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

TRIAL OPINION

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August 31, 2022

ANDREWS, U.S. DISTRICT JUDGE:

United Therapeutics Corporation ("UTC") brought this action against Liquidia Technologies, Inc. for infringement of U.S. Patent Nos. 9,593,066 ("the '066 patent"), 9,604,901 ("the '901 patent"), and 10,716,793 ("the '793 patent") under 35 U.S.C. § 271(e)(2)(A). (D.I. 1, 16). I held a four-day bench trial. (D.I. 402–405).[1] The disputes at trial were related to the infringement and validity of claims 1, 2, 3, 6, 8, and 9 of the '066 patent and claims 1, 4, 6, 7, and 8 of the '793 patent. The '901 patent is no longer at issue.

I have considered the parties' post-trial submissions. (D.I. 406, 407, 408, 409, 411, 412, 413, 414, 415, 416, 423, 424). Having considered the documentary evidence and testimony, I make the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

I. BACKGROUND

UTC is the holder of New Drug Application ("NDA") No. 022387 for Tyvaso®, an inhaled solution formulation of treprostinil approved for the treatment of pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease. (D.I. 322-1, Ex. 1, ¶¶ 5, 12). The '066 and '793 patents are listed in the FDA's Orange Book for Tyvaso®. (*Id.*, ¶ 14). The '066 patent discloses an improved process for preparing treprostinil. (*See* JTX 2). The '793 patent discloses a method of administering treprostinil by inhalation. (*See* JTX 3).

Liquidia submitted NDA No. 213005 under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act seeking FDA approval for the manufacture, use, and sale of its proposed product LIQ861 (Yutrepia™). (D.I. 322-1, Ex. 1, ¶ 2). LIQ861 is a dry powder formulation of

[1] I cite to the trial transcript as "Tr." The trial transcript is consecutively numbered.

treprostinil sodium. (*Id.*, ¶ 16). The FDA tentatively approved LIQ861 for the treatment of pulmonary arterial hypertension. (*Id.*, ¶¶ 17–18).

Liquidia's NDA contains Paragraph IV certifications alleging that both the '066 and '793 patents are invalid and/or will not be infringed by the manufacture, use, or sale of its proposed product. (*Id.*, ¶ 8). UTC received notice of Liquidia's Paragraph IV certifications and initiated the present lawsuit. (*Id.*, ¶ 9).

II. INFRINGEMENT OF THE '066 PATENT

A. Legal Standard

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent." 35 U.S.C. § 271(a). Determining infringement is a two-step analysis. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *Id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *Id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). The patent owner bears the burden of proving infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab'ys Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

In a Hatch-Waxman case, the plaintiff's infringement claim is based on the accused infringer's future conduct, rather than past acts of infringement. Under § 271(e)(2), the "infringement inquiry . . . is focused on the product that is likely to be sold following FDA approval." *Abbott Lab'ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). "Because drug manufacturers are bound by strict statutory provisions to sell only those products that

comport with the []NDA's description of the drug, an []NDA specification defining a proposed [] drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Id.* For product-by-process claims, the infringement inquiry is focused "on the process of making the product as much as it is on the product itself." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1370 (Fed. Cir. 2009). Thus, "a product-by-process claim is not infringed by a product made by a process other than the one recited in the claim." *Id.*

B. Asserted Claims of the '066 patent

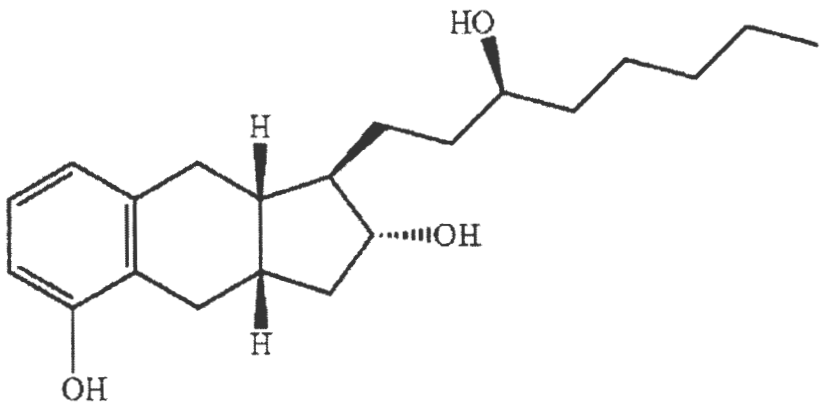
1. A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil 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.

2. The pharmaceutical composition of claim 1, wherein the salt is isolated in crystalline form.

3. The pharmaceutical composition of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

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

8. A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising alkylating a triol intermediate of the formula:



hydrolyzing the resulting compound to form treprostinil, forming a salt of treprostinil stable at ambient temperature, storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage, wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical product prepared by the process of claim 8.

C. Findings of Fact

1. A POSA would be either a chemical engineer or process research chemist with 3-5 years of experience in API and drug manufacturing or a master's degree in chemistry or chemical engineering who collaborated with individuals having 3-5 years of experience in API drug manufacturing.

2. Yonsung, based in South Korea, manufactures the treprostinil sodium API used to make Liquidia's LIQ861 product. (Tr. at 74:21–75:5 (Nuckolls); PTX 20 at 7). Yonsung has a Drug Master File ("DMF") for the treprostinil sodium used in LIQ861. (PTX 112 (Open DMF); PTX 201 (Restricted DMF)).

3. Yonsung synthesizes the treprostinil sodium by alkylating a batch of benzindene triol ("BTO") to provide a batch of "TN01" (PTX 201 at 7, 22, 35 (DMF Step 10)), then performing a hydrolysis step to provide a batch of treprostinil ("TN02") (*id.* at 8, 23, 36 (DMF Step 11)), and performing a salt formation step by combining the treprostinil with a base (sodium) to yield treprostinil sodium ("TN") (*id.* at 8, 24, 37 (DMF Step 12); Tr. at 75:19–76:20 (Nuckolls); Tr. at 407:2–408:21 (Winkler)).

4. LGM is a U.S. based administrative intermediary between Yonsung and Liquidia. (Tr. at 346:7–10 (Kindig); Tr. at 439:2–5 (Winkler)). Yonsung's shipments of treprostinil sodium sometimes go through LGM to Liquidia; however, LGM does not manufacture treprostinil sodium, nor is it involved in the development or administration of Liquidia's LIQ861 product. (Tr. at 331:14–21 (Kindig); Tr. at 366:5–16 (Lenox)).

5. A POSA would understand that the impurities limitations in claim 1 of the '066 patent refer to any impurities generated during the process steps of alkylating and hydrolyzing a batch of BTO (including from side reactions, impurities in reagents, solvents, or starting materials).

6. Yonsung's analytical testing of treprostinil sodium is a reliable and accurate measure of impurities in the pharmaceutical composition resulting from the alkylation and hydrolysis steps; Liquidia's processing of the TN into the pharmaceutical composition (LIQ861 bulk powder) does not affect those impurities.

7. Liquidia's proposed LIQ861 product will be prepared by a process which lowers the level of one or more impurities resulting from prior alkylation and hydrolysis steps as claimed in the '066 patent. The percentage of total "related substance" impurities and the amount of total "related substance" impurities increase during the alkylation and hydrolysis steps from BTO to the starting batch of treprostinil (TN02), and then decrease in the TN batch after the salt formation and isolation steps.

8. Liquidia's NDA and Yonsung's DMF require treprostinil sodium to be stored at 2°C to 8°C.

9. Liquidia will not use treprostinil sodium batches which have been stored at ambient temperature for GMP manufacturing.

10. Liquidia begins preparing a pharmaceutical product during Step 1 of its PRINT process.

D. Conclusions of Law

1. Claims 1, 2, and 3

Liquidia only disputes infringement of the impurities limitations in claims 1, 2, and 3. Claim 1 recites "providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps . . . wherein said alkylation is alkylation of benzindene triol." As a preliminary issue, the parties dispute the proper construction of "impurities resulting from prior alkylation and hydrolysis steps." Liquidia argues that the claimed impurities must result from alkylation and hydrolysis of "BTO," not the alkylation and

hydrolysis of any compound that may be present in the reaction vessel. (D.I. 411 at 3). UTC argues that the claimed impurities encompass any impurities generated during the process steps of alkylating and hydrolyzing a batch of BTO (including from side reactions, impurities in reagents, solvents, or starting materials). (D.I. 408 at 7–8).

UTC's construction is correct. The claim language requires that the impurities result from the "prior alkylation and hydrolysis *steps*." A POSA would understand that the alkylation step involves alkylating all materials in a batch of BTO, not just the single alkylation reaction of BTO. (*See* Tr. at 110:23–111:10 (Nuckolls); Tr. at 810:16–19, 818:18–22 (Scheidt); *see also* Tr. at 423:15–20 (Winkler) ("[A] real batch of – a bottle of benzindene triol could contain impurities.")). Thus, I find that a POSA would understand that any impurities generated during the alkylation and hydrolysis steps (including from side reactions) are within the scope of the claim.

Claim 1 further recites: "whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition." UTC has identified the LIQ861 bulk powder as the "pharmaceutical composition" and Yonsung's TN02 as the "starting batch of treprostinil." Liquidia argues that UTC cannot prove infringement of this limitation because UTC's experts only compared the impurities between TN02 and TN, not the LIQ861 powder. (D.I. 411 at 2). UTC responds that Yonsung's impurities testing for TN is a proper measure of impurities in the pharmaceutical composition resulting from the alkylation and hydrolysis steps because Liquidia's processing of TN into LIQ861 bulk powder has no effect on the impurities from these steps. (D.I. 416 at 4). Once Liquidia receives the TN from Yonsung,

Liquidia uses its proprietary PRINT process[2] to prepare the LIQ861 bulk powder using the TN as the API. (DTX 204; PTX 20). In simple terms, Liquidia puts the TN in solution, adds excipients, and dries this formulation into the powder. (DTX 204 at 2–6; Tr. at 741:7–16 (Gonda)).

UTC's expert Dr. Nuckolls testified that he "wouldn't expect" Liquidia's processing of TN to impact the impurities from the alkylation and hydrolysis steps. (Tr. at 157:7–17 (Nuckolls); *see also* PTX 66 at 96 ("Treprostinil sodium drug substance process impurities are controlled by the manufacturer, Yonsung Fine Chemicals Co., Ltd. (Yonsung)."). Dr. Nuckolls also testified that it would be difficult for a POSA to test the impurities resulting from the alkylation and hydrolysis steps in the LIQ861 bulk powder because the composition has been mixed with other excipients. (Tr. at 133:25–134:3 (Nuckolls)). Liquidia has not provided any expert testimony to rebut these opinions; thus, I will credit Dr. Nuckolls' testimony on this point. I therefore find that the TN impurities are representative of the impurities in the "pharmaceutical composition" (LIQ861 bulk powder) resulting from the prior alkylation and hydrolysis steps. *Cf. Vectura Ltd. v. GlaxoSmithKline LLC*, 397 F. Supp. 3d 579, 587–88 (D. Del. 2019) (finding that comparison testing supported the jury's infringement verdict where there was evidence that the tested products were representative of the accused products), *aff'd*, 981 F.3d 1030 (Fed. Cir. 2020).

To prove infringement of the impurities limitations, UTC compared the (1) amount of total impurities; (2) number of total impurities; and (3) amount of *epi*-treprostinil in BTO, TN02, and TN.

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[2] PRINT stands for Particle Replication in Nonwetting Templates. (DTX 204 at 2).

First, Dr. Nuckolls analyzed the total "related substance" impurities data provided by Yonsung in its DMF. (*See* PTX 201 at 270–72).[3] For two of the three DMF validation batches (TN117I010, TN117K010), the percentage of total "related substance" impurities increased between BTO and TN02, and then decreased in TN.[4] (Tr. at 77:23–80:18 (Nuckolls); PTX 201 at 270–72; PTX 326 at 4 (identifying the corresponding BTO, TN01, and TN02 batch numbers for each TN batch number)). Dr. Nuckolls opined that these changes in the percentage of total "related substance" impurities between BTO, TN02, and TN show infringement of the impurities limitations. (Tr. at 77:23–80:18 (Nuckolls)).

