IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELTIS USA, INC., LABORATORIOS LEON FARMA, S.A., CHEMO IBERICA, S.A., and CHEMO RESEARCH, S.L., Plaintiffs, v. LUPIN LTD. and LUPIN PHARMACEUTICALS, INC., Defendants.	Civil Action No. 22-434-RGA

TRIAL OPINION

Martina Tyreus Hufnal, Douglas E. McCann, Gregory R. Booker, Nitika Gupta Fiorella, Jonathan A. Bell, FISH & RICHARDSON P.C., Wilmington, DE,

Attorneys for Plaintiffs.

John C. Phillips, Jr., David A. Bilson, PHILLIPS, MCLAUGHLIN & HALL, P.A., Wilmington, DE; Michael Nutter, MCGUIREWOODS LLP, Chicago, IL; Merritt Westcott, MCGUIREWOODS LLP, Houston, TX; Corinne S. Hockman, MCGUIREWOODS LLP, Raleigh, NC; Daniel Withers, MCGUIREWOODS LLP, Dallas, TX; Dennis D. Gregory, MCGUIREWOODS LLP, Austin, TX,

Attorneys for Defendants.

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/s/ Richard G. Andrews

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs Exeltis USA, Laboratorios Leon Farma, Chemo Iberica, and Chemo Research ("Exeltis") brought this action against Defendants Lupin and Lupin Pharmaceuticals ("Lupin") under 35 U.S.C. § 271(e)(2), § 271(a), § 271(b), and § 271(c) for infringement of U.S. Patent Nos. 11,123,299 ("the '299 patent"), 11,291,632 ("the '632 patent"), 11,351,122 ("the '122 patent"), 11,413,249 ("the '249 patent"), and 11,478,487 ("the '487 patent"). (D.I. 78 ¶¶ 1, 11, 22–51). I held a three-day bench trial February 26–28, 2024, with closing arguments the following day.[1] By the time of trial, there were only six claims at issue: claim 14 of the '299 patent, claims 12 and 21 of the '632 patent, claim 29 of the '122 patent, claim 7 of the '249 patent, and claim 19 of the '487 patent.

I have considered the parties' post-trial submissions. (D.I. 334–37, 349–52, 355–56). I make the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

I. BACKGROUND

Exeltis holds New Drug Application ("NDA") No. 211367 for SLYND® tablets in 4 mg dosage form. (D.I. 275-1 ¶¶ 71, 78). "SLYND® is indicated for use by females of reproductive potential to prevent pregnancy." (*Id.* ¶ 77). The active ingredient of SLYND® is drospirenone. (*Id.* ¶¶ 78–79). The Food and Drug Administration ("FDA") approved Exeltis's NDA on May 23, 2019. (*Id.* ¶ 72).

On January 6, 2022, Lupin submitted Abbreviated New Drug Application No. 216936 to the FDA for approval to manufacture, import, market, and sell its generic versions of SLYND® ("Lupin's ANDA Product"). (D.I. 320 at 1). Lupin's ANDA Product is a 4 mg drospirenone

[1] The trial transcript ("Tr. at ___") is available at D.I. 338–41. It is consecutively paginated.

tablet. (D.I. 275-1 ¶ 88). The FDA tentatively approved Lupin's ANDA Product on November 3, 2022. (*Id.* ¶ 89).

Lupin sent Paragraph IV certifications to Exeltis alleging that Exeltis's patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Lupin's ANDA Product. (*See id.* ¶¶ 8, 10, 12, 13, 15, 17). Exeltis initiated the present suit on April 1, 2022, alleging Lupin infringed the '299 patent and U.S. Patent Nos. 9,603,860 ("the '860 patent"), 10,179,140 ("the '140 patent"), 10,603,281 ("the '281 patent"), 10,849,857 ("the '857 patent"), and 10,987,364 ("the '364 patent"). (*Id.* ¶¶ 8–9). On June 6, 2022, Exeltis amended its complaint, additionally asserting infringement of the '632 patent and U.S. Patent No. 11,291,633 ("the '633 patent"). (*Id.* ¶¶ 10–11). Exeltis amended its complaint again on August 23, 2022, additionally asserting infringement of the '122 and '249 patents. (*Id.* ¶¶ 12–14). Exeltis amended its complaint another time on January 6, 2023, additionally asserting infringement of the '487 patent and U.S. Patent Nos. 11,439,598 ("the '598 patent"), 11,452,695 ("the '695 patent"), 11,491,113 ("the '113 patent"), and 11,504,334 ("the '334 patent"). (*Id.* ¶¶ 15–16).

Prior to trial, the parties narrowed the issues to infringement and the following invalidity arguments: obviousness, written description, and indefiniteness. (*See id.* at 5–9 of 25). Exeltis narrowed its asserted claims to six claims in five patents. (*Id.* ¶ 19).[2] The patents at issue—the '299, '632, '122, '249, and '487 patents—are all listed in the FDA's Orange Book for SLYND®. (*Id.* ¶¶ 25, 31, 41, 49, 55).

[2] The pretrial order (D.I. 275 at 2, adopted at D.I. 282) included an additional claim, which was claim 33 of the '140 patent. Exeltis stopped asserting that claim after an adverse claim construction ruling. (*See* D.I. 302, 305).

II. LEGAL STANDARDS

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 to 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. Indefiniteness

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those

skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc*., 572 U.S. 898, 901 (2014). Inferring indefiniteness because a claim's scope is broad, however, is "legally incorrect: 'breadth is not indefiniteness.'" *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1367 (Fed. Cir. 2017) (quoting *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1341 (Fed. Cir. 2005)). The party raising indefiniteness bears the burden of proving it by clear and convincing evidence. *See id.* at 1365.

C. Written Description

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

For a genus claim, the written description requirement can be satisfied by the "disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350. "[A]n adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the

genus from other materials." *Id.* However, "merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." *Id.*

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

D. 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 (cleaned up).

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 Pat. 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 claim 14 of the '299 patent, claims 12 and 21 of the '632 patent, claim 29 of the '122 patent, claim 7 of the '249 patent, and claim 19 of the '487 patent. Claim 14 of the '299 patent depends from claim 1. The claims state,

> 1. A pharmaceutical composition comprising:
> drospirenone[3] in the form of particles that have: (i) a median particle size ranging from 10 micrometers (μm) to 30 μm; (ii) a d90 particle size of less than 100 μm; and (iii) a d10 particle size of more than 3 μm, wherein the drospirenone is present in an amount ranging from 3 milligrams (mg) to 4.5 mg; and
> one or more pharmaceutically acceptable excipients,
> wherein the pharmaceutical composition does not comprise estrogen; and
> wherein the pharmaceutical composition is formulated such that no more than 50% of the drospirenone initially present in the pharmaceutical composition is dissolved within 30 minutes if subjected to an in vitro dissolution test according to the USP XXIII Paddle Method.
>
> . . .
>
> 14. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is formulated as a tablet or a capsule.

(JTX-004 ('299 patent) at 61:38–56, 62:40–42). Claim 12 of the '632 patent depends from claim 1. The claims state,

> 1. A pharmaceutical composition comprising:
> drospirenone in the form of particles that have: (i) a median particle size ranging from 10 micrometers (μm) to 60 μm; (ii) a d90 particle size of less than 100 μm; and (iii) a d10 particle size of more than 3 μm, wherein the drospirenone is present in an amount ranging from 3 milligrams (mg) to 4.5 mg; and
> one or more pharmaceutically acceptable excipients,

[3] The claims other than claim 1 of the '249 patent all identify drospirenone by its chemical formula, which is 6β, 7β:15β, 16β-Dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone. For convenience, I have replaced the formula with "drospirenone" wherever the formula appears in the claims.

wherein the pharmaceutical composition does not comprise estrogen; and
wherein the pharmaceutical composition is formulated such that no more than 50% of the drospirenone initially present in the pharmaceutical composition is dissolved within 30 minutes if subjected to an in vitro dissolution test according to the USP XXIII Paddle Method.

. . .

12. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is formulated as a tablet.

(JTX-005 ('632 patent) at 61:21–39, 62:20–21). Claim 21 of the '632 patent, which depends from claims 1 and 20, states,

20. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is formulated to provide a pharmacokinetic profile for drospirenone if orally administered to a patient under fasting conditions, the pharmacokinetic profile comprising:
a mean T_{max} ranging from 2.2 hours to 6 hours; and (ii) a mean C_{max} of less than 30 ng/ml.

21. The pharmaceutical composition of claim 20, wherein the pharmacokinetic profile for drospirenone further comprises an $AUC_{0h\text{-}tlast}$ of at least 300 ng*h/ml.

