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

Before me is Plaintiff's Motion for Presumption under 35 U.S.C. § 295. (D.I. 311). I have reviewed the parties' briefing. (D.I. 312, 343, 352). For the reasons stated below, this motion is DENIED.

I. BACKGROUND

This action arises from Defendant Liquidia's submission of New Drug Application No. 213005 to the FDA, seeking approval for its treprostinil inhalation product LIQ861. On June 4, 2020, Plaintiff United Therapeutics Corporation ("UTC") filed suit against Liquidia for infringement of UTC's patents covering Tyvaso®, including U.S. Patent No. 9,593,066 ("the '066 patent"). The '066 patent discloses a process for preparing treprostinil, which can be used for the treatment of pulmonary arterial hypertension.

UTC asserts claims 1, 2, 3, 6, 8, and 9 of the '066 patent. Claims 1 and 6, for example, recite:

> 1. A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising

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providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

6. The pharmaceutical composition of claim 1, wherein the isolated salt is stored at ambient temperature.

II. LEGAL STANDARD

In actions alleging infringement of a "process patent," the court may impose a presumption that the accused infringer's product was made by the patented process and may shift the burden of proving non-infringement to the accused infringer if the court finds: "(1) that a substantial likelihood exists that the product was made by the patented process, and (2) that the plaintiff has made a reasonable effort to determine the process actually used in the production of the product and was unable to so determine." 35 U.S.C. § 295.

As to the first requirement, "the burden for establishing a substantial likelihood of infringement has been described as 'less than . . . proving successfully at a trial by a fair preponderance of the evidence that a product in question was in fact made by the patented process but would be more than a slight possibility that the product was so made.'" *LG Display Co. v. AU Optronics Corp.*, 709 F. Supp. 2d 311, 335 (D. Del. 2010) (citation omitted). In other words, the patentee "need only present evidence that would support a reasonable conclusion that the imported product was made by the patented process." *Id.*

In assessing the second requirement, "courts examine the patentee's discovery efforts and consider whether the patentee followed all of the avenues of discovery likely to uncover the defendant's process, including written discovery requests, facility inspections, first-hand

observation of the process, independent testing of process samples, the use of experts, and depositions of the defendant's officials." *Id.* (cleaned up).

III. DISCUSSION

The API (treprostinil sodium) used in Liquidia's proposed product is manufactured by Yonsung Fine Chemicals Co., Ltd. ("Yonsung"), a third-party based in Korea. (D.I. 312 at 3). UTC asserts that because Yonsung is outside the Court's discovery powers, UTC has been unable to determine the actual process used by Yonsung. (*Id.* at 1). UTC therefore asks this Court to apply a presumption under § 295 that Liquidia's proposed product is made using the process claimed in the '066 patent. (*Id.*).

As a preliminary matter, Liquidia briefly argues that § 295 does not apply to asserted claims 1, 2, 3, 6, and 9 because these claims are product-by-process claims, not pure process claims. (D.I. 343 at 10). Section 295 applies to "actions alleging infringement of a process patent based on the importation, sale, offer for sale, or use of a product which is made from a process patented in the United States." 35 U.S.C. § 295. The issue before the Court is whether the term "process patent" includes product-by-process claims. I conclude that it does.

"[P]roduct-by-process claims are limited by and defined by the process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). The Federal Circuit has held, "[P]rocess terms in product-by-process claims serve as limitations in determining infringement." *Abbott Lab'ys v. Sandoz, Inc.*, 566 F.3d 1282, 1293 (Fed. Cir. 2009) (quoting *Atl. Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 846 (Fed. Cir. 1992)). Because the process steps in product-by-process claims are specific claim limitations and define the scope of the patent protection, the term "process patent" necessarily includes product-by-process claims. Practicing a product-by-process claim results in

"a product which is made from a process patented in the United States" in accordance with § 295. Thus, the plain language of the statute includes product-by-process claims.

Further, applying § 295 to product-by-process claims advances the policy of the statute. The legislative history provides, "This presumption addresses the great difficulties a patentee may have in proving that the patented process was used in the manufacture of the product in question where the manufacturer is not subject to the service of process in the United States." S. REP. NO. 100-83, at 57 (1987). To establish infringement of product-by-process claims, the patentee must prove that the accused infringer practiced the process limitations. Thus, a patentee asserting infringement of product-by-process claims faces the same difficulties as a patentee asserting infringement of pure process claims because both patentees need to determine the process used by the accused infringer. There is no logical reason why the benefit of the § 295 presumption should only apply to patentees proving infringement of pure process claims and not to patentees who must prove infringement of claims with both process and product limitations. Thus, I hold that the § 295 presumption can be applied to product-by-process claims.

I decline to apply the § 295 presumption here, however, because UTC has failed to show that it was unable to determine the actual process used by Yonsung to produce the API. UTC has received extensive discovery regarding Yonsung's manufacturing process. Liquidia produced the open and closed portions of Yonsung's Drug Master File ("DMF"). (D.I. 344, Exs. 1–2). The open portion of the DMF details Yonsung's twelve-step manufacturing process. (D.I. 344-1, Ex. 1, at 10–15). It also provides impurity test results detecting various impurities

in the final treprostinil sodium (*id.* at 39–314) and reports the data from stability tests performed on 600 g batches of treprostinil sodium. (*Id.* at 521–625).

The closed portion of the DMF provides additional impurity data, including the percentages of impurities in the intermediates (BTO03, BTO, TN01, TN02), starting materials (TSE, TSW, methyl bromoacetate), and the final API. (D.I. 344-2, Ex. 2, at 269–80).

