NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PACIRA PHARMACEUTICALS, INC., and PACIRA BIOSCIENCES, INC., *Plaintiffs,* **v.** **eVenus PHARMACEUTICALS LABORATORIES, INC., JIANGSU HENGRUI PHARMACEUTICALS CO., LTD., and FRESENIUS KABI USA, LLC,** *Defendants.*	**Civil Action No. 21-19829** **OPINION**

ARLEO, UNITED STATES DISTRICT JUDGE

THIS MATTER arises from the filing of an Abbreviated New Drug Application ("ANDA") by Defendants Jiangsu Hengrui Pharmaceuticals Co., Ltd. ("Jiangsu Hengrui") and eVenus Pharmaceuticals Laboratories, Inc. ("eVenus"), seeking to market a generic copy of Exparel pursuant to the Hatch-Waxman Act, see 35 U.S.C. § 271(e).[1] On November 8, 2021, Plaintiffs Pacira Pharmaceuticals, Inc., and Pacira Biosciences, Inc. ("Pacira" or "Plaintiffs"), brought this action alleging infringement of U.S. Patent No. 11,033,495 (the "'495 Patent"). Defendants dispute that its proposed generic product infringes upon Exparel and further argue that

[1] Defendant Fresenius Kabi USA, LLC ("Fresenius Kabi" and together with Jiangsu Hengrui and eVenus, "Defendants") is party to a license agreement with Jiangsu Hengrui to commercialize the proposed ANDA products. Amend. Ans., ECF No. 73 at 4–5.

Pacira's patent is invalid for obviousness, anticipation, and lack of enablement, as well as unenforceable due to inequitable conduct. At issue in this matter is Claim 7 of the '495 Patent.[2]

The Court held a five-day bench trial in February 2024. See ECF Nos. 333–45. Thereafter, the parties submitted post-trial briefing and proposed findings of fact and responsive post-trial

[2] Although this case originally involved broader claims of infringement and a second patent, Plaintiffs have since stipulated to only asserting infringement of Claim 7 against Defendants. See Pre-trial Order, ECF No. 298, Tab 2; Pls.' Proposed Findings of Fact and Conclusions of Law, ECF No. 369.1 at 2 n.2.

Claim 7 is dependent on Claim 1. The claims are as follows:

1. A composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process, the commercial scale process comprising:
    a. mixing a first aqueous solution comprising phosphoric acid with a volatile water-immiscible solvent solution to form a water-in-oil first emulsion, wherein the volatile water-immiscible solvent solution comprises bupivacaine, 1, 2-dierucoylphosphatidylcholine (DEPC), 1, 2-dipalmitoylsn-glycero-3 phospho-rac-(1-glycerol) (DPPG), and at least one neutral lipid;
    b. mixing the water-in-oil first emulsion with a second aqueous solution to form a water-in-oil-in-water second emulsion, wherein the second aqueous solution comprises lysine and dextrose;
    c. removing the volatile water-immiscible solvent from the water-in-oil-in-water second emulsion to form a first aqueous suspension of bupivacaine encapsulated MVLs having a first volume;
    d. reducing the first volume of the first aqueous suspension of bupivacaine encapsulated MVLs by microfiltration to provide a second aqueous suspension of bupivacaine encapsulated MVLs having a second volume;
    e. exchanging the aqueous supernatant of the second aqueous suspension with a saline solution by diafiltration to provide a third aqueous suspension of bupivacaine encapsulated MVLs having a third volume; and
    f. further reducing the third volume of the third aqueous suspension by microfiltration to provide a final aqueous suspension of bupivacaine encapsulated MVLs having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL;

    wherein all steps are carried out under aseptic conditions; and

    wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C. for one month.
7. The composition of claim 1, wherein the erucic acid concentration in the composition is about 99 µg/mL or less after the composition is stored at 25° C. for six months.

briefing and proposed findings of fact.[3] ECF Nos. 365–71. The parties appeared before the undersigned for closing arguments on May 7, 2024. ECF No. 379.[4]

Pursuant to Federal Rule of Civil Procedure 52(a), and having considered the entire record in this case as well as the applicable law, the Court concludes that (1) Claim 7 of the '495 Patent is invalid as obvious in view of the prior art and (2) Claim 7 of the '495 Patent is also invalid as anticipated in view of the prior art.[5] The Court's findings of fact and conclusions of law are set forth in detail below.

I. FINDINGS OF FACT

A. Multivesicular Liposomes

Liposomes are drug delivery tools that allow for the sustained release of a drug product encapsulated within the liposome. Hall Tr. 75:20–76:4. The liposome is an external membrane composed of phospholipids, which surrounds an internal core consisting of a liquid pharmaceutical ingredient. Id. There are three types of liposomes: unilamellar, multilamellar, and multivesicular. Id. 76:9–24. While unilamellar and multilamellar liposomes comprise one or more, respectively, concentric phospholipid membranes that surround the liquid pharmaceutical core, the structure of a multivesicular liposome ("MVL") is more akin to that of a honeycomb or pomegranate—multiple, individual, non-concentric chambers, each of which comprise an external membrane and an internal liquid core, which combine to form one MVL particle. Id.; Grigsby Tr.

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[3] The Court would like to extend its gratitude to all counsel for their excellent trial preparation, briefing, and oral argument. The advocacy on both sides was outstanding, and all the lawyers exhibited the highest standard of professionalism.

[4] On July 18, 2024, upon Plaintiffs' request, this Court reopened the trial record for the parties to submit additional exhibits and findings of fact. See ECF Nos. 393, 395, 396, 397. The Court considered this new evidence but does not discuss it in detail as it does not move the needle on the theories upon which this Court relies to resolve this Matter.

[5] In light of this conclusion, the Court does not reach Defendants' alternative arguments of enablement and inequitable conduct, see Hospira, Inc. v. Fresenius Kabi USA, LLC, 343 F. Supp. 3d 823, 826 n.2 (N.D. Ill. 2018), nor the issue of infringement, ZUP, LLC v. Nash Mfg., 896 F.3d 1365, 1368 (Fed. Cir. 2018).

148:24–149:9; Schwendeman Tr. 385:20–25, 386:9–15. Once an MVL is injected into a person, the body's physiology causes the phospholipids that make up the external layer to degrade, allowing for the sustained release of the liquid pharmaceutical. Hall Tr. 77:14–78:6.

B. Exparel

Exparel is an MVL drug product. Id. 75:16–18. The active ingredient in Exparel—i.e., the internal pharmaceutical core—is bupivacaine, an analgesic used for local pain relief. Id. 74:21–24. The bupivacaine is surrounded by a phospholipid membrane, the main lipid component of which is 1, 2-dierucoylphosphatidylcholine ("DEPC"). DTX-3115.23–24, JTX-4205.19; Grigsby Tr. 152:22–23; Schwendeman Tr. 486:8–10. Exparel has been successful on the market as an alternative to opioids—it is injected into a patient before surgery and provides sustained pain relief for three to five days post-injection, after which the patient can manage residual pain with non-opioid pain medications such as ibuprofen and acetaminophen. Hall Tr. 79:14–81:5.

The United States Food and Drug Administration ("FDA") approved Exparel in 2011 as a local, post-surgical analgesic. Hall Tr. 91:14–15. Exparel's recommended storage temperature is about five degrees Celsius (i.e., refrigerated). JTX-4205.27; DTX-3115.37; Grigsby Tr. 154:20–22. Exparel's shelf life at this temperature is 24 months. Hall Tr. at 86:15–23. Exparel became commercially available in 2012, and since then, Pacira has sold 2,589 batches, or about 10.5 million vials. DTX-3109; Schwendeman Tr. 452:2–12.

When it first became commercially available, Pacira produced Exparel on 45-Liter skids or manufacturing units. Hall Tr. 92:6–93:23. In response to an increased demand for Exparel following the opioid epidemic, Pacira pursued two different methods that could sustain increased production of Exparel: a spray method and a 200-Liter skid process. Id. 93:6–94:6. Pacira eventually abandoned the spray method and, after about seven years, began successfully producing

Exparel using the 200-Liter skid process. Id. 97:11–22; Grigsby Tr. 151:3–5. Pacira continues to produce and sell Exparel using both the 200-Liter process ("200L Exparel") and the 45-Liter process ("45L Exparel"), and both are currently on the market with the same 24-month shelf life at refrigerated conditions. Grigsby Tr. 163:4–5; Schwendeman Tr. 454:9–14; JTX-4205 (45L Exparel prescribing information); DTX-3115 (200L Exparel prescribing information).

