IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

OTSUKA PHARMACEUTICAL CO., LTD., Plaintiff, v. LUPIN LIMITED and LUPIN PHARMACEUTICALS, INC., Defendants.	Civil Action No. 21-900-RGA

TRIAL OPINION

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July 31, 2024

/s/ Richard G. Andrews
ANDREWS, U.S. DISTRICT JUDGE:

Plaintiff Otsuka Pharmaceutical Co., Ltd. ("Otsuka") brought this patent infringement action under 35 U.S.C. § 271(e)(2)(A), § 271(a), and § 271(g) against Defendants Lupin Limited and Lupin Pharmaceuticals, Inc. (collectively, "Lupin"). (D.I. 37 ¶¶ 43, 45, 62; D.I. 120, Ex. 2 ¶¶ 5–8). The remaining issues in this case are infringement and invalidity for obviousness of the asserted claims of U.S. Patent No. 8,501,730 (the "'730 patent") and U.S. Patent No. 8,273,735 (the "'735 patent"). (*See* D.I. 142 at 1–3; D.I. 143 at 1–2).

I held a three-day bench trial from December 18 to December 20, 2023. (D.I. 145–47). I have considered the parties' post-trial submissions. (D.I. 141–44, 148–54). For the following reasons, I find the asserted claims of the '730 patent not infringed and not invalid. I find the asserted claims of the '735 patent not infringed and invalid for obviousness.

I. BACKGROUND

Otsuka holds New Drug Application ("NDA") No. 204441 for JYNARQUE® tablets in 15, 30, 45, 60, and 90 mg dosage forms. (D.I. 120, Ex. 1 ¶ 6). JYNARQUE® is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease ("ADPKD"). (*Id.* ¶ 9). The FDA approved NDA No. 204441 on April 23, 2018 and granted JYNARQUE® orphan drug exclusivity until April 23, 2025. (*Id.* ¶¶ 7–8).

The active ingredient of JYNARQUE® is tolvaptan. (*Id.* ¶ 18). The '730 patent claims highly pure tolvaptan synthesized by certain claimed processes and is listed in the FDA's Orange Book for JYNARQUE®. (*Id.* ¶¶ 10, 21). The '735 patent claims processes for preparing tolvaptan. (*Id.* ¶ 28).

Lupin Limited submitted ANDA No. 216063 ("Lupin's ANDA") to the FDA under § 355(j) of the Federal Food, Drug, and Cosmetic Act seeking FDA approval to engage in the

commercial manufacture, use, offer for sale or sale in the United States, and/or importation into the United States, of generic versions of JYNARQUE® tablets ("Lupin's ANDA products"). (*Id.* ¶ 14). The active ingredient in Lupin's ANDA products is tolvaptan. (*Id.* ¶ 18).

Otsuka brought a complaint alleging Lupin infringed the '730 patent and U.S. Patent No. 10,905,694 ("the '694 patent"). (D.I. 1 ¶ 1). Otsuka later amended its complaint to add the '735 patent. (*See* D.I. 37 ¶ 1). The parties stipulated to dismissal of the claims and counterclaims based on the '694 patent. (D.I. 74). Prior to trial, the parties narrowed the issues to infringement, invalidity for obviousness, and unenforceability due to inequitable conduct. (*See* D.I. 120 ¶ 81; *id.*, Ex. 2, ¶¶ 72–77; *id.*, Ex. 3, at 4–5, 8; Tr. at 25:14–15). At trial, I granted Otsuka's motion for a Rule 52(c) judgment that the asserted patents were not unenforceable due to inequitable conduct. (Tr. at 333:7–334:16).

II. LEGAL STANDARD

A. Infringement

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 ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Id.*

B. Obviousness

A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007). "As patents are presumed valid, a defendant bears the burden of proving invalidity by clear and convincing evidence." *Shire, LLC v. Amneal Pharms., LLC*, 802 F.3d 1301, 1306 (Fed. Cir. 2015) (cleaned up). "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *KSR*, 550 U.S. at 406 (citations and quotation marks omitted).

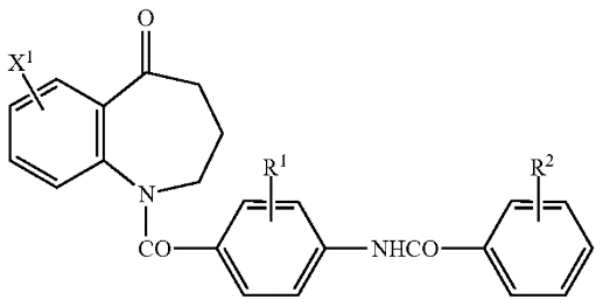
A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d

1063, 1078–79 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

III. DISCUSSION

A. The Asserted Claims

The claims at issue are claims 1, 2, 4, and 5 of the '730 patent and claims 7, 8, and 10 of the '735 patent. They are:

> 1. A highly pure 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine having a purity of more than 99.5%, or a salt thereof, which is produced by the process which comprises reducing a benzazepine compound of the formula (1):
>
> (1)
>
> 
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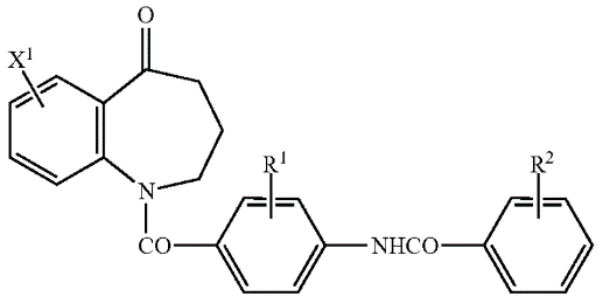
>
> wherein X^1 is a halogen atom, R^1 and R^2 are independently a lower alkyl group, or a salt thereof in the presence of a hydrogenating agent selected from the group consisting of lithium aluminum hydride, sodium borohydride, zinc borohydride, and diborane in an amount of 0.25 to 1 mole per 1 mole of the compound (1).

('730 patent, 29:9–32).

> 2. 7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine or a salt thereof, which is substantially free from at least one of the benzazepine compounds selected from 7-chloro-5-hydroxy-1-{2-methyl-4-[N-(2-methylbenzoyl)-N-(2-methyl-4-(2-methylbenzoylamino)benzoylamino]-benzoyl}-2,3,4,5-tetrahydro-1H-1-benzazepine (Compound A), 7-chloro-5-hydroxy-1-{2-methyl-4-[2-methyl-4-(2-methylbenzoylamino)benzoyl-amino]benzoyl}-2,3,4,5-tetrahydro-1H-1-benzazepine (Compound B), 7-chloro-5-[2-methyl-4-(2-methylbenzoylamino)benzoyloxy]-1-[2-methyl-4-(2-

methylbenzoylamino)benzoyl]-2,3-dihydro-1H-1-benzazepine (Compound C), and 7-chloro-5-[2-methyl-4-(2-methylbenzoylamino)-benzoyloxy]-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetra hydro-1H-1-benzazepine (Compound D), which is produced by the process which comprises reducing a benzazepine compound of the formula (1):

(1)

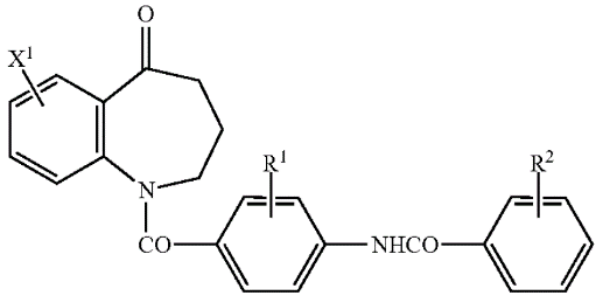


wherein X^1 is a halogen atom, R^1 and R^2 are independently a lower alkyl group, or a salt thereof in the presence of a hydrogenating agent selected from the group consisting of lithium aluminum hydride, sodium borohydride, zinc borohydride, and diborane in an amount of 0.25 to 1 mole per 1 mole of the compound (1).

('730 patent, 29:33–30:2).

4. 7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine or a salt thereof as set forth in claim 1 or 2, which is produced by the process which comprises reducing a benzazepine compound of the formula (1):

(1)

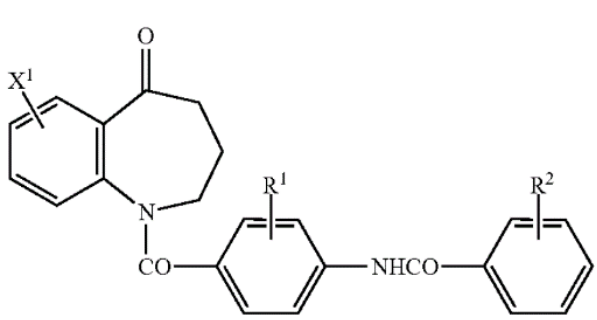


wherein X^1 is a halogen atom, R^1 and R^2 are independently a lower alkyl group, or a salt thereof in the presence of a sodium borohydride hydrogenating agent in an amount of 0.25 to 1 mole per 1 mole of the compound (1).

('730 patent, 30:27–48).

5. 7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine or a salt thereof as set forth in claim 1 or 2, which is

produced by the process which comprises reducing a benzazepine compound of the formula (1):



(1)

wherein X^1 is a halogen atom, R^1 and R^2 are independently a lower alkyl group, or a salt thereof, in the presence of a sodium borohydride hydrogenating agent in an amount of 0.25 to 0.5 mole per 1 mole of the compound (1).

('730 patent, 30:49–31:4).

7. The process according to claim 6, wherein the hydrogenating agent is sodium borohydride which is used in an amount of 0.25 to 1 mole per 1 mole of the compound (1).

('735 patent, 32:34–36).

8. The process according to claim 7, wherein the hydrogenating agent is sodium borohydride which is used in an amount of 0.25 to 0.5 mole per 1 mole of the compound (1).

('735 patent, 32:37–39).