Liquidia also produced executed batch production records, quality control testing documentation, and certificates of analysis ("COAs") for batches of the API, intermediates, and starting materials. (*See* D.I. 314-1, Ex. 1, ¶ 63). The batch production records provide step-by-step instructions for the chemical synthesis of the API and handwritten notes from Yonsung chemists detailing, among other things, the temperatures, pressures, reagent and solvent weights, and start and end times during the synthesis. (*See, e.g.*, D.I. 345, Exs. 47–48).

The COAs for batches of API disclose impurity test results detecting 15-*epi*-treprostinil, treprostinil ethyl ester, BTO, any other impurity, residual solvents, and microorganisms. (*See, e.g.*, D.I. 345-3, Ex. 5, at 2–4). The COAs for batches of intermediates and starting materials include impurity test results detecting 15-*epi*-BTO, 15-*epi*-TN01, TN02, any other impurity, and/or total impurities. (D.I. 345-4, Ex. 6, at 2–3; D.I. 345-5, Ex. 7, at 2–3).

Finally, Liquidia also provided temperature logging data for two GMP fridges where Liquidia stored the API (D.I. 345, Exs. 39–40), and samples of its proposed product and its treprostinil sodium API. (*See* D.I. 345-6, Ex. 8).

Yet UTC contends that this voluminous discovery is insufficient. First, UTC asserts that it does not have "documents sufficient to show each impurity present throughout the steps of [Yonsung's] manufacturing process." (D.I. 312 at 3). This information is relevant to

establishing infringement of the limitation in claim 1 requiring a "starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps." UTC argues that because the quality control test sheets and COAs for the intermediates only tracked two impurities by name and because UTC was unable to obtain any samples of Yonsung's TN02 intermediate,[1] its experts "were unable to definitively glean . . . the specific synthetic origin of the impurities analyzed." (D.I. 352 at 3–4).

I do not think this problem is a result of the API manufacturer being located in Korea. Instead, this problem relates to UTC's ability to prove infringement, not its failure to understand the actual process used by the Korean supplier. Liquidia has produced the DMF, quality control testing documents, and COAs which all provide impurity data for the intermediates and the final API. It is UTC's burden to use these documents to prove that Liquidia's process meets the claim limitations.

Second, UTC contends that it has "limited information concerning the storage temperatures used throughout the manufacturing and shipping" of the API. (D.I. 312 at 3). This information is relevant to the limitations in claims 6 and 8 which require that the treprostinil salt is stored at ambient temperature. I find that Liquidia has produced sufficient information relating to the storage conditions of the treprostinil sodium. For example, UTC has access to the temperature logger data for Liquidia's GMP fridges that stored the API. (*See* D.I. 345, Exs. 39–40). UTC also has the COAs, which provide that the treprostinil sodium should be "stored at

[1] UTC sought a representative sample of TN02. (D.I. 313-1, Ex. E, RFP No. 7). In response, Liquidia stated that it did not have any samples of TN02 and that Yonsung does not maintain samples of TN02. (D.I. 345-10, Ex. 12, at 2).

2°C to 8°C." (D.I. 344-1, Ex. 1, at 447, 449, 451, 518; D.I. 345-33, Ex. 35, at 3; *see also* D.I. 345-3, Ex. 5, at 5 (indicating that the API's storage condition is "cold storage")).

I find that the voluminous documentation produced by Liquidia is sufficient for UTC to reasonably determine the process actually used by Yonsung to manufacture the API. *See, e.g.*, *Nutrinova Nutrition Specialties & Food Ingredients GmbH v. Int'l Trade Comm'n*, 224 F.3d 1356, 1360 (Fed. Cir. 2000) (declining to apply the § 295 presumption where "a reasonable plaintiff would be able to determine the process used"). The open and closed portions of the DMF,[2] executed batch production records, quality control testing documentation, and COAs provide extensive details regarding the twelve-step chemical synthesis, the impurities present at each step, and the storage conditions of the API.

This extensive documentation is in stark contrast to the extremely limited documentation received by the patentees in the cases applying the § 295 presumption. *See, e.g.*, *Creative Compounds, LLC v. Starmark Lab'ys*, 651 F.3d 1303, 1315 (Fed. Cir. 2011) (patentee received no documentation regarding the process performed by the foreign manufacturer); *Dasso Int'l, Inc. v. MOSO N. Am., Inc.*, 2021 WL 4427168, at *6 (D. Del. Sept. 27, 2021) (same); *Syngenta Crop Prot., LLC v. Willowood, LLC*, 2017 WL 1133378, at *8–*11 (M.D.N.C. Mar. 24, 2017) (patentee received "some information about the manufacturing process," but did not receive "any

[2] Congress has recognized that the DMF is a useful source for determining the process actually used by foreign manufacturers. *See* S. REP. NO. 100-83, at 44 ("The DMF is complied [sic] from information supplied directly to the FDA from the manufacturer and from inspections by FDA personnel in the factories of the manufacturer. However, if the file can be obtained by the U.S. courts under a protective order without violating any other provisions of law, it could be used to assist the court in resolving whether the patented process was used in making the goods in question. It might alleviate the need to rely on indirect forms of evidence, such as chemical analysis, to trace the process used.").

manufacturing or batch records" to confirm the foreign supplier's testimony), *aff'd in part, vacated in part, rev'd in part on other grounds*, 944 F.3d 1344 (Fed. Cir. 2019).

The documentation provided here is sufficient for UTC to determine the actual process used. It is UTC's burden to use this documentation to prove whether the accused process meets the claim limitations. Thus, I decline UTC's request to apply the § 295 presumption.

IV. CONCLUSION

An appropriate order will issue.

Entered this 22 day of March, 2022.

United States District Judge