There are four general steps in manufacturing Exparel: first emulsion, second emulsion, sparge, and diafiltration. Hall Tr. 88:13–21. These general steps are used to manufacture both 200L and 45L Exparel. Id. 118:20–119:2. Although Pacira originally believed that they could not produce a stable Exparel using the 200-Liter process, JTX-4121.20 (21:51–55), Pacira adjusted certain parameters within the two emulsion steps—which are considered the most critical steps—in order to yield a stable product. Klibanov Tr. 739:4–8, 745:1–9. These parameters include reducing mixing speeds during the second emulsion, adding a second mixing blade for both emulsion steps, and using separate mixers for the first and second emulsion steps. Hall Tr. 106:10–111:1; Grigsby Tr. 151:17–152:14, 166:22-167:6.

C. Erucic Acid

Pacira determines the stability of Exparel by measuring the erucic acid concentration in the product. Grigsby Tr. 156:9–157:4. DEPC—the main lipid component forming the MVL—hydrolyzes or degrades over time into erucic acid and Lyso-DEPC, the latter of which further degrades into erucic acid. JTX-4121.17 (15:3–10). Excess lipid degradation can lead to a change in the release kinetics of the MVL particle and negatively impact the sustained release of bupivacaine over time. Grigsby Tr. 152:24–154:1. As such, Pacira uses erucic acid concentration, which is depicted as a rate of hydrolysis, as a marker to assess the stability of Exparel. Id.; id. 159:4–13.

Pacira tests stability by measuring the erucic acid concentration in batches of Exparel at various time points and under various conditions. Although the recommended storage temperature and shelf life are five degrees Celsius and 24 months respectively, Pacira also conducts accelerated stability studies. Id. 155:2–13. The accelerated stability study conditions that are specifically at issue in this case are storage at 25 degrees Celsius (room temperature) for one month and six months. Id. 154:8–18. Pacira conducted these accelerated stability studies and unexpectedly discovered that at six months some batches of 200L Exparel contained less erucic acid than other batches of 45L Exparel. Id. 159:7–13, 170:9–20. Pacira conducted further tests to understand the mechanisms that led to this lower erucic acid concentration and found that these batches of 200L Exparel had higher lysine, dextrose, and internal pH. Id. 163:6–168:7; DTX-2262.3. Pacira then relied on this data in their application for the '495 Patent, asserting that they now produced a new, more stable Exparel. JTX-4121.

D. The '495 Patent

The United States Patent and Trademark Office (the "USPTO") issued the '495 Patent, titled "Manufacturing of Bupivacaine Multivesicular Liposomes," on June 15, 2021, with a priority date of January 22, 2021. Id. 4121.1. The specification explains that the '495 Patent discloses "new and improved commercial scale manufacturing processes for making bupivacaine encapsulated [MVLs]," and details that "[t]he newly developed processes provide up to 5 folds increase in final product volume as compared to the current process . . . which is disclosed in U.S. Patent No. 9,585,838" (the "'838 Patent"). Id. 4121.11 (4:26–40). The specification explains that the new processes "allow for improved product operability" and "yield[] a more stabilized form of bupivacaine encapsulated MVLs." Id. Indeed, "[t]he improved lipid stability (as indicated by the

erucic acid concentration) observed in the bupivacaine MVLs prepared by the presently described process was surprisingly unexpected." Id. 4121.20 (21:52–55).

Claim 1 of the '495 Patent claims "[a] composition of bupivacaine encapsulated multivesicular liposomes (MVLs) prepared by a commercial scale process . . . having a target concentration from about 12.6 mg/mL to about 17.0 mg/mL . . . wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C. for one month." Id. 4121.20–21 (22:43–23:12). Claim 1 also discloses process limitations that constitute the "commercial scale process" by describing the first emulsion, second emulsion, sparge, and diafiltration steps—in total, six manufacturing steps and that each step must be "carried out under aseptic conditions." Id. (22:45–23:9). Claim 7 is for "[t]he composition of claim 1, wherein the erucic acid concentration in the composition is about 99 µg/mL or less after the composition is stored at 25° C. for six months." Id. 4121.21 (23:29–31). Although the specification discloses a range of volumes that includes 200 liters, id. 4121.18 (17:26–30), the '495 Patent does not disclose a specific volume limitation, see id. 4121.20–21 (22:42–24:32).

E. Scope and Content of the Prior Art

The heart of the parties' obviousness dispute is based on prior art—that which was "in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention." 35 U.S.C. § 102(a). As noted, Pacira originally manufactured Exparel using a 45-Liter process before developing a 200-Liter process to meet increased demand, with the new, 200-Liter process being the basis for the '495 Patent. Now, Pacira continues to manufacture both 45L and 200L Exparel. Defendants maintain that the prior art, specifically the combination of the '838 Patent and the stability study results of certain prior art batches of 45L Exparel, render Claim 7 of the '495 Patent obvious. Pacira, on the other hand, argues that a person of ordinary skill in

the art ("POSA")[6] would not have been motivated to combine the references, in part because other prior art references—a published study by Kapoor et al., and FDA guidance—teach away from the claimed invention, and thus Defendants do not prove by clear and convincing evidence that the Claim 7 is obvious. The Court reviews the relevant prior art in turn.

i. '838 Patent[7]

The USPTO issued the '838 Patent, titled "Production of Multivesicular Liposomes," on October 11, 2007, with a priority date of February 25, 2007. JTX-4089.1. The specification of the '838 Patent explains that "[a] new process for preparing MVLs has been invented. This process is suitable for manufacturing at commercial scales." Id. 4089.21 (3:27–29). The specification further explains that there are two aspects to the invention: (1) "the invention provides a process for producing MVL by providing a water in oil (w/o) emulsion," and (2) "the invention provides a way to accurately and quickly scale up reactions 10 fold." Id. (3:31–64). The specification also describes the four primary steps for manufacturing MVLs: first emulsion, second emulsion, sparge, and diafiltration. Id. 4089.23 (7:15–20:45); see also Klibanov Tr. 736:25–737:8 (noting that the '838 Patent teaches the general double emulsification process used to manufacture Exparel at a commercial scale). Pacira has used and continues to use the process disclosed by the '838 Patent

[6] "The POSA is patent law's hypothetical, legal construct akin to the reasonable person used as a reference in negligence determinations." McCoy v. Heal Sys., LLC, 850 F. App'x 785, 787–88 (Fed. Cir. 2021) (internal quotation marks omitted) (quoting In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998)). The legal construct presumes that the theoretical person has access to all prior art references in the field of the invention. In re Rouffet, 149 F.3d at 1357. A POSA in this case would have a bachelor's, master's, or Ph.D degree in the pharmaceutical sciences or a related discipline such as biology, chemistry, or chemical engineering. Schwendeman Tr. 384:2–17; Yaman Tr. 554:17–555:2. Such a POSA would also have an understanding of the importance, use, and characterization of liposomal drugs in the pharmaceutical industry and at least several years of experience developing, formulating, characterizing, analyzing, and/or manufacturing controlled-release drugs, such as liposomes, including experience in scaling up production of liposomal products or access to consult with someone having such experience. Id. Both parties provided similar definitions for the qualifications of a POSA in this case, and the experts all testified that their opinions remained the same regardless of which definition they used. Schwendeman Tr. 384:1–385:5; Klibanov Tr. 694:17–695:15.

[7] Production of Multivesicular Liposomes, U.S. Patent No. 9,585,838 (filed Feb. 25, 2007) (issued Oct. 11, 2007). JTX-4089.

to manufacture and sell 45L Exparel since its approval in 2011. Hall Tr. 118:5–22; Grigsby Tr. 167:7–12, 183:2–185:24.

ii. Prior Art Batches of Exparel[8]

Defendants identified 10 batches of Exparel that were commercially available before January 22, 2021, and thus constitute prior art (the "Prior Art Batches"). The Prior Art Batches were stability tested under accelerated conditions (25 degrees Celsius), the results of which ranged from less than 20[9] to 29 µg/mL of erucic acid after one month and from 110 to 127 µg/mL of erucic acid after six months. DTX-3111.

iii. Kapoor[10]

In 2017, as a result of substantial growth in the research of and regulatory submissions for liposomal drug products, the Kapoor study sought "to identify the pain points in development and manufacturing of liposomal drug products." JTX-4210.1. The authors conducted a retrospective analysis on regulatory submissions for new and generic liposomal drug products, identified "major challenges" in the development of liposomal drug products, and concluded that focusing on these challenges could achieve "a faster and more efficient development of liposomal drug products." Id.

Specifically, Kapoor notes that "[d]espite the popularity of the liposome platform, developability, manufacturability, scalability, and stability are key challenges with the technology." Id. 4210.1–2. "Some examples of deviations in [the] manufacturing process and

[8] Batch Nos. 14-4012, 14-4013, 14-4015, 14-P004, 16-3088, 16-3089, 16-3090, 18-P003, 18-P004, and 18-P063. DTX-3111 (summary table of Prior Art Batches).

[9] While the precise erucic acid concentration could not be measured below 20 µg/mL, such a result satisfies the 23 µg/mL or less limitation. Schwendeman Tr. 416:2–4; 417:25–418:2.