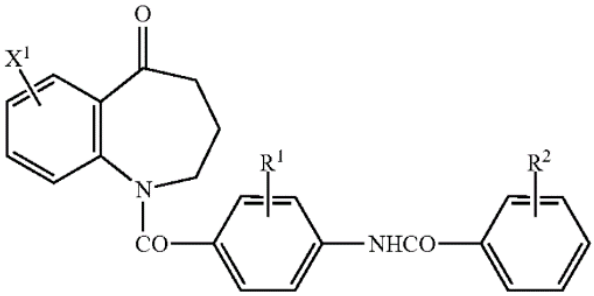
10. The process according to any one of claims 6, 7, and 8, wherein the 2,3,4,5-tetrahydro-1H-1-benzazepine compound (10) is 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzyol]-2,3,4,5-tetrahydro-1H-1-benzazepine, or a salt thereof.

('735 patent, 32:44–48).

Claim 6 of the '735 patent, which claims 7, 8, and 10 of the same patent depend on, recites:

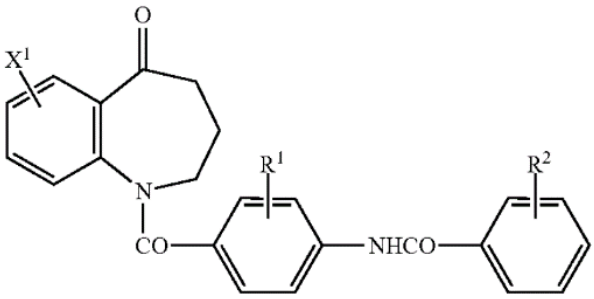
6. A process for producing a 2,3,4,5-tetrahydro-1H-1-benzazepine compound of the formula (10):

(1)



wherein X^1 is a halogen atom, R^1 and R^2 are independently a lower alkyl group, or a salt thereof, which comprises reducing a benzazepine compound of the formula (1):

(1)



wherein R^1, R^2 and X^1 are as defined above, or a salt thereof in the presence of a hydrogenating agent selected from the group consisting of lithium aluminum hydride, sodium borohydride, zinc borohydride, and diborane in an amount of 0.25 to 1 mole per 1 mole of the compound (1).

('735 patent, 31:61–32:33).

B. Person of Ordinary Skill in the Art

1. Findings of Fact

1. A person of ordinary skill in the art ("POSA") is a person who possesses a doctorate degree in chemistry, medicinal chemistry, organic or synthetic chemistry, or a related field, and at least two years of experience in the synthesis, research, and development of medicinal compounds. (Tr. at 206:13–206:21).[1]

2. A POSA may have had an education level lower than a doctorate degree if he or she had commensurately more relevant experience. (Tr. at 206:22–207:6). A POSA may also have worked as a part of a multi-disciplinary team and drawn

[1] The transcript is available at D.I. 145–47. It is consecutively paginated.

upon not only his or her own skills, but also consulted with others on the team, having specialized skills, to solve a given problem. (Tr. at 206:22–207:6).

3. A POSA does not need to have had a minimum of two years of experience related to process chemistry for the large-scale synthesis and purification of pharmaceutical compounds for use in a drug product. (Tr. at 207:19–208:6; '730 patent, 29:9–30:2, 30:27–31:4; '735 patent, 32:34–39, 32:44–38).

4. Dr. William R. Roush, Otsuka's technical expert, qualifies as a POSA. (Tr. at 47:21–49:6, 57:3–58:9, 61:15–62:21; 64:15–17).

5. Dr. William Dichtel, Lupin's technical expert, qualifies as a POSA. (Tr. at 178:2–182:19, 208:12–209:20, 304:24–305:21).

2. Conclusions of Law

The parties dispute whether a POSA must have experience in the large-scale synthesis and purification of pharmaceutical compounds.

"Factors that may be considered in determining the ordinary level of skill in the art include: 1) the types of problems encountered in the art; 2) the prior art solutions to those problems; 3) the rapidity with which innovations are made; 4) the sophistication of the technology; and 5) the educational level of active workers in the field." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666–67 (Fed. Cir. 2000).

As an initial matter, Otsuka acknowledges that the claims are not limited to industrial scale synthesis. (D.I. 150 at 8). I disagree with Otsuka's suggestion that the claims are not relevant to determining the level of experience required of a POSA. (*See id.* at 7–8 (citing *Ruiz*, 234 F.3d at 666–67, for the proposition that claim language is excluded from the list of factors considered)). The Federal Circuit's language in *Ruiz* indicates the stated list of factors is not exclusive. It is counterintuitive to argue that the claims, which "define the scope of the patent grant," do not provide insight into the experience a POSA in the field of the claimed invention would hold. *Markman*, 517 U.S. at 373.

Otsuka argues the "'730 and '735 patents' background section, description of the field of the invention, and summary of the inventors' objectives all make clear that an industrial-scale synthesis for highly pure tolvaptan was needed in the field." (D.I. 150 at 16). I disagree with Otsuka's interpretation of the patent specifications. The patent specifications focus on the chemical reactions behind the claimed invention. (*See generally* '730 patent, '735 patent). The specifications' descriptions of the relevant "technical field" do not discuss industrial-scale synthesis at all. (*See* '730 patent, 1:9–42; '735 patent, 1:5–40). The background section describes a starting compound that was "hardly obtainable in high yield and in high purity, and hence, the method [in the prior art] is not suitable as an industrial process." ('730 patent, 2:41–45; '735 patent, 2:55–58). In contrast, it describes the present invention as producing tolvaptan "in high yield and in high purity on industrial scale and hence is suitable as an industrial process." ('730 patent, 3:13–18; '735 patent, 3:27–32). It is clear the industrial applicability of the claimed invention stems from the nature of the chemical reaction, namely that it produces tolvaptan in high yield and high purity. The "types of problems" encountered are tied to the underlying chemical reactions and are not unique to industrial-scale synthesis. I am unconvinced that a POSA must have experience in industrial-scale processes to provide relevant and reliable opinions on infringement or validity.

Otsuka contends Dr. Dichtel's infringement and invalidity testimony is not reliable or relevant because he does not qualify as a POSA under either party's definition. (D.I. 143 at 6–7; D.I. 150 at 8–9). Otsuka failed to raise its objection to Dr. Dichtel's testimony before or during trial. Otsuka maintains it did not object because Lupin offered him as an expert in "organic chemistry and organic synthesis" rather than as an expert "in the synthesis research, and development of medicinal compounds." (D.I. 152 at 5 (citing Tr. at 182:15–19)). Even

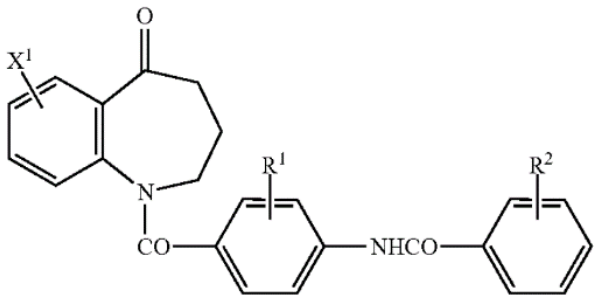
accepting Otsuka's rationale, Otsuka still failed to object to any of Dr. Dichtel's testimony during trial, including to his testimony regarding a POSA's perspective. If a party wants to preserve an objection, the party needs to make the objection in a timely fashion. Fed. R. Evid. 103(a). Since Otsuka did not do so, I reject Otsuka's belated challenge to the admissibility of Dr. Dichtel's testimony.

C. Infringement of the '735 and '730 Patents

1. Findings of Fact

1. The tolvaptan in Lupin's ANDA products is produced by a process which involves reducing a benzazepine compound of the following formula, wherein X^1 is chlorine and R^1 and R^2 are methyl groups (the "ketone precursor" or "TLV-III"):

(1)



(D.I. 120, Ex. 1 ¶ 45).

2. The tolvaptan in Lupin's ANDA products is produced by a process of reducing the ketone precursor in the presence of sodium borohydride. (*Id.* ¶ 46).

3. Sodium borohydride is a hydrogenating agent. (*Id.* ¶ 47).

4. The tolvaptan in Lupin's ANDA products is substantially free from Compounds A–D, which are defined in claim 2 of the '730 patent. (*Id.* ¶ 48; '730 patent, 29:33–30:2).

5. Lupin's Drug Master File ("DMF") describes adding at least 1.2 molar equivalents of sodium borohydride per 1 mole of ketone precursor during the reduction step. (JTX-014.0012; JTX-015.0041–43; JTX-019.0007, 0016, 0039; Tr. at 186:24–188:9). The process involves making a solution of the required amount of sodium borohydride in water and adding that solution to a solution of the required amount of the ketone precursor, which is stored in a reactor. (JTX-014.0012; JTX-015.0041–43; JTX-019.0007, 0016, 0039; Tr. at 186:24–188:9).

Lupin adds the sodium borohydride solution to the reactor containing the ketone precursor solution over 30 to 240 minutes, which it does at a uniform rate. (JTX-014.0012; Tr. at 165:18–166:10, 191:11–19).

6. After the sodium borohydride solution has been added, Lupin's process involves stirring the reaction mixture for 15 minutes, and then taking a sample. (JTX-014.0012; JTX-015.0041–43; Tr. at 191:20–24). Lupin then stirs the reaction mixture for another 75 minutes, and then takes a second sample. (JTX-014.0012–13; JTX-015.0041–43; Tr. at 192:10–17).

7. Lupin conducts in-process quality check tests on the samples collected. (JTX-014.0012, 13; JTX-015.0041–43; Tr. at 192:5–17). The quality checks assess the samples to measure the concentration of the ketone precursor that is remaining in the reaction mixture. (JTX-014.0012–13; JTX-019.0016, 0040–41; Tr. at 192:10–22).

8. If quality checks indicate that either of the samples contains the ketone precursor in an amount of 0.05 percent of its starting amount or less, Lupin moves on to the next step and quenches the reaction by adding water and dilute hydrochloric acid to the reactor containing the reaction mixture. (JTX-014.0013, 0018–20; JTX-019.0016, 0040–41; Tr. at 140:17–141:11, 188:4–189:6, 192:18–193:14).