(*Id.* at 62:49–60). Claim 29 of the '122 patent depends from claims 1 and 23. The claims state,

1. A pharmaceutical composition comprising:
drospirenone, and
one or more pharmaceutically acceptable excipients, wherein the drospirenone is present in an amount ranging from 2 milligrams (mg) to 6 mg; and
wherein the pharmaceutical composition is formulated such that:
(1) when orally administered under fasting conditions, the pharmaceutical composition provides a pharmacokinetic profile for the drospirenone comprising:
(i) a mean T_{max} ranging from about 2.2 hours to about 6 hours; and
(ii) a mean C_{max} which is less than about 30 ng/ml; and
(iii) a mean $AUC_{0h\text{-}tlast}$ of at least about 300 ng*h/ml; and
(2) no more than 50% of the drospirenone initially present in the pharmaceutical composition is dissolved within 30 minutes if subjected to an in vitro dissolution test according the USP XXIII Paddle Method; and
wherein the pharmaceutical composition does not comprise estrogen.

. . .

23. The pharmaceutical composition of claim 1, wherein when orally administered under fasting conditions, the pharmaceutical composition provides a pharmacokinetic profile for the drospirenone comprising:
(i) a mean T_{max} ranging from 2.2 hours to 6 hours;
(ii) a mean C_{max} which is less than 30 ng/ml; and
(iii) a mean $AUC_{0h\text{-}tlast}$ of at least 300 ng*h/ml.

. . .

29. The pharmaceutical composition of claim 23, wherein the amount of drospirenone present is 4.0 mg.

(JTX-007 ('122 patent) at 61:30–55, 63:6–13, 64:17–19). Claim 7 of the '249 patent depends from claim 1. The claims state,

1. A method of providing effective contraception in a female patient, the method comprising:
orally administering to the patient a daily pharmaceutical composition for 24 consecutive days, followed by orally administering to the patient a daily placebo dosage unit for 4 consecutive days,
wherein the pharmaceutical composition comprises from 2 mg to 6 mg drospirenone and is formulated such that:
(1) when orally administered under fasting conditions, the pharmaceutical composition provides a pharmacokinetic profile for the drospirenone comprising:
(i) a mean T_{max} ranging from 2.2 hours to 6 hours;
(ii) a mean C_{max} which is less than 30 ng/ml; and
(iii) a mean $AUC_{0h\text{-}tlast}$ of at least 300 ng*h/ml; and
(2) no more than 50% of the drospirenone initially present in the pharmaceutical composition is dissolved within 30 minutes if subjected to an in vitro dissolution test according to the USP XXIII Paddle Method; and
wherein the pharmaceutical composition does not comprise estrogen.

. . .

7. The method of claim 1, wherein the amount of the drospirenone present is 4.0 mg.

(JTX-008 ('249 patent) at 61:27–62:12, 62:26–27). Claim 19 of the '487 patent depends from claims 1 and 16. The claims state,

1. A pharmaceutical composition comprising:
particles comprising drospirenone; and
one or more pharmaceutically acceptable excipients,

wherein the pharmaceutical composition does not comprise estrogen; and
wherein the particles have a diameter less than 200 micrometers (μm), and the pharmaceutical composition is formulated such that:
(1) when orally administered to a patient under fasting conditions, the pharmaceutical composition provides a pharmacokinetic profile for the drospirenone comprising:
(i) a mean T_{max} ranging from 2.2 hours to 6 hours; and
(ii) a mean C_{max} of less than 30 ng/ml; and
(2) no more than 50% of the drospirenone initially present in the pharmaceutical composition is dissolved within 30 minutes if subjected to an in vitro dissolution test according to the USP XXIII Paddle Method.

. . .

16. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises from 2 milligrams (mg) to 6 mg of the drospirenone.

. . .

19. The pharmaceutical composition of claim 16, wherein the pharmaceutical composition comprises 4.0 mg of the drospirenone.

(JTX-011 ('487 patent) at 62:2–23, 63:14–17, 63:26–29).

I construed "an in vitro dissolution test according to the USP XXIII Paddle Method" as "an in vitro dissolution test using the USP XXIII Paddle Method." (D.I. 298 at 5). I ruled that the claims do not require specific test conditions. (*Id.* at 5–7). I construed "particle size" as the "plain and ordinary meaning: particle size as determined by any means." (*Id.* at 7–8). I ruled that the claims are not limited to volume-based techniques only. (*Id.* at 7–10). I construed "[drospirenone] in the form of particles" / "particles comprising [drospirenone]" as "[drospirenone] in the form of discrete units of material" ('299 patent, claim 14; '632 patent, claims 12 and 21) and "discrete units of material which include drospirenone" ('487 patent, claim 19). (*Id.* at 10–11).

B. Indefiniteness

1. Findings of Fact

1. The priority date for all asserted claims is July 28, 2010. (D.I. 275-1 ¶ 68).

2. Combination oral contraceptives ("COCs") contain progestin and estrogen. Progestin-only pills ("POPs") contain progestin, but they do not contain estrogen. (Tr. at 52:16–19, 56:10–57:6).

3. A person of ordinary skill in the art ("POSA") includes a person having a doctoral degree in pharmaceutical sciences, a field of chemistry relating to drug formulation or development, or a related field with at least two years of experience formulating solid dosage forms. A POSA also includes a gynecologist or obstetrician or other medical professional in women's healthcare, with at least two years of experience prescribing oral contraceptives. (D.I. 275-1 ¶ 70).

4. A POSA may have an education level lower than a doctoral degree in pharmaceutical sciences, chemistry, or a related field if the POSA has commensurately more relevant work experience. A POSA may have also worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also consulted with others on the team having specialized skills to solve a problem. (D.I. 275-1 ¶ 70).

5. The asserted claims do not require a single approach to practicing the USP XXIII Paddle Method. (*See, e.g.*, JTX-004 ('299 patent) at 61:38–56, 62:40–42).

6. Exeltis's expert, Dr. Bugay, used the following Paddle Method parameters to test Lupin's ANDA Product: 900 mL of water, 37°C, and a paddle speed of 50 rpm. (Tr. at 132:15–25).

7. The following prior art references appear in the intrinsic record of the asserted patents: U.S. Patent Publication No. 2005/0220825 ("Funke"), WIPO Publication No. 2009/138224 ("Helm"), WIPO Publication No. 2006/015956 ("Sandrone"), and WIPO Publication No. 2005/087199 ("WO199"). (DTX-019 at SLYND_0008401–06, SLYND_0009081–9100, SLYND_0009958).

8. Funke describes a paddle speed of "50–100 rpm, such as 50 or 75 rpm," which is broader than the speed used by Dr. Bugay. (DTX-353 at [0027]).

9. Helm discloses a paddle speed of 100 rpm and a temperature of 39±0.5°C, both of which are different than Dr. Bugay's parameters. (PTX-562.0016).

10. WO199 discloses a stirring speed of 50 or 100 rpm, 900 or 1,000 mL of a dissolution medium, and the use of either water or an aqueous solution of sodium dodecyl sulfate as the dissolution medium. (DTX-019 at SLYND_0009092).

11. Sandrone teaches the use of a surfactant and hydrochloric acid (HCl) to obtain dissolution profiles of drospirenone using the Paddle Method. (DTX-374 at 17:28–32).

12. The file history thus discloses multiple approaches to practicing the Paddle Method. (DTX-353 at [0027] (Funke); PTX-562.0016 (Helm); DTX-374 at 17:28–32 (Sandrone); DTX-019 at SLYND_0009092 (WO199)).

13. The specification of the asserted patents discloses only one set of Paddle Method parameters. (JTX-004 ('299 patent) at 19:55–63, 38:26–31, 45:4–5).[4]

14. During prosecution of the asserted patents, Dr. Blatnik performed dissolution testing in 900 mL of water at 37°C and 50 rpm. (PTX-089B.0003; Tr. at 717:16–718:15).

15. A POSA would understand that the Paddle Method of the asserted claims should be performed using 900 mL of water at 37°C with a stirring speed of 50 rpm. (Tr. at 109:8–110:15). A POSA would not lack reasonable certainty about which Paddle Method parameters to select.

16. "Sink conditions" occur when the dosage of a drug dissolves in one-third of the available dissolution medium. (Tr. at 209:13–15).

17. A POSA practicing the asserted claims does not need to choose Paddle Method parameters that meet sink conditions. (DTX-350 at SLYND_1184015; DTX-502 at Lupin_Slynd_0080899).

18. The asserted claims do not require a particular method of measuring particle size. (*See, e.g.*, JTX-004 ('299 patent) at 61:38–56, 62:40–42; Tr. at 319:22–23).

19. The specification of the asserted patents teaches different ways of measuring particle size: sieve analysis, laser diffraction, photoanalysis, and optical counting. (JTX-004 ('299 patent) at 22:46–50; Tr. at 315:1–316:7, 319:19–21).