Second, Dr. Nuckolls analyzed the number of total impurities detected in Yonsung's validation batches. To do so, Dr. Nuckolls looked at Yonsung's underlying high-performance liquid chromatography (HPLC) data. (Tr. at 81:8–84:19 (Nuckolls)). HPLC separates components in a mixture by running the mixture down a column. (Tr. at 81:8–23 (Nuckolls)). The mixture's components are separated based on how they interact with the column, so each component will elute at different retention times, depicted by peaks on a chromatogram. (*Id.*; Tr. at 176:3–18 (Toste)).

To determine the number of impurities, Dr. Nuckolls counted the number of HPLC peaks in the chromatograms for BTO, TN02, and TN, excluding the peaks for "the material of interest"

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[3] Because Liquidia relies on the same impurities data in its NDA, I find these data to be reliable. (*See* PTX 66 at 96; PTX 105 at 7–11).

[4] For validation batch TN117I010, the percentage of "related substance" impurities was 0.07% in BTO, 0.20% in TN02, and 0.03% in TN. (PTX 201 at 270–72). For validation batch TN117K010, the percentage of "related substance" impurities was 0.08% in BTO, 0.20% in TN02, and 0.01% in TN. (*Id.*). These results are consistent with Yonsung's acceptance criteria, which allow for a greater percentage of "related substance" impurities in TN02 than in TN. (*Id.* (2.0% for TN02; 0.5% for TN)). For validation batch TN117K020, the percentage of "related substance" impurities was 0.38% in BTO, 0.21% in TN02, and 0.01% in TN. (*Id.*).

(e.g., BTO, TN02, and TN) and for the "known impurities" that were "labeled as missing or not detected." (Tr. at 81:24–83:4 (Nuckolls)). For example, the chromatogram for TN02 for validation batch TN117I010 reported six peaks. (PTX 1540 at 79–80). One of these peaks identified TN02, which is the material of interest, not an impurity. (*Id.*). Thus, this peak was excluded from the impurities count. The chromatogram also identifies "15-epi-Treprostinil" and "Treprostinil ethyl ester" as "Peak Names," but reports these impurities as "Missing." (*Id.*). Because these known impurities were not detected in this sample, they are also excluded from the impurities count. Accordingly, Dr. Nuckolls identified three "related substance" impurities in this batch of TN02. (Tr. at 82:3–83:4 (Nuckolls)). Dr. Nuckolls testified that for two validation batches (TN117I010, TN117K010), the number of "related substance" impurities increased between BTO and TN02, and then decreased in TN.[5] (Tr. at 81:24–84:19 (Nuckolls)). Dr. Nuckolls testified that this decrease shows that one or more impurities resulting from the alkylation and hydrolysis steps are lowered from TN02 to TN. (*Id.*).

Liquidia argues that Dr. Nuckolls has failed to show a reduction in impurities "resulting from prior alkylation and hydrolysis steps . . . wherein said alkylation is alkylation of benzindene triol." (D.I. 411 at 4). Liquidia argues that the reported "total impurities" relied on by Dr. Nuckolls in his amount of total impurities analysis include "residual solvents and any impurity

[5] For validation batch TN117I010, one "related substance" impurity was identified in BTO, three "related substance" impurities were identified in TN02, and one "related substance" impurity was identified in TN. (Tr. at 82:3–83:4 (Nuckolls); PTX 1536 at 51 (BTO); PTX 1539 at 77 (TN); PTX 1540 at 79–80 (TN02)). For validation batch TN117K010, two "related substance" impurities were identified in BTO, three "related substance" impurities were identified in TN02, and one "related substance" impurity was identified in TN. (PTX 1410 at 59–62 (BTO); PTX 1157 at 33–34 (TN02); PTX 1543 at 83–84 (TN)). The underlying HPLC chromatogram for validation batch TN117K020 was not available to Dr. Nuckolls. (Tr. at 84:14–19 (Nuckolls)).

contained in the reagents or starting materials, not just impurities resulting from the claimed process steps." (*Id.*). Liquidia similarly faults Dr. Nuckolls' number of impurities analysis. Liquidia argues that since Dr. Nuckolls failed to correlate the unidentified HPLC peaks to any specific impurity, he cannot show that these impurities resulted from the alkylation and hydrolysis steps. (*Id.*).

These arguments, however, rely on Liquidia's improper interpretation of the impurities limitations. As concluded above, a POSA would understand that the claimed impurities include any impurities generated during the alkylation and hydrolysis steps, including impurities originating from starting materials or reagents. Thus, Liquidia's arguments rest on an infirm foundation.

As described in its DMF, Yonsung uses a twelve-step process to manufacture TN. (PTX 201 at 3). Step 10 of this process is the alkylation step—BTO is reacted with the alkylating agent to produce TN01. (Tr. at 75:20–76:2, 76:11–13 (Nuckolls); PTX 201 at 7). Next, in Step 11—the hydrolysis step—TN01 is hydrolyzed to produce TN02. (Tr. at 76:1–3, 13–15 (Nuckolls); PTX 201 at 8). In Step 12, TN02 is treated with a base to form TN. (Tr. at 76:3–5, 15–18 (Nuckolls); PTX 201 at 8). Thus, Dr. Nuckolls opined that any increased impurities in TN02 as compared to BTO resulted from the alkylation and hydrolysis steps, because those were the steps that were run to synthesize TN02 from BTO. (Tr. at 80:4–18, 82:3–15 (Nuckolls)). He further opined that the impurities that were generated during the alkylation and hydrolysis steps (Steps 10 and 11) were reduced during the final salt formation step (Step 12), as shown by the reduced levels of impurities in TN as compared to TN02. (*Id.*). I credit Dr. Nuckolls' testimony over Dr. Winkler's contrary testimony, which relied on Liquidia's erroneous construction. (*See* Tr. at 427:19–429:17 (Winkler)).

Based on the total impurities analyses conducted by Dr. Nuckolls, I find that UTC has proven that Liquidia will meet the impurities limitations of claim 1.[6] I therefore find that UTC has proven by a preponderance of the evidence that Liquidia's proposed LIQ861 product will infringe claims 1, 2, and 3 of the '066 patent.[7]

2. Claim 6

Claim 6, which depends from claim 1, further requires that "the isolated salt is stored at ambient temperature" before it is used to prepare a pharmaceutical composition. I construed "ambient temperature" as "room temperature (equal to or less than the range of 15°C to 30°C)." (D.I. 119). I construed "stored"/"storing"/"storage" to have its plain and ordinary meaning. (*Id.*).

Liquidia has represented to the FDA that it will store treprostinil sodium between 2°C and 8°C. Yonsung's DMF, which is incorporated in Liquidia's NDA (*see* PTX 105 at 3), specifies the following storage conditions for TN: "STORAGE: Should be kept in a tight container, protected from moisture and light and stored at 2°C to 8°C." (PTX 112 at 517). The certificates of analysis for TN and Yonsung's 2017 List of Finished and Intermediate Products also include these storage requirements. (*Id.* at 448, 450 ("Storage condition: Should be kept in a tight container, protected from moisture and light and stored at 2 °C to 8 °C (Long-term storage)."); DTX 43 at 6 (specifying TN's "Storage Conditions" as "Refrigerated")). LGM, an intermediary between Yonsung and Liquidia, stores TN in accordance with Yonsung's set

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[6] Because I find UTC's first two analyses sufficient to show infringement, I need not consider UTC's third analysis, which compares the amount of *epi*-treprostinil in TN02 and TN.

[7] "To be sure, if at the end of the day, an act that would have been an infringement . . . pertains to a patent that is shown to be invalid, there is no patent to be infringed." *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 644 (2015). Since I ultimately conclude that claims 1, 2, and 3 of the '066 patent are invalid as anticipated, there is ultimately no infringement.

storage conditions. (Tr. at 365:23–366:4, 367:9–15, 368:2–7 (Lenox); *see also* DTX 105). Liquidia's raw material specification for treprostinil sodium states: "Storage Conditions: 2° - 8°C, protected from light and moisture." (DTX 9 at 1; *see also* Tr. at 374:12–15, 396:7–10 (Fuson) (testifying that the FDA would expect Liquidia to follow the temperature storage conditions set in its raw material specification and Yonsung's DMF); DTX 407 at 3 (FDA pre-approval inspection report wherein the FDA checked Liquidia's compliance with the 2°C to 8°C storage conditions)).

Despite these clear statements to the FDA, UTC argues that Liquidia's NDA and Yonsung's DMF permit storage of TN at ambient temperature because Yonsung's stability data show that TN is stable at ambient temperature. (*See* PTX 112 at 519–61). The parties' FDA experts Mr. Matto and Mr. Fuson both agree that if there were an out-of-specification temperature excursion (e.g., TN was exposed to ambient temperatures), Liquidia would need to conduct a full investigation before using that TN to make LIQ861. (Tr. at 272:9–274:3 (Matto); Tr. at 378:1–15 (Fuson)). But the fact that Liquidia might, in some circumstances, be permitted to use TN exposed to ambient temperatures is insufficient to show that Liquidia will do so.[8] *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1329 (Fed. Cir. 2010) ("[I]t is not enough to simply

[8] UTC argues that Liquidia infringes as a matter of law under *Sunovion*. (D.I. 408 at 10–11). *Sunovion* is inapposite. The patent claim at issue in that case limited the concentration of a particular isomer to "less than 0.25%," and the amended ANDA specified a product containing "[not more than] 0.6%" concentration of the same isomer. *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1274–75 (Fed. Cir. 2013). Since the ANDA specification of not more than 0.6% necessarily included products meeting the claim limitation of less than 0.25%, the Court held that Defendant had sought "FDA approval to market a generic compound within the scope of a valid patent," and thus infringed as a matter of law. *Id.* at 1280. In contrast, here, Liquidia asks the FDA to approve sales that fall outside the scope of the '066 patent. Liquidia's NDA (through incorporation of Yonsung's DMF) specifically provides that TN should be stored at 2°C to 8°C, not ambient temperature.

show that a product is capable of infringement; the patent owner must show evidence of specific instances of direct infringement.").

UTC further argues that the isolated salt (TN) used to make LIQ861 is stored at ambient temperature at three points in the process: before acceptance into Yonsung's warehouse; during shipment from Yonsung to Liquidia; and during Step 1 of Liquidia's PRINT process. (D.I. 408 at 10). I will address each argument in turn.

First, UTC asserts that TN is stored at ambient temperature in "finished product storage containers" before acceptance into Yonsung's warehouse. Relying on Yonsung's 2017 batch production record for TN117I010, Dr. Nuckolls claimed that Yonsung stored the TN at ambient temperature for 43 days between production and acceptance into the warehouse. (Tr. at 96:10–97:24 (Nuckolls); PTX 1409 at 47–50, 70). Dr. Nuckolls, however, only based his opinion on the lack of temperature notation in this batch record. The absence of temperature notation on a single batch record does not show storage at ambient temperature by a preponderance of the evidence. Rather, Yonsung's List of Finished/Intermediate Products from 2017 required TN to be stored at refrigerated temperatures. (DTX 43 at 6). Further, batch production records from 2019 indicate that TN is "refrigerated" between production and acceptance into the warehouse. (DTX 413 at 12).

Second, UTC contends that TN is stored at ambient temperature when it is shipped from Yonsung to Liquidia.[9] Three batches of TN (TN120C010, TN120G010, and TN120I010)[10]

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[9] Liquidia argues that the plain and ordinary meaning of "stored" does not include shipping. (D.I. 412 at 8 n.2). I disagree. A POSA would understand that a material can be stored during shipment. (Tr. at 137:6–138:11 (Nuckolls)).

