IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	Civil Action No. 20-755-RGA

MEMORANDUM OPINION

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ANDREWS, U.S. DISTRICT JUDGE:

Before me is the issue of claim construction of multiple terms in U.S. Patent No. 9,593,066 ("the '066 patent") and U.S. Patent No. 9,604,901 ("the '901 patent"). The parties submitted a Joint Claim Construction Brief (D.I. 75), and I heard oral argument on June 4, 2021 (D.I. 161). The parties argued for constructions of five claim terms, and I construed three terms at the hearing. (D.I. 119). I requested supplemental briefing on the remaining two terms, which the parties have provided. (D.I. 125). I now construe the remaining two terms, which appear in the '901 patent.

I. BACKGROUND

The '901 patent relates to "an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil." ('901 patent, abstract). Plaintiff filed this action for infringement of the '066 patent and the '901 patent based on Defendant's submission of New Drug Application No. 213005. (D.I. 1). Defendant petitioned for IPR of both patents. (D.I. 76-1, Exs. P1 & P2). The PTAB denied institution of IPR for the '066 patent and granted institution of IPR for the '901 patent. (D.I. 76-1, Ex. P3). On October 8, 2021, the PTAB issued a final written decision, finding claims 1–5, 8, and 9 of the '901 patent to be unpatentable. *Liquidia Techs., Inc. v. United Therapeutics Corp.*, No. IPR2020-00770, 2021 WL 4860733, at *1 (P.T.A.B. Oct. 8, 2021). The PTAB also found that Defendant had not established that claims 6 and 7, which depend from claim 1, were unpatentable. *Id.*

The disputed terms appear in independent claim 1 and are also fully set forth in method claim 8. The following claims are thus the most relevant for purposes of this Markman:

Claim 1 of the '901 patent

> 1. A *pharmaceutical batch* consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to

form a solution comprising treprostinil, (c) *contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil*, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and wherein the *pharmaceutical batch* contains at least 2.9 g of treprostinil or its salt.

Claim 8 of the '901 patent

8. A method of preparing a *pharmaceutical batch* as claimed in claim 1, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) *contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil*, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

II. LEGAL STANDARD

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324) (alteration in original). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977–80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312–13 (citations and internal quotation marks omitted). "[T]he ordinary meaning of a

claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a determination of law. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 331 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317–19 (internal quotation marks omitted). Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

III. CONSTRUCTION OF DISPUTED TERMS

1. "pharmaceutical batch" (claims 1–4, 6, and 8)

a. *Plaintiff's proposed construction*: "a specific quantity of treprostinil (or its salt) that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture, wherein the uniform character and quality is such that it still contains impurities resulting from the method by which it is produced"

b. *Defendant's proposed construction*: "pharmaceutical batch made according to the process recited in steps (a) – (d) and optionally (e), wherein no purification steps appear between alkylation and salt formation"

c. *Court's construction*: plain and ordinary meaning

Plaintiff's proposed construction imports a definition from an FDA regulation, which defines "batch" as "a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture." 21 C.F.R. § 210.3(b)(2).

Plaintiff's expert Dr. Robert Ruffolo asserts that a person of ordinary skill in the art would have understood the term "pharmaceutical batch" to incorporate this regulatory definition since the '901 patent is "a pharmaceutical patent that is related to the commercial manufacturing of a pharmaceutical API of an FDA-approved marketed drug." (D.I. 76-1, Ex. P4, ¶ 75).[1] But I am not convinced that a POSA would interpret the term "pharmaceutical batch" to incorporate an FDA regulatory definition, especially because there are no references to the FDA or to FDA regulations in the '901 patent. Thus, I deny Plaintiff's attempt to import this FDA regulatory guidance into the plain and ordinary meaning of this term.

Defendant's proposed construction simply adds a limitation to the plain and ordinary meaning of "pharmaceutical batch"—i.e., that no purification steps appear between alkylation and salt formation. In support of this construction, Defendant points to statements made by Plaintiff during the IPR of the '901 patent. For example, in its Patent Owner Preliminary

[1] Plaintiff also argues that "pharmaceutical batch" is distinct from "batch." Plaintiff claims that a POSA would understand that the claimed process includes a "pharmaceutical batch," while the prior art process includes a "batch." (D.I. 75 at 45–46). Plaintiff reasons that the claimed process involves commercial manufacturing, while the prior art process describes a smaller-scale drug development process. (*Id.* at 46; D.I. 76-1, Ex. P4, ¶ 86). I am unclear as to how this distinction is reflected in Plaintiff's proposed construction. To the extent that Plaintiff is arguing that "pharmaceutical" denotes a commercial character, I cannot agree. The '901 patent specification expressly defines "pharmaceutically acceptable" as "being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use." ('901 patent, 5:27-31; *see also* D.I. 78-1, Ex. D9 at 113:12–115:20). This definition includes no reference to a "commercial" character. It does not seem consistent with Plaintiff's argument that a POSA would understand "pharmaceutical batch" to import an FDA definition.