20. Alan Rawle, Malvern Instruments Limited, *Basic Principles of Particle Size Analysis* ("Rawle"), teaches that different ways of measuring particle size produce different answers. (DTX-153 at 5).

21. Rawle teaches that a POSA may interconvert number, volume, and length measurements of particle size. (DTX-153 at 3).

22. Based on the teachings of Rawle, a POSA could accurately convert number-based measurements to volume-based measurements, and vice versa.

[4] Mentions of "the specification" throughout this opinion refer to the common specification that all asserted patents share. (*See* D.I. 350 at 4 n.1).

23. Lupin has failed to prove that the results of a number-based method of measuring particle size would be materially different from the results of a volume-based method of measuring particle size.

24. Laser diffraction testing of Exeltis's drospirenone batches produced inconsistent results. (DTX-243 at SLYND_0423013; DTX-254 at SLYND_0425281–82).

25. Inconsistent results of the same measurement technique do not support a finding of indefiniteness.

26. Particle agglomeration is the most common cause of erroneous results for laser diffraction measurements. (Tr. at 465:23–466:5).

2. Conclusions of Law

a. Dissolution Limitations

The asserted claims each have a dissolution limitation requiring that no more than 50% of the drospirenone initially present in the pharmaceutical composition dissolve within thirty minutes when subjected to an in vitro dissolution test in accordance with the USP XXIII Paddle Method. (JTX-004 ('299 patent) at claim 1; JTX-005 ('632 patent) at claim 1; JTX-007 ('122 patent) at claim 1; JTX-008 ('249 patent) at claim 1; JTX-011 ('487 patent) at claim 1).

As a threshold matter, Lupin argues that Exeltis's positions at trial were inconsistent with my claim construction order, which declined to limit the Paddle Method parameters in the asserted claims' dissolution limitations to a particular medium, volume, temperature, and stirring speed. (D.I. 335 at 5–6 (citing D.I. 298 at 5–7)). Exeltis contends that its positions were consistent with the order, and that regardless, the claim construction order is not dispositive. (D.I. 349 at 8–10). Although I previously ruled that the claims do not require specific parameters for the Paddle Method, it is nevertheless possible that a POSA would know with reasonable certainty which parameters to use. *See Javelin Pharms., Inc. v. Mylan Lab'ys Ltd.*, 2017 WL 4511352, at *4 (D. Del. Oct. 10, 2017) (finding a claim term was not indefinite where "the patent describes one set of testing conditions that—even if not required by the claims—a

person of skill in the art could use"). I do not think that Exeltis's positions at trial were inconsistent with my claim construction order.

Lupin argues that even if Exeltis's arguments were consistent with my claim construction order, the claims would be indefinite under the two-prong test in *Dow Chemical Co. v. Nova Chemicals Corp.*, 803 F.3d 620 (Fed. Cir. 2015). In *Dow*, the Federal Circuit held,

> Although . . . "[s]ome modicum of uncertainty" may be tolerated, the patent and prosecution history must disclose a single known approach or establish that, where multiple known approaches exist, a person having ordinary skill in the art would know which approach to select.

Id. at 630 (citations omitted).

Lupin argues the claims do not meet the first *Dow* prong because the specification and file history do not disclose a "single known approach" to using the Paddle Method. (D.I. 335 at 7). Dr. Bugay testified that a POSA would know to use 900 mL of water, at 37°C, with a paddle speed of 50 rpm. (Tr. at 109:8–110:15).

The prosecution history,[5] viewed as a whole, does not disclose a single known approach. Funke describes a broader range of paddle speed options than the speed Dr. Bugay used. (DTX-353 at [0027]). Helm discloses both a different paddle speed and a different temperature than Dr. Bugay used. (PTX-562.0016). WO199 discloses a different medium and more options for stirring speed and volume. (DTX-019 at SLYND_0009092). Sandrone teaches the use of a surfactant and HCl. (DTX-374 at 17:28–32). All of these prior art references appear in the asserted patents' file history. (DTX-019 at SLYND_0008401–06, SLYND_0009081–9100, SLYND_0009958).

[5] DTX-019 is the file history for U.S. Patent Application No. 13/171,410 ("the '410 application"). All of the asserted patents claim priority back to the '410 application. (*See* D.I. 275-1 ¶¶ 22, 28, 38, 46, 52).

The file history thus discloses multiple ways to use the Paddle Method. The evidence nevertheless shows that a POSA would know which approach to select when practicing the asserted patents. The specification discloses only one set of Paddle Method parameters. The "Detailed Description of the Invention" section states,

> The in vitro dissolution rate of any active drug of the present invention, including drospirenone, may be assessed by anyone [sic] of well-known methods described in the prior art. The in vitro dissolution rate of drospirenone is preferably assessed by the USP XXIII Paddle Method. Briefly, a tablet consisting of the contraceptive composition comprising drospirenone to be tested is placed in 900 mL of water at 37° C. (±0.5° C.). The dissolution test is performed using a USP dissolution test apparatus 2 at a stirring rate of 50 rpm.

(JTX-004 ('299 patent) at 19:55–63). Consistent with this disclosure, Example 2 and Example 5 describe dissolution tests performed according to the Paddle Method with 900 mL of water, a stirring rate of 50 rpm, and a temperature of 37±0.5°C. (*Id.* at 38:26–31, 45:4–5). These examples further support the use of one set of parameters. *Cf. Vifor Fresenius Med. Care Renal Pharma Ltd. v. Lupin Atlantis Holdings SA*, 2019 WL 4222673, at *4 (D. Del. Sept. 5, 2019) ("If a specification describes one, and only one, reference or method to calculate a claimed measurement as part of an example, . . . it may be (as it is here) that the record reveals no reason to believe a skilled artisan (or the Court) would look to any other method of measurement." (footnote omitted)); *Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc.*, 554 F.3d 1010, 1022 (Fed. Cir. 2009) (finding the term "reduction in bacterial density in the wound by at least 50%" was not indefinite where "several methods for calculating reduction in bacterial density are available but the specification discloses one particular method").

Exeltis's statements during prosecution of the asserted patents are also consistent with this set of parameters. Dr. Blatnik, in a declaration, stated that she performed

dissolution testing in 900 mL of water at 37°C and 50 rpm. (PTX-089B.0003; Tr. at 717:16–718:15). Dr. Koleng testified that formulations needed to be tested "in the same way using the same parameters and conditions" to properly determine which ones would meet the dissolution profile of the asserted claims. (Tr. at 718:1–719:1).[6] Thus, although Dr. Buckton testified that a POSA would generally consider factors such as "the drug in the formulation, the solubility of the drug in the dissolution fluid . . . [and] the characteristics of that formulation" (Tr. at 207:21–208:17), the specification and file history teach a specific set of Paddle Method parameters for the asserted patents.

Lupin's reliance on *Dow* and *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335 (Fed. Cir. 2015), is unpersuasive.

In *Dow*, the Federal Circuit held that the term "slope of strain hardening coefficient" was indefinite. 803 F.3d at 633–35. Assuming that the slope needed to be measured at its maximum value, the Federal Circuit noted that "three methods existed to determine the maximum slope." *Id.* at 633. Dow's expert developed a fourth method for the purpose of the case. *Id.* Neither the claims nor the specification, however, "discusse[d] the four methods or provide[d] any guidance as to which method should be used." The parties also did not argue that the prosecution history provided any guidance. *Id.* at 634.

In *Teva*, the parties agreed that the term "molecular weight" could mean one of three things: M_p, M_w, or M_n. 789 F.3d at 1341. None of the three options were mentioned in the specification. *Id.* Although the parties did not point to relevant

[6] FDA guidance from 2010 is consistent with the specification and Exeltis's statements during prosecution, though the guidance was directed toward COCs. (*See* PTX-027J.0021; Tr. at 110:7–15, 133:9–18).

evidence in the prosecution history of the asserted patent, the court considered statements made during the prosecution of two continuations of the asserted patent. *Id.* at 1343. During one prosecution, the patentee argued that "molecular weight" meant M_w. During the other prosecution, the patentee argued that "molecular weight" meant M_p. *Id.* at 1344. The Federal Circuit held that "molecular weight" was indefinite. *Id.* at 1345.

Dow and *Teva* differ from the present case because the specifications in those cases did not provide any guidance about methods of determining slope or the appropriate measure of molecular weight, respectively. The specification in the present case, meanwhile, consistently teaches one set of Paddle Method parameters. Exeltis's statements during prosecution support its position, unlike *Dow*, which did not include helpful prosecution history evidence, and *Teva*, where the prosecution history provided conflicting guidance.