[10] Kapoor et al., Liposomal Drug Product Development and Quality: Current US Experience and Perspective, 19 AAPS J. 632 (2017). JTX-4210.

their effect on liposome product quality/performance are as follows:" the effect of freezing and drying temperatures on morphology, residual water content, and stability of lyophilized liposomes; the effect of aqueous phase temperature on liposome particle size and size distribution; the effect of homogenization speed, time, and temperature on particle size and product performance; and the effect of lipid phase transition temperatures on drug loading or leakage. Id. 4210.3. Kapoor also generally notes that "scalability of liposomal drug products . . . is one of the key challenges with the development of these complex formulations" but acknowledges that "a thorough understanding of the manufacturing process and the use of appropriate in-process controls result in a well-controlled manufacturing process that is less likely to experience failures during scale-up." id. 4210.8; see also id. ("The understanding and identification of appropriate controls can be achieved by applying principles of quality by design (QbD) in early phases of product development."); id. 4210.2–3 ("[A] control strategy should be developed to obtain desired product quality despite subtle changes during" formulation and development by, among other things, "developing [a] manufacturing process that provides adequate control of the variables that affect" certain attributes such as lipid degradation products.).

iv. FDA Guidance for Industry[11]

In 2018, the FDA published guidance for what information should be included in new drug applications ("NDA") and abbreviated new drug applications ("ANDA") for liposome drug products. PTX-362.4. In it, the FDA generally notes that "[l]iposome drug products are sensitive to changes in the manufacturing conditions, including changes in scale (size of batches)" and that "[l]iposome drug products are complex and sensitive formulations and response to [chemistry,

[11] U.S. FOOD & DRUG ADMIN., LIPOSOME DRUG PRODUCTS CHEMISTRY, MANUFACTURING, AND CONTROLS; HUMAN PHARMACOKINETICS AND BIOAVAILABILITY; AND LABELLING DOCUMENTATION: GUIDANCE FOR INDUSTRY (2018). PTX-362.

manufacturing, and control] changes is less predictable than with more conventional formulations." Id. 362.8, 362.13. Like Kapoor, the FDA also notes that such changes can be anticipated and controlled for and offers guidance on how "[p]rior knowledge can be leveraged and risk assessments can be used to identify manufacturing process parameters that potentially affect finished product quality." Id. 362.8; see id. ("Appropriate process controls should be established during product development.").

F. Non-Prior Art Evidence

The heart of the parties' anticipation dispute is based on evidence that does not qualify as prior art—i.e., it was not "available to the public before the effective filing date of the claimed invention." 35 U.S.C. § 102(a). Defendants maintain that this non-prior art evidence—specifically the combination of Pacira's NDA, the stability study results of certain non-prior art batches of 45L Exparel, and the stability study results of certain non-prior art batches of 200L Exparel—render Claim 7 of the '495 patent anticipated. The Court reviews the relevant non-prior art in turn.

v. Pacira's NDA[12]

Pacira's NDA, filed in 2010, includes information regarding the stability, manufacturing process, and justification of specifications for 45L Exparel. See DTX-2498; JTX-4174; JTX-4264.

The NDA states that the concentration of bupivacaine in the tested batches all met the acceptance criterion of 12.6–14.0 mg/mL. DTX-2498.9; see also JTX 4174.2–3 (outlining manufacturing steps that yield a target 13.3mg/mL bupivacaine concentration); Grigsby Tr. 185:6–9. Furthermore, "[a]t 25° C, . . . [a]ll results met the acceptance criterion of [no more than] 310 µg/mL," with "a range of 78 to 127 µg/mL." DTX-2498.11.

[12] The Court only discusses the relevant sections of New Drug Application No. 022496: sections 3.2.P.3 Manufacture (JTX-4174), 3.2.P.5 Control of Drug Product (JTX-4264), and 3.2.P.8 Stability (DTX-2498).

The NDA also sets the erucic acid specification at no more than 310 µg/mL. JTX-4264.5. This is equivalent to 10% nominal DEPC degradation. Id. The NDA further states that "[t]his level of erucic acid was observed to have no effect on the in vitro release of [Exparel]." Id. In fact, "[s]tudies . . . indicate that up to 15% [DEPC] degradation . . . does not significantly alter the bilayer permeability," such that a comparison of tested lots "with approximately 310µg/mL" to lots with lower erucic acid content "showed comparable pharmacokinetic profiles, demonstrating that product with erucic acid vales up to 310 µg/mL will maintain product performance." Id. Dr. Grigsby confirmed this and testified that an increase of 15 µg/mL erucic acid would amount to "about half a percent of DEPC hydrolysis." Grigsby Tr. 191:22–192:24.

vi. Batches of non-prior art Exparel[13]

Defendants identified 14 batches of 45L Exparel that were stability tested but not commercially available before January 22, 2021 (the "Non-Prior Art Batches"). The Non-Prior Art Batches were stability tested under accelerated conditions (25 degrees Celsius), the results of which ranged from less than 20 to 25 µg/mL of erucic acid after one month and from 78 to 100 µg/mL of erucic acid after six months. DTX-3110. The Non-Prior Art Batches were manufactured during the same time period using the same process, components, and equipment as prior art 45L Exparel. Grigsby Tr. 190:8–20; Schwendeman Tr. 451:3–22; 527:24–528:1; JTX-4044.11 (FDA guidance instructing that "the manufacturing process used . . . should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing"). They also shared the same physical properties as

[13] Batch Nos. 037188, 037189, 037190, 037191, 037192, 037193, 047903, 13-2204, 13-2205, 13-2206, 18-SS-020, 18-SS-021, 18-SS-022, and 18-SS-024. DTX-3110 (summary table of all batches of 45L Exparel tested before January 22, 2021).

prior art 45L Exparel and were used in regulatory submissions to represent and obtain approval for commercial 45L Exparel. Grigsby Tr. 190:8–20; Schwendeman Tr. 451:3–22; 527:24–528:1.

vii. Batches of 200L Exparel[14]

Defendants identified nine batches of 200L Exparel that were stability tested but not commercially available before January 22, 2021 (the "200L Batches"). The 200L Batches were stability tested under accelerated conditions (25 degrees Celsius). DTX-3114. Four of the 200L Batches exhibited results ranging from less than 20 to 23 µg/mL of erucic acid after one month and from 92 to 99 µg/mL of erucic acid after six months. Id. Five of the 200L Batches exhibited results ranging from 26 to 37 µg/mL of erucic acid after one month and from 106 to 133 µg/mL of erucic acid after six months.

II. DISCUSSION

A. Obviousness

Defendants argue that Claim 7 of the '495 Patent is invalid as obvious in view of the prior art. Specifically, Defendants maintain that Claim 7 is obvious because the claimed erucic acid concentration at the six-month time point after storage at 25 degrees Celsius, 99 µg/mL (the "Six-Month Erucic Acid"), is so close to the range of erucic acid disclosed by the Prior Art Batches that a POSA would have expected the two to have the same properties. Defs.' Invalidity Br., ECF No. 365 at 37. Defendants argue that this creates a prima facie case of obviousness, which Plaintiffs fail to rebut with evidence of non-obviousness. Id. at 38–41.

In response, Plaintiffs assert that no prima facie case of obviousness exists because the Six-Month Erucic Acid does not overlap with the range disclosed by the Prior Art Batches. Pls.'

[14] Batch Nos. 129855, 129856, 129860, 120862, 120863, 120864, 21-2001, 21-2002, and 21-2003. DTX-3114 (summary table of tested batches of 200L Exparel).

Invalidity Br., ECF No. 369 at 23–26. Instead, Plaintiffs argue that Defendants fail to prove obviousness under the traditional Graham factors test for obviousness because a POSA would not be motivated to modify 45L Exparel nor have a reasonable expectation of success in achieving the improved stability of 200L Exparel as embodied in Claim 7. Id. at 22–23. Furthermore, Plaintiffs argue that any prima facie case of obviousness under the range theory is defeated by evidence of critical range and other objective indicia of non-obviousness, such as a long-felt, unresolved need for a larger scale, stable Exparel. Id. at 26–32.

For the reasons discussed below, the Court finds that Claim 7 of the '495 Patent is invalid as obvious.

i. Legal Standard

Patents are presumed to be valid, and "[e]ach claim of a patent . . . shall be presumed valid independently of the validity of other claims." 35 U.S.C. § 282; Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed. Cir. 2006). In accordance with "the U.S. Patent Act, an invention cannot be patented if the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." P & G v. Teva Pharms. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (internal citation omitted); 35 U.S.C. § 103(a).

Traditionally, a party seeking to invalidate a patent based on obviousness must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Pfizer, Inc. v. Apotex, Inc., 480

F.3d 1348, 1361 (Fed. Cir. 2007).[15] Obviousness is a question of law and is traditionally based on several underlying factual determinations known as the Graham factors: (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) secondary considerations of obviousness, such as commercial success and unexpected results. Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966).