[10] These batches are not listed as "Representative Treprostinil Sodium Drug Substances Batches" in the NDA. (PTX 105 at 8).

experienced ambient temperatures for nine days during shipment from Yonsung to LGM. (PTX 19 at 17, 19–21, 26–27; Tr. at 98:1–13 (Nuckolls)). LGM notified Liquidia that these batches experienced temperature excursions, stating, "[O]ur QC released the shipment because Yonsung has long-term stability showing the Treprostinil is stable at room temperature for 6 months." (PTX 2020 at 475–78). Liquidia accepted these shipments, marking "Requirements Met" for "Transport Conditions (Temperature-if applicable)" on the receiving reports. (PTX 19 at 1; PTX 104 at 1).

UTC provides no evidence showing that Liquidia used these batches in GMP manufacturing to make a pharmaceutical composition, as is required by claim 6. Instead, the evidence shows that Liquidia only used these batches for R&D. Liquidia's Executive Director of Analytical Operation, Mr. Kindig, testified that TN120C010 was ordered specifically for use in R&D, not GMP manufacturing. (Tr. at 309:1–4, 321:1–13 (Kindig)). Mr. Kindig also testified that TN120G010 and TN120I010 were rejected by Liquidia's Quality Unit for GMP use and were relegated to R&D use only. (Tr. at 317:1–320:20 (Kindig)).[11] The fact that Liquidia accepted these out-of-specification batches instead of requesting a refund from Yonsung is not persuasive evidence of infringement, as Liquidia had another use for these batches.

UTC also asserts that three other batches of TN (TN116J010, TN117K010, and TN117I010) were stored at ambient temperature during shipment and were subsequently used for clinical trials. (*See* PTX 105 at 8 (listing these batches as "Representative Treprostinil Sodium

[11] Nevertheless, UTC again argues that the FDA will permit Liquidia to use these batches because of Yonsung's stability data. (D.I. 408 at 13–14). But, as discussed above, this does not show by a preponderance of the evidence that Liquidia will use batches exposed to ambient temperatures to prepare pharmaceutical compositions. Liquidia rejected these batches for GMP manufacturing because they were exposed to ambient temperatures, and UTC has failed to provide evidence showing that Liquidia will not continue to do so.

Drug Substances Batches")). While the temperature data loggers for these batches do show a spike to ambient temperature, this spike directly corresponds with Liquidia's receipt of the batches. (PTX 116; PTX 117; Tr. at 324:11–327:24 (Kindig); Tr. at 150:17–153:22 (Nuckolls) (confirming that receipt date and spike date were both December 11, 2017)). Once Liquidia receives the TN shipment, an employee will open the box, set aside the data logger and paperwork, and transfer the TN to the GMP refrigerator. (Tr. at 321:18–323:7 (Kindig)). Because the temperature logger does not automatically stop once the box is opened, the employee will later press the button to stop the data logging when dealing with the paperwork. (Tr. at 322:15–323:2; 327:18–328:8 (Kindig)). This explains why the data loggers immediately spiked into ambient temperature on the date Liquidia received and opened the box. Thus, the temperature data loggers for these three batches do not prove storage at ambient temperature.

The remaining shipments that UTC points to did not include temperature data loggers. (PTX 123; PTX 124; PTX 127; PTX 823; *see also* PTX 126 at 24 (temperature logger showing a maximum temperature of 6.1°C)). Contrary to UTC's assertion, the lack of temperature data is not persuasive evidence that these batches were stored at ambient temperature.

Third, UTC argues that TN is stored at ambient temperature in a drybox during Step 1 of Liquidia's PRINT process. Liquidia's PRINT process has six steps: (1) "Preparation of aqueous stock solution"; (2) "Preparation of engineered particles (particle fabrication)"; (3) "Dry collection of engineered particles as bulk LIQ861 inhalation powder"; (4) "Drying and packaging of bulk LIQ861 inhalation powder"; (5) "Drug Product Primary Packaging – encapsulation of bulk LIQ861 inhalation powder in [HPMC] capsules"; and (6) "Drug Product Secondary Packaging – blister packaging and assembly of commercial drug product kit." (DTX

204 at 2). After Step 4, the LIQ861 bulk powder is shipped to Xcelience for encapsulation and packaging (Steps 5 and 6). (*Id.* at 12).

During Step 1, a sample of TN is placed in a drybox and used to make a stock aqueous solution. (PTX 70 at 9–17). Dr. Nuckolls claims that TN is "stored" in the drybox for three hours. (Tr. at 99:24–100:7 (Nuckolls) (relying on the time stamps in Step 2-2 (8:12am) and Step 2-17 (11:46am) of the Batch Production Record (PTX 70))). A POSA, however, would understand that TN is being used, not stored, during Step 1 of the PRINT process. (*See* DTX 204 at 2 (referring to the PRINT process as "[t]he manufacturing process"). Thus, evidence that Liquidia places TN in a drybox does not prove infringement of the storage limitation.

Liquidia has represented to the FDA that it will store treprostinil sodium at 2°C to 8°C. UTC has failed to prove that Liquidia will go against these representations and store isolated treprostinil sodium at ambient temperature before it is used to prepare a pharmaceutical composition. *See In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1378 (Fed. Cir. 2011) ("We cannot assume that [the NDA filer] will not act in full compliance with its representations to the FDA."). Accordingly, I find that UTC has failed to prove by a preponderance of the evidence that Liquidia's proposed LIQ861 product will infringe claim 6.

3. Claims 8 and 9

Liquidia only disputes infringement of the temperature storage limitation in claims 8 and 9. Claims 8 and 9 require "storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage." UTC asserts that the three instances of storage discussed above with respect to claim 6 apply equally to claims 8 and 9. (D.I. 408 at 16). This evidence fails to show storage of TN at ambient temperature for the reasons discussed above.

Because claims 8 and 9 require storage of "the treprostinil salt," whether isolated or not, UTC points to three additional instances of storage at ambient temperature to show infringement. Specifically, UTC contends that the LIQ861 bulk powder, which contains the treprostinil salt after it is mixed with excipients, is stored at ambient temperature between PRINT Steps 1 and 2; between PRINT Steps 2 and 3; and between PRINT Steps 3 and 4. (*Id.*).

Claim 8 recites a method for "preparing a pharmaceutical product," while claim 6 recites a "pharmaceutical composition." UTC contends that the LIQ861 bulk powder is the "pharmaceutical composition" and LIQ861 is the "pharmaceutical product." (*Id.*). UTC asserts that Liquidia prepares the pharmaceutical composition during PRINT Steps 1–4 and begins "preparing a pharmaceutical product" at PRINT Step 5. (*Id.*). I disagree. I find that a POSA would understand that Liquidia begins preparing the LIQ861 product at PRINT Step 1, not Step 5.[12] Steps 5 and 6 simply involve encapsulating and packaging the LIQ861 inhalation powder produced in Step 4, i.e., putting it in final dosage form. (Tr. at 455:9–12 (Winkler); DTX 204 at 2). A POSA would understand that the encapsulation and packaging performed during these steps would not change the chemical properties of the bulk LIQ861 inhalation powder produced in Step 4. (Tr. at 455:5–18 (Winkler)). Accordingly, a POSA would understand that Liquidia begins preparing a pharmaceutical product before the final packaging steps.

Any "storage" between steps in the PRINT process thus cannot meet the limitations of claims 8 and 9, which require storage before preparing a pharmaceutical product. I therefore

[12] While I agree with UTC that a POSA would understand the "pharmaceutical product" of claim 8 to be distinct from the "pharmaceutical composition" of claim 6, this does not mean that the preparation of the pharmaceutical composition and pharmaceutical product cannot begin at the same point.

find that UTC has failed to prove infringement of claims 8 and 9 by a preponderance of the evidence.[13]

III. INVALIDITY OF THE '066 PATENT

A. Product-by-Process Claims (Claims 1, 2, 3, 6, and 9)

1. Legal Standard

"In determining validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). "That is because of the . . . long-standing rule that an old product is not patentable even if it is made by a new process." *Id.* at 1370. "If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). However, there is an exception to this general rule when "the process by which a product is made imparts 'structural and functional differences' distinguishing the claimed product from the prior art." *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012) (quoting *Amgen*, 580 F.3d at 1370). "The party asserting anticipation bears the burden of proving that the process limitations do not result in an invention distinguishable from the prior art." *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 668 (D. Del. 2014) (citing *Amgen*, 580 F.3d at 1370), *aff'd*, 805 F.3d 1112 (Fed. Cir. 2015).

2. Findings of Fact

1. The priority date of the '066 patent is December 17, 2007.

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[13] Liquidia also argues that UTC has failed to show that Liquidia uses "a salt of treprostinil stable at ambient temperature" as required by claims 8 and 9. (D.I. 411 at 12). Because I have found that UTC has failed to prove infringement of the storage limitation, I need not address this argument.

2. Treprostinil is also known as UT-15 or treprostinil free acid. (DTX 258 at 1; DTX 674 at 4; Tr. at 408:16–17, 459:5–6, 461:5–6 (Winkler); Tr. at 742:5–9 (Gonda)).

3. A 2004 *Journal of Organic Chemistry* article by Moriarty et al., in relevant part titled "Synthesis of UT-15 (Treprostinil)" ("Moriarty"), teaches the synthesis of 99.7% pure treprostinil free acid, via alkylation and hydrolysis.

4. Moriarty is prior art.

5. The UT-15 treprostinil taught by Moriarty is the same chemical structure as the treprostinil product of claims 1–3, 6, and 9 of the '066 patent.

6. The average purity of UTC's batches of UT-15 treprostinil made by Moriarty and the '066 process are the same: 99.7%.

7. There are no structural or functional differences between the UT-15 treprostinil taught by Moriarty and the treprostinil claimed in the '066 patent.

3. Conclusions of Law

Claims 1, 2, 3, 6, and 9 are product-by-process claims, which claim a "pharmaceutical composition[/product] comprising treprostinil or a pharmaceutically acceptable salt thereof." Liquidia argues that these claims are invalid because the claimed product is the same product previously disclosed in the prior art by the 2004 Moriarty publication.[14] (D.I. 406 at 3).

[14] UTC faults Liquidia for failing to assert Moriarty as a § 102(a) anticipating reference. (D.I. 413 at 14 & n.10). This argument misunderstands Liquidia's invalidity theory. Liquidia claims that Moriarty anticipates under product-by-process law, not that Moriarty anticipates the claimed process steps. UTC did not object to the admission of evidence relating to this anticipation theory at trial. Thus, UTC cannot now argue that Moriarty is not prior art because Liquidia failed to disclose it as such. UTC also (newly) argues that Liquidia has failed to show that Moriarty was enabled. (*Id.* at 15–16). However, it is UTC's burden to prove that Moriarty is not enabled. *Apple Inc. v. Corephotonics, Ltd.*, 861 F. App'x 443, 450 (Fed. Cir. 2021) (nonprecedential) ("[R]egardless of the forum, prior art patents and publications enjoy a presumption of enablement, and the patentee/applicant has the burden to prove nonenablement for such prior art."); *In re Antor Media Corp.*, 689 F.3d 1282, 1289 (Fed. Cir. 2012) ("[D]uring patent prosecution, an examiner is entitled to reject claims as anticipated by a prior art publication or patent without conducting an inquiry into whether or not that prior art reference is enabling. As long as an examiner makes a proper prima facie case of anticipation . . . , the burden

The 2004 article published in the *Journal of Organic Chemistry* by Robert M. Moriarty et al., entitled, in relevant part, "Synthesis of UT-15 (Treprostinil)" ("Moriarty"), teaches the synthesis of treprostinil free acid by alkylation and hydrolysis of BTO. (DTX 258 at 8; Tr. at 461:17–25 (Winkler)). Liquidia argues that the treprostinil product claimed in the product-by-process claims is identical to the treprostinil free acid of Moriarty.