Because a POSA would know which set of Paddle Method parameters to select, it is irrelevant whether parameters other than 900 mL of water at 37°C and 50 rpm produce different dissolution results. Lupin has also not shown that Paddle Method parameters must meet sink conditions. The claims and specification do not describe sink conditions, and the evidence suggests that a dissolution medium may be acceptable even if it does not achieve sink conditions. (*See* DTX-350 at SLYND_1184015 ("A medium that fails to provide sink conditions may be acceptable if it is shown to be more discriminating or otherwise appropriately justified."); DTX-502 at Lupin_Slynd_0080899 ("Sink conditions are desirable but not mandatory.")). Although Dr. Buckton testified that a POSA would choose "a suitable dissolution fluid to achieve sink conditions" when performing the Paddle Method (Tr. at 208:2–17), the documentary evidence is more

equivocal, suggesting merely that sink conditions make it "more likely that dissolution results will reflect the properties of the dosage form" (DTX-350 at SLYND_1184015; *see also* DTX-502 at Lupin_Slynd_0080899). I thus credit the teachings of the claims and specification, along with the extrinsic evidence, over Dr. Buckton's testimony.

I conclude that Lupin has not shown that a POSA would lack reasonable certainty about which Paddle Method parameters to select. Lupin has failed to prove by clear and convincing evidence that the dissolution limitations of the asserted claims are indefinite.

b. Particle Limitations

The asserted claims of three of the patents have particle limitations that require: (1) that the pharmaceutical composition contain particles, and (2) that the particles have a diameter below 200 microns or that they fall within specific size distribution ranges. (*See* JTX-004 ('299 patent) at claim 1; JTX-005 ('632 patent) at claim 1; JTX-011 ('487 patent) at claim 1).

Lupin argues the asserted claims of the '299, '632, and '487 patents are indefinite because they do not require a specific method of measurement for particle size and particle size distribution, and different methods lead to different results that may or may not be within the scope of the claims. (D.I. 335 at 13). Exeltis argues a POSA would understand that the particle size distributions "are reported on a volume basis," making the claims definite. (D.I. 349 at 14).

The specification does not teach a volume-based measurement only. The specification states,

> The active drug (such as drospirenone) particle size distribution, in particular d90, d10 and d50 values, may be determined by well-known methods of the prior art such as sieve analysis, laser diffraction methods, photoanalysis or optical counting methods. Laser diffraction methods are particularly preferred. As illustrated in the Example 1, the particle size distribution may be determined by laser diffraction in wet dispersion. The dispersant is preferably water.

(JTX-004 ('299 patent) at 22:46–54). Although this language shows a preference for laser diffraction, it also makes clear that a POSA can practice other methods, such as sieve analysis, to determine particle size distributions.[7] These teachings are consistent with the asserted claims, as the claims do not specify a method of measurement. *Cf. Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 937 (Fed. Cir. 2024) (affirming a finding of no indefiniteness where the claims did not specify a measurement technique for average particle size and the specification disclosed that particle size could be measured in at least three ways).

Because different methods existed for measuring particle size distributions as of the priority date, and the asserted patents do not disclose only one technique, I consider whether "application of the different methods result[s] in materially different outcomes for the claim's scope such that a product or method may infringe the claim under one method but not infringe when employing another method." *Ball Metal Beverage Container Corp. v. Crown Packaging Tech., Inc.*, 838 F. App'x 538, 542 (Fed. Cir. 2020).

Lupin argues that different methods of measuring particle size distributions "yield substantially different results." (D.I. 335 at 16). Lupin argues that "one could not know with reasonable certainty whether their product falls inside or outside the claims." (*Id.*). Exeltis, on the other hand, argues a POSA would understand that results from different techniques would not be materially different if the techniques are done properly. (D.I. 349 at 15).

Lupin relies on *Kyowa Hakka Bio, Co. v. Ajinomoto Co.*, 2020 WL 3403207 (D. Del. June 19, 2020), and *Otsuka Pharm. Co. v. Torrent Pharms. Ltd.*, 151 F. Supp. 3d 525 (D.N.J. 2015). Both cases are distinguishable.

[7] The testimony of Drs. Bugay and Koleng—that particle size is usually presented on a volume basis in the pharmaceutical field—does not change the teachings of the specification. (Tr. at 114:24–115:5, 115:23–25, 726:20–24).

In *Kyowa*, the court adopted a Report and Recommendation finding the term "average particle size" to be indefinite. 2020 WL 3403207, at *9. The court reasoned that the term was "ambiguous" in light of "conflicting intrinsic evidence" and extrinsic evidence that "did not resolve this ambiguity." *Id.* The court summarized, "[T]he use of an arithmetic mean made sense in the context of the patent," but a figure in the specification seemed to disclose a different technique, and the plaintiff had made statements in European proceedings that an average particle size was synonymous with a volume weighted average. *Id.* at *4. *Kyowa* is thus inapposite, as it focused on a different issue than the present case. Unlike *Kyowa*, the specification of the asserted patents teaches that multiple ways of measuring particle size distribution are possible. The specification does not offer conflicting guidance about choosing only one method. Instead, the parties' dispute is whether the different methods disclosed in the specification lead to materially different results.

In *Otsuka*, the court held the term "mean particle size" to be indefinite, reasoning that a POSA would not know whether to use a "volume weighted mean" or a "surface weighted mean" to report measurements. 151 F. Supp. 3d at 548. The court found, "The choice of 'volume' or 'surface' matters because each type le[a]ds to a different result." *Id.* *Otsuka* differs from the present case because Lupin has not shown that different particle size measurement techniques, such as laser diffraction and sieve analysis, lead to different results. In other words, Lupin has not shown that the results of a number-based method would be materially different from the results of a volume-based method.

Dr. Buckton, relying on the Rawle paper (DTX-153), testified that each method of measuring particle size leads to a different result. (Tr. at 317:1–318:11). Dr. Buckton created a data set to illustrate his opinion that converting from a number-based distribution to a volume-

based distribution skews the distribution because "the larger particles count more." (Tr. at 320:23–321:21). He testified, "They aren't measured data set, I've just literally written particle sizes of 1 to 10 along the x-axis on the bottom." (Tr. at 320:24–321:1). Exeltis's expert, Dr. Koleng, offered a different view, testifying that he has never had any concern over the accuracy of a conversion from a number-based measurement to a volume-based measurement. (Tr. at 727:4–9). I find that Rawle is consistent with Exeltis's position. Rawle explains "that each measurement technique produces a different answer because it is measuring a different dimension of our particle." (DTX-153 at 5). Rawle does not stop there, however, as the paper discusses interconversions between number, length, and volume measurements. For example, Rawle explains that if an electron measurement technique is subject to a ±3% error rate, then a conversion from a number mean size to a mass mean size could produce a ±27% variation. On the other hand, if laser diffraction measures a volume mean with an error of ±0.5%, then a conversion from a volume mean to a number mean would result in a variation of less than 1%. (*Id.* at 3). Rawle concludes,

> In practice this means that if we are using an electron microscope and what we really want is a volume or mass distribution, the effect of ignoring or missing one 10µ particle is the same as ignoring or missing one thousand 1µ particles. Thus we must be aware of the great dangers of interconversion.

(*Id.*). Rawle thus suggests that conversions from number-based measurements to volume-based measurements, or vice versa, can be accurate if done properly.

I credit the teachings of Rawle, along with Dr. Koleng's testimony, over Dr. Buckton's testimony, which was largely speculative. Dr. Buckton did not analyze Dr. Bugay's testing data (*see* Tr. at 247:12–14 ("I don't have access to the equipment to open it.")), and Lupin has not offered any evidence showing materially different results. Lupin has therefore failed to show by clear and convincing evidence that the particle limitations are indefinite. *Cf. Janssen*, 97 F.4th at

937 (declining to find a term indefinite where the defendant "did point to evidence that, for particles in general, different particle-size measurement techniques can yield different results," but "did not present evidence that different measurement techniques would typically yield different particle-size measurements of paliperidone palmitate"); *Takeda Pharm. Co. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359, 1367 (Fed. Cir. 2014) (declining to find a term indefinite where "there was no evidence in this case that different measurement techniques in fact produced significantly different results for the same sample").

Lupin's references to inconsistent results in Exeltis's drospirenone batches do not make the particle limitations indefinite. The two batches were tested using the same technique: laser diffraction. (DTX-243 at SLYND_0423013; DTX-254 at SLYND_0425281–82; Tr. at 323:10–324:16). Dr. Velada testified that particle agglomeration may occur during laser diffraction (Tr. at 465:23–466:5), and Exeltis thus argues that a POSA would question at least one of those values (D.I. 349 at 19). Lupin contends that Exeltis "provided no response beyond conjecture for why their own documents show incredibly inconsistent particle size results utilizing the same method for the same sample," but Lupin does not otherwise address Dr. Velada's testimony. (D.I. 356 at 9). Absent contrary evidence, I credit Dr. Velada's testimony that particle agglomeration may lead to erroneous laser diffraction results. Regardless, even if the results in Exeltis's drospirenone batches vary more than the diameters in *Takeda*, *see* 743 F.3d at 1367 n.3, an inconsistency in the use of the same method does not suggest that different particle size measurement techniques lead to different results.