Whether a separate test or one subsumed by the Graham factors, the Federal Circuit has articulated a burden-shifting framework applicable in overlapping range cases (the "Range Framework"): "[a] prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." E.I. du Pont de Nemours & Co. v. Synvina C.V., 904 F.3d 996, 1006 (Fed. Cir. 2018) (alteration in original) (quoting In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003)).[16] This rule is based on the underlying legal principle that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Id. (quoting In re Aller, 220 F.2d 454, 456 (C.C.P.A. 1955).

Although "such overlap creates a presumption of obviousness," it may be rebutted by evidence (1) of "a new and unexpected result which is different in kind and not merely degree from the results of the prior art," i.e., critical range, id. (quoting Aller, 220 F.2d at 456); (2) "that the prior art [teaches] away from the claimed range," id.; and (3) of other "secondary considerations," such as commercial success and a long-felt, unresolved need for the product, Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006). "Where there is a range

[15] The Supreme Court has described "clear and convincing" as evidence which produces in the mind of the trier of fact "an abiding conviction that the truth of [the] factual contentions are highly probable." Colorado v. New Mexico, 467 U.S. 310, 316 (1984).

[16] This burden-shifting framework applies both before the United States Patent and Trademark Office (the "PTO") and in district court. E.I. du Pont de Nemours & Co., 904 F.3d at 1007.

disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with [such] evidence." Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 738 (Fed. Cir. 2013). Nevertheless, this "does not shift the burden of persuasion to the patentee to prove nonobviousness by, for example, pointing to evidence of criticality or unexpected results." E.I. du Pont de Nemours & Co., 904 F.3d at 1008. In other words, "absent a reason to conclude otherwise, a factfinder is justified in concluding that a disclosed range does just that—discloses the entire range." Id.

With these principles in mind, and in light of Plaintiffs' argument to the contrary, the Court first determines whether the Range Framework applies in this case. The Court finds that it does. The Court then sets out and weighs Defendants' evidence of obviousness against Plaintiffs' evidence of non-obviousness before finally concluding that Claim 7 of the '495 Patent is invalid as obvious.

ii. Application of the Range Framework

Defendants solely rely on the Range Framework, arguing that the Six-Month Erucic Acid is so close to the range disclosed by the Prior Art Batches such that there exists a prima facie case of obviousness. Plaintiffs counter that the Range Framework does not apply here because (1) the Six-Month Erucic Acid does not overlap with the range disclosed by the Prior Art Batches and (2) the one case cited by Defendants with non-overlapping ranges is non-precedential and distinguishable from this case. See Pls.' Invalidity Br. at 24–25 (collecting overlapping range cases and citing Ortho-McNeil Pharmaceutical v. Teva Pharmaceuticals Industries, 344 F. App'x 595 (Fed. Cir. 2009)).

Contrary to Plaintiffs' arguments, the Range Framework applies here despite the non-overlapping nature of the ranges at issue. The Court may consider non-precedential

cases—especially those from the Federal Circuit—as persuasive despite being non-binding. See In re Hartman, No. 15-7093, 2016 WL 7189826, at *3 n.5 (D.N.J. Dec. 12, 2016) ("[A]lthough 'non-precedential opinions of the Third Circuit are not binding upon this Court,' the Court 'is certainly permitted to consider and find persuasive their reasoning.'"). Furthermore, the Federal Circuit—in published, binding opinions—has held that the Range Framework also applies in cases involving ranges that, while not overlapping, "are so close that prima facie one skilled in the art would have expected them to have the same properties." In re Brandt, 886 F.3d 1171, 1178 (Fed. Cir. 2018) (collecting cases) (quoting Titanium Metals Corp. v. Banner, 778 F.2d 775, 783 (Fed. Cir. 1985)).

The Court, therefore, must determine whether Defendants have satisfied their burden to show that the Six-Month Erucic Acid and the range of erucic acid disclosed by the Prior Art Batches "are so close that prima facie one skilled in the art would have expected them to have the same properties." See id. Against Defendants' evidence of obviousness, the Court must weigh Plaintiffs' evidence of (1) critical range, (2) teaching away, and (3) secondary considerations, such as commercial success and long-felt, unresolved need.

iii. Defendants' evidence of obviousness

The Six-Month Erucic Acid is 99 µg/mL after storage at 25 degrees Celsius for six months. JTX-4121.20–21. The erucic acid concentration disclosed by the Prior Art Batches after storage at 25 degrees Celsius for six months ranged from about 110 to 127 µg/mL. DTX-3111; Schwendeman Tr. 449:1–9. Plaintiffs' witness Dr. Grigsby confirmed that the 11 µg/mL difference in erucic acid between the low end of the prior art range and the Six-Month Erucic Acid would amount to less than half a percent DEPC degradation in the MVL lipid membrane. Grigsby Tr. 191:22–192:24 (confirming that an increase of 15 µg/mL erucic acid would amount to "about

half a percent of DEPC hydrolysis"). This is further supported by the NDA, which discloses to the FDA that 310 µg/mL is equivalent to 10% DEPC degradation. JTX-4264.5. Dr. Schwendeman testified that this difference is so small that a POSA would reasonably expect 45L Exparel and 200L Exparel to have the same properties. Schwendeman Tr. 453:17–459:16. For example, a POSA would not expect such a small difference to impact the effective properties of Exparel, such as release rate of bupivacaine and pharmacokinetics. Schwendeman Tr. 459:11–16. This lack of impact on the drug's efficacy is further supported by the NDA, which asserts that an erucic acid concentration up to 310 µg/mL would not affect product performance.[17] JTX-4264.5; see also Schwendeman Tr. 457:13–20. Finally, the erucic acid concentration in batches of prior art Exparel after storage at 25 degrees Celsius for one month ranged from less than 20 µg/mL to 29 µg/mL. DTX-3111; Schwendeman Tr. 453:11–17. This directly overlaps with the erucic acid concentration in Claim 1, about 23 µg/mL or less, JTX-4121.20–21, and "[w]hen compounds share significant structural and functional similarity, those compounds are likely to share other properties, including optimal formulation for longterm stability," Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc., 955 F.3d 25, 32–33 (Fed. Cir. 2020).

Taken together, this evidence demonstrates that the Six-Month Erucic Acid is so close to the range disclosed by the Prior Art Batches that a POSA "would have expected them to have the same properties." In re Brandt, 886 F.3d at 1178. As such, the Court must consider Plaintiffs' evidence of critical range, teaching away, and secondary considerations.

[17] While the Court agrees with Plaintiffs that their FDA filings are not prior art, the Court is not relying on them and other extrinsic evidence to come to a conclusion that requires prior art—i.e., that the disclosed range overlaps or is so close to the claimed range as to be obvious. The batches of prior art Exparel establish obviousness. Thus, the Court relies on this extrinsic evidence much in the same way it relies on witness testimony that is not prior art—to determine what a POSA would or would not understand in the field of invention and expect of the product's properties. See Endo Pharms., Inc. v. Actavis LLC, 922 F.3d 1365, 1372 (Fed. Cir. 2019) (citing Phillips v. AWH Corp., 415 F.3d 1303, 1319 (Fed. Cir. 2005)).

iv. Critical range

Evidence of critical range is evidence that a new and unexpected result "is different in kind and not merely degree from the results of the prior art." E.I. du Pont de Nemours & Co., 904 F.3d at 1006 (quoting Aller, 220 F.2d at 456). "A difference of degree is not as persuasive as a difference in kind"—i.e., a difference in kind is one that produces a new property dissimilar to the known property, whereas a difference in degree is one that produces a predictable result but to an unexpected extent. UCB, Inc. v. Actavis Labs. UT, Inc., 65 F.4th 679, 693 (Fed. Cir. 2023) (quoting Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014)). Here, the evidence of critical range must demonstrate that the Six-Month Erucic Acid produces a new property dissimilar to the range of erucic acid disclosed in the Prior Art Batches.

At trial, Plaintiffs' expert, Dr. Klibanov, testified that the Six-Month Erucic Acid yielded numerous benefits for Pacira: they could seek FDA approval for (1) a tighter erucic acid specification, (2) a longer shelf life, and (3) longer and more extreme temperature excursions. Klibanov Tr. 715:15–716:5. Furthermore, Pacira could obtain approval in countries with stricter erucic acid requirements. Id. Defendants counter that this speculation about what Pacira could do does not constitute a difference in kind. The Court agrees with Defendant.