As a preliminary matter, UTC argues that Moriarty cannot invalidate the product-by-process claims because it only discloses treprostinil, not a "pharmaceutical composition[/product] comprising treprostinil." (D.I. 413 at 8–9). The '066 patent, however, makes no distinction between treprostinil and a pharmaceutical composition/product comprising treprostinil. The specification only describes the steps for synthesizing treprostinil or treprostinil salt. (*See* JTX 2 at 9:46–14:54 (Examples 1–5), 17:23 (Example 6, step 51, final yield is "UT-15"); *see also id.* at 5:57–59 ("The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process.")). There is no description of combining treprostinil or treprostinil salt with excipients. Thus, a POSA reading the '066 patent specification would understand that treprostinil is a "pharmaceutical composition[/product] comprising treprostinil." This reading is confirmed by the testimony of both parties' experts. (Tr. at 104:22–105:8 (Nuckolls) (stating that the pharmaceutical composition in claim 1 "could be Treprostinil or the pharmaceutically acceptable [salt thereof]"); Tr. at 462:15–24 (Winkler) (confirming that the product claimed by the product-by-process claims "could just be Treprostinil")).

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shifts to the applicant to submit rebuttal evidence of nonenablement."). UTC has failed to submit such evidence.

Liquidia's expert Dr. Winkler testified that the UT-15 treprostinil disclosed in Moriarty and the '066 treprostinil were structurally and functionally the same. (Tr. at 457:6–480:2 (Winkler)). Specifically, the UT-15 treprostinil disclosed in Moriarty has the same chemical structure as the treprostinil product of claims 1, 2, 3, 6, and 9. (Tr. at 462:25–463:2, 467:3–5 (Winkler). *Compare* DTX 258 at 3 (depicting the chemical structure of UT-15 treprostinil as compound 7), *with* JTX 2 at 14:20–30 (depicting the chemical structure of treprostinil)). Claims 1, 2, 3, 6, and 9 do not claim any purity percentage, impurity profile, or commercial scale production.[15] (Tr. at 460:8–16 (Winkler)). The specification discloses that the treprostinil generated by the claimed process has a purity ranging from 99.7% to 99.9%. (JTX 2 at 14:55–65). The patent further advises, "In one embodiment, the purity of [treprostinil free acid] is at least 90.0%, 95.0%, 99.0%, 99.5%." (*Id.* at 9:22–23). The UT-15 treprostinil disclosed in Moriarty has a purity of 99.7%, which falls within the disclosures of the '066 patent specification. (DTX 258 at 13; Tr. at 462:9–14 (Winkler)).

Dr. Winkler also testified that UTC manufactured UT-15 treprostinil according to both processes. (Tr. at 463:20–22 (Winkler)). He testified that UTC used the Moriarty process in Chicago starting in 1997,[16] and in 2007, UTC moved the manufacturing process to Silver

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[15] UTC argues that the claim limitation requiring that the "level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition" defines the claimed product. (D.I. 413 at 7–8 (citing *In re Nordt Dev. Co.*, 881 F.3d 1371, 1376 (Fed. Cir. 2018))). I disagree. This impurities limitation is a process limitation that requires comparing the level of certain process impurities in the starting batch of treprostinil and the pharmaceutical composition, as shown in the infringement analysis above. This limitation merely describes the process and does not impart any structural or functional differences in the claimed pharmaceutical composition (as shown in Dr. Winkler's analysis discussed *infra*). *See In re Nordt*, 881 F.3d at 1375–76; *Greenliant*, 692 F.3d at 1268–69.

[16] UTC argues that Dr. Winkler failed to show that UTC's former Chicago process was the same process disclosed in Moriarty. (D.I. 413 at 17–19). In reaching this conclusion, Dr. Winkler compared the Moriarty paper and the description of the Chicago process and determined that

Spring, Maryland and changed to the '066 process. (Tr. at 464:15–465:2 (Winkler) (citing DTX 627A); Tr. at 546:1–4 (Batra); DTX 619). UTC told the FDA that the products made by both processes were the "same" and "equivalent." (DTX 70 at 3 ("[T]he lots of treprostinil API produced by the new process in Silver Spring are of the same high quality and purity as the commercial lots of API produced by the existing process at the Chicago facility."); DTX 619 at 10 ("The release data for the drug substance batch prepared by the revised route of synthesis indicate that it is of equivalent quality to the batches produced by the current synthetic route, particularly with respect to the assay and purity profile."); DTX 646 at 4–5 ("[T]he simplified chemical synthesis of treprostinil will provide API that meets the same acceptance criteria as API obtained from the 20-step chemical synthesis, with a very similar impurity profile and similar acceptance criteria.")).

UTC used both processes to make treprostinil free acid for its drug Remodulin®. (Tr. at 467:17–468:3 (Winkler); Tr. at 545:7–19 (Batra); JTX 2 (titled "Process to Prepare Treprostinil, The Active Ingredient in Remodulin®")). UTC never represented to the FDA that the UT-15 treprostinil made according to the '066 patent in Silver Spring was safer, less toxic, or purer than the UT-15 treprostinil made according to Moriarty in Chicago. (Tr. at 469:7–14, 478:23–479:21 (Winkler)). Based on this, Dr. Winkler concluded that a POSA would understand there not to

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they recited the same reactions. (Tr. at 519:18–22, 520:9–21 (Winkler)). Dr. Winkler also relied on one of the inventors, Dr. Batra, who testified that "Moriarty's process" "might be one of the terms" used to describe the Chicago process. (Tr. at 546:5–10 (Batra); *see also* JTX 2 at 1:28–31 ("Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty . . . .")). No UTC witness disputed Dr. Winkler's statement that the Moriarty process was used in Chicago. In fact, UTC's witnesses relied on documents comparing the Chicago and Silver Spring products to demonstrate a structural difference. (*See* Tr. at 783:21–786:17 (Bunce); Tr. at 793:16–794:12, 799:4–802:19 (Walsh)). I therefore credit Dr. Winkler's testimony that the "Chicago process" and "Moriarty process" are the same.

be any "efficacy, toxicity," or "biological activity" differences between the treprostinil made according to Moriarty and the '066 treprostinil. (Tr. at 479:12–21 (Winkler)).

Dr. Winkler further testified that UTC had identical specification limits (with respect to unidentified impurities, identified impurities, and total related substances) on allowable impurities between the two processes' products. (Tr. at 469:15–471:23 (Winkler). *Compare* DTX 151 at 1 (Silver Spring Product Certificate of Analysis from 2020), *and* DTX 627A at 5–6 (Silver Spring Process Optimization Batches Release Testing Data), *with* DTX 627A at 7 (Chicago Release Testing Data)). UTC increased its purity assay range from 97–101% (Chicago) to 98–102% (Silver Spring). (Tr. at 784:23–786:9 (Bunce); DTX 70 at 3; DTX 151 at 1; DTX 627A at 7). But Dr. Winkler testified that the purity of 96 batches of treprostinil made by the Chicago process was 98.9%–100.3%, within both the 97–101% and 98–102% ranges. (Tr. at 470:21–473:5 (Winkler)). Dr. Winkler testified, and UTC did not refute, that the average purity of UTC's batches of UT-15 treprostinil made by the Chicago process and the Silver Spring process were the same: 99.7%. (Tr. at 473:16–477:18 (Winkler) (relying on the purity data submitted during the IPR for UTC's U.S. Patent No. 8,497,393 (DTX 664 at App. A ("Sample of product of Moriarty process")))).

No UTC expert or fact witness rebutted Dr. Winkler's opinions or provided testimony identifying any structural or functional difference between the Moriarty treprostinil free acid and the claimed treprostinil free acid product/composition. UTC only provided evidence relating to the functional and structural differences between the Moriarty treprostinil free acid and the claimed treprostinil salt product/composition. Dr. Walsh (inventor and former UTC employee) testified that the '066 process greatly reduced the 3AU90 impurity (an isomer of treprostinil) as compared to UTC's former Chicago process. (Tr. at 793:2–794:5, 795:12–796:12, 797:11–

802:19 (Walsh)). Dr. Walsh, however, did not compare the Moriarty treprostinil free acid prepared in Chicago and the claimed treprostinil free acid product/composition. Instead, he compared the treprostinil free acid prepared at the Chicago facility and the treprostinil diethanolamine salt prepared by the '066 process. (Tr. at 803:1–12 (Walsh)). Dr. Walsh confirmed that treprostinil diethanolamine salt is a different compound from treprostinil free acid. (Tr. at 804:17–19 (Walsh)). Thus, Dr. Walsh's testimony fails to identify any structural or functional differences between the treprostinil products.

UTC also argues that the '066 patent's "capability for making a pharmaceutical composition from treprostinil salt that had been stored at ambient temperature is novel over the prior art." (D.I. 413 at 24). UTC is improperly focusing on the process limitations of the claims. The storage and stability limitations in claims 6 and 9 relate to the intermediate salt generated during the process steps, not the final composition/product. The claims do not cover any stability or storage of the final treprostinil product. Nor is this "capability" a structural or functional difference which appears in the claimed product. Instead, UTC admitted that the claimed treprostinil free acid was not stable at room temperature, which presents no improvement over the Moriarty UT-15 treprostinil. (Tr. at 964:19–965:7 (UTC Closing)).

The product-by-process claims recite a "pharmaceutical composition[/product] comprising treprostinil *or* a pharmaceutically acceptable salt thereof." Thus, if the treprostinil product is anticipated, then the claims are invalid, regardless of whether the treprostinil salt is anticipated. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art."). UTC has not provided any evidence or expert testimony which compares the

claimed treprostinil free acid to the Moriarty UT-15 treprostinil, instead choosing to focus on the claimed treprostinil salt. Accordingly, there is no record evidence that contradicts Dr. Winkler's testimony that the claimed treprostinil product and Moriarty UT-15 treprostinil are the same.

Liquidia has shown by clear and convincing evidence that the claimed treprostinil product is functionally and structurally the same as the UT-15 treprostinil disclosed in Moriarty. Thus, I find that claims 1, 2, 3, 6, and 9 of the '066 patent are invalid as anticipated.

B. Written Description (Claims 1, 2, 3, and 6)

1. Legal Standard

The written description requirement contained in 35 U.S.C. § 112 requires that the specification "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "When determining whether a specification contains adequate written description, one must make an 'objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.'" *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (quoting *Ariad*, 598 F.3d at 1351).

The written description inquiry is a question of fact. *Ariad*, 598 F.3d at 1351. "A party must prove invalidity for lack of written description by clear and convincing evidence." *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 682 (Fed. Cir. 2015).

2. Findings of Fact

1. A POSA reading the '066 patent specification would have understood that the alkylation step results in a light brown material, the hydrolysis step

results in a pale yellow material, and the salt formation step results in an off-white material, indicating the generation and lowering of impurities from the alkylation and hydrolysis steps.

2. TLC may be used to qualitatively see the presence of impurities generated as the reaction proceeds. A POSA would have understood from the specification disclosure that monitoring the progress of a reaction by TLC would include identification of impurities generated during the reaction step.

3. Conclusions of Law

Liquidia asserts that there is no written description support for claim 1's limitation requiring that "a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition." Claim 1 further requires "a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps . . . wherein said alkylation is alkylation of benzindene triol."

The specification provides adequate written description support for the impurities limitation. Specifically, the specification provides, "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." (JTX 2 at 17:29–32). Liquidia argues that this passage does not provide adequate written description support because it does not specify whether the impurities that are reduced are from the alkylation and hydrolysis of BTO. (D.I. 406 at 12–13). This argument, however, is based on Liquidia's narrow claim construction, which I rejected above. A POSA would understand that claim 1 encompasses any impurity generated during the alkylation and hydrolysis steps. Thus, based on this language in the specification, a POSA would understand that the inventors were in possession of the impurities limitation. (*See* Tr. at 818:1–22 (Scheidt)).