C. Infringement

1. Findings of Fact

1. Lupin's ANDA Product has a mean C_{max} of 19.4 ng/ml, a mean T_{max} of 4.46 hours, and a mean $AUC_{0h\text{-}tlast}$ of 519 ng*hr/ml. (Tr. at 96:5–97:12).

2. Dr. Bugay tested Lupin's ANDA Product using the USP XXIII Paddle Method. (PTX-306; Tr. at 132:15–21, 134:14–16).

3. Dr. Bugay applied the following Paddle Method parameters: 900 mL of water, 37°C, and a paddle speed of 50 rpm. (Tr. at 132:15–25).

4. Dr. Bugay's testing showed that no more than 50% of Lupin's ANDA Product dissolves within thirty minutes. (PTX-306; Tr. at 108:8–11, 110:16–111:15, 134:14–135:8).

5. Based on Dr. Bugay's testing, Dr. Taft concluded that Lupin's ANDA Product infringes the asserted claims' dissolution limitations. (Tr. at 88:23–89:1, 91:20–92:25).

6. Raman spectroscopy is a chemical analysis technique that can be used to differentiate the chemical identity of components in a formulation. (Tr. at 116:10–15).

7. Raman spectroscopy can distinguish individual components in a formulation from mixtures or complexes of multiple components. (Tr. at 119:25–120:15).

8. Scanning electron microscopy ("SEM") is a physical technique that can be used to determine if a formulation contains particles. (Tr. at 116:16–21).

9. Dr. Bugay tested Lupin's ANDA Product using Raman spectroscopy and SEM. (Tr. at 116:1–24).

10. Atsushi Kuriyama & Yukihiro Ozaki, *Assessment of Active Pharmaceutical Ingredient Particle Size in Tablets by Raman Chemical Imaging Validating Using Polystyrene Microsphere Size Standards*, 15:2 AAPS PHARMSCITECH 375 (2014) ("Kuriyama"), describes the use of chemical spectroscopy and physical analysis to determine the particle size of active pharmaceutical ingredients. (PTX-483).

11. Raman spectroscopy and SEM testing are well-established techniques. (Tr. at 116:25–117:1, 458:25–459:6; PTX-483).

12. Dr. Bugay used Raman spectroscopy to obtain images showing the identity and location of drospirenone in Lupin's ANDA Product. (Tr. at 117:20–23, 120:16–121:24).

13. Dr. Bugay found that the drospirenone in Lupin's ANDA Product was not co-located with an excipient such as Eudragit. He did not observe shifts in the peaks of the Raman spectra corresponding to the components of Lupin's ANDA Product that would indicate that drospirenone was co-located with any excipients. (Tr. at 119:25–120:15, 121:6–10, 123:14–16, 158:25–159:2).

14. Using SEM, Dr. Bugay concluded that particles were present in Lupin's tablets. (Tr. at 122:5–20).

15. Dr. Bugay relied on software to calculate the size of drospirenone particles. (Tr. at 123:3–13).

16. Dr. Bugay determined that exhibit batch L190049 of Lupin's ANDA Product had a particle size distribution with a d10 of 6.42 μm, a d50 of 16.64 μm, and a d90 of 32.89 μm; exhibit batch L190051 had a particle size distribution with a d10 of 6.46 μm, a d50 of 15.28 μm, and a d90 of 28.64 μm; and exhibit batch L190053 had a particle size distribution with a d10 of 5.67 μm, a d50 of 12.30 μm, and a d90 of 24.50 μm. (Tr. at 123:17–124:7; PTX-332; PTX-335; PTX-338).

17. Based on Dr. Bugay's testing, Dr. Taft concluded that Lupin's ANDA Product meets the particle limitations of the asserted claims. (Tr. at 87:10–21, 88:6–89:10, 89:15–90:6, 91:4–19).

18. Dr. Buckton did not perform any testing on Lupin's ANDA Product to assess the presence of drospirenone particles or the particle size of drospirenone particles. (Tr. at 213:18–214:7). Nor did Dr. Buckton analyze Dr. Bugay's Raman chemical images using Raman software or consider the raw particle size data generated by Dr. Bugay. (Tr. at 246:8–247:15).

2. Conclusions of Law

The parties dispute whether Lupin's ANDA Product meets the asserted claims' dissolution limitations and whether it meets the particle limitations in the asserted claims of the '299, '632, and '487 patents. The asserted claims of the '122, '249, and '487 patents, along with claim 21 of the '632 patent, also recite pharmacokinetics limitations, or PK limitations, which include some or all of a "mean T_{max} ranging from 2.2 to 6 hours," a "mean C_{max} less than 30 ng/ml," and an "$AUC_{0h\text{-}tlast}$ of at least 300 ng*h/ml." Lupin stipulated to infringement of the PK limitations for claims 20 and 21 of the '632 patent, claim 23 of the '122 patent, claim 1 of the '487 patent, and claim 1 of the '249 patent, but did not stipulate to infringement of the PK limitation in claim 1 of the '122 patent. (D.I. 320 ¶¶ 1–15). Dr. Taft testified that Lupin's ANDA Product meets the PK limitation in claim 1 of the '122 patent, from which asserted claim 29 depends. (Tr. at 94:16–19, 97:13–24). Lupin did not rebut this testimony. (*See* D.I. 351 at

3–12). Absent any contrary evidence, I credit Dr. Taft's testimony and find that Lupin's ANDA Product meets the PK limitation in claim 1 of the '122 patent.

a. Dissolution Limitations

To prove infringement of the dissolution limitation in each of the asserted claims, Dr. Bugay used the USP XXIII Paddle Method to test Lupin's ANDA Product. Dr. Bugay applied only one set of parameters: 900 mL of water, 37°C, and a paddle speed of 50 rpm. He concluded that no more than 50% of Lupin's ANDA Product dissolved within thirty minutes. (PTX-306; Tr. at 108:8–11, 110:16–111:15, 132:15–133:8, 134:14–135:8). Lupin argues that Exeltis tested Lupin's ANDA Product using parameters that a POSA would not use. (D.I. 351 at 11). Lupin argues that under appropriate parameters, more than 50% of the drospirenone in its product dissolves within thirty minutes. (*Id.* at 10–11).

I have already found that the specification teaches a POSA to practice the Paddle Method in 900 mL of water at 37°C and a speed of 50 rpm. Dr. Bugay's testing shows that Lupin's ANDA Product meets the dissolution limitations under those parameters. Lupin has not offered any testing data to suggest otherwise. I therefore conclude that Exeltis has proven by a preponderance of the evidence that Lupin's ANDA Product infringes the asserted claims' dissolution limitations.

b. Particle Limitations

To prove infringement of the particle limitations in the asserted claims of the '299, '632, and '487 patents, Dr. Bugay tested Lupin's ANDA Product using Raman spectroscopy and SEM.

Lupin argues Dr. Bugay never showed he was only measuring drospirenone, rather than drospirenone co-located with Eudragit. (*Id.* at 6). Dr. Bugay testified that he used Raman spectroscopy to obtain images showing the identity and location of drospirenone in Lupin's

ANDA Product. (Tr. at 117:20–23, 120:16–121:24). This analysis involved a determination of whether Eudragit or a combination of drospirenone and Eudragit were present. (Tr. at 121:6–10). Dr. Bugay testified that "if there was a drospirenone with Eudragit, that would not have been counted because that wasn't a drospirenone particle." (Tr. at 159:7–18). Lupin could have presented evidence of its own testing to rebut Dr. Bugay's findings. It did not. I find Dr. Buckton's testimony to be less convincing than Dr. Bugay's testimony.

Lupin further argues that its product does not contain drospirenone particles because the drospirenone is an "amorphous dispersion" in a polymer film. (D.I. 351 at 3). Whereas Dr. Bugay used SEM to conclude that particles were present in the tablets, Lupin did not test its own product to determine if it has particles of drospirenone. (Tr. at 168:1–168:17).[8] Instead, Dr. Buckton speculated about what he thought would have happened if there were particles. He testified that amorphous particles would crystallize over time. (Tr. at 188:3–189:2, 191:3–17). Because testing did not reveal crystalline drospirenone, Lupin argues that amorphous particles were not present either. (D.I. 351 at 5). Dr. Buckton also testified that "the dissolution rate for an amorphous drug substance initially would be very fast" (Tr. at 188:25–189:2), and that Lupin's manufacturing method cannot give rise to particles (Tr. at 183:22–184:10). Absent evidence that Lupin's ANDA Product does not contain particles, however, I credit Dr. Bugay's testing data over Dr. Buckton's speculative opinions. I thus conclude Exeltis has met its burden of proving by a preponderance of the evidence that Lupin's ANDA Product contains particles of drospirenone.

