effective technique for purifying a prostacyclin compound (Ex. 1007, 6).

In addition, for the same reasons set forth with respect to the rationale to combine Moriarty, Phares, Kawakami, and Eğe, we find that Kawakami's methanoprostacyclin derivative and treprostinil are sufficiently similar that an ordinarily skilled artisan would have had a reasonable expectation of success in using the salt formation and free acid regeneration prostacyclin purification procedure taught by Kawakami to purify treprostinil. In this regard, we recognize, but do not find persuasive, UTC's contention that differences in the particular stereoisomers and other impurities removed from treprostinil and Kawakami's methanoprostacyclin derivative using salt formation and free acid regeneration would have foreclosed any reasonable expectation of success. *See In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985) ("Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness.").

Accordingly, we find that an ordinarily skilled artisan would have a reasonable expectation of success in combining Moriarty, Phares, Kawakami, and Eğe to produce treprostinil.

d. Recited Process Steps

UTC reasserts its contention, addressed in Parts II.C.2.b. and II.D.2.e., above, that the treprostinil products of the challenged claims exhibit structural and functional differences compared to prior art treprostinil. PO Resp. 33–34. In particular, UTC argues that the performance of step (d) as required by claims 6, 10, 15, 21, and 22 imparts a higher overall purity, as well as an improved purity profile relative to the treprostinil produced by Moriarty. *Id*. at 33. UTC also asserts that "Phares' diethanolamine salt of

treprostinil is structurally and functionally distinct from the free acid substance formed by step (d) of claims 6, 15 and 21." *Id*. UTC relies on the same evidence and reasoning addressed previously in making these arguments. In addition, UTC contends that even if a "close relationship" exists between Moriarty treprostinil and the treprostinil of the challenged claims, "conducting a salt-formation purification step on the known treprostinil free acid of Moriarty would not have been obvious, so the mere existence of a 'close relationship' in the products cannot be used to deny patentability." *Id*. at 45.

As explained in Parts II.C.2.b. and II.D.2.e., above, we find that the evidence of record does not support the existence of any structural or functional differences between prior art treprostinil and that produced according to the '393 patent. Furthermore, we observe that UTC's argument concerning the effect of a "close relationship" between Moriarty treprostinil and that of the challenged claims is a non-sequitur. As explained previously, we find that no structural or functional differences exist between Moriarty treprostinil and '393 patent treprostinil, and, therefore, conclude that the process steps recited in the '393 patent are not entitled to patentable weight. Moreover, even were the recited process steps entitled to patentable weight, as explained-in-part above, and addressed further below, we nevertheless determine that the recited process steps would have been obvious to a relevant skilled artisan.

e. Claims 6, 15, and 21

Claims 6, 15, and 21 each recite the product of either claim 1 or claim 9, subject to additional process steps. Claim 6 recites "[t]he product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4." Claim 15 similarly recites "[t]he product of claim 9, wherein the acid in step (d) is HCl." Claim 21 simply recites "[t]he product of claim 1, wherein step (d) is performed."

UTC does not offer evidence or argument to suggest that the additional process steps recited in claims 6, 15, and 21 impart structural or functional differences to the claimed product beyond that discussed above in Parts II.C.2.b, II.D.2.e, and II.E.3.d. Rather, UTC reiterates the argument, addressed above, that a relevant skilled artisan "would not have looked to Eğe to further purify a complex carboxylic acid such as treprostinil from its stereoisomers and other impurities and would have no reasonable expectation of success by using HCl based on this disclosure." PO Resp. 46 (quoting Ex. 2020 ¶ 115).

It is undisputed that Eğe discloses the conversion of the carboxylate salt sodium benzoate back to the carboxylic acid benzoic acid by treatment with the acid HCl. Ex. 1008, 8; *see* PO Resp. 46 ("Eğe cites HCl as an example in the conversion of benzoic acid"). Moreover, as detailed in Parts II.E.3.b.–c. above, we find that an ordinarily skilled artisan at the time of invention of the '393 patent would have had reason to, and a reasonable expectation of success in, combining Moriarty, Phares, Kawakami, and Eğe. Accordingly, we do not find UTC's position persuasive.

f. Claim 10

Claim 10 recites "[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%." Ex. 1001, 20:47–48.