9. If quality checks indicate that both samples contain the ketone precursor in an amount greater than 0.05 percent of its starting amount, Lupin adds additional sodium borohydride to the reactor containing the reaction mixture. (JTX-014.0013–15; JTX-019.0016, 40–41; Tr. at 193:20–194:6). Lupin then repeats the process of waiting additional periods of time and conducting additional quality check testing. (JTX-014.0013–15; JTX-019.0016, 0040–41; Tr. at 193:20–194:6).

10. A POSA would understand that the reduction reaction in Lupin's DMF process proceeds throughout the addition of at least 1.2 molar equivalents of sodium borohydride. (Tr. at 140:10–142:10, 201:12–202:5, 205:7–20, 287:16-19, 288:20-292:4).

11. A POSA would understand that the reduction reaction does not stop when the ketone precursor level reaches 0.05 percent. (Tr. at 201:12–202:5). A POSA would instead understand the 0.05 percent level specified by Lupin's DMF to be an acceptance criterion. (Tr. at 194:7–20, 288:20–292:4).

12. Lupin's Experiments 109 and 115 showed that 0.02 percent and 0.01 percent of tolvaptan remained after 0.91 molar equivalents of sodium borohydride were added. (D.I. 143 at 7; JTX-017.0113–14, 0019–20; JTX-020.0019, 0029; PTX-1050; Tr. at 80:13–84:2, 85:11–86:4, 91:4-21).

13. A POSA would understand the reduction reaction to reach practical completion when the synthesis process proceeds to the quenching step. (Tr. at 140:10–142:10, 201:12–202:5, 205:7–20, 287:16-19, 288:20-292:4).

14. Experiments 109 and 115 were performed under different conditions than the reduction reaction in Lupin's DMF process, including different starting ketone precursor concentration, temperature, scale, pH, and solvent compositions. (JTX-014.0009–20; JTX-017.0113, 0114, 0119–20; JTX-019.0039–40; Tr. at 91:23–25, 92:13–17, 93:16–24, 96:7–98:13, 124:5–125:21, 175:23–25, 195:18–197:24).

15. The underlying experimental data for Experiments 109 and 115 contained anomalies that may have resulted from an unspecified margin of error or a lack of appropriate quality control. (Tr. at 88:9–16, 89:14–25, 118:3–120:12, 121:1–22, 123:10–23).

16. Experiments 109 and 115 do not provide reliable insight regarding when the ketone precursor level reaches 0.05 percent during the reduction reaction in Lupin's DMF process. (Tr. at 197:6–24).

2. Conclusions of Law

The core of the parties' dispute revolves around the claim limitation requiring reduction in the presence of a hydrogenating agent used "in an amount of 0.25 to 1 mole per 1 mole of the [ketone precursor]." ('730 patent, 29:31–32). This limitation, or a variant requiring 0.25 to 0.5 molar equivalents of a hydrogenating agent, is present in all asserted claims. At the Markman Hearing, I explained this "amount" of hydrogenating agent referred to "the amount while the [reduction] reaction is taking place." (D.I. 64 at 27:25–28:1). The parties now dispute when the reduction reaction is "taking place."[2]

Otsuka maintains that the term refers to the amount of hydrogenating agent added before the reduction reaction reaches "practical completion" or is "complete in a practical sense." (D.I. 143 at 3). Lupin argues that "so long as unreacted ketone precursor and sodium borohydride are present, the reaction will continue to proceed." (D.I. 148 at 7). I agree with Otsuka that "absolute completion," which is only a theoretical possibility (Tr. at 102:10–103:17, 147:10–148:1), cannot define the endpoint of the reaction. I agree with Otsuka that, in "the practical

[2] I understand the parties' dispute to be one over the plain and ordinary meaning of the term "amount." (*See* D.I. 143 at 2–7; D.I. 148 at 1–5).

time course of doing something in a laboratory where the objective is to make this batch and move onward towards the drug product," there must be some point when the reaction is considered complete. (Tr. at 103:12–15). I understand the reduction reaction to be "taking place" until it reaches some point of practical completion.

Otsuka nevertheless fails to prove its assertion that the reaction reaches practical completion when 0.05 percent of the ketone precursor remains. (D.I. 143 at 5). The DMF's process involves quality checks performed at described time intervals, rather than constant monitoring of the ketone precursor level. The moment "when an experimentalist decides [the reaction] is done and wants to work it up" is therefore the point at which the chemist overseeing the tolvaptan synthesis initiates the quenching step following a passed quality check. (Tr. at 134:6–8). The point occurs, at the earliest, after the first set of quality of checks and therefore after the addition of at least 1.2 molar equivalents of sodium borohydride.

Otsuka posits that the reaction reaches practical completion when "so little precursor ketone remains that no further reduction is observed." (D.I. 143 at 1). Nothing in the DMF indicates that, at the 0.05 percent ketone precursor level, the reaction is "moving so slowly that people of ordinary skill in the art would understand that it's . . . for all practical purposes, over." (Tr. at 595:11–19). The DMF suggests that 0.05 percent operates as an acceptance criterion for the quality checks, not the point at which chemists no longer observe any further reduction. Otsuka fails to show by a preponderance of the evidence that the reduction reaction is complete when 0.05 percent of the ketone precursor remains in the reaction mixture.

Even assuming Lupin's reduction reaction reaches practical completion at the 0.05 percent ketone precursor level, Otsuka fails to show that no more than 1 molar equivalent of sodium borohydride or less has been added by that point.

Otsuka conducted no experiments to replicate Lupin's process. (Tr. at 100:2–14, 124:2–4). Otsuka instead relies on Experiments 109 and 115, two Lupin experiments conducted under different conditions from Lupin's DMF process. Based on the differences in starting ketone precursor amount and temperature, Dr. Roush opined that Lupin's DMF process would proceed 4-fold faster than the Lupin experiments. (Tr. at 93:16–95:20, 98:16–99:25, 109:7–23). He opined that the other differences were immaterial. (Tr. at 91:23–98:13). Dr. Dichtel testified that these differences were meaningful and that, given the closeness between 0.91 molar equivalents and 1 molar equivalent and the decreased speed of the reaction as it nears completion, even small discrepancies in Dr. Roush's assumptions could cause this practical completion point to fall outside the claimed range. (Tr. at 197:6–24). Dr. Roush admitted that the underlying data for Experiments 109 and 115 contained anomalies that might be accounted for by some unspecified "margin of error" or a lack of "appropriate quality control." (Tr. at 88:9–16, 89:14–25, 118:3–120:12, 121:1–22, 123:10–23). After evaluating the expert testimony, I conclude that Otsuka has not demonstrated by a preponderance of the evidence that Experiments 109 and 115 provide reliable results that are representative of Lupin's DMF process. Otsuka fails to meet its burden of showing that Lupin's DMF process reaches the 0.05 percent ketone precursor level before more than 1 molar equivalent of sodium borohydride has been added.

For the reasons stated, Otsuka fails to prove by a preponderance of the evidence that the reduction reaction in Lupin's tolvaptan synthesis process reaches completion before more than 1

molar equivalent of sodium borohydride has been added.[3] I find that Lupin's DMF process does not infringe the asserted claims of the '735 and '730 patents.

D. Invalidity of the '735 Patent

1. Findings of Fact

1. The priority date for the '735 patent is September 2, 2005. (D.I. 120, Ex. 1 ¶ 49).

2. Kazumi Kondo et al., *7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino) benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine (OPC-41061): A Potent, Orally Active Nonpeptide Arginine Vasopressin V2 Receptor Antagonist*, Bioorganic & Med. Chem. 7 (1999) 1743-1754 ("Kondo") published in August 1999 and is prior art to the Asserted Patents under pre-AIA 35 U.S.C. § 102(b). (*Id.* ¶ 50).

3. U.S. Patent No. 4,410,520 ("Watthey '520") issued on October 18, 1983. (*Id.* ¶ 51). U.S. Patent No. 4,473,575 ("Watthey '575") issued on September 25, 1984. (*Id.* ¶ 52). U.S. Patent No. 4,575,503 ("Watthey '503") issued on March 11, 1986. (*Id.* ¶ 53). Watthey '520, Watthey '575, and Watthey '503 (collectively, "Watthey") are prior art to the Asserted Patents under pre-AIA 35 U.S.C. § 102(b). (*Id.* ¶¶ 51–53).

4. U.S. Patent No. 4,952,573 ("LeClerc") issued on August 28, 1990, and is prior art to the Asserted Patents under pre-AIA 35 U.S.C. § 102(b). (*Id.* ¶ 54).

5. Kondo disclosed a process for synthesizing tolvaptan that consists of eleven linear steps through the following route: 1a → 2a → 3a → 4a → 6a → 7a → 8a → 9a → 27c → 28c → 29c → 32. (JTX-005.0002–0004, 0009, 0011; Tr. at 213:9-20; 351:17 – 353:6, 380:21 – 381:5).

6. Kondo's reduction step is Step 29c → 32 and is made up of two stages, a reduction stage wherein the precursor ketone is reduced using sodium borohydride, and an isolation (purification) stage wherein recrystallization is used to isolate the tolvaptan from solution. (JTX-005.0002–04; Tr. at 358:9–359:1, 378:18–379:9).

7. Kondo's reduction step involves reducing the ketone precursor to tolvaptan in the presence of sodium borohydride in an amount of 1.5 moles per 1 mole of the ketone precursor. (JTX-005.0004, 0009, 0011; Tr. at 211:12–25, 213:9–214:23, 422:13–15). Kondo's reduction step thus disclosed each limitation of the

[3] Otsuka, consequently, also fails to show by a preponderance of the evidence that no more than 0.5 molar equivalents of sodium borohydride have been added before Lupin's tolvaptan synthesis process reaches completion, as required by claim 8 of the '735 patent and claim 5 of the '730 patent.

Asserted Claims of the '735 patent except for the claimed amounts of sodium borohydride. (JTX-005.0004, 0009, 0011; Tr. at 213:9–214:23, 421:8–13).

8. Reactions involving the reduction of ketone precursors in the presence of sodium borohydride have been known since the 1930s. (D.I. 120, Ex. 1 ¶ 57; DTX–2060: Tr. at 215:6–11).