First, Dr. Klibanov testified that Pacira could seek to tighten its erucic acid stability specification from the current limit of 310 µg/mL to a more stringent specification, such as the 130 µg/mL specification in the European Union. Id. at 716:7–717:8. But Dr. Klibanov did not testify as to how this change in stability specification would amount to a difference in kind. Pacira might seek a more stringent specification, but there is no evidence that this change in a regulatory parameter indicates the existence of a new property in the product. In fact, the evidence shows otherwise: (1) Dr. Schwendeman testified, and Pacira's NDA confirmed, that the small difference

in erucic acid would not impact the efficacy of the product, Schwendeman Tr. 457:13–459:16; JTX-4264.5; (2) Pacira's NDA further supports the finding that an erucic acid concentration up to 310 µg/mL, the United States specification, would not affect product performance, JTX-4264.5; (3) Defendants' and Plaintiffs' witnesses testified that all batches of Exparel, 45L and 200L, that are currently on the market have the same shelf life of two years at refrigerated conditions, Grigsby Tr. 163:4–5; Schwendeman Tr. 454:6–15; Klibanov Tr. 767:9–14; see also JTX-4205; DTX-3115; and (4) Pacira continues to sell 45L and 200L Exparel interchangeably, without identifying any additional properties or shelf-life improvements, Schwendeman Tr. 454:9–14; JTX-4205; DTX-3115. Furthermore, the 110 µg/mL erucic acid concentration disclosed in the prior art—and even the 127 µg/mL—already fell within the stricter 130 µg/mL specification in the European Union, and Plaintiff produces no other evidence of why it is only the Six-Month Erucic Acid that now allows them to seek such a tighter stability specification.

Second, Dr. Klibanov testified that Pacira could seek a longer shelf life in light of the improved Six-Month Erucic Acid and that this longer shelf life would lead to less product waste. Klibanov 717:9–15. Plaintiffs support Dr. Klibanov's testimony with that of Dr. Xin, who testified that longer shelf life is beneficial and a property worth pursuing. Xin Tr. 158:18–159:1 (JTX-4291). But other than noting that improved shelf life is desirable, Plaintiffs do not produce evidence of how and to what extent the difference between the Six-Month Erucic Acid and the range of erucic acid disclosed in the Prior Art Batches yields such an improved shelf life. Given the countervailing evidence of non-critical range discussed above, and for the same reasons, the Court finds that the ability to seek a longer shelf life is also not indicative of a difference in kind.

Finally, Plaintiffs produce testimony by Dr. Grigsby and Dr. Klibanov that, although Exparel is normally stored at refrigerated conditions for up to two years, the improved Six-Month

Erucic Acid could allow hospitals and other users of Exparel, such as the military, to store the product at room temperature for longer than the currently recommended period of 30 days. Grigsby Tr. 160:1–6; Klibanov Tr. 718:9–719:9. But again, this speculation is not supported by additional evidence of what that difference looks like. As with stability and shelf life, such speculation is outweighed by the abundance of evidence that indicates that the difference between the Six-Month Erucic Acid and the range disclosed in the Prior Art Batches is one of degree, not kind.

In sum, there is insufficient evidence to show that the Six-Month Erucic Acid (the "new property") is dissimilar to the range of erucic acid concentration disclosed in the prior art (the "known property"), such that it constitutes a difference in kind. See UCB, Inc., 65 F.4th at 693. Therefore, the Court finds that Plaintiffs have produced evidence that merely demonstrates a difference in degree.

v. Teaching away[18]

A prior art reference teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken." Galderma Lab'ys., L.P. v. Tolmar, Inc., 737 F.3d 731, 738 (Fed. Cir. 2013) (quoting DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1327 (Fed. Cir. 2009)). Conversely, a reference does not teach away "if it merely expresses a general preference for an alternative invention but does not criticize, discredit or otherwise discourage investigation into the invention claimed." Id. Here, the evidence must show

[18] Although Plaintiffs do not argue in their brief that prior art references teach away from the Six-Month Erucic Acid, see Pls.' Invalidity Br. at 26–32, the Court nonetheless engages in this analysis because, while Plaintiffs bear the burden of production in Range Framework cases, they do not bear the burden of persuasion, see E.I. du Pont de Nemours & Co., 904 F.3d at 1008.

that prior art references teach away by discouraging a POSA from manufacturing liposome drug products at larger scales[19] or leads a POSA down a divergent path by "criticiz[ing], discredit[ing] or otherwise discourag[ing] investigation into" a product with the Six-Month Erucic Acid. See id.

Dr. Klibanov testified that it is well known in the art that MVLs are difficult to manufacture at a larger scale while maintaining stability. Klibanov Tr. 722:16–725:8. To support his testimony, Dr. Klibanov discussed the Kapoor study, which states that "[d]espite the popularity of the liposome platform, developability, manufacturability, scalability, and stability are key challenges with the technology." JTX-4210.1–2; Klibanov Tr. 723:1–4. Dr. Klibanov also cited the FDA Guidance for Industry, which states that "[l]iposome drug products are sensitive to changes in the manufacturing conditions, including changes in scale (size of batches)" and that "[l]iposome drug products are complex and sensitive formulations and response to [chemistry, manufacturing, and control] changes is less predictable than with more conventional formulations." PTX-362.8, 362.13; Klibanov Tr. 723:15–24.

But these references do not rise to the level of teaching away—they neither discourage a POSA from manufacturing liposome drug products at larger scales nor lead a POSA down a divergent path by "criticiz[ing], discredit[ing] or otherwise discourag[ing] investigation into" a product with the Six-Month Erucic Acid. See Galderma Lab'ys., L.P., 737 F.3d at 738 (quoting DePuy Spine, Inc., 567 F.3d at 1327. Neither of these references mention erucic acid, and while both generally discuss degradation and stability of lipid components, they do not specifically indicate any negative correlation between stability and large-scale manufacturing. See generally PTX-362; see also JTX-4210.3 (scaled-up manufacturing and its purported impact on erucic acid,

[19] The Court does not consider whether prior art references specifically teach away from producing liposome drug products at a 200-liter scale because, as the Court previously held, there is no volume limitation contained in the claims of the '495 Patent. See Markman Op., ECF No. 187 at 20 n.12.

other degradation products, or stability in general not included in a list of "examples of deviations in manufacturing process and their effect on liposome product quality/performance"). These references merely note that there are general challenges in scaling up manufacturing of liposome drug products and that such products are sensitive to changes in manufacturing conditions, including increased scale. See PTX-362.8 (noting that liposome drugs are sensitive to changes in manufacturing conditions, such as changes in batch size); JTX-4210.8 (noting that the use of appropriate in-process controls can mitigate failures during scale-up of manufacturing).

In fact, the purpose of the FDA Guidance for Industry is to provide guidance and recommendations for the large-scale production of liposome products, see generally PTX-362, and Kapoor similarly counsels developing a "control strategy" to "obtain desired product quality despite subtle changes during formulation or overall product development" by, among other things, "developing [a] manufacturing process that provides adequate control of the variables that affect" certain attributes such as lipid degradation products, see JTX-4210.2–4. Relatedly, the '838 Patent—which also does not criticize, discredit, or discourage investigation into a product with the Six-Month Erucic Acid—discloses its own large-scale manufacturing process, using the same basic manufacturing steps and same materials as the process disclosed by the '495 Patent, for production of a stable liposome drug product. JTX-4089; Hall Tr. 118:5–119:2; Grigsby Tr. 167:7–12, 183:2–185:24.

Taken together, the evidence shows that the prior art references do not teach away from the Six-Month Erucic Acid or even from general large-scale production of liposome drug products. At most, the prior art references teach that large-scale manufacturing of liposome drug products is complex yet achievable.

vi. Secondary considerations

Secondary considerations such as commercial success and long-felt, unresolved need "'may have relevancy' as indicia of obviousness."[20] Ormco Corp. Inc., 463 F.3d at 1311 (quoting Graham, 383 U.S. at 17–18). "When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." Id. (quoting J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997)). As for long-felt, unresolved need, courts look to the availability and sufficiency of the prior art methods to meet the need of the claimed invention—not merely whether there was a motivation to improve upon an existing method. See In re Couvaras, 70 F.4th 1374, 1381 (Fed. Cir. 2023) (emphasis added) ("Here, such indicia of nonobviousness do not exist. Rather, as the Board correctly held, there was no long-felt, unmet need, given the admitted availability of antihypertensive agents and a lack of evidence that the available antihypertensive treatments were somehow insufficient to meet patients' needs."); see also Celgene Corp. v. Peter, 931 F.3d 1342, 1352 (Fed. Cir. 2019) ("The fact that there is no long-felt, unmet need does not necessarily mean that there is no motivation to improve a system."). Furthermore, for purposes of long-felt, unresolved need, the Court focuses on technical inadequacies, not economic forces. See Friskit, Inc. v. RealNetworks, Inc., 306 F. App'x 610, 618 (Fed. Cir. 2009). Here, the evidence

[20] Although Plaintiffs do not specifically argue that commercial success militates against obviousness in their brief, the Court nonetheless engages in the analysis because Plaintiffs, who do not bear the burden of persuasion, have produced relevant evidence of commercial success.