[8] The only testing Lupin completed was internal stability testing over the shelf life of Lupin's ANDA Product. The test results showed a lack of crystalline particles. (DTX-108 at Lupin_Slynd_0081740).

Lupin further argues that Dr. Bugay's method of determining particle size is flawed. (D.I. 351 at 9). Lupin argues that Dr. Bugay measured different parts of each "particle" because he examined a rough tablet surface instead of a smooth interior surface. (*Id.*). Lupin also argues that Dr. Bugay provided confusing and inconsistent testimony about images of particles. (*Id.*).

Dr. Buckton's criticism of particle images is unpersuasive. Dr. Buckton testified that he only looked at images in Dr. Bugay's report; he did not review the underlying data. (Tr. at 241:18–22). While Dr. Bugay may not have explained the images from his report in a clear way, Dr. Buckton's opinion did not address the underlying data on which Dr. Bugay relied. (Tr. at 130:7–131:5 ("[I]f you looked at the tabular data that was presented in the Excel spreadsheet, that's the real data to be looking at to make any arguments.")).

Dr. Buckton's testimony criticizing Dr. Bugay's analysis of a rough tablet surface instead of a smooth surface (Tr. at 194:8–195:21) is similarly unpersuasive. Kuriyama teaches the use of Raman spectroscopy and physical analysis to determine particle size. (PTX-483). Although Kuriyama focused on a "smooth, flat surface" (PTX-483.0002), Lupin does not point to anything in Kuriyama that discourages the use of a rough surface. Dr. Buckton testified that for a rough surface, he was concerned "whether you can spatially be confident in what you're measuring by virtue of measuring on a peak, on a slope and in the plane." (Tr. at 195:14–18). Dr. Bugay, however, testified,

> But the instrument has an auto-focus feature such that I'm always in focus as I move across that rough surface, which is one of the beautiful components of a Renishaw system, that it has a live focus feature. So at every one of those positions, even though there is some topography on that surface, the laser is staying in focus to get high-quality spectra from each one of the 660,000 positions.

(Tr. at 121:14–22). I conclude that Dr. Buckton's testimony is too speculative to discredit Dr. Bugay's testimony and testing.[9]

Lastly, Lupin argues that Dr. Bugay's particle size findings are illogical in light of differences between the microcrystalline cellulose ("MCC") substrate and the Eudragit-drospirenone-plasticizer coating in Lupin's ANDA Product. (D.I. 351 at 8–9). Lupin contends that Dr. Buckton explained why the particle sizes are infeasible, but the cited testimony does not address this issue. Dr. Buckton testified,

> So this slide describes the process that I've already talked to and other people have talked to already, which is a microcrystalline cellulose particle with a median size of 90 microns. The spray of the drospirenone and Eudragit and the plasticizer coating onto the drospirenone. The drospirenone is in a thin film in Eudragit onto the microcrystalline cellulose.
>
> The issue is how, with anything other than would happen [sic], given the only way these materials are going to land is to land onto the microcrystalline cellulose particle. And there is no mechanism that I can think of which gives rise to the particles of a D90 of 28 which is what Dr. Bugay talked about.
>
> There's no mechanism by which the drospirenone can separate out and can separates [sic] out into such a large lump, separate to the microcrystalline cellulose particle.

(Tr. at 188:5–20). This testimony does not show that Dr. Buckton compared various particles in the way Lupin suggests. Lupin's contention about the feasibility of particles coating the MCC granules boils down to attorney argument. I do not credit it.[10]

[9] Dr. Buckton's testimony about the unreliability of Dr. Bugay's particle size distributions (Tr. at 201:21–203:5) is unpersuasive, too. Dr. Buckton relied on Rawle to opine that conversions from number-based distributions to volume-based distributions are unreliable, but as I explained in the context of indefiniteness, Rawle does not teach that conversions are inherently unreliable.

[10] Exeltis is also correct in arguing that Lupin mischaracterizes Dr. Koleng's testimony. Dr. Koleng testified that Lupin uses a fast-dissolving form of drospirenone that is similar to micronized drospirenone; he did not testify that Lupin's ANDA Product contains micronized drospirenone. (Tr. at 706:19–707:4).

I thus conclude that Lupin's ANDA Product contains particles of drospirenone in the claimed size distributions. Exeltis has proven by a preponderance of the evidence that Lupin infringes the particle limitations in claim 14 of the '299 patent, claims 12 and 21 of the '632 patent, and claim 19 of the '487 patent.

D. Written Description

1. Findings of Fact

1. The state of the art for slow-release formulations and for drospirenone formulations was well-established as of 2010. (Tr. at 746:2–7).

2. Excipients like Eudragit were well-known in 2010 as a way of delaying release. (Tr. at 221:2–222:4, 646:25–647:21).

3. Lupin's ANDA Product is not meaningfully different from the compositions described in the specification. (Tr. at 706:9–22).

4. The specification discloses that the dissolution and PK profiles are central aspects of the invention. (JTX-008 ('249 patent) at 13:20–33; Tr. at 700:7–20).

5. Besides the manipulation of particle size to achieve the claimed dissolution and PK limitations, the specification of the asserted patents teaches multiple well-known methods of achieving those targets. (JTX-008 ('249 patent) at 29:54–30:2).

6. The data disclosed in the specification of the asserted patents shows that the inventors had possession of the novel dissolution and PK limitations. (JTX-008 ('249 patent) at 10:60–11:24, 11:56–61, 37:32–49:10; Tr. at 496:14–507:17, 700:12–20).

7. Given the knowledge in the art regarding drospirenone and slow-release formulations, a POSA, with the claimed PK and dissolution parameters in mind, could reasonably predict which formulations would achieve those claimed parameters. (Tr. at 709:9–11).

2. Conclusions of Law

Lupin argues that the asserted claims of the '122 and '249 patents, which do not include particle limitations, are directed to a broad, functionally claimed genus: any 4 mg formulation that meets the claimed dissolution and PK limitations. (D.I. 335 at 27). Lupin argues that the

specification does not show that the inventors had possession of the full scope of the genus. Lupin contends the specification discloses only one way of achieving the dissolution and PK limitations: manipulation of drospirenone particle size. (*Id.* at 28). Lupin argues the specification only spends two paragraphs on describing other ways of achieving the dissolution and PK limitations. (*Id.* at 29). Lupin argues the paragraphs are merely "an invitation to experiment with different techniques." (*Id.*).

Exeltis argues that the specification supports the novel aspects of its invention—the dissolution and PK profiles. (D.I. 349 at 34). Exeltis contends that the specification describes in detail the "unique approach" of using particle size to achieve the dissolution and PK limitations, but that the specification "understandably" does not discuss the well-known and routine task of using excipients to achieve a slow release. (*Id.* at 34–35). Exeltis argues that the specification did not need to identify representative species or common structural features of the claimed formulations because they were known in the art. (*Id.* at 37). For example, Exeltis argues that the specification did not need to describe Eudragit, which Lupin's ANDA Product uses, because Eudragits were well-known in the art. (*Id.* at 38–39).

"[D]etermining whether a patent complies with the written description requirement will necessarily vary depending on the context." *Ariad*, 598 F.3d at 1351. "Specifically, the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* "For generic claims, we have set forth a number of factors for evaluating the adequacy of the disclosure, including 'the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.'" *Id.* (citation omitted).

The state of the art for slow-release formulations and for drospirenone formulations was well-established as of 2010. (Tr. at 746:2–7). The specification teaches oral administration in the form of tablets, capsules, and granules (JTX-008 ('249 patent) at 29:5–9; Tr. at 703:3–10), and it teaches multiple methods of manufacturing such products, including dry granulation, direct compression, and wet granulation (JTX-008 ('249 patent) at 29:24–27). Drs. Koleng and Buckton testified that compositions containing drospirenone were well-known in various forms, including spray-dried, amorphous, micronized, and molecularly dispersed drospirenone. (Tr. at 218:14–219:18, 686:5–22). Dr. Koleng also testified that slow-release drug delivery systems have a physical structure in common. (Tr. at 704:23–705:1).