9. Because the borohydride anion of sodium borohydride contains four hydrogen atoms, each equivalent of sodium borohydride can reduce up to four equivalents of a ketone precursor. (Tr. at 138:5–139:3, 215:18–216:13). Thus, above the 0.25 low-end value, the claimed ranges of sodium borohydride recite molar excess of reducing equivalents. (Tr. at 138:5–139:3, 217:21–25).

10. A POSA in September 2005 would have been familiar with reactions involving the reduction of ketone precursors using sodium borohydride and the relevant stoichiometry and reactivity of sodium borohydride in reduction reactions. (Tr. at 218:1–8, 223:18–24).

11. A POSA in September 2005 would have known that he or she could reduce the 1.5 molar equivalents of sodium borohydride used in Kondo's reduction step to between 0.25 and 1 molar equivalents. (Tr. at 218:9–14).

12. Watthey disclosed the reduction of a 5-oxo benzazepine precursor, structurally similar to the claimed ketone precursor, to a 5-hydroxy benzazepine compound, structurally similar to tolvaptan, using 0.5 molar equivalents of sodium borohydride. (JTX-045.0021; JTX-046; JTX-047; Tr. at 219:2–25).

13. LeClerc disclosed the reduction of a 5-oxo benzazepine precursor, structurally similar to the claimed ketone precursor, to a 5-hydroxy benzazepine compound, structurally similar to tolvaptan, using 0.76 molar equivalents of sodium borohydride. (JTX-048.0010–11; Tr. at 220:3–25).

14. A POSA would have recognized Kondo as reporting the promising pharmacologic properties of tolvaptan and a viable synthesis method for the promising pharmaceutical. (Tr. at 211:19–25, 224:10–226:8).

15. U.S. Patent Publication No. 2007/0185323 ("Zard") is not prior art to the Asserted Patents but it is dated near the earliest priority date of the Asserted Patents and is therefore contemporaneous to them. (PTX-1153.0002).

16. Zard described Kondo's tolvaptan synthesis method as "the synthetic pathway currently used to obtain [tolvaptan]." (PTX-1153.0003; Tr. at 382:8–383:10, 439:13–441:21).

17. Kondo was the standard method for synthesizing tolvaptan in the relevant prior art time frame. (Tr. at 440:18–441:21).

18. A POSA would have recognized Kondo's method as a viable starting point for a tolvaptan synthesis process. (Tr. at 224:10–226:8).

19. A POSA would have recognized that reducing the amount of molar excess of sodium borohydride would reduce the cost of synthesizing tolvaptan. (Tr. at 221:1–17).

20. Separating and isolating the tolvaptan during post-processing is easier if there are fewer by-products in the reaction mixture. (Tr. at 221:14–24). A POSA would have recognized that reducing the amount of sodium borohydride would reduce the amount of by-products generated by the reaction. (*Id.*).

21. A POSA would have known that sodium borohydride reacts exothermically with water and acid to generate heat and hydrogen gas. (D.I. 120, Ex. 1 ¶ 77; DTX-2232; JTX-041; Tr. at 221:25–223:4, 387:21–25). The use of sodium borohydride poses a known fire and explosion risk. (*Id.*). A POSA would have recognized that reducing the amount of sodium borohydride used in Kondo's reduction step would thus improve safety. (*Id.*).

22. A POSA would have believed that the low yield in Step 29c → 32 was the result of the isolation stage, not the reduction stage. (Tr. at 358:9–359:1, 378:11–379:9, 383:15–22).

23. A POSA would have believed that the risk of reduced yield from modification of the reduction stage was low because the amount of sodium borohydride remained greater than 0.25 and would therefore be in molar excess. (Tr. at 215:18–218:18, 226:9–11, 226:21–227:12).

24. The fourteen prior art references identified by Otsuka (PTX-1154; PTX-1152; PTX-1144; PTX-1161; PTX-1159; PTX-1160; PTX-1114; PTX-1127; PTX-1133; PTX-1134; PTX-1162; PTX-1163; PTX-1135; JTX-005) do not demonstrate an industry convention or standard of using more than 1 molar equivalent of sodium borohydride to reduce a precursor ketone to a hydroxy compound.

25. A POSA would have been motivated to improve the reduction step of Kondo's method and reduce the amount of sodium borohydride used in Kondo's reduction step to the claimed ranges to reduce costs, simplify post-processing, and improve the safety of the tolvaptan synthesis. (Tr. at 221:1–17, 385:5–16, 386:19–387:3).

26. A POSA would have been motivated to combine Kondo with Watthey or LeClerc due to the similarities between the reactions in Kondo and the two references. (Tr. at 218:15–220:25).

27. A POSA would have reasonably expected to successfully synthesize tolvaptan by reducing the amount of sodium borohydride used in Kondo's reduction step to the claimed ranges. (Tr. at 223:18–24, 422:16–423:4).

28. Kondo was addressed by the USPTO during prosecution of the application leading to the ’735 patent. (JTX-002.1198).

29. In response to the USPTO’s rejection of the pending claims in view of Kondo, Otsuka submitted a declaration from one of its chemists, Hirotaka Yukawa. (D.I. 120 ¶ 90; JTX-002.1501, 1518–28). In the declaration, Yukawa purported to compare test results from a tolvaptan sample reported in the specification of the application leading to the ’735 patent with results from tests performed on a tolvaptan sample purportedly synthesized according to Kondo’s method, except that Yukawa used 3 molar equivalents of sodium borohydride in his reduction step instead of the 1.5 molar equivalents disclosed in Kondo. (JTX-002.1523).

30. Otsuka argued to the USPTO that the comparison in the Yukawa declaration showed that the claimed reduction step was nonobvious over Kondo because the reduction step produced tolvaptan “possess[ing] unexpectedly superior advantages that are not taught or suggested by KONDO.” (JTX-002.1513–14). The USPTO withdrew its rejection based on Kondo and allowed the claims. (JTX-002.1539, 1558).

31. Otsuka’s internal documents report the presence of a dechlorinated impurity when using 2 molar equivalents of sodium borohydride in the reduction step, but not when using 1.5 molar equivalents as disclosed in Kondo. (DTX-2114; Tr. at 248:8–249:24, 251:19–252:3).

32. Yukawa’s use of 3 molar equivalents of sodium borohydride was a material difference to the 1.5 molar equivalents disclosed in Kondo. (Tr. at 245:8–18).

33. Otsuka began selling JYNARQUE® in the United States in 2018. (Tr. at 526:4–6.) JYNARQUE® is also available in Europe and Japan, with Japan being the first to grant marketing authorization for tolvaptan, as used for treating ADPKD, in 2016. (Tr. at 462:2–12).

34. JYNARQUE® is a marketplace success. (Tr. at 474:6–16, 491:24–492:8).

35. In 1993, Otsuka received U.S. Patent No. 5,258,510 (“the ’510 patent”), which claimed the tolvaptan compound and expired on November 2, 2010. (JTX-043; JTX-051.0001-2; Tr. at 212:4–213:5, 252:7–11, 401:23–402:7, 507:16–508:3, 534:20–536:15, 569:1–21). The ’510 patent is a blocking patent to the ’735 patent.

36. In 1998, Otsuka received U.S. Patent No. 5,753,677 (“the ’677 patent”), which claimed the use of tolvaptan to treat ADPKD and expired in 2020. (JTX.044; JTX-051.0005-6; JTX-052.0001, 0003; Tr. at 402:2–7, 408:11–16, 510:20–511:10, 569:1–25, 570:17–571:10, 572:21–574:5). The ’677 patent is not a blocking patent to the ’735 patent.

37. The ’510 patent deterred others between 1993 and 2010 from investing the resources needed to make, develop, and market the tolvaptan synthesis methods and

tolvaptan compounds covered by the Asserted Claims. (Tr. at 405:3–406:3, 507:16–508:3, 534:20–536:15, 538:11–17, 569:3–21, 572:21–574:5).

38. The nexus between JYNARQUE®'s commercial success and the claimed invention is weak.

39. The efficacy, safety, and tolerability of JYNARQUE® in treating ADPKD is due to the prior-art tolvaptan compound. (Tr. at 466:16–20, 520:1–5, 543:8–14, 567:6–568:11).

40. At most, only a small portion of JYNARQUE®'s marketplace success is attributable to the claimed invention.

41. As of September 2, 2005, there was a long-felt but unmet need for an ADPKD treatment, but not for an industrial scale process for synthesizing tolvaptan. (Tr. at 460:11–461:19).

42. The Yukawa declaration does not establish that the claimed process of the '735 patent produces tolvaptan with unexpected properties.

2. Conclusions of Law

The parties agree that Kondo discloses each limitation the asserted '735 patent claims except for the claimed ranges of sodium borohydride added during the reduction stage.[4] Lupin argues the claimed invention would have been an obvious modification of Kondo based on a POSA's general knowledge or in view of either Watthey or LeClerc. (D.I. 142 at 8). Otsuka makes several challenges to Lupin's invalidity theories, including arguing that a POSA would not have had (1) the motivation to select Kondo as a starting point; (2) the motivation to select the reduction step of Kondo for modification; (3) the motivation to reduce the amount of sodium

[4] The parties' briefing focuses on the 0.25 to 1 molar equivalent range described in claim 7 of the '735 patent. Neither party raises different arguments in relation to the smaller 0.25 to 0.5 molar equivalents range described in claim 8 of the '735 patent or otherwise indicates this range raises separate issues. I therefore accept that the same invalidity analysis applies to both ranges and consider any argument contrary to this conclusion waived. Even absent waiver, I find the rationale set forth below, which supports finding the 0.25 to 1 molar equivalent range obvious, also supports finding the 0.25 to 0.5 molar equivalent range obvious. Accordingly, while I focus my analysis below on the parties' arguments, which address the broader range in claim 7, my reasoning applies to the narrower range in claim 8 in almost equal force.

borohydride used in the reduction step; and (4) a reasonable expectation of success. (D.I. 150 at 20–32). Otsuka further notes that Kondo was considered during prosecution of the '735 patents and raises three objective indicia of nonobviousness. (*Id.* at 32–40).