UTC advances the same argument addressed above, in Part II.D.2.f., concerning claim 2, concerning the comparability of the 99.7% purity reported by Moriarty and that recited in claim 10. PO Resp. 46. In addition, UTC reasserts its contentions, addressed above, in Parts II.E.3.b.–c., that Moriarty does not perform steps (c) or (d) of the challenged claims, and that a relevant skilled artisan would not have had reason to, or a reasonable expectation of success in, looking to Phares, Kawakami, or Eğe to improve the purity of treprostinil. *Id.*

For the same reasons set forth with regard to claim 2, we find that the 99.7% purity reported by Moriarty is reliable, and thus, performing the additional purification steps disclosed by Phares, Kawakami, and Eğe on Moriarty would yield a product having at least as high a purity as the starting Moriarty treprostinil. Furthermore, as explained above, we find that an ordinarily skilled artisan would have had reason to, and a reasonable expectation of success in, combining Moriarty, Phares, Kawakami, and Eğe, in order to produce a treprostinil product of greater purity.

g. Claim 22

Claim 22 recites "[t]he product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d)."

UTC asserts that the cited combination fails to disclose the additional salt formation step recited in claim 22, but does not offer evidence or argument to suggest that this process step imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.C.2.b., II.D.2.e., and II.E.3.d.

It is undisputed that the cited combination discloses treprostinil diethanolamine salt. Moreover, as explained previously, we find that the evidence of record does not support the existence of any structural or functional differences between prior art treprostinil diethanolamine salt and that produced according to the '393 patent.

h. Objective Indicia of Nonobviousness

UTC reasserts its position, addressed in Part II.D.2.h., above, that objective indicia of nonobviousness, including evidence of a long-felt but unmet need for treprostinil having greater overall purity and an improved impurity profile compared to treprostinil produced by known methods, as well as evidence that treprostinil produced according to the process steps of the challenged claims unexpectedly yields a product having increased purity as compared to prior art processes establish the nonobviousness of the challenged claims. PO Resp. 47–49.

As explained in detail above, however, upon full consideration of the evidence of record respecting the objective indicia of nonobviousness in this case, we are persuaded that nonobvious is not established by that evidence.

4. Conclusion

For the foregoing reasons, therefore, we determine SteadyMed has demonstrated, by a preponderance of the evidence, that the combination of Moriarty, Phares, Kawakami, and Eğe would have rendered obvious to one with ordinary skill in the art the subject matter recited in claims 6, 10, 15, 21, and 22.

F. SteadyMed's Motion to Exclude Evidence

SteadyMed moves to exclude the Ruffolo Declaration (Ex. 2022), concerning the existence of a long-felt but unmet need for the claimed invention because, according to SteadyMed, Dr. Ruffolo applied an incorrect legal standard in rendering his opinions. Paper 63, 1. SteadyMed contends that Dr. Ruffolo's opinions are "unreliable, confusing, and not helpful to the trier of fact." *Id*.

Even without excluding the Ruffolo Declaration, however, we have determined that SteadyMed has demonstrated, by a preponderance of the evidence, that claims 1–22 of the '393 patent are unpatentable.

Accordingly, SteadyMed's Motion to Exclude is *dismissed* as moot.

G. UTC's Motion to Exclude Evidence

UTC seeks to exclude the following: (1) certain portions of the Winkler Declaration (Ex. 1009); (2) a website printout entitled "Getting Started in HPLC,' Section 4D: Precision and Accuracy" (Ex. 1017); (3) certain portions of the Rogers Declaration (Ex. 1022); and (4) certain portions of the Deposition Transcript of Dr. Robert M. Williams, Ph.D.