Response, Plaintiff argued that the prior art did not permit large-scale synthesis. Plaintiff told the PTAB, "This perspective is critical in the context of the claimed pharmaceutical composition, in which, e.g., no purification steps appear between alkylation and salt formation." (D.I. 77-1, Ex. D5 at 56; *see also* Ex. D7 at 58 ("Rather, the POSA must have been motivated to combine the prior art in the way claimed in the '901 patent (e.g., not purified before salt formation), and had a reasonable expectation of success in doing so.")). Defendant argues that these statements amount to a disclaimer of an intermediate purification step. (D.I. 75 at 47).

The Federal Circuit has held, "[S]tatements made by a patent owner during an IPR proceeding, whether before or after an institution decision, can be considered for claim construction and relied upon to support a finding of prosecution disclaimer." *Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1362 (Fed. Cir. 2017). "Of course, to invoke the doctrine of prosecution disclaimer, any such statements must 'be both clear and unmistakable.'" *Id.* at 1361. Plaintiff withdrew the purported disavowals before the PTAB took any steps in reliance on them. (*See* D.I. 125-1, Ex. J1; Ex. J2 at 36:7–8, 69:14). Thus, I find no clear and unmistakable disclaimer of claim scope.

Defendant's construction is also inconsistent with the '901 patent specification, which discloses examples where there are purification steps between alkylation and salt formation. (*See* D.I. 76-1, Ex. P4, ¶¶ 54, 92). Example 2, "Hydrolysis of Benzindene Nitrile," describes removing impurities with ethyl acetate; washing with water, a solution of $NaHCO_3$, and a solution of NaCl; and filtering with Celite® 545. ('901 patent, 11:58–12:14). Thus, I decline to adopt Defendant's proposed construction.

I instead apply the plain and ordinary meaning, which is, as always, the default in claim construction. *Phillips*, 415 F.3d at 1316.

2. "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil" (claims 1 and 8)

a. *Plaintiff's proposed construction*: plain and ordinary meaning

b. *Defendant's proposed construction*: "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, wherein the salt is formed without isolation of treprostinil after alkylation and hydrolysis"

c. *Court's construction*: "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, wherein the salt is formed without isolation of treprostinil after alkylation and hydrolysis"

In its final written decision, the PTAB construed this term and agreed with Defendant that, based on the intrinsic evidence, "treprostinil is not isolated from the solution formed in step (b) before forming a salt in step (c)." *Liquidia*, No. IPR2020-00770, 2021 WL 4860733, at *12. "The PTAB's construction is not binding on this Court, but, where the construction is similar to that of a district court's review, it is appropriate for me to take the PTAB's claim construction into consideration." *Genuine Enabling Tech., LLC v. Sony Corp.*, 2020 WL 1140910, at *7 (D. Del. Mar. 9, 2020) (internal quotation marks and citation omitted). Here, it is appropriate for me to consider the PTAB's construction of this term because the PTAB applied "the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b)"—i.e., the *Phillips* standard. *Liquidia*, No. IPR2020-00770, 2021 WL 4860733, at *7 (quoting 37 C.F.R. § 42.100(b)).

I find the PTAB's reasoning to be persuasive. First, the claim language supports a construction excluding an intermediate isolation step. Step (c) of claim 1 requires "contacting *the solution comprising treprostinil from step (b)* with a base to form a salt of treprostinil." ('901 patent, 17:27–29 (emphasis added)). This claim language dictates that the solution of treprostinil from step (b)—not treprostinil isolated as a solid from step (b)—is what is used to form a salt in step (c).

Second, the '901 patent specification supports this construction. Example 2 provides, "The filtrate (pale-yellow) was reduced to volume of 35-40 L by evaporation in vacuo at 50-55° C *for direct use in next step*." (*Id.*, 12:15–17 (emphasis added)). Example 3 describes the next step, conversion of treprostinil to treprostinil diethanolamine salt. It provides, "A 50-L, cylindrical reactor . . . was charged with *a solution of treprostinil* in ethyl acetate (*35-40 L from the previous step*) . . . ." (*Id.*, 13:13–17 (emphasis added)). These examples are consistent with the claim language and show that the solution of treprostinil formed in step (b) is used immediately in step (c), with no isolation of treprostinil between the steps.[2]

Plaintiff argues that Defendant's construction improperly reads out a preferred embodiment of the claimed invention. (*See* D.I. 75 at 64; D.I. 161 at 68:10–71:14). Example 2 provides that the treprostinil is formed in an aqueous layer and then "extracted with ethyl acetate . . . to remove impurities soluble in ethyl acetate." ('901 patent, 11:58–60). The treprostinil is transferred from the aqueous layer to the organic layer (ethyl acetate). (*Id.*, 11:62–12:3). The organic solution is then used in the salt formation step. (*Id.*, 12:15–17; D.I. 161 at 67:8–15, 69:20–70:19). Plaintiff contends that, in this example, treprostinil is isolated before the salt formation step, so Defendant's construction is improper. (*See* D.I. 161 at 73:3–74:23).