For the reasons stated below, I find Lupin has shown by clear and convincing evidence that a POSA would have found the claimed invention obvious based on Kondo either in view of a POSA's background knowledge or in view of Watthey or LeClerc.

a. Motivation

i. Motivation to Select Kondo

Otsuka asserts that a POSA would not have selected Kondo as a starting point for modification. (D.I. 150 at 20). In particular, Otsuka argues a POSA would have recognized that "Kondo's process is for synthesizing small amounts of tolvaptan, and no aspect of Kondo's process is appropriate for industrial-scale synthesis." (*Id.* at 21).

As an initial matter, whether a POSA would be motivated to select Kondo as a starting point is a relevant inquiry as Lupin asserts theories based on combinations of prior art. "Whether a skilled artisan would be motivated to make a combination includes whether he would select particular references in order to combine their elements." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016). While Lupin maintains this sentence is dicta (D.I. 153 at 4), the Federal Circuit has cited this premise as good law. *See, e.g.*, *Yeda Rsch. v. Mylan Pharms. Inc.*, 906 F.3d 1031, 1044 (Fed. Cir. 2018); *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1070 (Fed. Cir. 2018); *Vicor Corp. v. SynQor, Inc.*, 869 F.3d 1309, 1324 (Fed. Cir. 2017).

Whether Kondo's process is appropriate for industrial-scale synthesis, however, is not the appropriate consideration for assessing motivation. The patent challenger's burden is one of demonstrating "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d

1348, 1361 (Fed. Cir. 2007). Differences between the prior art and unclaimed aspects of patented invention are generally irrelevant to the obviousness analysis. *See McCarty v. Lehigh Valley R. Co.*, 160 U.S. 110, 116 (1895) ("[W]e know of no principle of law which would authorize us to read into a claim an element which is not present, for the purpose of making out a case of novelty or infringement."); *Smith & Nephew, Inc. v. Rea*, 721 F.3d 1371, 1381 (Fed. Cir. 2013) ("[A]n unclaimed and undisclosed feature such as the 'specialized screw' cannot be the basis for finding Synthes's patent to be non-obvious over the prior art."); *Soverain Software LLC v. Newegg Inc.*, 705 F.3d 1333 (Fed. Cir. 2013) ("The distinction proposed by Dr. Shamos and advanced by Soverain is not embodied in the claims and not reflected in the claim construction.").

"In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls." *KSR*, 550 U.S. at 419. "[T]he problem motivating the patentee may be only one of many addressed by the patent's subject matter." *Id.* at 420; *see Janssen Pharm., Inc. v. Teva Pharm. USA, Inc.*, 97 F.4th 915, 929 (Fed. Cir. 2024) ("A motivation 'may be found in many different places and forms.'" (quoting *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013)). "What matters is the objective reach of the claim." *KSR*, 550 U.S. at 419.

The asserted claims are not limited to industrial-scale synthesis. Otsuka's desire for an industrial-scale synthesis process does not force Lupin to assert the same motivation. Dr. Dichtel testified that a POSA would have selected Kondo because it reports the promising pharmacologic properties of and a viable synthesis method for tolvaptan. I find this testimony sufficient to establish a POSA's motivation to select Kondo as a viable starting point.

Furthermore, the record demonstrates a POSA would have considered Kondo a suitable starting point for industrial-scale synthesis. Otsuka's expert acknowledged that Kondo was one of two known synthesis methods as of the priority date of the asserted patents. (Tr. at 440:13–

20). Dr. Roush further conceded that Zard, the primary reference that Otsuka relies on, recognizes Kondo as the standard method in use at the time. (Tr. at 441:18–442:21). While Zard describes various inefficiencies with the Kondo process and an alternative method for synthesizing tolvaptan (Tr. at 382:4–383:10), this does not indicate a POSA would reject Kondo, the industry standard, as a viable starting point. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.").

Lupin has presented clear and convincing evidence that a POSA would have recognized Kondo as a viable starting point

ii. Motivation to Select Reduction Stage

Otsuka argues that Lupin fails to explain why a POSA would have been motivated to modify the reduction step of the Kondo synthesis process, as opposed to one of the other eleven steps. (D.I. 150 at 24). Otsuka further maintains that if a POSA would have been motivated to modify the reduction step, the motivation would have been to modify the isolation stage, and not the reduction stage, of the reduction step. (*Id.*).

Otsuka does not argue that the prior art teaches away from modification of the reduction step or reduction stage; in fact, Dr. Roush testified that a POSA would look at the reduction step as "one of the many [steps] that a person would have attempted to improve." (Tr. at 429:7–16). Rather, Otsuka's position is that Lupin does not explain why a POSA would have selected one step for modification, when the POSA might have been motivated to modify other steps in the process as well. Otsuka, in essence, advocates for the incorrect premise that a POSA cannot have sufficient motivation to make a modification if there is some other modification that may lead to an equal or more desirable improvement. "[A] particular combination [need not] be the

preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). "The question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *Id.* (cleaned up). That other steps in Kondo could also be improved does not suggest a POSA would have been discouraged or dissuaded from modifying the reduction step or the reduction stage.

Dr. Dichtel describes several motivations (cost reduction, post-processing simplification, and safety improvements) linked to modification of the reduction stage. (Tr. at 221:1–233:4). I find these motivations sufficient to satisfy Lupin's burden of showing a POSA would have been motivated to modify the reduction stage of the Kondo process.

iii. Motivation to Reduce Amount of Sodium Borohydride

Dr. Dichtel testified that a POSA would have been motivated to reduce the amount of sodium borohydride used in Kondo's reduction step to the claimed ranges to reduce costs, simplify post-processing, and improve the safety of the tolvaptan synthesis.[5] (Tr. at 221:1–233:4). Otsuka challenges Lupin's proffered motivations on several bases. (D.I. 150 at 25).

Otsuka challenges Lupin's proffered motivations as "generic." (*Id.* (citing *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012))).[6] The Federal Circuit recently clarified its position on generic motivations:

> [*Activevideo*], however, didn't denounce energy efficiency as per se insufficient as the Board's decision suggests. Such a rationale is not inherently suspect merely

[5] As indicated in footnote 4, I am satisfied that these motivations support reducing the amount of sodium borohydride to both the ranges of claim 7 and claim 8 of the '735 patent.

[6] I note that *ActiveVideo*'s holding is specific to a POSA's motivation to combine references. *See ActiveVideo*, 694 F.3d at 1328.

> because it's generic in the sense of having broad applicability or appeal. Quite the opposite. Even before KSR, we held that *because* such improvements are "technology-independent," "universal," and "even common-sensical," "there exists in these situations a motivation to combine prior art references *even absent any hint of suggestion* in the references themselves."
>
> Of course, "generic" might also have a different sense: conclusory. Certainly, "[c]onclusory expert testimony does not qualify as substantial evidence," as demonstrated in *ActiveVideo*. But unlike *ActiveVideo*, this isn't a case "where the motivation of increased efficiency is asserted so generically as to be legally insufficient." The testimony in *ActiveVideo* bore "no relation to any specific combination of prior art elements ... from specific references" and didn't explain why a skilled artisan would have combined them "in the way the claimed invention does," but here Intel's expert indicated precisely how and why a skilled artisan would have combined the references.

Intel Corp. v. Qualcomm Inc., 21 F.4th 784, 797 (Fed. Cir. 2021) (citations omitted).

Based on the expert testimony, I understand a POSA would generally be interested in reducing the costs, simplifying the post-processing, and improving the safety of conducting a reaction. I understand a POSA would, based on general knowledge and common sense, believe a POSA could accomplish these goals by decreasing the amount of a reagent, which is at least partially responsible for various by-products and safety hazards, used in the reaction. Dr. Dichtel's proffered motivations are the exact type of acceptable generic motivations contemplated by the *Intel* court. *See Janssen*, 97 F.4th at 929–30 ("A motivation 'may be found explicitly or implicitly in market forces; design incentives; the interrelated teachings of multiple patents; any need or problem known in the field of endeavor at the time of invention and addressed by the patent; and the background knowledge, creativity, and common sense of the person of ordinary skill.'" (quoting *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1365 (Fed. Cir. 2022)).

Otsuka argues that Lupin's identified motivations are not suitable options. (D.I. 150 at 25; *see Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014) ("Our

precedent does not require the motivation be the best option, only that it be a suitable option from which the prior art did not teach away." (citations omitted)). As stated above, Lupin's motivations, on their face, appear suitable based on their identification of generic benefits. I therefore turn to Otsuka's challenges to suitability.

Otsuka submits that there were more expensive reagents used in the reaction that a POSA might consider reducing. (D.I. 150 at 26). This fact does not prevent cost reduction being a suitable motivation for decreasing the amount of sodium borohydride. *See In re Fulton*, 391 F.3d at 1200. Dr. Roush further argues that a POSA would understand that reducing the amount of sodium borohydride would reduce yield, thus rendering the Kondo synthesis even less efficient and more costly. (Tr. at 379:10–380:4). I am persuaded by Dr. Dichtel's testimony that the risk of reduced yield from modification of the reduction stage was low because the amount of sodium borohydride remained in molar excess. (Tr. at 215:18–218:18, 226:9–227:12). This opinion is consistent with Dr. Roush's opinion that a POSA would believe "the amount of sodium borohydride is not the culprit" for the low yield and that issues with yield resulted from the isolation stage, not the reduction stage. (Tr. at 358:9–359:1, 378:11–379:9). I find that a POSA would understand that decreasing the amount of sodium borohydride used would decrease the overall cost of conducting a reaction.

Otsuka argues there was no need to further simplify post-processing of the Kondo synthesis because any byproducts can be easily removed by extraction. (D.I. 150 at 26; Tr. at 386:11–387:7). Dr. Roush, however, does not dispute Dr. Dichtel's assertion this modification would simplify post-processing or that simplifying post-processing is beneficial. In other words, Dr. Roush does not contest Dr. Dichtel's assertion that such a motivation exists here; rather, he

challenges the strength of such a motivation. The fact that a motivation is not "the best option" does not teach away from it or otherwise make it unsuitable. *Par*, 773 F.3d at 1198.