Multiple experts testified that excipients like Eudragit were well-known in 2010 as a way of delaying release. (Tr. at 221:2–222:4, 646:25–647:21). Dr. Koleng testified that Lupin's ANDA Product is not meaningfully different from the compositions described in the specification. (Tr. at 706:9–22). This testimony contradicts Lupin's contention that the specification does not describe anything similar to Lupin's ANDA Product, and, as I held above, the dissolution characteristics of the parties' products are comparable given that Lupin infringes Exeltis's patents.

Besides the method of manipulating particle size to achieve the claimed dissolution and PK limitations, the specification lists multiple other well-known methods of achieving those targets. The specification states,

> A DRSP [i.e., drospirenone] containing composition with such an in vitro dissolution profile or the in vivo pharmacokinetic profile fully-described above may be achieved by various other ways.
>
> By routine experiments and in view of his general knowledge, one skilled in the art may modify (i) the particle size distribution of DRSP and (ii) the amounts and the nature of excipients in order to obtain other alternative compositions displaying the in vitro dissolution profile and the in vivo pharmacokinetic profile

> described in the present application. For example, one skilled in the art may conceive a composition comprising (i) micronized DRSP together with (ii) a slow release agent in order to diminish the dissolution rate of said DRSP.
>
> One skilled in the art may also combine (i) large particles of DRSP together with (ii) a surfactant and/or a wetting agent in order to ensure the dissolution of said DRSP. Generally, non-micronized and essentially crystallized form DRSP is preferably used for preparing the pharmaceutical composition of the invention.

(*See* JTX-008 ('249 patent) at 29:50–30:2). This portion of the specification provides sufficient detail regarding methods that were well-known as of 2010. *See Bos. Sci. Corp.*, 647 F.3d at 1366 ("Because the specification is viewed from the perspective of one of skill, in some circumstances, a patentee may rely on information that is 'well-known in the art' for purposes of meeting the written description requirement.").

Contrary to Lupin's argument, this case is not "strikingly similar" (D.I. 335 at 30) to *Lipocine Inc. v. Clarus Therapeutics, Inc.*, 541 F. Supp. 3d 435 (D. Del. 2021). The claims at issue in *Lipocine* were notably broader than the asserted claims here. For instance, the broadest claims in *Lipocine* did not contain any PK requirements, and the claims allowed for dose adjustments of 40% after titration. *Id.* at 448. The specification in *Lipocine* also emphasized "the importance of the choice of excipients to the invention's ability to achieve the recited therapeutic objectives," but ten of the claims did not require any particular excipients at all. *Id.* at 449–51. The data examples only supported the PK limitations for a "small subset" of the formulations within the scope of the claims. *Id.* at 451. Unlike *Lipocine*, the asserted claims of the '122 and '249 patents are narrower in scope, the examples in the specification disclose the claimed dissolution and PK ranges, and the claims require the aspects of the invention that the specification emphasizes: dissolution and PK parameters.

The specification shows that a POSA could have made formulations that met the claimed PK limitations in 2010. The specification states, "[T]he present invention provides a

drospirenone-containing composition with a slow dissolution rate of drospirenone in vitro and which exhibits a similar mean AUC value (Area Under the Curve) as compared to Yasminelle® when orally administered to female patients." (JTX-008 ('249 patent) at 13:23–28). It also states, "[T]he present invention relates to DRSP-containing compositions which also display a significantly mean reduced C_{max} value (Maximum Plasma Concentration) associated with a delayed mean t_{max} value for drospirenone as compared to Yasminelle®." (*Id.* at 13:29–33). Exeltis is correct that the data disclosed in the specification teaches a POSA that the inventors had possession of the novel dissolution and PK profiles in the claims. (*See id.* at 37:32–49:10). Dr. Koleng's testimony is consistent with the specification. (*See* Tr. at 702:15–22 ("[O]nce I know the pharmacokinetic profile, for instance, the type of curves in Figure 3A or 3B for instance, I can readily envision and make products that would meet those PK profiles and the corresponding dissolution limitation – and meet the corresponding dissolution limitations."); *see also* Tr. at 707:14–18).

Thus, Lupin has failed to prove by clear and convincing evidence that the asserted claims of the '122 and '249 patents are invalid for lack of written description.

E. Obviousness

1. Findings of Fact

1. In the 1970s, drospirenone was invented at Schering, which obtained patent protection for the compound's use in oral contraception in 1980. (DTX-054 at 5:18–6:7). In the late 1990s and early 2000s, Schering filed patent applications directed to pharmaceutical compositions containing drospirenone. The applications contain similar disclosures. They include Funke, E.U. Patent No. 1214076 ("Heil 076"), E.U. Patent No. 1611892 ("Heil 892"), and U.S. Patent Publication No. 2003/0114429 ("Hilman") (collectively "Schering references"). (*See* DTX-353; DTX-426; DTX-139; DTX-115).

2. The Schering references are section 102(b) prior art to the asserted patents. Most of the references are directed to rapid-release COCs containing drospirenone,

estrogen, and excipients. (DTX-426 at claims 1, 3; DTX-115 at claims 1, 8; DTX-353 at [0017], [0027]).

3. WIPO Publication No. 2008/031631 ("Huempel") was published on March 20, 2008. Huempel is section 102(b) prior art to the asserted patents. (DTX-054; *see also* D.I. 320 ¶ 30).

4. Funke teaches fast release. Funke describes the use of an enteric coat in the context of degradation. Funke does not teach a POSA to focus on slow-release drospirenone. (DTX-353 at [0003]–[0005], [0017], [0027]; Tr. at 686:5–22).

5. U.S. Patent Publication No. 2006/0275362 ("Davila") was published on December 7, 2006. Davila is section 102(b) prior art to the asserted patents. (DTX-049; *see also* D.I. 320 ¶ 30).

6. Davila does not teach slow release. (DTX-049 at [0081] and claims 1, 2, 18).

7. Huempel suggests that the degradation of drospirenone is only a concern during manufacturing. (DTX-054 at 20:17–21).

8. Sandrone teaches that the bioavailability of drospirenone is affected by degradation in the stomach. (DTX-374 at 2:8–12, 17:28–18:14, fig.16).

9. In light of Huempel, Sandrone, Davila, and Funke, the prior art did not teach away from slow-release drospirenone.

10. Some of the Davila claims are broad enough to encompass a 4 mg dose of a rapidly-dissolving drospirenone POP. (*See, e.g.*, DTX-049 at claims 1, 5).

11. Huempel is directed to the use of a new estrogen in a COC. Huempel does not teach the use of a drospirenone POP. (DTX-054 at 18:5–28).

12. As of 2010, POPs were disfavored because they were associated with unpredictable bleeding, a continuous dosing schedule, and a strict missed pill window. (Tr. at 57:24–58:8, 603:18–604:6).

13. A POSA would not have been motivated to combine Examples 1 and 2 of Davila (DTX-049 at [0074]–[0077]) with Example 3 of Davila (DTX-049 at [0078]–[0079]).

14. As of the priority date, a POSA would have been motivated to make a 4 mg dosage of a drospirenone formulation.

15. As of the priority date, a POSA would not have been motivated to make a slow-release drospirenone POP.

16. Huempel does not teach the asserted claims' T_{max} range of 2.2 to 6 hours. (DTX-054).

17. Nothing in Huempel suggests that the T_{max} values therein disclosed (1.7 hours and 10 hours) form a range.

18. As of the priority date, a POSA would not have been motivated to develop a product with the claimed PK limitations.

19. Davila teaches the particle sizes of the asserted claims. (DTX-049 at [0078]).

20. As of the priority date, a POSA would have been motivated to use particle size to achieve the dissolution and PK limitations of the asserted claims. (Tr. at 383:4–384:19, 385:8–386:4; DTX-049; DTX-059 at Lupin_Slynd_0027478).

21. Leena Anttila, Michael Kunz & Joachim Marr, *Bleeding Pattern with Drospirenone 3 mg+Ethinyl Estradiol 20 mcg 24/4 Combined Oral Contraceptive Compared with Desogestrel 150 mcg+Ethinyl Estradiol 20 mcg 21/7 Combined Oral Contraceptive*, 80 CONTRACEPTION 445 (2009), was published in 2009 ("Anttila"). Anttila is section 102(b) prior art to the asserted patents. (DTX-048; *see also* D.I. 320 ¶ 30).

22. Huempel and Anttila teach non-continuous dosing regimens in the context of COCs. Huempel and Anttila do not teach a non-continuous dosing regimen for a POP. (DTX-048 at Lupin_Slynd_0027296–97; DTX-054 at 8:8–11, 9:16–18).

23. Davila does not teach a non-continuous dosing regimen for a POP. (DTX-049 at [0070]–[0072] and claim 20).

24. As of the priority date, a POSA would not have been motivated to make a drospirenone POP with 24/4 dosing.

25. Even if a POSA would have had a motivation to modify the prior art to achieve the claimed limitations, Lupin has failed to show a reasonable expectation of success.