(Ex. 2059). Paper 65, 2. UTC additionally seeks to exclude the portions of the Petition and Petitioner's Reply to Patent Owner's Response that rely on these exhibits. *Id*. at 3.

1. Winkler Declaration (Ex. 1009)

UTC contends that paragraphs 3, 31, 46, 48, 54, 57, 63, 71, and 72 of the Winkler Declaration (Ex. 1009) should be excluded because the testimony in these paragraphs represent "purely legal conclusions or otherwise unsupported conclusory statements." PO Mot. Exclude 6.

SteadyMed responds that the testimony objected to merely summarizes Dr. Winkler's ultimate conclusions on issues of anticipation and obviousness, and is therefore admissible. Pet. Opp. Exclude 2.

We are not persuaded by UTC's arguments. It is blackletter law that "[a]n opinion is not objectionable just because it embraces an ultimate issue." Fed. R. Evid. 704(a). Furthermore, it is within our discretion to assign the appropriate weight to be accorded to evidence. In its motion, UTC has not explained adequately why we should exclude conclusory expert testimony, instead of giving it little or no weight. *See, e.g.*, *Donnelly Garment Co. v. NLRB*, 123 F.2d 215, 224 (8th Cir. 1941) ("One who is capable of ruling accurately upon the admissibility of evidence is equally capable of sifting it accurately after it has been received . . . .").

For the foregoing reasons, we decline to exclude any portion of the Winkler Declaration (Ex. 1009).

2. Website Printout: "Getting Started in HPLC,' Section 4D: Precision and Accuracy" (Ex. 1017)

UTC contends that Exhibit 1017, a website printout entitled "Getting Started in HPLC,' Section 4D: Precision and Accuracy," should be excluded as inadmissible hearsay. PO Mot. Exclude 7. UTC additionally asserts that Exhibit 1017 has not been authenticated, and should be excluded on that basis as well. UTC contends that Ex. 1017 itself, as well as paragraph 70 of the Winkler Declaration, and the portions of the Petition and Petitioner's Reply to Patent Owner's Response that rely on Exhibit 1017 or paragraph 70 of the Winkler Declaration should be excluded.

SteadyMed responds that Dr. Winkler's reliance on Exhibit 1017 to support his assessment of error in HPLC instrumentation was proper, irrespective of the Exhibit's status as hearsay. Pet. Opp. Exclude 5. SteadyMed argues also that Exhibit 1017 is not hearsay and is properly authenticated. *Id*. at 6.

As an initial matter, we determine that Dr. Winkler is entitled to rely on Exhibit 1017 as support for his opinions. Fed. R. Evid. 703. While we recognize UTC's contention that an expert in pharmaceutical purity would not rely on a general HPLC printout to determine instrumentation error rates (PO Reply Exclude 2), we do not find UTC's position persuasive. In this regard, we observe that Dr. Winkler relies on Exhibit 1017 solely as providing a baseline understanding of the relative standard deviation for HPLC instrumentation. Ex. 1009 ¶ 70. We also observe that it is within our discretion to assign the appropriate weight to be accorded to evidence, and UTC has not explained adequately why we should exclude Dr. Winkler's

testimony, instead of giving it little or no weight. *See, e.g.*, *Donnelly Garment Co.*, 123 F.2d at 224.

As to the portions of the Petition and Petitioner's Reply to Patent Owner's Response that UTC seeks to exclude as improperly relying on paragraph 70 of the Winkler Declaration or Exhibit 1017, we note that SteadyMed's pleadings rely exclusively on Dr. Winkler's opinions as set forth in paragraph 70 of his declaration, and not on Exhibit 1017 itself. Accordingly, because we determine that Dr. Winkler's opinions are admissible, we decline to exclude the portions of the Petition and Petitioner's Reply to Patent Owner's Response identified by UTC.

With respect to Exhibit 1017 itself, we do not rely on that Exhibit in our decision, and, therefore, determine that as it pertains to Exhibit 1017, UTC's motion to exclude is moot.