Otsuka contends that a POSA would not believe that reducing the amount of sodium borohydride from 1.5 molar equivalents to between 0.25 and 1 molar equivalents would make the Kondo synthesis safer. (D.I. 150 at 26). Dr. Roush conceded that the hydrogen gas generated from sodium borohydride reacting with acid during the quenching step presents potential safety hazards. (Tr. at 387:13–388:3). I understand a POSA would recognize, based on common sense, that decreasing the amount of sodium borohydride would decrease the amount of dangerous hydrogen gas produced. While the safety hazard might not be eliminated by this reduction (Tr. at 388:8–24), there is no reason a POSA could not be motivated to make a lesser safety improvement. Dr. Roush argues that engineering solutions for handling hydrogen gas already exist (Tr. at 387:25–388:3), but this assertion only suggests that improving safety may not be the strongest of motivations. *See Par*, 773 F.3d at 1198. I find that Lupin has identified suitable motivations not taught away from by the prior art.

Otsuka argues that Lupin fails "to address why a POSA would sacrifice yield to potentially reduce costs, simplify post-processing, and improve safety." (D.I. 150 at 26). "The fact that the motivating benefit comes at the expense of another benefit . . . should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another." *See Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 (Fed. Cir. 2000). "Instead, the benefits, both lost and gained, should be weighed against one another." *Id.* As explained above, Lupin has satisfied its burden of proving that the risk of reduced yield was low. The record demonstrates that Lupin has shown, by clear and convincing evidence, that its identified motivating benefits outweigh the potential downsides of reduced yield.

Otsuka maintains that "a POSA's 'first' priority would be to develop a synthesis to produce highly pure tolvaptan on an industrial scale" and that a POSA would therefore not prioritize reducing costs, simplifying post-processing, or improving safety. (D.I. 150 at 27–28). Even assuming industrial-scale synthesis would be a POSA's top priority, the existence of a "best" goal does not imply the undesirability of other motivations. *Par*, 773 F.3d at 1197–98.

Otsuka contends Lupin's asserted motivations of reducing cost and simplifying post-processing are "at odds with" Dr. Dichtel's assertion that a POSA would have been motivated to modify Kondo by using chromatography or recrystallization, which would increase the cost of and complexity of the reaction, to arrive at the '730 patent claims. (D.I. 150 at 28; D.I. 151 ¶ 96). That cost and complexity are outweighed as considerations for making one modification, however, does not mean they are necessarily outweighed as considerations for making another modification. For example, the additional benefit from the chromatography or recrystallization modification of "achiev[ing] certain levels of purity" demonstrates there are different tradeoffs at play as compared to sodium borohydride amount modification. (Tr. at 238:11–20). As stated, Lupin has satisfied its burden of showing the motivating benefits gained from reducing the amount of sodium borohydride used outweighs the benefits lost.

For the above reasons, Lupin has presented clear and convincing evidence that a POSA would have been motivated to reduce the amount of sodium borohydride used in the reduction stage of Kondo to the claimed ranges.

iv. Motivation to Combine Kondo with Watthey or LeClerc

Dr. Dichtel opined that, based on the similarities between the reactions in Kondo and Watthey and LeClerc, a POSA would have been motivated to modify Kondo in view of those

prior art references.[7] (Tr. at 218:15–220:25). Otsuka argues that Watthey and LeClerc would not have motivated a POSA to reduce the amount of sodium borohydride in Kondo's reduction stage. (D.I. 150 at 29).

Otsuka contends that Dr. Dichtel provides no explanation for why "a POSA would 'have plucked' these two references from the 'sea of prior art' teaching the use of more than 1 molar equivalent" when Watthey and LeClerc go against the "industry standard." (*Id.* (citing *WBIP*, 829 F.3d at 1337; *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988))). I do not agree that Otsuka's identification of fourteen references using more than one molar sodium borohydride establishes an industry standard. (*See* D.I. 150 at 29–30; D.I. 151 ¶ 94). As Lupin points out, none of these examples describe more than 1 molar equivalent as being the convention or standard in the industry or teaches away from using less than 1 molar equivalent. (D.I. 153 at 6). Furthermore, Otsuka's "industry standard" cut-off of 1 molar equivalent, which coincidentally matches the upper limit of the claimed range of 0.25 to 1 molar equivalents, appears rather arbitrary. Watthey, LeClerc, and the other fourteen pieces of prior art Otsuka identified showcase a wide range of molar equivalents, ranging from 0.5 molar equivalents to 10 molar equivalents. (D.I. 151 ¶ 94). While these references might imply that "the standard way that POSAs use sodium borohydride is to use it in excess" (Tr. at 389:9–10), Otsuka provides no explanation for why the conventional range should be defined to exclude Watthey's 0.5 molar equivalents and LeClerc's 0.76 molar equivalents. No evidence indicates these references use

[7] While LeClerc's 0.76 molar equivalents of sodium borohydride falls outside the range limitation of claim 8 of the '735 patent, Watthey's 0.5 molar equivalents matches the upper limit of the claim 8 range. Thus, the same rationale outlined in this section supports finding that a POSA would have been motivated to modify Kondo in view of Watthey to reach the process covered by claim 8 of the '735 patent.

unorthodox amounts of sodium borohydride. I am not convinced that there is an industry standard of using more than 1 molar equivalent of sodium borohydride.[8]

Otsuka notes that its fourteen prior art references involve structurally similar compounds to those in Kondo, but does not dispute that Watthey and LeClerc contain structurally similarly compounds as well. (*See* D.I. 150 at 30). Otsuka does not identify any sources teaching away from modifying Kondo's process based on Watthey or LeClerc. Under Dr. Dichtel's proffered motivations, it makes sense that a POSA would look to prior art utilizing low amounts of sodium borohydride. That neither Watthey nor LeClerc discuss the benefits of using less than 1 molar equivalent is inapposite. (*Id.* at 29). "A motivation may be found in many different places and forms, and it need not be expressly stated in the references at all, let alone originate from the reference to be modified." *Janssen*, 97 F.4th at 929 (cleaned up) (citations omitted). I am convinced that "the background knowledge, creativity, and common sense of the person of ordinary skill" sufficiently support Lupin's identified motivations. *Id.* at 929–30.

Otsuka argues, "A POSA seeking to meet [the need for an industrial-scale synthesis for tolvaptan] would not combine Watthey or LeClerc with Kondo." (D.I. 150 at 30). As stated above, the claims are not limited to industrial-scale synthesis. Ostuka's desire for an industrial-scale synthesis process does not limit Lupin's invalidity theory to relying on the same motivation. *See KSR*, 550 US at 419–20; *Senju Pharmaceutical Co. v. Lupin Ltd.*, 780 F.3d 1337, 1347 (Fed. Cir. 2015) ("Many of appellants' arguments on the lack of reasons to combine the teachings of these three patents rely on the fact that they do not disclose anything about corneal

[8] This determination ultimately does not affect my conclusion that Lupin satisfied its burden to show a motivation to combine references. The law does not require a POSA look only to prior art complying with an industry standard. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738–39 (Fed. Cir. 2013) ("A teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions.").

permeability of gatifloxacin solutions. As discussed above, this is not a limitation of claims 12–16 and, therefore, is not relevant to the obviousness determination."); *In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992) ("As long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor.").

Otsuka suggests, "Watthey's and LeClerc's silence regarding tolvaptan, Kondo, scale, yield, and purity would dissuade a POSA from combining them with Kondo." (D.I. 150 at 31). I agree with Otsuka's assertion that reasons not to combine should be balanced against those in favor of combining references. *See Winner*, 202 F.3d at 1349 ("Trade-offs often concern what is feasible, not what is, on balance, desirable. Motivation to combine requires the latter."). Silence, however, is not the same as teaching away from a combination. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) ("A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not 'criticize, discredit, or otherwise discourage' investigation into the invention claimed." (quoting *In re Fulton*, 391 F.3d at 1201)). I find that Lupin's proffered motivations to combine outweigh any reasons not to combine.

Otsuka argues that even if a POSA would combine Watthey or LeClerc with Kondo, Lupin fails to show a POSA would have been motivated to reduce the amount of sodium borohydride used in Kondo. (D.I. 150 at 31). Otsuka asserts, "[N]either Watthey nor LeClerc teaches that reducing the amount of sodium borohydride increases yield or purity." (*Id.*). Otsuka maintains that "neither Watthey nor LeClerc suggests that using less than 1 molar equivalent reduced costs, simplified post-processing, or improved safety." (*Id.* at 32). As explained above, Lupin's invalidity theory can rely on motivations that come from the common sense or background knowledge of a POSA and need not match Otsuka's original motivation. *See KSR*, 550 U.S. at

419–20; *Janssen*, 97 F.4th at 929. I find a POSA, relying on Watthey or LeClerc, would have been motivated to reduce the amount of sodium borohydride used in Kondo.

For the stated reasons, I conclude Lupin has shown by clear and convincing evidence that a POSA would have had the requisite motivation to combine Kondo with Watthey or LeClerc.

b. Reasonable Expectation of Success

Dr. Dichtel testified that a POSA would have reasonably expected to have been able to synthesize tolvaptan by reducing the amount of sodium borohydride in Kondo's reduction step to the claimed ranges based on a POSA's general knowledge regarding reduction reactions. (Tr. at 223:5–24). Dr. Roush agreed with this assessment. (Tr. at 422:16–423:4). Otsuka nevertheless argues that Lupin fails to show reasonable expectation success because "[t]here is no evidence that a POSA would have a reasonable expectation that reducing the amount of borohydride in Kondo's 29c → 32 [step] would result in highly pure tolvaptan." (D.I. 150 at 32). Otsuka's argument stems from the proposition that "the expectation-of-success analysis must match the highly desired goal." (*Id.* (quoting *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013))).