Yet, Liquidia argues that since the specification does not report the level of impurities generated during the alkylation and hydrolysis steps, the '066 patent does not provide any

written description of a "level of one or more impurities found in the starting batch of treprostinil" to compare to the pharmaceutical composition. (Tr. at 480:25–482:7 (Winkler); *see* JTX 2 at 9:49–10:37, 10:40–11:49). Liquidia argues, "[T]here is insufficient data and information in the specification of the '066 patent for a POSA to make such a comparison as claimed." (D.I. 406 at 10). This argument is not a written description argument; it might be an enablement argument. The specification need not report quantitative impurities data to provide written description support. While the '066 patent does not disclose quantitative impurities measurements, it provides qualitative measures that would alert a POSA to the generation and reduction of impurities as claimed.

As UTC's expert Dr. Scheidt testified, the '066 patent describes that the alkylation step results in a light brown material, the hydrolysis step results in a pale yellow material (i.e., the starting batch of treprostinil), and the salt formation step results in an off-white material. (Tr. at 810:13–811:1 (Scheidt); JTX 2 at 9:49–10:37 (alkylation of benzindene triol), 10:40–11:49 (hydrolysis of benzindene nitrile), 14:1–54 (conversion of treprostinil diethanolamine salt to treprostinil)). Dr. Scheidt credibly testified that a POSA would understand that these color changes indicate the generation and lowering of impurities from the alkylation and hydrolysis steps. (Tr. at 811:17–812:5, 817:5–25, 819:7–18 (Scheidt); *see also* Tr. at 484:2–8, 488:3–15, 532:16–24 (Winkler) (acknowledging that changes in color can indicate the presence of an impurity)). Liquidia faults Dr. Scheidt's analysis because the color differences do not show the specific impurity or the amount of impurity removed. (D.I. 406 at 11). This argument, however, relies on Liquidia's erroneous construction. A POSA would understand that claim 1 encompasses any impurity generated during the alkylation and hydrolysis steps. Further, the

claim simply requires the lowering of the impurities, so the specification need not disclose the specific amount of impurities removed to provide adequate written description support.

The '066 patent specification also provides that the progress of the alkylation and hydrolysis reactions were monitored by thin layer chromatography ("TLC"). (JTX 2 at 10:30–32, 11:13–16). TLC may be used to qualitatively see the presence of impurities generated as the reaction proceeds. (Tr. at 812:9–814:16 (Scheidt)). Although the patent does not disclose the use of TLC to identify or measure impurities, I credit Dr. Scheidt's testimony that a POSA would understand that the TLC would include identification of impurities generated during the reaction steps. (*Id.*).

I find that these disclosures in the '066 patent "reasonably convey[] to those skilled in the art that the inventor had possession" of the impurities limitation.[17] *Ariad*, 598 F.3d at 1351. Liquidia has not proven by clear and convincing evidence that claims 1, 2, 3, and 6 of the '066 patent are invalid for lack of written description.

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[17] Liquidia relies on inventor testimony to show that the inventors did not possess the impurities limitation. (D.I. 406 at 10, 12–13). This inventor testimony does not alter my conclusion. The test for written description "requires an objective inquiry into the four corners of the specification." *Ariad*, 598 F.3d at 1351. The disclosures in the '066 patent reasonably convey possession of the claimed impurities limitation. I therefore see no reason to look beyond the four corners of the specification. *See Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 28 F.4th 1194, 1202 (Fed. Cir. 2022) (Lourie, J., dissenting from the denial of the petition for rehearing en banc) ("Where the disclosure in a patent's specification plainly corresponds to what is claimed, extrinsic evidence should not be used to cast doubt on the meaning of what is disclosed."). Even if I were to consider the inventor testimony, I would find that it does not provide clear and convincing evidence that the claims lack written description.

IV. INFRINGEMENT OF THE '793 PATENT

A. Legal Standard

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). To prevail on a claim of induced infringement, the plaintiff must show (1) "that there has been direct infringement," and (2) "that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018) (internal citation omitted).

In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed []NDA product were marketed, it would infringe the [asserted claims]." *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018). For method-of-treatment patents, if an NDA applicant's "proposed label instructs users to perform the patented method[,] . . . the proposed label may provide evidence of [the NDA applicant's] affirmative intent to induce infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). In that setting, the Federal Circuit has explained, "The label must encourage, recommend, or promote infringement." *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). Evidence that a proposed label will "inevitably lead some consumers to practice the claimed method" can suffice to support a finding of specific intent to induce infringement. *AstraZeneca*, 633 F.3d at 1060.

B. Asserted Claims of the '793 patent

> **1.** A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

4. The method of claim 1, wherein the inhalation device is a dry powder inhaler.

6. The method of claim 4, wherein the formulation is a powder.

7. The method of claim 6, wherein the powder comprises particles less than 5 micrometers in diameter.

8. The method of claim 1, wherein the formulation contains no metacresol.

C. Findings of Fact

1. A POSA would have a medical degree with a specialty in pulmonology or cardiology, plus at least two years of experience treating patients with PH as an attending, including with inhaled therapies, or equivalent degree or experience.

2. LIQ861 is administered "3 to 5 times per day." Each administration is a single event dose.

3. LIQ861 is administered in a single event dose that is therapeutically effective.

4. Treprostinil is a vasodilator that reduces vasoconstriction in the pulmonary vasculature, causing vasodilation (widening of vasculature) and reduction of pulmonary artery pressure ("PAP") and pulmonary vascular resistance ("PVR").

5. A single administration of treprostinil will improve a patient's hemodynamics.

6. A single administration of LIQ861 will have positive hemodynamic effects, i.e., reduce PAP and PVR.

7. Liquidia has knowledge of the '793 patent.

8. Liquidia's proposed LIQ861 label teaches all elements of the asserted claims of the '793 patent.

9. Knowing that the method of administering LIQ861 is infringing, Liquidia will encourage, recommend, and promote use of LIQ861 in an infringing manner, including by providing the label, patient instructions, and additional training and other information to physicians and patients.

D. Conclusions of Law

1. Act of Direct Infringement

Liquidia argues that UTC has failed to prove that LIQ861 is administered in "a therapeutically effective single event dose," as required by claim 1 and therefore every asserted claim.[18]

Liquidia argues that claim 1 is limited to one single event dose per day rather than multiple doses per day. (D.I. 411 at 13). Liquidia reasons that claim 1 recites a "single event dose" rather than simply a "dose." (*Id.*). Liquidia's argument lacks merit. The term "single" modifies "event," not "dose." The experts agree that "single event dose" refers to a dose that is delivered in a single treatment session (i.e., a "single event"), including a session that involves multiple breaths. (Tr. at 675:4–15 (Waxman); Tr. at 704:25–705:9 (Hill)).

The claim language does not limit the number of single event doses per day. The claim recites the administration of "a" single event dose. The Federal Circuit "has repeatedly emphasized that an indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising.'" *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000). There is no language in the claims or specification that necessitates a departure from this general rule. *See Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342–43 (Fed. Cir. 2008) ("An exception to the general rule that 'a' or 'an' means more than one only arises where the language of the claims themselves, the specification, or the prosecution history necessitate a departure from the rule.").

[18] Liquidia does not dispute infringement of the remaining limitations in claims 1, 4, 6, 7, and 8. (*See* D.I. 411 at 12–17).

The specification is consistent with the general meaning of "a." The specification expressly states, "Treprostinil can be administered a single time per day or several times per day." (JTX 3 at 8:1–2). Further, based on treprostinil's three- to four-hour half-life, a POSA would understand that a patient would need to receive more than one single event dose per day. (Tr. at 704:9–24 (Hill)). Accordingly, I conclude that the scope of claim 1 is not limited to one single event dose per day. I find that LIQ861 is administered in a single event dose. The proposed LIQ861 label states that LIQ861 "should be administered 3 to 5 times per day." (PTX 469 at 4). Each administration is a single event dose. (*See* Tr. at 676:15–20 (Waxman); Tr. at 705:1–9, 707:5–22 (Hill)).

The parties agree that claim 1 requires that each "single event dose" be "therapeutically effective." (Tr. at 651:5–22 (Waxman); Tr. at 683:2–9 (Hill)). The parties, however, dispute the plain and ordinary meaning of "therapeutically effective." UTC's expert Dr. Waxman testified that a therapeutically effective single event dose is one that causes a positive change in a patient's hemodynamics—i.e., "a therapeutically effective dose should cause a reduction in pulmonary artery pressure and cause a reduction in pulmonary vascular resistance." (Tr. at 651:3–22 (Waxman)). In contrast, Liquidia's expert Dr. Hill testified that a single event dose is therapeutically effective when it causes an "improvement in symptoms, in function, and/or in survival." (Tr. at 685:15–21 (Hill)). Based on the teachings of the '793 patent, I agree with Dr. Waxman that a POSA would understand the plain and ordinary meaning of "therapeutically effective single event dose" to be a dose given in a single treatment session that causes an improvement in a patient's hemodynamics (reduced PAP or PVR).

The examples in the specification studied the hemodynamic effects after a single event dose of treprostinil. (*See, e.g.*, JTX 3 at 8:57–18:11; 9:11–21 ("Pulmonary hemodynamics and

blood gases were measured at defined time points . . . . [Inhaled treprostinil sodium] doses of 30 µg, 45 µg and 60 µg reduced pulmonary vascular resistance (PVR) . . . . Reduction of PVR by a single inhalation of the two higher doses outlasted the observation period of 120 minutes."); 11:62–66 ("The application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution.")). The examples in the patent do not report long-term measures like patient survival rate. (*See* Tr. at 702:12–20 (Hill)). A POSA reading the '793 patent would thus understand that a single event dose is therapeutically effective when it improves a patient's hemodynamics.

I find that UTC has proven by a preponderance of the evidence that LIQ861 is administered in a therapeutically effective single event dose. Treprostinil is a vasodilator that reduces vasoconstriction in the pulmonary vasculature, causing vasodilation (widening of vasculature) and reduction of PAP and PVR. (Tr. at 650:20–25 (Waxman); Tr. at 700:13–17 (Hill) (acknowledging that "the goal of using a vasodilator such as Treprostinil is to reduce the pulmonary arterial pressure and/or pulmonary vascular resistance")). Both experts agree that the '793 patent shows that the claimed single-event dosing of treprostinil improves a patient's hemodynamics. (Tr. at 637:22–25 (Waxman); Tr. at 702:1–4 (Hill) (agreeing that the '793 patent shows hemodynamic effectiveness from treprostinil); *see also* Tr. at 702:5–11 (Hill) (agreeing that on average, "a single administration of Treprostinil to someone suffering from pulmonary hypertension results in a beneficial reduction of pulmonary arterial pressure and/or vascular resistance")).

Liquidia argues that these disclosures are not evidence that a single event dose of LIQ861 will have hemodynamic effects because LIQ861 is administered in a completely different form than Tyvaso®. (D.I. 411 at 15). LIQ861 is a dry powder formulation, while Tyvaso® is a

liquid formulation delivered to the patient via a nebulizer. (Tr. at 696:6–12 (Hill)). But, as Dr. Hill acknowledged, Tyvaso® and LIQ861 involve the same molecule (treprostinil). (Tr. at 711:4–6 (Hill)). Dr. Hill testified that, because they involve the same molecule, he would expect Tyvaso® and LIQ861 to have similar effects on PAP and PVR. (Tr. at 711:4–11 (Hill); *see also* Tr. at 694:20–695:2 (Hill) (after a single event dose of LIQ861, "There might be a transient improvement in hemodynamics. There might be no effect on the hemodynamics, but in the longer term, the effect would dissipate within hours, and you would expect no therapeutic effect beyond those first few hours.")). In fact, Liquidia relied on Tyvaso®'s safety and efficacy data in its NDA. (PTX 573 at 7 ("The NDA for LIQ861 inhalational powder . . . rel[ies] on the FDA's previous finding of safety and effectiveness for Tyvaso, the selected reference listed drug (RLD) for demonstration of the effectiveness of treprostinil in the treatment of PAH."); *see also* PTX 1213 (demonstrating that LIQ861 and Tyvaso® have the same bioavailability)).