For the foregoing reasons, we decline to exclude paragraph 70 of the Winkler Declaration (Ex. 1009), as well as the portions of the Petition and Petitioner's Reply to Patent Owner's Response identified by UTC. We further determine that the Motion to Exclude is moot as to Exhibit 1017.

3. Rogers Declaration (Ex. 1022)

UTC seeks to exclude paragraphs 44–48 and 84–87 of the Rogers Declaration (Ex. 1022). PO Mot. Exclude 8–9. UTC asserts that paragraphs 44–48 constitute new opinions concerning the melting point of treprostinil diethanolamine salt Form A, and paragraphs 84–87 improperly rely on facts not in the record. *Id*.

SteadyMed responds that the paragraphs in question directly respond to UTC's challenges concerning the melting point of Phares treprostinil, and that Dr. Rogers' opinions regarding the equipment used to generate Phares' data was proper. Pet. Opp. Exclude 8–9.

We are not persuaded by UTC's arguments. Dr. Rogers' testimony pertains directly to UTC's challenges on melting point. *See* Ex. 1022 ¶¶ 44–48, 84–87. Moreover, Dr. Rogers' reliance on personal knowledge concerning the instrumentation and software used by Phares is appropriate, because such knowledge is of the sort that a polymorph expert would rely on in providing opinions on compound purity. *See* Fed. R. Evid. 702, 703.

In addition, it is within our discretion to assign the appropriate weight to be accorded to evidence. In its motion, UTC has not explained adequately why we should exclude Dr. Rogers' testimony, instead of giving it little or no weight. *See, e.g.*, *Donnelly Garment Co.*, 123 F.2d at 224.

For the foregoing reasons, we decline to exclude any portion of the Rogers Declaration (Ex. 1022).

4. Williams Deposition Transcript (Ex. 2059)

UTC contends that "Petitioner's Reply to Patent Owner's Response includes a number of statements and references that misrepresent certain testimony from the deposition transcript of Dr. Williams (Ex. 2059)." PO Mot. Exclude 9. On this basis, UTC seeks to exclude several excerpts from Dr. Williams' deposition and corresponding portions of Petitioner's Reply to Patent Owner's Response. *Id*. at 9–10.

SteadyMed responds that "a motion to exclude is not a proper vehicle for a party to argue that the other party's arguments are incorrect." Pet. Opp. Exclude 9 (quoting *Hopkins Manufacturing Co., v. Cequent Performance Products, Inc.*, IPR2015-00609, Paper 32, at *23 (PTAB July 28, 2016)). SteadyMed additionally asserts that UTC's arguments go to weight, not admissibility of the evidence. Lastly, SteadyMed points out that, with one exception, UTC failed to object to the disputed portions of Dr. Williams' testimony during his deposition. *Id*. at 10.

We are not persuaded by UTC's arguments. Rather, we agree with SteadyMed that a motion to exclude is not an appropriate means for expressing disagreement with an opposing party's arguments. We also agree with SteadyMed that any concerns regarding the mischaracterization or misrepresentation of Dr. Williams' testimony go to the weight attributable to, and not the admissibility of, that testimony and SteadyMed's arguments. We further observe that to the extent UTC did not object to the disputed questions during Dr. Williams' deposition, any objections to those questions have been waived.

In addition, it is within our discretion to assign the appropriate weight to be accorded to evidence.

For the foregoing reasons, we decline to exclude any portion of Petitioner's Reply to Patent Owner's Response (Paper 51), or the Deposition Transcript of Dr. Robert M. Williams, Ph.D. (Ex. 2059).

III. CONCLUSION

For the foregoing reasons, we determine that SteadyMed has shown by a preponderance of the evidence that claims 1–22 are unpatentable.

IV. ORDER

It is

ORDERED that claims 1–22 of the ’393 patent are unpatentable;

FURTHER ORDERED that SteadyMed’s Motion to Exclude Evidence is dismissed.

FURTHER ORDERED that UTC’s Motion to Exclude Evidence is denied.

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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