The "highly desired goal" for the '735 patent claims is one of producing tolvaptan using the claimed process. "[T]he person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention." *Allergan*, 726 F.3d at 1292. The asserted claims of the '735 patent are directed towards "[a] process for producing a 2,3,4,5-tetrahydro-1H-1-benzazepine compound." ('735 patent, 31:61–62). The claimed invention does not include any purity requirement. Thus, Lupin does not bear a burden of showing that a POSA would have reasonably expected the produced tolvaptan be highly pure. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1368 (Fed. Cir. 2016) ("[The Petition's failure to

explain why a POSA would have expected a quantitative deblocking criterion to be satisfied] is irrelevant to a finding that there was no reasonable expectation of success in meeting the claims of the ′537 patent, which do not require quantitative deblocking at all . . . .”). I conclude that Lupin has satisfied its burden of establishing reasonable expectation of success.

c. Arguments Made During Prosecution

“When no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job . . . .” *PowerOasis, Inc. v. T–Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984), *abrogated on other grounds by Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011)). “That high burden is reflected in the clear and convincing evidence burden for proving invalidity.” *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012). “[T]here is no heightened burden of proof when a reference was previously considered by the PTO, and no lowered burden of proof if a defendant raises a new reference or argument during litigation.” *Id.* “If the PTO did not have all material facts before it, its considered judgment may lose significant force and the burden to persuade the finder of fact by clear and convincing evidence may, therefore, be easier to sustain.” *Id.* (cleaned up) (citations omitted).

During prosecution of the ’735 patent, the Patent Examiner rejected the pending claims based on Kondo.[9] The Examiner withdrew the rejection after Otsuka submitted the Yukawa

[9] It is not clear that Lupin relies on “no prior art other than that which was considered by the PTO.” *PowerOasis*, 522 F.3d at 1304. The prosecution history only contains discussion regarding Kondo. (*See* JTX-002.1198). While Watthey ’520 is cited on the face of the ’735 patent, Watthey ’575, Watthey ’503, and LeClerc are not. *See Shire LLC v. Amneal Pharmaceuticals, LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015) (“AU ’168 is listed on the face of

declaration, which purportedly demonstrated the "surprisingly unexpected properties" of the claimed process. (JTX-002.1514). The parties dispute the level of insight to be drawn from the Examiner's consideration of the Yukawa declaration. (D.I. 142 at 19–20; D.I. 150 at 32–33).

Based on the evidence presented, I find that the deference owed to the PTO's review of Kondo does not overcome the evidence weighing in favor of obviousness. Lupin presented evidence and expert testimony providing important facts and context not considered by the PTO, such as information from Otsuka's internal documents. (*See* DTX-2114). As explained in further detail below, this testimony and evidence undermine the Yukawa declaration's unexpected results evidence as they suggest that the Yukawa experiments followed processes that contained material differences from Kondo's process. *See* Section III.D.2.d. I conclude that the "theories presented during [prosecution] prove[] too weak when challenged in a judicial forum to rise to the level of unexpected results sufficient to rebut a strong case of obviousness." *Senju Pharm.*, 780 F.3d at 1351–53.

d. Objective Indicia of Nonobviousness

Otsuka offers evidence of three secondary considerations of nonobviousness: commercial success, long-felt but unmet need, and unexpected results. (D.I. 150 at 33–40).

A patentee is not required to present evidence of secondary considerations. *See Prometheus Lab'ys., Inc. v. Roxane Lab'ys., Inc.*, 805 F.3d 1092, 1101–02 (Fed. Cir. 2015). There must be enough evidence, however, for a finding that a given secondary consideration exists by a preponderance of the evidence. *See Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, then the probative value of each secondary

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the patents-in-suit and therefore the examiner is presumed to have considered it."). Since Lupin does not raise this issue, I consider the argument waived.

consideration will be considered in light of the evidence produced. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer*, 480 F.3d at 1359. That burden stays always with the patent challenger. *Id.* at 1359-60.

i. Commercial Success

Otsuka points to the commercial success of its JYNARQUE® product. (D.I. 150 at 33). Lupin does not dispute that JYNARQUE® is a successful product. (*See* D.I. 142 at 30–31). Lupin instead argues the evidence of commercial success is weak in light of economic disincentives from blocking patents and a weak nexus between JYNARQUE®'s success and the claimed invention.

Lupin contends Otsuka's '510 and '677 patents were blocking patents that disincentivized others from investing resources into making, developing, and marketing the '735 patent's claimed invention. (D.I. 153 at 13). The '510 patent claimed the tolvaptan compound and the '677 patent claimed a method of treating ADPKD using tolvaptan.[10]

"A patent has been called a 'blocking patent' where practice of a later invention would infringe the earlier patent." *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018). "The existence of such a blocking patent may deter non-owners and non-

[10] Otsuka contends that Lupin offers no technical expert opinion on the scope of the '510 and '677 patents. (D.I. 150 at 34). This argument serves no purpose as there is no dispute over the scope of these patents; rather, Otsuka's experts appear to adopt Lupin's characterizations of patent scope. (*See* Tr. at 401:23–402:7, 408:11–16, 507:16–508:3, 510:20–511:10). Furthermore, Dr. Dichtel did testify on the scope of the '510 patent. (Tr. at 252:7–11). Lupin's experts also relied on Otsuka's own representations to the FDA regarding the scope of the '510 and '677 patents. (Tr. at 212:4–213:5, 568:22–25, 569:19–570:4; *see Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 688 F.3d 766, 768 (Fed. Cir. 2012) (noting a company submitting patent information to the FDA must certify under penalty of perjury that its submission is accurate and complete); 21 C.F.R. § 314.53(c)(2)(i)(Q), (ii)(R)).

licensees from investing the resources needed to make, develop, and market such a later, 'blocked' invention, because of the risk of infringement liability and associated monetary or injunctive remedies." *Id.* "If the later invention is eventually patented by an owner or licensee of the blocking patent, that potential deterrent effect is relevant to understanding why others had not made, developed, or marketed that 'blocked' invention and, hence, to evaluating objective indicia of the obviousness of the later patent." *Id.* Where "market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak." *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed.Cir.2005).

As the '510 patent covers the tolvaptan compound, "no one other than [Otsuka] could have practiced the invention of the ['735 patent] without facing liability for patent infringement." *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 2017 WL 1199767, at *38 (D. Del. Mar. 31, 2017), *aff'd in part, dismissed in part*, 903 F.3d 1310 (Fed. Cir. 2018). In contrast, it is possible to practice the '735 patent's synthesis process without infringing the '677 patent's method of treatment claims. The '510 patent is a blocking patent while the '677 patent is not.

Otsuka submits that some entities did invest resources into developing and marketing tolvaptan and tolvaptan synthesis processes. (D.I. 150 at 35). The Zard group filed a French patent application claiming a process of synthesizing tolvaptan in 2004. (PTX-1171–73; Tr. at 381:21–382:7, 403:17–25, Tr. 498:11–20). Otsuka also points to several groups that filed patent applications or published articles describing tolvaptan synthesis methods after the '735 patent's priority date, ten companies that submitted DMFs for tolvaptan prior to the '677 patent's expiration, and five companies that filed ANDAs for generic tolvaptan products. (D.I. 150 at 35–36).

The relevant inquiry is whether the '510 patent caused a deterrent effect, not whether all others were dissuaded from resource investment. Aside from the Zard group, only the Galapagos Genomics group filed patent applications or published articles close to the asserted patents' priority date.[11] (PTX-1181, PTX-1182). Hetero filed a patent application on October 5, 2010, a month before the '510 patent expired. (PTX-1175). All other identified patent applications, publications, ANDAs, and DMFs were submitted in 2013 or later, close to a decade after the priority date of the asserted patents and three years after the '510 patent expired. (PTX-1155, PTX-1184; PTX-1167, PTX-1519–PTX-1524).

That only two groups investigated methods of synthesizing tolvaptan close to the priority date of the '735 patent suggests Otsuka's competitors experienced disincentives in investing resources into this area. This lack of investigation occurred despite what Otsuka characterizes as other pharmaceutical companies "know[ing] that tolvaptan had vasopressin antagonistic activity and was considered a promising pharmaceutical compound." (D.I. 150 at 36). The inference that the '510 patent had a deterrent effect is further supported by the wave of entities developing tolvaptan synthesis methods and seeking to commercialize tolvaptan products that began near the expiration date of the '510 patent. I find that the '510 patent deterred investment of resources into making, developing, and marketing the claimed invention.

I also find the claimed invention has a weak nexus to JYNARQUE®'s commercial success. "For secondary considerations to have probative value, the decision maker must determine whether there is a nexus between the merits of the claimed invention and the

[11] Though Otsuka states that Zard is the only patent application or published article pre-dating the '735 patent's priority date (D.I. 150 at 35), the two Galapagos Genomics patent applications appear to have been filed on May 21, 2004 and April 26, 2005 respectively (*see* PTX-1181, PTX-1182). This discrepancy does not change my conclusion on the commercial success secondary consideration.

secondary considerations." *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 n. 42 (Fed. Cir. 1985). "[T]he patented invention 'need not be solely responsible for the commercial success' of the accused products in order for a nexus to exist." *IOENGINE, LLC v. Paypal Holdings, Inc.*, 607 F. Supp. 3d 464, 508 (D. Del. 2002) (citing *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991)). Commercial success can be attributable to "manufacturing processes as critical steps in the chain of success." *Janssen Prod., L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 671 (D.N.J. 2014), *modified*, 2016 WL 1029269 (D.N.J. 2016); *see Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1361 (Fed. Cir. 1999) (finding a nexus for commercial success based on the success of a product made by a patented method). "Whether or not there is a nexus between the novel features of the patented product and the commercial success must be evaluated in terms of what is driving sales." *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 393 (D.N.J.), *aff'd*, 603 F. App'x 999 (Fed. Cir. 2015).