UTC's evidence shows that a single administration of treprostinil will improve a patient's hemodynamics, and thus proves by a preponderance of the evidence that a single administration of LIQ861 at the claimed doses will improve a patient's hemodynamics. I therefore find that UTC has proven by a preponderance of the evidence that the administration of LIQ861 will directly infringe claims 1, 4, 6, 7, and 8 of the '793 patent.

2. Specific Intent to Induce Infringement

Liquidia argues that it lacks specific intent to induce infringement because the proposed LIQ861 label does not encourage administration of a "therapeutically effective single event dose." (D.I. 411 at 16–17). Liquidia argues that the label does not "instruct[] that LIQ861 produces hemodynamic changes after a single event dose" because the label does not contain any

hemodynamic data or instruction to doctors to measure hemodynamic changes after a single event dose. (*Id.*). The label, however, does not need to provide hemodynamic data to induce infringement. It just needs to instruct doctors and patients to administer a single event dose that is therapeutically effective. *See AstraZeneca*, 633 F.3d at 1060 (finding that evidence that a proposed label will "inevitably lead some consumers to practice the claimed method" can suffice to support a finding of intent to induce infringement). The LIQ861 label does so by instructing doctors and patients to administer LIQ861 "3 to 5 times per day" at the claimed doses. (*See* PTX 469 at 4–6). As discussed above, UTC has proven that a single administration of LIQ861 will be therapeutically effective. Thus, the label's instructions will "inevitably lead" to the administration of a "therapeutically effective single event dose."[19] UTC has met its burden to show intent to induce infringement.

I therefore find that UTC has proven by a preponderance of the evidence that Liquidia will induce infringement of claims 1, 4, 6, 7, and 8 of the '793 patent.

On July 19, 2022, the PTAB issued a Final Written Decision in the IPR of the '793 patent, invalidating all claims of the '793 patent as obvious. *Liquidia Techs., Inc. v. United Therapeutics Corp.*, No. IPR2021-00406, 2022 WL 2820717 (P.T.A.B. July 19, 2022). Liquidia argues that it therefore cannot be liable for induced infringement under the Supreme Court's decision in *Commil*. (D.I. 427).

[19] Liquidia also argues that the label does not encourage patients to use LIQ861 as a "single event dose" because the label instructs doctors and patients to administer LIQ861 "3 to 5 times per day." (D.I. 411 at 16–17). But, as discussed above, claim 1 is not limited to one single event dose per day. The LIQ861 label instructs and encourages the administration of LIQ861 as a "single event dose."

In *Commil*, the Supreme Court held that an accused infringer's "belief regarding patent validity" is not a defense to a claim of induced infringement. *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 642 (2015). The Supreme Court also stated, "[I]f . . . an act that would have been an infringement or an inducement to infringe pertains to a patent that is shown to be invalid, there is no patent to be infringed." *Id.* at 644. The Supreme Court further explained, "An accused infringer can, of course, attempt to prove that the patent in suit is invalid; if the patent is indeed invalid, and shown to be so under proper procedures, there is no liability." *Id.* The Supreme Court never stated, however, that a PTAB decision invalidating patent claims in an IPR will preclude liability before it becomes final and nonappealable. *Id.* at 644–45. The Court simply stated that an IPR proceeding is one procedure through which an accused infringer can pursue an invalidity challenge. *Id.* at 645. I therefore do not think that *Commil* compels this Court to treat the '793 patent as invalid for purposes of assessing Liquidia's induced infringement. (*See* D.I. 427 at 1).

Instead, the Federal Circuit has indicated that an IPR decision does not have collateral estoppel effect until that decision is affirmed or the parties waive their appeal rights. *See XY, LLC v. Trans Ova Genetics*, 890 F.3d 1282, 1294 (Fed. Cir. 2018) ("[A]n affirmance of an invalidity finding, whether from a district court or the Board, has a collateral estoppel effect on all pending or co-pending actions."); *Papst Licensing GMBH & Co. KG v. Samsung Elecs. Am., Inc.*, 924 F.3d 1243, 1249 (Fed. Cir. 2019) (finding IPR decision became final after appeals were voluntarily dismissed). Further, the PTAB's FWD does not cancel claims. The claims are cancelled when the Director issues a certificate confirming unpatentability, which only occurs after "the time for appeal has expired or any appeal has terminated." 35 U.S.C. § 318(b); *see*

also Fresenius USA, Inc. v. Baxter Int'l, Inc., 721 F.3d 1330, 1346 (Fed. Cir. 2013) ("[I]t could hardly be clearer that Congress meant for cancellation to terminate pending suits.").

Therefore, I find that the PTAB's decision—which is not yet final—has no impact on my finding of induced infringement.

V. INVALIDITY OF THE '793 PATENT

A. Legal Standard

A patent's specification must enable the claimed invention. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999). For a patent claim to be enabled, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]" 35 U.S.C. § 112(a). "The enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (citation omitted). Factors for assessing whether a disclosure would require undue experimentation include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

"Enablement is a question of law based on underlying facts." *Wyeth & Cordis Corp. v. Abbott Lab'ys*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). The party challenging validity must prove lack of enablement by clear and convincing evidence. *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013).

B. Findings of Fact

1. The '793 patent has a priority date of May 15, 2006.

2. With respect to treating PH, a POSA would have a medical degree with a specialty in pulmonology or cardiology, plus at least two years of experience treating patients with PH as an attending, including with inhaled therapies, or equivalent degree or experience. With respect to inhaled formulations used in treating PH, a POSA would have a Ph.D. in pharmaceutical science or a related discipline like chemistry or medicinal chemistry, plus two years of experience in pharmaceutical formulations, including inhaled products, or equivalents (e.g., an M.S. in the same fields, plus five years of experience).

3. A POSA would understand "treating pulmonary hypertension," as claimed, to encompass treating all five WHO Groups of pulmonary hypertension ("PH"), including both isolated Group 2 (also referred to as isolated postcapillary Group 2) and pre- and postcapillary combined Group 2.

4. Treprostinil is a member of the family of compounds referred to as prostacyclins or prostacyclin analogs. (JTX 3 at 5:37–39; Tr. at 573:21–22 (Hill)). Prostacyclins dilate, or widen, the blood vessels of the lungs. (Tr. at 574:10–15 (Hill)).

5. A POSA would understand that the claimed administration of treprostinil vasodilates the pulmonary vasculature and reduces PAP and PVR, even in Group 2 PH patients.

6. The processes involved in developing dry powder formulations were well known as of 2006 and utilized routine techniques for both manufacturing and analysis.

7. Numerous dry powder inhaler ("DPI") devices were available by 2006.

8. By 2006 it was common for a POSA to develop a powder blend and then choose an available DPI for delivery of the powder formulation. Not all DPI devices need to be separately developed or specifically chosen for a given patient population.

9. Using well-known and routine techniques, Dr. Smyth prepared treprostinil free acid and treprostinil diethanolamine dry powder formulations that delivered doses within the claimed 15–90 μg range with three weeks of testing. Dr. Smyth's testing demonstrated that PH patients could effectively inhale these dry powder formulations using a DPI.

10. Selecting a suitable form of treprostinil was routine as of 2006. Methods for determining suitable forms, including salt forms, of a particular API were well known and routine for several decades prior to 2006.

11. Lactose was the only FDA-approved carrier in 2006 and was also the most common excipient for use in dry powder inhalers.

12. The Maillard reaction was well known and understood as of 2006. A POSA would have understood how to monitor any Maillard reaction between treprostinil diethanolamine and lactose.

13. Meyer (PTX 1980) was available before the priority date and discloses that PH patients were able to obtain maximum inspiratory efforts of 5.2 kPa in females and 6.8 kPa in males, which is enough to use a DPI.

C. Conclusions of Law

1. Enablement of "Treating Pulmonary Hypertension"

The asserted claims of the '793 patent recite: "A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof . . . ." Liquidia argues that the full scope of "treating pulmonary hypertension" is not enabled.

Before addressing enablement, I must first resolve the parties' claim construction dispute. Liquidia asserts that the phrase "treating pulmonary hypertension" encompasses treating all five WHO groups of pulmonary hypertension ("PH"). (D.I. 406 at 14). UTC argues that the claims are limited to treating precapillary PH. (D.I. 413 at 29–30).

PH refers to abnormally high blood pressure in the lungs. (Tr. at 562:13–14, 563:18–21 (Hill); Tr. at 629:9–630:1, 677:21–678:7 (Waxman)). PH includes a range of conditions classified in five different WHO groups: Group 1, pulmonary arterial hypertension; Group 2, pulmonary venous hypertension, i.e., PH related to left heart disease; Group 3, PH associated with disorders damaging the lungs; Group 4, PH caused by chronic thrombotic or embolic disease, including chronic blood clots in the lungs; and Group 5, a miscellaneous category for conditions that do not fit well into the other four groups. (JTX 3 at 1:41–46; Tr. at 564:19–566:7, 575:22–576:4 (Hill); Tr. at 609:18–610:11 (Rubin); DTX 385 at 2).

PH Groups 1, 3, and 4 are classified as "precapillary" PH as they are characterized by conditions affecting the pulmonary arteries or precapillary vessels. (Tr. at 564:18–566:4, 591:24–592:1 (Hill)). In contrast, the high blood pressure in the lungs of Group 2 PH patients has a different underlying cause. Defects in the left side of the heart cause elevated pressure in the postcapillary veins which reflects back as high pressure in the pulmonary arteries. (Tr. at 565:4–16, 571:17–24 (Hill)). Because the left heart is downstream (in terms of blood flow) of the pulmonary capillaries, Group 2 PH is sometimes referred to as "postcapillary" PH. (Tr. at 564:5–17, 565:4–16 (Hill); Tr. at 630:10–17 (Waxman)). Group 2 PH patients can suffer from isolated postcapillary PH or combined pre- and postcapillary PH. (Tr. at 571:10–14 (Hill); Tr. at 659:8–14 (Waxman)). In combined Group 2 PH patients, the precapillary vessels undergo changes similar to those in precapillary Group 1 PH. (Tr. at 571:10–572:8 (Hill)).

Because the cause of postcapillary PH is the left heart, not precapillary resistance, the "mainstay of treatment" by POSAs for postcapillary PH is a diuretic, not a vasodilator like treprostinil. (Tr. at 636:1–5 (Waxman); *see also* Tr. at 587:5–588:5, 600:2–9 (Hill) (stating that treating postcapillary PH patients with a vasodilator would be "stupid" because vasodilation can lead to pulmonary edema)).

Claim 1 requires "treating pulmonary hypertension comprising administering . . . treprostinil," a vasodilator. Based on this language, UTC argues that a POSA would understand claim 1 to be limited to "treating varieties of PH where using a vasodilator addresses the cause of the disease." (D.I. 413 at 30). Thus, because both experts agree that a POSA would not treat postcapillary PH with treprostinil, UTC contends that a POSA would read the claim to be limited to the treatment of precapillary PH.

This expert testimony, however, is no substitute for the clear disclosures in the '793 patent specification. The specification expressly includes all five Groups when describing "pulmonary hypertension." (JTX 3 at 1:41–45 ("Pulmonary hypertension may occur due to various reasons and the different entities of pulmonary hypertension were classified based on clinical and pathological grounds in 5 categories according to the latest WHO convention." (citing DTX 385)); *see also id.* at 1:37–38 ("Generally, pulmonary hypertension is defined through observations of pressures above the normal range . . . .")). The specification does not contain any disclosures which limit the scope of "pulmonary hypertension" to any particular subset of PH patients. Instead, the specification refers to both "precapillary pulmonary hypertension" and "pulmonary hypertension," demonstrating that the inventors viewed precapillary PH as a subset of the broadly claimed "pulmonary hypertension." (*Id.* at 9:36–37, 12:64–65, 16:64–65).