That said, despite other secondary considerations considered by courts—such as failure of others and industry praise—the Court focuses on commercial success and long-felt, unresolved need due to the lack of evidence in this case on other secondary considerations. See E.I. du Pont de Nemours & Co., 904 F.3d at 1006 (burden of production falls on patentee to present "other pertinent evidence of nonobviousness").

must show significant sales of 200L Exparel and that 45L Exparel was either unavailable or insufficient to meet an unresolved technical need.

Although Plaintiffs present evidence of Exparel's market success, Hall Tr. 79:14–19, there is no evidence of whether this success is attributable to 200L Exparel or 45L Exparel because both are still on the market and indistinguishable, see Schwendeman Tr. 454:9–14; JTX-4205; DTX-3115. Furthermore, the evidence does not attribute any of Exparel's success to its stability—improved or otherwise. See Hall Tr. 78:14–81:5 (success is due to greater period of pain relief, ability to provide sustained pain relief without the use of opioids, and lower likelihood of addiction, nausea, and fall risk); see also JTX-4121.10 (1:25–36). This is insufficient evidence of commercial success because it neither ties commercial success to 200L Exparel specifically nor the claimed attribute of stability in general. See Ormco Corp. Inc., 463 F.3d at 1311 (quoting J.T. Eaton & Co., 106 F.3d at 1571) (patentee must be able to demonstrate that "the successful product is the invention disclosed and claimed in the patent").

Plaintiffs also present evidence that there was a long-felt, unresolved need for a larger scale, stable Exparel. See Klibanov Tr. 722:4–8, 726:11–17. Plaintiffs assert that the '495 Patent describes this need: "[g]iven the addictive nature of opioids and the opioid epidemic that has been affecting countries around the world, there is an urgent need for new and improved large scale productions of Exparel to meet the substantial and growing market demand." JTX-4121.10 (1:32–36); see also Hall Tr. 93:6–94:6 (noting that Pacira initially added additional manufacturing skids in order to meet the increased demand for Exparel that arose as a result of the opioid epidemic but that the additional skids were not enough to meet the demand). Dr. Klibanov testified that 200L Exparel satisfied this need because more of it could be produced. Klibanov Tr. 727:11–15; see also Hall Tr. 92:23–93:5 (noting that Pacira produced 150,000 vials of Exparel in its first year

with the 45-liter process but was able to produce 1.7 million vials of Exparel in a year using the 200-liter process). Finally, Plaintiffs point to a paper by Dr. Schwendeman acknowledging the inadequacies in the technical knowledge of Exparel and noting that "the unique structure of MVLs pose challenges to the development and assessment of generic versions." PTX-425.1; Schwendeman Tr. 478:19–480:18.

As a preliminary matter, a need that arose from the opioid epidemic is economic in nature, not a need arising from a technological inadequacy. Nevertheless, Plaintiffs present evidence of technological inadequacies in the manufacturing of MVL structures. But this evidence does not rise to the level of demonstrating that the previous manufacturing process or any resulting product with a higher erucic acid concentration were either unavailable or inadequate to meet such need. At best, the evidence shows that there was "motivation to improve a system." See Celgene Corp., 931 F.3d at 1353. Even if the Court had read a 200-liter volume limitation into the claims, such a larger-scale process arguably meets an economic need, but it merely scales up an existing commercial manufacturing process that already produced a viable, stable, and effective product. See id. at 1352 (no long-felt, unresolved need "because existing systems were available and adequate").

Although there is some evidence of a long-felt, unresolved need for a stable Exparel produced by a larger-scale manufacturing process, the weight of the evidence leads the Court to conclude that the resolution of this need was largely a motivation to improve an existing, available, and adequate manufacturing process.

* * *

"When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over." In re Piasecki, 745 F.2d 1468, 1472 (Fed. Cir. 1984) (quoting In

re Rinehart, 531 F.2d 1048, 1052 (C.C.P.A. 1976)). A decision of prima facie obviousness should not "be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability." Id.

Defendants present reliable testimony and supportive documentary evidence that Claim 7 is obvious because the Six-Month Erucic Acid is so close to the range of erucic acid disclosed by the Prior Art Batches that a POSA would reasonably expect the two products to have the same properties. See supra at 17–18. Against this, Plaintiffs produce evidence that (1) there is a difference in kind between the Six-Month Erucic Acid and the range of erucic acid disclosed by the Prior Art Batches, (2) prior art references disclose the difficulty of manufacturing liposome drug products, (3) Pacira's 45L and 200L Exparel products have enjoyed commercial success, and (4) the larger-scale production of Exparel improved upon the existing process and met an increased demand for Exparel. See supra at 18–26. But, as discussed above, these arguments do not rise to the level sufficient to defeat Defendants' strong case of obviousness.

"The patentability of a product does not depend on its method of production. If the product in the 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) (internal citations omitted). Taking all the evidence together, the manufacturing process disclosed in the '495 Patent appears to yield a product with the Six-Month Erucic Acid that is obvious from the six-month erucic acid range disclosed by the prior product. Plaintiffs' evidence to the contrary does not outweigh Defendants' strong case for obviousness. Thus, Defendants have asserted a prima facie case of obviousness upon which this Court may rely. See E.I. du Pont de Nemours & Co., 904 F.3d at 1008 ("[A]bsent a reason to conclude otherwise, a factfinder is justified in concluding that a disclosed range does just that—discloses the entire

range."). For the reasons discussed above, the Court finds that Defendants have established, by clear and convincing evidence, that Claim 7 of the '495 Patent is invalid as obvious.

B. Anticipation

Defendants argue that Claim 7 of the '495 Patent is also invalid as anticipated in view of the prior art. Specifically, Defendants maintain that Claim 7 is anticipated because at least one prior art reference of 45L Exparel practices all the limitations of Claim 7. Defs.' Invalidity Br. at 29. In making this argument, Defendants rely on the stability test results for the Non-Prior Art Batches and argue that such results are representative of prior art batches of 45L Exparel, both of which were made by the same process. Id. at 30–32.

Plaintiffs do not dispute that the stability test results for the Non-Prior Art Batches practice Claim 7. Instead, Plaintiffs argue that it is improper to rely on non-prior art evidence for purposes of anticipation. Pls.' Invalidity Br. at 13–19. Plaintiffs also argue that, even if such evidence is proper, the evidence does not account for the structural differences that result from 200L Exparel being "prepared by a commercial scale process" and that the non-prior art batches are not representative of prior art. Pls.' Invalidity Br. at 9–13; 19–21.

For the reasons discussed below, the Court finds that Claim 7 of the '495 Patent is also invalid as anticipated.

i. Legal Standard

"'Anticipation' in patent terms means that the claimed invention is not new; that is, the invention as claimed was already known." Ericsson Inc. v. Intellectual Ventures I, LLC, 890 F.3d 1336, 1338 (Fed. Cir. 2018). "Anticipation is a question of fact, and a finding of anticipation requires that every limitation of the claim is present in a single prior art reference." Id. In an anticipation analysis of a product-by-process claim, "the focus is on the product and not on the

process of making it." Amgen Inc. v. F. Hoffmann-La Roche, Ltd., 580 F.3d 1340, 1369 (Fed. Cir. 2009). "As a result, a product-by-process claim can be anticipated by a prior art product that does not adhere to the claim's process limitation." Id. at 1370.

"Anticipation under [35 U.S.C.] § 102(a) generally requires the presence in the prior art of each and every limitation of the claimed invention." Id. at 1366 (citing Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282 (Fed. Cir. 2000)); see also 35 U.S.C. § 102(a) (patent claim is invalid for anticipation if "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention"). In addition to anticipation by the explicit teaching of a limitation in the prior art, prior art can inherently anticipate. Arbutus Biopharma Corp. v. Modernatx, Inc., 65 F.4th 656, 663 (Fed. Cir. 2023). "[T]he 'critical question' for inherent anticipation is 'whether the [prior art] patent sufficiently describes and enables one or more embodiments—whatever the settings of their operational features—that necessarily include or result in the subject matter of [the] limitation. . . .'" Id. at 664 (alterations in original) (quoting Toro Co. v. Deere & Co., 355 F.3d 1313, 1321 (Fed. Cir. 2004)).

Although Plaintiffs argue otherwise, courts may rely on extrinsic evidence in an inherency analysis to determine whether a feature or characteristic is necessarily present in a prior art reference. Monsanto Tech. LLC v. E.I. DuPont De Nemours & Co., 878 F.3d 1336, 1345 (Fed. Cir. 2018). Such extrinsic evidence may, and often does, include non-prior art. See, e.g., id. at 1345–46; Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1377–78 (Fed. Cir. 2003); see also Hospira, Inc. v. Fresenius Kabi USA, LLC, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (affirming a finding of inherent obviousness—a stricter form of inherent invalidity—that relied on stability test results of non-prior art batches). As such, "extrinsic evidence need not antedate the critical

date of the patent at issue nor have contemporaneous recognition by a [POSA]." Monsanto Tech. LLC, 878 F.3d at 1345 (internal citations omitted).