The demand for JYNARQUE® stems from the need for an ADPKD treatment. (*See* Tr. at 460:11–461:19). All experts agree that efficacy, safety, and tolerability of JYNARQUE® in treating ADPKD arises from the properties of the tolvaptan compound. (Tr. at 466:16–20, 520:1–5, 543:8–14, 567:6–568:11). It appears the key driver behind JYNARQUE®'s success are the properties inherent to the compound, rather than the claimed process. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005) ("Assuming that the active ingredient in the formulation was previously patented, the commercial success of ACULAR may heavily derive from subject matter that does not on the whole contribute to the patentable distinctiveness of these claims."). Furthermore, the claimed process is one step in a larger tolvaptan manufacturing process. (Tr. at 421:21–25). Dr. Roush testified that Otsuka scientists had to modify several other steps of the Kondo process, steps that are not covered by the '735 patent, to

achieve an acceptable tolvaptan synthesis process. (Tr. at 344:2–347:11, 421:21–25). I find, at most, only a small portion of JYNARQUE®'s marketplace success attributable to the claimed invention. *See Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 666–67 (D. Del. 2014), *aff'd*, 805 F.3d 1112 (Fed. Cir. 2015); *cf. Janssen*, 109 F. Supp. 3d at 671. Otsuka has not proven by a preponderance of the evidence that the "properties outlined in the claims are responsible for [JYNARQUE®'s] market success, as opposed to the 'inherent properties' of [the tolvaptan compound]." *Cubist*, 75 F. Supp. 3d 641 at 666.

For the above reasons, I find that the commercial success of JYNARQUE® offers minimal probative value on the issue of nonobviousness.

ii. Long-Felt but Unmet Need

Otsuka argues there was a long-felt but unmet need for an industrial-scale synthesis process for tolvaptan. (D.I. 150 at 38). Trial testimony focused largely on tolvaptan's role in fulfilling a long-felt but unmet need for an ADPKD treatment.[12] (*See* Tr. at 457:1–461:19). Otsuka's experts, Dr. Roush and Dr. Gansevoort, did testify about the amount of JYNARQUE® prescribed world-wide and the need for an industrial-scale process to meet this number of prescriptions. (*See* Tr. at 415:3–416:2, 462:2–463:7). This testimony, however, provides little insight regarding the existence of a need for a method of synthesizing tolvaptan on an industrial scale existed as of the priority date of the asserted patents, over a decade before Otsuka began selling JYNARQUE®. *See Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) ("Under *Monarch* [*Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998)], we look to the [priority] filing date of the challenged invention to

[12] It appears to be undisputed that a long-felt but unmet need for an ADPKD treatment existed. (*See* D.I. 142 at 35; D.I. 150 at 38). Otsuka does not argue that a sufficient nexus exists between this need and the claimed invention. (*See* D.I. 150 at 38).

assess the presence of a long-felt and unmet need."). In addition, Dr. Gansevoort agreed that "in 2005, there would not have been a need for a process to manufacture tolvaptan," let alone a need for an industrially suitable process. (Tr. at 468:5–9). Otsuka fails to establish by a preponderance of the evidence the existence of a long-felt need for an industrial-scale tolvaptan synthesis process.

iii. Unexpected Results

Otsuka argues the claimed invention produces tolvaptan with an unexpectedly high yield and high purity, making it suitable for industrial scale process. (D.I. 150 at 38). Otsuka bases its position on the Yukawa declaration, which reports a purity of 99.3 percent and yield of between 30 and 52.2 percent making tolvaptan by Kondo's process and a purity of 99.5 percent and yield of between 82 and 93 making tolvaptan by the claimed process. (PTX-1478.0002–0010).

Lupin and Dr. Dichtel argue the Yukawa declaration does not accurately report the results of Kondo because Yukawa used 3 molar equivalents of sodium borohydride in his experiments, as opposed to the 1.5 molar equivalents used in Kondo. (D.I. 143 at 19–20, 36). Dr. Dichtel opines that doubling the amount of sodium borohydride is a meaningful difference and notes that Otsuka's internal documents report the presence of a dechlorinated impurity when using 2 molar equivalents of sodium borohydride in the reduction step, but not when using 1.5 molar equivalents as disclosed in Kondo. (Tr. at 245:8–18, 248:8–249:24, 251:19–252:3; *see* DTX-2114). Otsuka and Dr. Roush maintain the difference is immaterial. (D.I. 150 at 33). Otsuka notes that Lupin's FDA submissions state that "the use of more than 1.2 molar equivalents of sodium borohydride leads to the formation of the dechlorinated impurity." (Tr. at 279:14–280:11; *see* JTX-015.0044).

I find Dr. Dichtel's testimony more credible. The sole improvement from the claimed invention over Kondo is decreasing the amount of sodium borohydride used from 1.5 molar equivalents to between 0.25 and 0.5 molar equivalents or between 0.25 and 1 molar equivalents. Given Otsuka's claims regarding the yield and purity improvements from this change, I am skeptical of Otsuka's assertion that doubling the amount makes no difference at all. I also find curious Otsuka's choice to rely on an experiment using 3 molar equivalents of sodium borohydride, rather than to conduct an experiment using 1.5 molar equivalents. Otsuka fails to meet its burden to show that the Yukawa declaration accurately reports the results of the Kondo process.

Otsuka asserts that a POSA would expect reducing the amount of sodium borohydride to cause yield to decrease and to have no impact on tolvaptan's purity. (D.I. 150 at 39). Otsuka's failure to establish the yield and purity expected to result from producing tolvaptan by Kondo's process proves fatal to its ability to show that the claimed invention produced tolvaptan with properties that deviated from the expected results. *See Pfizer*, 480 F.3d at 1371 ("[I]n order to properly evaluate whether a superior property was unexpected, the court should [consider] what properties were expected."); *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). I find that Otsuka has not met its burden of proving unexpected results by a preponderance of the evidence.

For the foregoing reasons, I conclude the secondary considerations do not overcome the strong evidence in favor of obviousness. *See W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1371 (Fed. Cir. 2010) ("[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness."); *Dow Chemical Co. v. Halliburton Oil Well Cementing Co.*, 324 U.S. 320, 330 (1945) ("[Secondary] considerations are relevant only in

a close case where all other proof leaves the question of invention in doubt."). I find the asserted '735 patent claims invalid for obviousness.

E. Invalidity of the '730 Patent

1. Findings of Fact

1. The priority date for the '730 patent is September 2, 2005. (D.I. 120, Ex. 1 ¶ 49).

2. Kondo disclosed tolvaptan. (JTX-005; Tr. at 230:12).

3. Tolvaptan made by any process, including the Kondo process and the claimed process, consists of many tolvaptan molecules. (Tr. at 348:13–349:1, 414:1–6).

4. The process limitation in the '730 patent claims impart structural differences over the Kondo tolvaptan because the claimed process results in the synthesis of highly pure tolvaptan containing "minimal amounts of dechlorinated impurity" that is suitable "for use as a pharmaceutical agent." (*Id.*).

5. The process limitation in the '730 patent claims impart functional differences over the Kondo tolvaptan because the tolvaptan synthesized according to the claims can be easily purified, in contrast to the Kondo tolvaptan. (Tr. at 349:2-8).

6. A POSA would not have had a reasonable expectation of success of using the claimed process limitation to obtain (1) tolvaptan with a purity greater than 99.5 percent and (2) tolvaptan substantially free from at least one of Compounds A-D.

2. Conclusions of Law

The asserted claims of the '730 patent are product-by-process claims. The parties dispute whether an invalidity analysis of these claims requires consideration of the process limitation. (D.I. 142 at 27; D.I. 150 at 9).

"In determining validity of a product-by-process claim, the focus is on the product and not the process of making it." *Amgen Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed.Cir.2009)." The Federal Circuit recognized an exception to this general rule: "if the process by which a product is made imparts 'structural and functional differences' distinguishing the claimed product from the prior art, then those differences are relevant as evidence of [nonobviousness] although they 'are not explicitly part of the claim.'" *Greenliant Sys., Inc. v.*

Xicor LLC, 692 F.3d 1261, 1268 (Fed. Cir. 2012) (quoting *Amgen*¸ 580 F.3d at 1370); *see also Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1354 (Fed. Cir. 2016).

The parties dispute who bears the burden of proof of establishing structural and functional differences between the claimed product and the prior art. (D.I. 150 at 9; D.I. 153 at 7 n. 1). The case law makes clear "[t]he party asserting [obviousness] bears the burden of proving that the process limitations do not result in an invention distinguishable from the prior art." *Cubist*, 75 F. Supp. 3d at 668; *see Amgen*, 580 F.3d at 1370 ("To prove invalidity, [the patent challenger] had to show that recombinant EPO was the same as urinary EPO, even though urinary EPO was not made recombinantly.").

Lupin fails to satisfy its burden of proof. In its opening brief, Lupin merely asserts that Otsuka's expert presented no evidence in support of Otsuka's position on the presence of structural and functional differences and provides no analysis of its own. (D.I. 142 at 27–28). In its reply brief, Lupin challenges Otsuka's arguments as flawed because the "relevant analysis is the structure and function of the claimed product—tolvaptan—not the separate impurity." (D.I. 153 at 8). I need not credit Lupin's argument as it was raised for the first time in its reply brief. *See In re: Niaspan Antitrust Litigation*, 67 F.4th 118, 135 (3d Cir. 2023). Furthermore, I agree with prior case law from this Court that suggests impurities can lead to structural or functional differences. *See Cubist*, 75 F. Supp. 3d at 669 (finding elimination of certain impurities did not qualify as structural and functional differences based on the facts of the case and only after a thorough analysis considering expert testimony and prosecution history). I find the process limitation does impart structural and functional differences that differentiate the claimed product of the '730 patent from the prior art.

Lupin contends that, even with consideration of the process limitation, the '730 patent claims are obvious because they contain the same reduction step present in the '735 patent claims. (D.I. 142 at 28). The '730 patent claims, however, include purity limitations that are absent from the '735 patent claims. Lupin's reasonable expectation of success analysis for the '735 patent relies on the lack of a purity limitation in the asserted claims of the '735 patent. (*See* D.I. 142 at 13). Lupin offers no analysis on a POSA's expectation of success of using the claimed process to achieve (1) tolvaptan with a purity greater than 99.5 percent and (2) tolvaptan substantially free from at least one of Compounds A-D. Lupin therefore fails to present clear and convincing evidence that a POSA would have reasonably expected to successfully synthesize tolvaptan in compliance with the purity limitations of the asserted '730 patent claims. I conclude the asserted claims of the '730 patent are not invalid for obviousness.

IV. CONCLUSION

For the foregoing reasons, I find the asserted claims of the '735 patent not infringed and invalid for obviousness under 35 U.S.C. § 103. I find the asserted claims of the '730 patent not infringed and not invalid.

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