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[2] Defendant also argues that Plaintiff disclaimed an intermediate isolation step through statements made during the IPR of the '901 patent. (*See, e.g.*, D.I. 77-1, Ex. D7 at 11 ("[C]laim 1 requires the solution in which treprostinil is formed be used directly in the next salt-forming step without isolating treprostinil in between."); *id.* at 15 ("Each claim of the '901 patent further requires forming the salt without isolating the intermediate acid."). Plaintiff later withdrew these statements. (D.I. 125-1, Ex. J2 at 22:10–14, 26:12–13). The PTAB dismissed Plaintiff's request to withdraw these statements as moot because it construed the "contacting" term based solely on the intrinsic evidence. *Liquidia*, No. IPR2020-00770, 2021 WL 4860733, at *22. Since the PTAB did not rely on these withdrawn statements, I find no clear and unmistakable disclaimer of claim scope. Regardless, the intrinsic evidence supports Defendant's construction, and thus I would reach the same result whether I considered the statements or not.

Defendant responds that this example involves purification, not isolation, and that Plaintiff and its expert are conflating the terms "purification" and "isolation." (*Id.* at 71:19-72:6). I agree. At oral argument, Plaintiff referred to Example 2's steps as "purification steps," not "isolation steps." (*See, e.g.*, *id.* at 66:4–6 ("There are purification and work-up steps that are identified in example two . . . ."); *id.* at 67:15–17 ("[T]here are purification steps in between."); *id.* at 71:12–14 ("[W]e just saw that there's purification steps that are occurring there.")). Dr. Ruffolo also referred to these steps as "purification steps" in his initial declaration. (D.I. 76-1, Ex. P4, ¶ 54; Ex. P5, ¶ 17).

In his supplemental declaration, Dr. Ruffolo states, "[A] POSA would understand that a compound can be purified to isolation, even while it is maintained in a solvent, which is often done for practical considerations (e.g., material transfer) in manufacturing plants." (*Id.*, Ex. P5, ¶ 21; *see also id.*, ¶ 15 ("[I]t is common for compounds to be isolated (i.e., separated from many impurities and other contaminants resulting from previous chemical reactions) and retained in a solution state in commercial manufacturing processes for practical reasons, such as facilitating material transfer."); *id.*, ¶ 17 ("It is clear that these many purification steps result in isolation of treprostinil (from many impurities and contaminants) prior to the salt formation step, regardless of whether the isolated treprostinil is in an aqueous phase, organic phase or solid phase.")). But Dr. Ruffolo's assertions that isolation and purification are essentially the same and that a compound can be isolated even when it is still in solution are inconsistent with the use of the terms "isolation" and "purification" in the '901 patent.

The '901 patent specification uses both terms, but in different contexts. (*See, e.g.*, '901 patent, 16:67–17:1 ("The purification of benzindene nitrile by column chromatography is eliminated."); 17:8–10 ("[T]he treprostinil salts can be synthesized from the solution of

treprostinil without isolation."). There are no places in the '901 patent where these terms appear to be used as synonyms. Thus, I think it is reasonable to conclude that these terms have different meanings in the '901 patent. *See Amgen Inc. v. Sandoz Inc.*, 923 F.3d 1023, 1031 (Fed. Cir. 2019) ("[D]ifferent claim terms are presumed to have different meanings." (quoting *Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1382 (Fed. Cir. 2008))).

The patent specification uses the terms "isolation" and "isolating" in the context of isolating a compound as a solid. For example, step (d) in claim 1 requires "isolating the salt of treprostinil." ('901 patent, 17:29). The specification explains that the salt is isolated as a solid. (*Id.*, 13:24–27 ("The treprostinil diethanolamine salt was collected by filtration using Aurora filter equipped with filter cloth, and the solid was washed with ethyl acetate (2x8 L)."")). Thus, Defendant's construction does not read out Example 2, because Example 2 discloses purification steps, not the isolation of treprostinil as a solid. (*See* D.I. 161 at 70:20–71:2 ("The only difference is that it's never reduced to dryness. So, you don't ever have in this specific example a solid form . . . .")).

I will therefore adopt Defendant's proposed construction, as it is consistent with the claim language and the specification.

IV. CONCLUSION

Within five days the parties shall submit a proposed order consistent with this Memorandum Opinion.