Based on these clear disclosures in the specification, I conclude that the scope of "treating pulmonary hypertension" includes treating all five Groups of PH.

Returning to enablement, Liquidia argues that it would require undue experimentation to practice the full scope of the claimed "treating pulmonary hypertension," specifically treating Group 2 PH patients. (D.I. 406 at 15–19). Dr. Hill testified that as of May 15, 2006, a POSA would have had significant safety concerns about administering inhaled treprostinil to treat Group 2 PH patients. (Tr. at 592:3–593:18 (Hill)). Several studies have indicated that Group 1 PH therapies like prostacyclins could exacerbate symptoms in Group 2 PH patients. In the FIRST trial, patients with Group 2 PH were treated intravenously with the prostacyclin epoprostenol. (Tr. at 582:12–583:23 (Hill)). Because more people died in the epoprostenol treatment group than in the control group, the study was prematurely stopped. (Tr. at 583:4–13,

585:10–14, 585:21–586:2 (Hill); DTX 358 at 1, 8–9 ("[C]hronic epoprostenol infusion in severe left ventricular failure resulted in increased mortality rates and no evidence of improved quality of life."); *see also* DTX 385 at 2 (citing the FIRST study when noting "epoprostenol therapy in patients with pulmonary venous hypertension [Group 2 PH] can be harmful")).

The label for Ventavis® (iloprost), which was the only inhaled prostacyclin approved for treatment of Group 1 PH as of May 15, 2006, similarly warned that treatment should be stopped if signs of pulmonary edema occur, as this may be a sign of pulmonary venous hypertension. (DTX 345 at 6; Tr. at 586:6–587:22 (Hill)). Dr. Hill testified that, based on this warning and the results of the FIRST trial, a POSA would have been extremely cautious about using intravenous and inhaled prostacyclins, like treprostinil, in Group 2 PH patients, as such use could create a potentially life-threatening situation in these patients. (Tr. at 587:5–588:5 (Hill)). Prostacyclins dilate the precapillary vessels, which allows more blood to flow through the capillaries and into the pulmonary veins. (*Id.*). According to Dr. Hill, this increased blood flow "could increase the pulmonary venous pressure, the pressure filling the left heart, and that increase in the capillaries can cause leakage of fluid into the gas exchanging areas of the lungs, interfering with oxygenation and creating a potentially life-threatening situation." (*Id.*).

The experts agree that the '793 patent only describes treating Groups 1, 3, and 4 PH, which are all precapillary. (*See* JTX 3 at 8:57–18:20; Tr. at 579:25–580:23, 590:25–592:2 (Hill); Tr. at 634:22–635:13 (Waxman)). Because there are no disclosures in the '793 patent or the prior art establishing the feasibility or safety of treating Group 2 PH patients with inhaled treprostinil, Dr. Hill concluded that a POSA would have had to conduct undue experimentation to treat Group 2 PH with treprostinil. (Tr. at 592:13–593:18 (Hill)). Specifically, a POSA would have had to "start at square one," conducting additional preclinical and clinical trials to

determine whether the treprostinil formulation was safe and effective in treating Group 2 PH patients. (Tr. at 593:2–18 (Hill)).

I have no doubt that a physician would have certain safety concerns about treating Group 2 PH patients—particularly isolated Group 2 PH patients—with treprostinil. (*See* Tr. at 635:16–636:10 (Waxman)). But the fact that a POSA would have safety concerns does not necessarily show a lack of enablement. The claims do not require "*safely and effectively* treating pulmonary hypertension," as Liquidia seems to be arguing. The claims instead require "treating pulmonary hypertension comprising administering . . . a therapeutically effective single event dose of a formulation comprising treprostinil."

As discussed above, a POSA would understand "a therapeutically effective single event dose" to be a dose given in a single treatment session that causes an improvement in a patient's hemodynamics (reduced PAP or PVR). Applying this construction, Liquidia has not shown by clear and convincing evidence that a POSA would have to conduct undue experimentation to practice the claimed method of treating PH.

There is no dispute that the '793 patent enables treatment of patients with Groups 1, 3, 4, and 5 PH. (*See* D.I. 406 at 16–17). The '793 patent describes the invention including the specific drug, conditions the invention is intended to treat (PH), dosages (15–90 µg), and mode and method of treatment (1–3 breaths by inhalation). (JTX 3 at 6:41–45, 7:7–12, 7:55–58, 7:64, 8:20–31, 18:1–6). The '793 patent also describes the improved hemodynamics that result from the use of the claimed invention, and the absence or reduction of side effects. (*Id.* at 8:57–18:11; Tr. at 637:22–638:3 (Waxman); Tr. at 702:1–11 (Hill)).

The record demonstrates that the claimed administration of treprostinil vasodilates the pulmonary vasculature and reduces pulmonary blood pressure, even in isolated Group 2 PH

patients. (*See* Tr. at 582:11–19, 583:14–585:23, 587:5–588:5 (Hill); Tr. at 637:18–640:5 (Waxman); DTX 358). The FIRST study, involving Flolan® (epoprostenol), showed that treating isolated Group 2 PH patients with a prostacyclin had preliminary clinical evidence of benefit and a statistically significant acute hemodynamic improvement, including a reduction of mean PAP, wedge pressure, and PVR, and improvements in exercise duration and dyspnea score. (Tr. at 582:11–19, 583:14–585:23 (Hill); DTX 358 at 1, 5–7). Thus, even with a risk of pulmonary edema, a POSA would understand that the claimed administration of treprostinil would vasodilate the pulmonary vasculature, affect hemodynamics, and treat a patient's elevated pulmonary blood pressure, i.e., treat PH. (*Id.*; JTX 3 at 1:33–40, 2:13–15, 2:30–38; Tr. at 587:5–588:5 (Hill); Tr. at 637:18–640:5 (Waxman)).

Liquidia has thus failed to show by clear and convincing evidence that it would require undue experimentation for a POSA to use treprostinil to improve a patient's hemodynamics, i.e., to treat PH as claimed. The fact that a physician might be cautious and need to monitor the patient more closely when administering treprostinil to isolated Group 2 PH patients does not change this result.

I therefore find that Liquidia has failed to show by clear and convincing evidence that claims 1, 4, 6, 7, and 8 of the '793 patent are invalid for lack of enablement.

2. Written Description of "Treating Pulmonary Hypertension"

Liquidia argues that the asserted claims of the '793 patent are invalid for lack of written description. Specifically, Liquidia contends that the '793 patent fails to convey with reasonable certainty that the inventors possessed the full scope of treating PH as claimed. Liquidia reasons that the '793 patent specification does not describe treating Group 2 PH patients with inhaled treprostinil and does not address the safety concerns that a POSA would have with respect to

treating Group 2 PH patients with treprostinil. (D.I. 406 at 19). But just like its enablement argument, Liquidia's position seems to be based on the flawed premise that the claims require "a method of safely and effectively treating pulmonary hypertension."

As the Federal Circuit has explained, to satisfy the written description requirement, "An inventor need not prove that a claimed pharmaceutical compound actually achieves a certain result. But when the inventor expressly claims that result, our case law provides that such result must be supported by adequate disclosure in the specification." *Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1343 (Fed. Cir. 2021) (cleaned up). The '793 patent claims require "treating pulmonary hypertension comprising administering . . . a therapeutically effective single event dose of a formulation comprising treprostinil." The only effectiveness that is claimed is "a therapeutically effective single event dose of . . . treprostinil." The '793 patent contains adequate written description support for this claimed result.

The '793 patent describes how administering inhaled treprostinil targets the lungs, dilates the blood vessels, and reduces blood pressure. (*See* JTX 3 at 2:29–43, 3:25–5:2, 5:13–36, 8:57–18:11; Tr. at 637:22–25 (Waxman); Tr. at 702:1–11 (Hill)). Even though a POSA might have safety concerns regarding the treatment of isolated Group 2 PH patients, a POSA would understand, based on these disclosures, that treprostinil would effectively vasodilate the pulmonary vasculature, affect hemodynamics, and treat a patient's elevated pulmonary blood pressure. (*Id.*). Accordingly, these disclosures "reasonably convey[] to those skilled in the art that the inventor had possession" of the full scope of treating PH as claimed.

I therefore find that Liquidia has failed to prove by clear and convincing evidence that claims 1, 4, 6, 7, and 8 of the '793 patent are invalid for lack of written description.

3. Written Description of Dry Powder Formulations and Dry Powder Inhaler

Claim 1 of the '793 patent recites using an inhaled "formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device." The parties agree that claim 1 encompasses inhaled liquid solutions delivered via nebulizers, soft mist inhalers, and metered dose inhalers, and dry powder formulations delivered via a dry powder inhaler ("DPI"). (*See* D.I. 406 at 21; D.I. 413 at 35). Further, dependent claims 4, 6, and 7 specifically recite the use of a DPI and a powder formulation of treprostinil. Liquidia argues that the '793 patent does not provide adequate written description support for the claimed dry powder formulation of treprostinil or corresponding DPI suitable for treating PH patients. (D.I. 406 at 21).

The '793 patent specification provides, "The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter." (JTX 3 at 7:22–26). Liquidia argues that this statement is nothing more than a "mere wish or plan" for a powder formulation and that the '793 patent contains no other disclosures relevant to developing a dry powder formulation of treprostinil that can be used for the claimed method of treating PH. (D.I. 406 at 22). I disagree.

The '793 patent describes the delivery of a therapeutically effective bolus dose of 15–90 μg of treprostinil by inhalation in 1–3 breaths without the expected negative side effects. (JTX 3 at Exs. 1 and 2, 17:4–24, 17:42–43, 18:4–6; Tr. at 832:19–833:6, 835:7–13, 836:17–21 (Clark)). The '793 patent demonstrates the efficacy of the claimed bolus dose by presenting data from the administration of a liquid formulation of treprostinil in 1–3 breaths using a soft mist inhaler and an ultrasonic nebulizer. (JTX 3 at Exs. 1 and 2; Tr. at 832:19–833:6 (Clark)).

Liquidia claims that this information regarding liquid formulations in the '793 patent does not inform the development of powder formulations, relying on testimony from the '793 patent inventors Drs. Rubin and Seeger. (D.I. 406 at 21). But Dr. Rubin merely stated that a solution could not be used in a DPI; he never stated that information about an inhaled solution cannot be used to develop a powder formulation. (Tr. at 612:4–5 (Rubin)). Further, Dr. Seeger merely testified, "[B]ringing something down as a powder may or may not be simply identical to bringing something down with the fluid solution." (Tr. at 297:12–23 (Seeger)). These statements are not clear and convincing evidence that information regarding liquid formulations cannot inform the development of powder formulations.

Rather, UTC's expert Dr. Clark credibly testified that the "starting point for developing a powder formulation" is determining the dose and whether it is "safe to deliver it in a single bolus." (Tr. at 833:10–20 (Clark)). Although the '793 patent does not contain any examples of dry powder formulations or DPIs, the '793 patent discloses the bolus dose and demonstrates its efficacy. The patent further states that the claimed bolus dose of treprostinil can be delivered using a DPI with a powder formulation consisting of particles less than ten microns and preferably less than five microns. (JTX 3 at 7:22–26; Tr. at 834:9–15 (Clark)). Numerous DPIs were available by 2006 and the process for developing dry powder formulations was well known and involved routine techniques. (Tr. at 758:8–10, 761:19–23 (Gonda); Tr. at 835:24–836:3, 837:19–838:1 (Clark); PTX 271 at 4; PTX 905).

Given the disclosures in the '793 patent and the state of the art, I find that a POSA would have understood that the inventors possessed a method of treating PH using a dry powder

formulation of treprostinil with a DPI.[20] (*See* Tr. at 832:19–835:16 (Clark)); *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) ("Because the specification is viewed from the perspective of one of skill, in some circumstances, a patentee may rely on information that is 'well-known in the art' for purposes of meeting the written description requirement.").