With these principles as background, the Court first considers whether Defendants' evidence establishes a successful case of inherent anticipation. The Court finds that it does. The Court then addresses Plaintiffs' counterarguments and why each is unavailing.

ii. Defendants' evidence of anticipation

In order to prove anticipation of Claim 7, Defendants must show that at least one prior art reference practiced every limitation of Claim 7, not including the process limitations. Because Claim 7 is dependent on Claim 1, those limitations are as follows:

> 1. a composition of bupivacaine encapsulated multivesicular liposomes . . . having a target concentration from about 12.6 µg/mL to about 17.0 µg/mL (the "Composition Limitation");
> 2. wherein the erucic acid concentration in the composition is about 23 µg/mL or less after the composition is stored at 25° C. for one month (the "One-Month Limitation"); and
> 3. wherein the erucic acid concentration in the composition is about 99 µg/mL or less after the composition is stored at 25° C. for six months (the "Six-Month Limitation").

JTX-4121.20–21 (22:43–23:30).

It is undisputed that 45L Exparel explicitly practices the Composition Limitation. DTX-2498.9; JTX-4174.2–3; Grigsby Tr. 185:6–9; see also Schwendeman Tr. 443:20–24, 444:8–3; JTX-4205; DTX-3115. Yet none of the prior art references before the Court explicitly practice Claim 7 because any prior art reference that also explicitly practices the One-Month

Limitation does not explicitly practice the Six-Month Limitation. DTX-3110.1–2; see also DTX-3111(at least six of the Prior Art Batches explicitly practice the One-Month Limitation but not the Six-Month Limitation). Therefore, Defendants rely on the following extrinsic evidence of non-prior art references practicing the One-Month and Six-Month Limitations: (1) Pacira has sold about 2,600 batches, or 10.5 million vials, of Exparel since its inception, but Pacira conducted stability testing on only 10, about 0.3%, of these prior art batches, DTX-3109; DTX-3111; Schwendeman Tr. 452:2–12, 524:6–17; (2) in addition to the testing on 10 prior art batches, Pacira also conducted stability testing on about 40 non-prior art batches for regulatory filings and bioequivalence studies, DTX-3110; Schwendeman Tr. 419:10–20; and (3) the stability test results show that the 14 Non-Prior Art Batches practiced the One-Month and Six-Month Limitations, DTX-3110; Schwendeman Tr. 418:6–419:4.[21]

To support their contention that the One-Month and Six-Month Limitations practiced by the Non-Prior Art Batches are necessarily present in at least one prior art reference, Defendants also produce the following extrinsic evidence as to why the Non-Prior Art Batches are representative of prior art 45L Exparel: (1) the Non-Prior Art Batches were manufactured during the same time period using the same process, components, and equipment as prior art 45L Exparel, Grigsby Tr. 190:8–20; Schwendeman Tr. 451:3–22; 527:24–528:1; JTX-4044.11; (2) the Non-Prior Art Batches shared the same physical properties as the prior art batches, Grigsby Tr. 190:8–20; Schwendeman Tr. 451:3–22; and (3) the Non-Prior Art Batches were used in regulatory

[21] Although batch 18-SS-024 has an erucic acid concentration at six months of 100 µg/mL and batches 037189 and 047903 have an erucic acid concentration at one month of 25 µg/mL, Dr. Schwendeman testified, and this Court agrees, that these erucic acid measurements satisfy the limitations of "about" 99 µg/mL and 23 µg/mL respectively. See Schwendeman Tr. 425:8–17; see also PPG Indus. v. Guardian Indus. Corp., 156 F.3d 1351, 1355 (Fed. Cir. 1998) ("[A]fter the court has defined the claim with whatever specificity and precision is warranted by the language of the claim and the evidence bearing on the proper construction, the task of determining whether the construed claim reads on the accused product is for the finder of fact.").

submissions to represent and obtain approval for the commercial product, JTX-4079; Hall Tr. 136:6–137:10; Schwendeman Tr. 393:4–11, 451:3–22, 527:20–528:5.

The ample documentary and testimonial evidence show that there were batches of Exparel that practiced the limitations of Claim 7. Although the batches in evidence are not technically prior art, the evidence compels this Court to conclude that the Non-Prior Art Batches are representative of prior art 45L Exparel. Although Plaintiffs make several arguments to the contrary, this evidence demonstrates that it is "highly probable" that at least one prior art reference of 45L Exparel practiced the limitations of Claim 7. Colorado, 467 U.S. at 316 (clear and convincing evidence produces "an abiding conviction that the truth of [the] factual contentions are highly probable").[22] The Court discusses below why each of Plaintiffs' arguments are unavailing.

Plaintiffs do not dispute that the Non-Prior Art Batches practice the Claim 7 limitations. Instead, Plaintiffs argue that this extrinsic evidence is not clear and convincing evidence of inherent anticipation because (1) Defendants have not produced any evidence of either prior art or the Non-Prior Art Batches containing the unclaimed structural features imparted by the limitation "prepared by a commercial scale process"; (2) the Non-Prior Art Batches are not representative of prior art 45L Exparel because they were prepared by a different process and, additionally, Defendants have not produced any statistical analysis to show that the Non-Prior Art Batches are representative of the nearly 2,600 untested commercial batches also practicing Claim 7; and (3) inherent anticipation is destroyed by one sample of prior art that does not practice all the limitations of Claim 7. The Court addresses each argument in turn.

[22] The Court also discusses below that Defendants have demonstrated by clear and convincing evidence that prior art Exparel practices the limitations of Claim 7 to the same extent as 200L Exparel. See infra 37–39.

iii. Unclaimed structural features

Plaintiffs and Defendants dispute the impact of this Court's construction of the limitation "prepared by a commercial scale process." Plaintiffs argue that because the Court construed this as "not a product-by-process limitation because it informs the structure and contains structural differences than the existing art," Defendants must produce evidence that the prior art also contained the unclaimed structural features imparted by this limitation: lower lipid hydrolysis byproducts, higher internal lysine, higher dextrose concentration, and a more desirable internal pH. See Pls.' Invalidity Br. at 9–13 (quoting Markman Op. at 19). Defendants counter that because the Court construed this as "not a product-by-process" limitation, the Court necessarily construed this as a structural limitation and, therefore, the Court must only take into account the claimed structural features—i.e., the erucic acid limitations. Defs.' Invalidity Br. at 34.

Both parties miss the mark. Defendants' semantic argument is unavailing. When it comes to considering unclaimed structural features, the Federal Circuit does not distinguish between product-by-process limitations that impart structural features and process limitations that are construed as structural limitations. Compare Amgen Inc. v. F. Hoffmann-La Roche, Ltd., 580 F.3d 1340, 1370 (Fed. Cir. 2009) (emphasis added) (courts should consider unclaimed structural "features imparted by a process limitation"), with In re Nordt Dev. Co., 881 F.3d 1371, 1374 (Fed. Cir. 2018) (emphasis added) ("If the process limitation connotes specific structure and may be considered a structural limitation, . . . that structure should be considered."). Therefore, Plaintiffs are correct that courts should consider any unclaimed structural features imparted by a process limitation, whether such limitation is construed as a structural limitation or a product-by-process limitation that imparts structural features.

Plaintiffs are incorrect, however, in their assertion that the Court must consider the unclaimed structural features noted in the Markman Opinion—"findings of fact that go to the question of validity of product-by-process claims do not automatically become part of claim construction." Amgen Inc. v. F. Hoffmann-La Roche, Ltd., 580 F.3d 1340, 1373 (Fed. Cir. 2009) (emphasis in original) (noting that even though the court construed the process limitation as imparting structural features, "[t]hat does not mean, however, that the court implicitly construed the source limitations to include those structural and functional differences. . . . Rather, the court construed the source as a limitation of the asserted claims and found that the source imparted structural and functional features . . ."). In fact, this Court explicitly noted in its Markman Opinion that "[v]alidity is not at issue at this stage, but . . . that the structure is what will ultimately determine that analysis." Markman Op. at 17 n.11; see also Pls.' Markman Br., ECF No. 99 at 15 ("While this classification [that "prepared by a commercial scale process" is not a product-by-process limitation] may potentially impact what the parties need to prove on the merits with respect to infringement and invalidity, neither party proposes, and the Court need not decide at this stage, what that impact may be."). Now that validity is at issue, Plaintiffs want the Court to consider certain unclaimed structural features: lower lipid hydrolysis byproducts, higher internal lysine, higher dextrose concentration, and a more desirable internal pH. But the evidence presented at trial shows that these structural features are directly tied to the key claimed structural feature at issue: erucic acid concentration. See Grigsby Tr. 153:5–8, 159:4–13 (erucic acid concentration is depicted as a rate of hydrolysis); Id. 163:6–164:19 (noting that Pacira pursued measurement of lysine and pH in order to explain erucic acid concentration); Id. 165:2–8 (noting the relationship between lysine and pH); Hall Tr. 110:1–13 (same); Grigsby Tr. 166:2–7, 167:19–168:7 (higher internal lysine was measured in batches with lower erucic acid

concentration); Id. 168:8–15 (noting that lipid degradation, which is measured by erucic acid concentration, is dependent upon pH and that higher lysine leads to higher pH, which leads to less erucic acid); DTX-2262.3 (higher internal pH is due to increase in lysine and dextrose). This distinguishes this case from a case like Amgen, in which the Federal Circuit upheld consideration of unclaimed structural features because, unlike here, there were no claimed features that were otherwise representative of those structural features. 580 F.3d at 1363–70 (emphasis added) (affirming district court's consideration of unclaimed higher molecular weight and different charge as "novel structures" that distinguish the prior art from the claimed invention).