I therefore find that Liquidia has failed to prove by clear and convincing evidence that claims 1, 4, 6, 7, and 8 of the '793 patent are invalid for lack of written description.

4. Enablement of Dry Powder Formulations and Dry Powder Inhaler

Liquidia argues that the '793 patent does not enable the claimed method of treating PH patients with a dry powder treprostinil formulation and corresponding DPI. (D.I. 406 at 23–28).

The '793 patent does not provide any examples of treprostinil dry powder formulations, methods of manufacture of such powders, or DPI devices for the delivery of such formulations. (Tr. at 729:22–731:14 (Gonda); Tr. at 847:22–25 (Clark)). The processes involved in developing a dry powder formulation, however, were well known as of 2006. (Tr. at 837:19–838:1, 838:15–841:3, 842:6–844:11, 845:17–846:14 (Clark); Tr. at 864:15–865:25, 867:8–870:15 (Smyth)).

Liquidia's expert Dr. Gonda testified that to develop a treprostinil dry powder formulation, a POSA would need to (1) identify a suitable form of treprostinil; (2) identify a suitable carrier that is safe and compatible with the API; and (3) identify a suitable DPI that can

[20] Liquidia also provides inventor testimony and evidence of UTC's agreement with MannKind to show that the inventors did not possess a dry powder formulation of treprostinil as of 2006. (*See* D.I. 406 at 22 & n.4). I have found, however, that the four corners of the specification reasonably convey possession of this limitation. Thus, this extrinsic evidence is irrelevant. *See Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 28 F.4th 1194, 1202 (Fed. Cir. 2022) (Lourie, J., dissenting from the denial of the petition for rehearing en banc) ("Where the disclosure in a patent's specification plainly corresponds to what is claimed, extrinsic evidence should not be used to cast doubt on the meaning of what is disclosed."); *Ariad Pharms.*, 598 F.3d at 1352 ("[T]he written description requirement does not demand . . . an actual reduction to practice[.]").

be used with the formulation to treat PH patients. (Tr. at 734:16–737:11 (Gonda)). Liquidia argues that a POSA would need to perform undue experimentation to perform these steps. (D.I. 406 at 24–25). Yet the experiments conducted by UTC's expert Dr. Smyth show otherwise.

With three weeks of testing, Dr. Smyth prepared treprostinil free acid and treprostinil diethanolamine dry powder formulations that delivered doses within the claimed 15–90 μg range. (Tr. at 863:6–864:14, 870:9–15, 876:18–879:8 (Smyth); PTX 1344; PTX 1345). Dr. Smyth used well-known and routine techniques for each step of his powder development process. (Tr. at 864:15–865:25, 867:8–876:17 (Smyth)). At a high level, Dr. Smyth's experiments involved jet milling the API several times, blending the formulations with lactose, adding the formulations to capsules, and testing the capsules using a DPI device and machine called a Next Generation Impactor, intended to mimic patient inhalation. (Tr. at 864:23–865:3 (Smyth)).

Based on this testing, I find that Liquidia has failed to prove by clear and convincing evidence that a POSA would need to perform undue experimentation to develop a treprostinil dry powder formulation. *See Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306, 352–53 (D. Del. 2020) (finding that defendants failed to prove lack of enablement where plaintiff's expert could successfully practice the claims), *aff'd sub nom. Bristol-Myers Squibb Co. v. Sigmapharm Lab'ys, LLC*, 858 F. App'x 359 (Fed. Cir. 2021).

First, Liquidia has failed to prove that a POSA would need to perform undue experimentation to identify a suitable form of treprostinil. The patent identifies the API to be used in the claimed invention: "treprostinil or a pharmaceutically acceptable salt thereof." (JTX 3 at claim 1; *see also id.* at 6:41–7:6 (defining what constitutes a "pharmaceutically acceptable salt" of treprostinil)). Methods for determining suitable forms, including salt forms, of a

particular API were well known and routine for several decades prior to 2006. (Tr. at 761:4–10 (Gonda); Tr. at 838:19–839:4, 841:4–21 (Clark)).

Dr. Smyth tested three forms of treprostinil: treprostinil free acid, treprostinil diethanolamine salt, and treprostinil sodium. Dr. Smyth was unable to develop a dry powder formulation of treprostinil sodium because it was too hygroscopic. (Tr. at 737:24–740:13 (Gonda); Tr. at 880:19–881:8 (Smyth)). Dr. Smyth attributed this to the lack of humidity control in his lab. (Tr. at 882:9–883:23 (Smyth)). I do not think Dr. Smyth's failure in developing a dry powder formulation of treprostinil sodium shows by clear and convincing evidence that a POSA would require undue experimentation to identify a suitable form of treprostinil. Dr. Smyth used routine techniques to determine that treprostinil sodium would not work. Further, Dr. Gonda testified that a POSA in 2006 would have a laboratory with temperature and humidity control. (Tr. at 762:4–14 (Gonda)).

Liquidia also faults Dr. Smyth's experiments with treprostinil free acid. Treprostinil free acid is not stable at room temperature and has the tendency to form dimers. (DTX 674 at 4; Tr. at 741:20–744:4 (Gonda)). Liquidia argues that despite this, Dr. Smyth did not test the stability of his treprostinil free acid powder formulation. (D.I. 406 at 27). Dr Smyth's failure to conduct additional testing is not clear and convincing evidence that undue experimentation would be required to select a suitable form of treprostinil. Dr. Gonda testified that "stability testing" was known and routine by 2006. (Tr. at 770:15–16 (Gonda)). Further, Liquidia did not perform extensive stability tests in selecting the API for LIQ861. (Tr. at 275:10–24 (Maynor)).

Second, Liquidia has failed to prove that a POSA would require undue experimentation to identify a suitable carrier. Although the '793 patent does not disclose any suitable carriers,

lactose was the only FDA-approved carrier for dry powder formulations as of 2006. (PTX 905 at 13; Tr. at 763:14–21 (Gonda); Tr. at 844:12–15 (Clark); Tr. at 866:1–4 (Smyth)). For this reason, Dr. Smyth selected lactose as the carrier for his dry powder formulations. (Tr. at 866:1–4 (Smyth)).

Dr. Gonda testified that "a POSA would have been reluctant to use lactose" as a carrier with treprostinil diethanolamine because lactose reacts with amines by the Maillard reaction. (Tr. at 754:1–11 (Gonda); *see also* DTX 481).[21] According to UTC's expert Dr. Clark, however, the Maillard reaction would not deter a POSA from attempting to formulate an amine drug with lactose unless the POSA witnessed an adverse reaction. (Tr. at 844:16–845:2 (Clark)). Dr. Clark reasoned that in 2006, the Physician's Desk Reference—which generally only describes approved drugs—described 72 examples of amine drugs formulated with lactose. (Tr. at 844:12–23 (Clark); Tr. at 866:5–867:7 (Smyth); PTX 47 at 2). Further, a POSA would have understood how to monitor any Maillard reaction between treprostinil diethanolamine and lactose. (Tr. at 844:16–845:2 (Clark); PTX 47 at 2; DTX 481 at 5). There is no evidence that Dr. Smyth noticed any Maillard reaction with treprostinil diethanolamine. (*See* Tr. at 867:22–870:15 (Smyth)). I am therefore not convinced that a POSA would require undue experimentation to select an appropriate carrier.

Third, Liquidia has not proven that identifying a suitable DPI for PH patients would require undue experimentation. A 2005 publication by Meyer et al. discloses that PH patients were able to obtain maximum inspiratory efforts of 5.2 kPa in females and 6.8 kPa in males,

[21] There is no amine in the treprostinil molecule itself, so a POSA would have no concern about the Maillard reaction with respect to combining treprostinil free acid and lactose. (Tr. at 767:23–768:8 (Gonda)).

which is enough to use a DPI. (PTX 1980 at 1; Tr. at 851:20–852:1, 852:14–854:20 (Clark)). Dr. Smyth's analytical testing involved the use of a Next Generation Impactor simulating a single breath at 4.0 kPa and 4.0L through a Plastiape RS01 low resistance inhaler (which was available as of 2006). (Tr. at 869:22–870:8 (Smyth); Tr. at 845:17–846:8 (Clark); PTX 905 at 7).[22] Dr. Smyth's testing resulted in an average emitted dose of 53.54 µg for treprostinil free acid and 52.60 µg for treprostinil diethanolamine, falling well within the claimed range of 15–90 µg. (PTX 1344 at 2; PTX 1345 at 2). Dr. Smyth's testing demonstrated that PH patients could effectively inhale his dry powder formulations using a DPI.

I find that a POSA reading the '793 patent would be able to develop a dry powder formulation of treprostinil and a corresponding DPI for treatment of PH with routine experimentation. Notably, Liquidia and its experts did not perform any experiments attempting to make dry powder formulations. Liquidia instead tries to discredit Dr. Smyth's testing. But, for the reasons discussed above, these efforts do not amount to clear and convincing evidence that a POSA would require undue experimentation. That Dr. Smyth would not administer his dry powder formulations to PH patients without conducting more studies makes no difference. (*See* D.I. 406 at 28). Of course, there is no expectation that Dr. Smyth test his formulations on actual patients for purposes of patent litigation.

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[22] Liquidia challenges Dr. Smyth's testing on the basis that he "assumed large inhaled volumes and flow rates." (D.I. 406 at 28). Dr. Smyth did not explicitly set forth his assumed inspiratory effort (4.0 kPa) and inhaled volume (4.0 L) in his testimony, but these values were set forth on a demonstrative exhibit. (DDX 5.4). Liquidia argues that these values were too high as a 2021 article by Faria-Urbina et al. reported that PAH patients have a maximum inspiratory pressure of 2.6 ± 1.2 kPa and inhale a total volume of 1.4 ± 0.03 L. (DTX 468 at 4 (Table 2); Tr. at 751:14–754:13 (Gonda); Tr. at 854:16–20 (Clark)). I nevertheless find Dr. Smyth's testing to be credible. The assumed inspiratory pressure of 4.0 kPa is consistent with the maximum inspiratory pressure reported in Meyer (5.2 kPa in females, 6.8 kPa in males). Meyer was available to a POSA as of 2006, unlike the 2021 Faria-Urbina publication.

Liquidia also argues that UTC is improperly "attempting to use a POSA's knowledge as an entire substitute for a deficient specification." (*Id.* at 26 (citing *Trs. of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018); *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1283 (Fed. Cir. 2007))). I do not think that is the case. The '793 patent teaches a POSA that a bolus dose of 15–90 μg of treprostinil delivered by inhalation in 1–3 breaths provides therapeutic efficacy without the expected negative side effects. (JTX 3 at Exs. 1 and 2, 17:4–24, 17:42–43, 18:4–6; Tr. at 832:19–833:6, 835:7–13, 836:17–21 (Clark); *see also* JTX 3 at 2:60–62 ("Currently, there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device such as a metered dose inhaler.")). UTC's experts Dr. Smyth and Dr. Clark supplemented these disclosures by showing that a POSA at the time of the invention would have been able to use well-known and routine techniques to make the claimed dry powder formulations. *See AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) ("[T]he artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.").

I therefore find that Liquidia has failed to prove by clear and convincing evidence that claims 1, 4, 6, 7, and 8 of the '793 patent are invalid for lack of enablement.

VI. CONCLUSION

UTC failed to prove by a preponderance of the evidence that Liquidia will infringe claim 8 of the '066 patent. Liquidia proved by clear and convincing evidence that claims 1, 2, 3, 6, and 9 of the '066 patent are invalid. UTC proved by a preponderance of the evidence that Liquidia will induce infringement of claims 1, 4, 6, 7, and 8 of the '793 patent.

The parties shall submit a final judgment consistent with this memorandum opinion within one week.