Although the Court construed the limitation "prepared by a commercial scale process" as imparting structural features, the Court finds, based on the evidence presented at trial, that any structural features imparted by the limitation "prepared by a commercial scale process" are embodied in the claimed erucic acid limitations. As such, the Court finds that any lack of evidence of these particular asserted unclaimed features does not defeat a finding of inherent anticipation.

iv. Non-Prior Art Batches as representative of prior art

Plaintiffs also argue that the Non-Prior Art Batches are not representative of prior art 45L Exparel. First, Plaintiffs argue that the Non-Prior Art Batches were made for regulatory purposes, not commercial sale, and that the processes for the two differ significantly. Second, Plaintiffs argue that Dr. Schwendeman's opinion that there is no difference between 45L Exparel and 200L Exparel is ipse dixit because Defendants produce no statistical analysis to support their claim that the Non-Prior Art Batches are representative of prior art batches. The Court disagrees.

First, Plaintiffs rely on evidence that four of the Non-Prior Art Batches were manufactured with an additional step not included in the manufacturing process for prior art 45L Exparel and that the remaining Non-Prior Art Batches were manufactured before the FDA had approved or

qualified the manufacturing line. See Schwendeman Tr. 526:13–529:13. But Dr. Schwendeman also testified that the extra manufacturing step used in those four Non-Prior Art Batches should have no impact on the erucic acid level of the final product, id. at 526:20–22, and the evidence shows that there is no significant difference between the manufacturing line used for the Non-Prior Art Batches and prior art 45L Exparel, JTX-4044.11 (FDA instructing that "the manufacturing process used . . . should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing"); JTX-4121.19 (showing that Pacira relied on non-prior art batches of 45L Exparel to compare against 200L Exparel for purposes of prosecuting the '495 Patent); see also Schwendeman Tr. 451:3–13; Grigsby Tr. 190:8–20.

Second, an expert's opinion is ipse dixit if is without any reliable foundation. See Bracco Diagnostics, Inc. v. Amersham Health, Inc., 627 F. Supp. 2d 384, 441–42 (D.N.J. 2009) (collecting cases). But "an expert need not take into account every possible factor in rendering an opinion." Id. at 442. Rather, the expert only "must consider enough factors to make his or her opinion sufficiently reliable in the eyes of the court." MicroStrategy Inc. v. Business Objects, S.A., 429 F.3d 1344, 1355 (Fed. Cir. 2005). Here, Dr. Schwendeman's opinions that the Non-Prior Art Batches are representative of prior art batches of 45L Exparel and that "[t]here is no difference" between 45L and 200L Exparel, see Schwendeman Tr. 450:11–452:12, 462:16–18, are based on her consideration of the ample evidence Defendants' produced to support their inherent anticipation argument, see supra 30–31. While a statistical analysis is helpful evidence in some cases, there is no evidentiary requirement for such analysis in every case, and the Court fails to see how Dr. Schwendeman's reliable expert opinion based on this abundance of other evidence is ipse dixit.

For these reasons, the Court finds that the Non-Prior Art Batches are sufficiently representative of prior art batches of 45L Exparel and may be considered for purposes of inherent anticipation.

v. One non-practicing sample of prior art

Plaintiffs argue that inherent anticipation "is defeated by a single example in which the features are not present." Pls.' Invalidity Br. at 12 (citing Par Pharm. Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1194–95 (Fed. Cir. 2014). Plaintiffs, therefore, assert that Defendants' inherent anticipation case should fail because "[t]he '495 Patent itself contains such an example." Id. Although Plaintiffs point to the unclaimed structural features that this Court finds to be embodied in the Six-Month Limitation, this argument would apply with equal force to the Six-Month Limitation because the same examples contained in the '495 Patent do not practice the Six-Month Limitation.

Plaintiffs' reliance on Par Pharm. is misplaced. Par Pharm. is a case involving obviousness and does not stand for the proposition that inherent anticipation is defeated by a single prior art reference that fails to practice all the limitations. 773 F.3d at 1194–95. Instead, Par Pharm. merely illustrates that defendants must meet a "high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis." Id. at 1195–96 (emphasis added) ("We have, however, also explained that the use of inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of obviousness."). For inherent anticipation, the critical question is "whether the prior art patent sufficiently describes and enables one or more embodiments—whatever the settings of their operational features—that necessarily include or result in the subject matter of the limitation." Arbutus Biopharma Corp., 65 F.4th at 664 (cleaned up) (quoting Toro Co., 355 F.3d at 1321). In fact, contrary to Plaintiffs'

argument, "[t]o anticipate, the prior art need only meet the inherently disclosed limitation to the same extent as the patented invention." Id. (emphasis added); see also King Pharms., Inc. v. Eon Labs., Inc., 616 F.3d 1267, 1276 (Fed. Cir. 2010) (quoting King Pharms., Inc. v. Eon Labs, Inc., 593 F. Supp. 2d 501, 509 (E.D.N.Y. 2009)) ("As the district court aptly stated, 'to inherently anticipate, the prior art need only give the same results as the patent, not better.'"). The Court, therefore, need only determine whether practicing the limitations of the '838 Patent would necessarily result in Exparel that practices the Composition, One-Month, and Six-Limitations to the same extent as Exparel produced by practicing the limitations of the '495 Patent. See Arbutus Biopharma Corp., 65 F.4th at 664–65. The evidence shows that it does.

First, the '838 Patent discloses a large-scale manufacturing process that uses the same basic manufacturing steps and same materials as the process disclosed by the '495 Patent to produce a stable, effective product that, as this Court discussed in the context of obviousness, is effectively the same as 200L Exparel, aside from the claimed improved stability of the One-Month and Six-Month Limitations. See supra at 17–26. Although Plaintiffs point out differences in the processes—such as a larger volume in the '495 Patent—the Court does not construe the '495 Patent to include a volume limitation. See Markman Op. at 20 n.12. Regardless, the focus for purposes of invalidity is on the product, not the process. See In re Thorpe, 777 F.2d at 697. The Court only looks to the process here to determine whether practicing the process limitations of the '838 Patent would necessarily yield a product that practices the structural limitations at issue to the same extent as 200L Exparel.

Second, as noted above, Defendants produce ample evidence to show that the claimed improved stability of the One-Month and Six-Month Limitations was practiced by the Non-Prior Art Batches and that such batches are representative of prior art batches of 45L Exparel. See supra

at 30–32. Specifically, the evidence shows that the Non-Prior Art Batches, which constituted about one-third of the around 40 tested non-prior art batches of 45L Exparel, practiced the One-Month and Six-Month Limitations. See id.; Schwendeman Tr. 447:23–448:2 ("[T]here is always a range of erucic acid concentration made by [the '838 Patent] process."). Additionally, Defendants produce evidence that, much like the Non-Prior Art Batches that constitute their extrinsic evidence, only four of the nine 200L Batches practice the One-Month and Six-Month Limitations. DTX-3114; Schwendeman Tr. 439:23–441:19, 462:15–20.

Taken together, the Court finds that the evidence shows that the '838 Patent "sufficiently describes and enables one or more embodiments" of Exparel "that necessarily include or result in" the Composition, One-Month, and Six-Month Limitations of Claim 7 to the same extent as an embodiment of Exparel produced by practicing the limitations of the '495 Patent. See Arbutus Biopharma Corp., 65 F.4th at 664.

* * *

For anticipation, Defendants bear the burden to show that Claim 7 would be practiced to the same extent by an Exparel product, regardless of how it was made. See id.; Amgen Inc., 580 F.3d at 1370. For the reasons discussed above, the Court finds that Defendants have satisfied this burden with clear and convincing evidence that Claim 7 of the '495 Patent is invalid as anticipated.

III. CONCLUSION

For the foregoing reasons, the Court finds that Defendants have shown, by clear and convincing evidence, that Claim 7 of the '495 Patent is invalid as obvious and anticipated. An appropriate Order accompanies this Opinion.

Date: August 9, 2024

s/ Madeline Cox Arleo
Hon. Madeline Cox Arleo
UNITED STATES DISTRICT JUDGE