26. Cerazette® is a desogestrel POP. It has been available in Europe since 2003. (Tr. at 289:19–24, 300:13–17).

27. Jean Michel Foidart, *The Benefits of Estetrol Addition to Drospirenone for Contraception*, AJOG Global Reports 1 (2023), addresses an Exeltis study that suggested SLYND® has a better bleeding profile than Cerazette® ("Foidart"). (DTX-140).

28. Robert L. Barbieri, *Drospirenone vs Norethindrone Progestin-Only Pills. Is There a Clear Winner?*, 34:2 OBG MANAGEMENT 10 (2022), was published in 2022 ("Barbieri"). (DTX-326).

29. SLYND® has a lower discontinuation rate than Cerazette®. (Tr. at 486:13–487:1; PTX-078; DTX-140 at 4).

30. The decline in unscheduled bleeding during SLYND®'s Phase III clinical trials "may be facilitated by a substantial dropout rate occurring from 2178 participants in cycle 1 to 726 in cycle 12." (DTX-140 at 3).

31. The bleeding profiles of SLYND® and Cerazette® are similar. (DTX-140 at 3).

32. Barbieri suggests that the bleeding profiles of a drospirenone POP and a norethindrone POP are similar. (DTX-326 at 11).

33. Exeltis has failed to prove that SLYND® has an unexpectedly better bleeding profile compared to Cerazette®.

34. Drospirenone does not have androgenic effects and therefore allows for a higher daily dose than earlier progestins. (Tr. at 274:8–276:7, 640:16–19).

35. Drospirenone remains in the blood after a four-day period of a patient not taking the drug. (Tr. at 391:1–18).

36. Exeltis has failed to prove that SLYND®'s twenty-four-hour missed pill window and 24/4 dosing schedule were unexpected results.

37. In 2010, COCs were understood to cause blood clots. (Tr. at 607:1–20, 610:25–611:14). COCs with drospirenone had black box warnings on their labels for serious cardiovascular side effects. (Tr. at 579:2–16, 614:18–615:16; PTX-431.0006).

38. As of 2010, drospirenone was associated with venous thromboembolism ("VTE") and hyperkalemia. (Tr. at 488:12–24, 607:1–608:13; PTX-133.0001; PTX-027 at SLYND_0400922).

39. SLYND®'s Phase III clinical trials did not report any cases of VTE. (Tr. at 578:20–579:1).

40. The lack of VTE cases among SLYND® users was an unexpected result.

41. SLYND®'s Phase III clinical trials did not show a difference in efficacy between high-BMI women and other women. (Tr. at 571:13–19, 572:13–573:8; PTX-463.0003).

42. Exeltis has shown that Finding #41 was an unexpected result.

43. SLYND® met a long-felt but unmet need for a safe and effective drug with a longer missed pill window and a 24/4 dosing regimen.

44. Exeltis's research and development team put experimental activities on hold until receipt of PK results. (Tr. at 467:16–469:19, 517:13–518:6).

45. Exeltis has not shown any evidence of industry skepticism.

46. The testimony of Drs. Colli and Velada is not reliable evidence of industry praise.

47. Barbieri discusses the benefits of SLYND®. (DTX-326 at 12).

48. Dr. Shoupe wrote positively about SLYND® in 2021. (PTX-195.0004).

49. Exeltis has shown weak evidence of industry praise.

50. SLYND® was the fifteenth entrant into the POP market. (Tr. at 653:1–6).

51. SLYND® has experienced a 19% growth in market share compared to other POPs. (Tr. at 652:15–653:10).

52. An expected market share for a fifteenth market entrant is closer to 6% or 7%. (Tr. at 653:1–6).

53. SLYND® ranked second in sales and prescriptions among the top twenty oral contraceptives after less than four years of sales. (Tr. at 594:14–596:8).

54. SLYND® is surpassing other COCs in revenue share. Its market share (as defined by prescriptions) relative to the top oral contraceptive, LO LOESTRIN FE®, has reached nearly 30%. (Tr. at 653:24–655:5, 655:21–656:10).

55. Total prescriptions for SLYND® are increasing at 13% per month, and new prescriptions are increasing by 11% per month. (Tr. at 661:2–23).

56. SLYND® costs about $190. LO LOESTRIN FE® has a similar price. Generic pills cost between $2 and $13. (Tr. at 662:25–663:10).

57. Exeltis has shown significant evidence of commercial success based on a combination of market share and sales.

58. SLYND® embodies the asserted claims' particle size limitations. (PTX-027H at .0039; Tr. at 732:24–733:14, 758:16–759:4).

59. SLYND® is coextensive with the asserted claims' dissolution and PK limitations. (PTX-027H.0025, .0078).

2. Conclusions of Law

The parties agree that a POSA in the pertinent art includes a person having a doctoral degree in pharmaceutical sciences, a field of chemistry relating to drug formulation or development, or a related field with at least two years of experience formulating solid dosage forms. A POSA also includes a gynecologist or obstetrician or other medical professional in

women's healthcare, with at least two years of experience prescribing oral contraceptives. (D.I. 275-1 ¶ 70). A POSA may have an education level lower than a doctoral degree in pharmaceutical sciences, chemistry, or a related field if the POSA has commensurately more relevant work experience. A POSA may have also worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also consulted with others on the team having specialized skills to solve a problem. (*Id.*).

Lupin argues that the combination of Huempel and Davila renders the asserted claims obvious. (D.I. 335 at 20). The parties disagree about whether these prior art references disclose all limitations of the asserted claims. Lupin makes various arguments about the differences between the prior art and the claimed invention. I address those arguments.

a. Teaching Away

Lupin argues that the prior art did not teach away from slow-release drospirenone. (*Id.* at 17).

Lupin contends that a finding of teaching away is foreclosed by Funke. Lupin argues that Funke taught the use of an enteric coat as an alternative to fast release. (*Id.* at 18–19). Lupin relies on *Bayer Schering Pharma AG v. Barr Laboratories Inc.*, 575 F.3d 1341 (Fed. Cir. 2009), to support its position. Lupin's argument regarding Funke is unpersuasive. Funke mentions enteric coatings in a background section describing ways to overcome drospirenone's degradation in the stomach. (DTX-353 at [0003] ("Enteric coatings may be suggested in consequence thereof."); Tr. at 386:22–388:5). Funke teaches that the in-vitro dissolution of micronized drospirenone is high, but that micronization techniques are expensive and "may be difficult to handle," so alternatives to micronized drospirenone may be necessary. (DTX-353 at [0004]–[0005]). An enteric coating is one such alternative. I conclude that the mentions of

enteric coating in Funke are consistent with fast release; Funke does not suggest that a POSA could or should focus on slow-release drospirenone. Lupin's citations to *Barr* are similarly unpersuasive. In *Barr*, Bayer argued that the prior art taught away from using micronized drospirenone in a normal tablet, while Barr argued that the prior art taught away from using an enteric coating. 575 F.3d at 1349. The Federal Circuit rejected the analysis of both sides, holding that the prior art merely presented two options to a POSA, both of which were obvious to try. *Id.* at 1349–50. This case differs to the extent that Funke does not present a POSA with the option of pursuing slow-release formulations. Funke is consistent with other prior art references, such as Davila, which taught fast release, not slow release. (DTX-049 at [0007], [0016], [0074], [0076]; Tr. at 689:7–21)).[11]

Lupin concedes Heil 076 taught that fast release was "an advantage" that led to "high bioavailability of the compound," as fast release avoided potential drug loss in the stomach. (DTX-426 at [0018]). Lupin argues, however, that teaching an advantage is different than teaching away. (D.I. 335 at 18). Lupin contends that by the priority date, degradation was no longer a concern, as Huempel taught that bioavailability loss does not occur in vivo. (*Id.* at 19). Lupin further argues that even if one ignores Huempel, a POSA in 2010 would have known that bioavailability could be increased by increasing the dosage, and that drospirenone could be dosed

[11] Lupin argues, "Davila teaches an exemplar DRSP-containing formulation with a slowed dissolution profile falling withing the claimed range." (D.I. 335 at 20). This formulation is found in Example 3, which describes a composition that falls outside the scope of the Davila claims. (Tr. at 413:1–6). The composition in Example 3 "released only about 20% of the drospirenone within 20 minutes." (DTX-049 at [0081]). Davila, however, claims rapidly-dissolving compositions. (*Id.* at claims 1, 2, 18). Because Example 3 is contrary to the claims of Davila, I find that Davila as a whole does not teach slow release.

at higher levels than previous progestins because it did not have any androgenic effects.[12] (*Id.* at 20 (citing Tr. at 274:8–276:7, 381:17–382:5)).

Huempel discloses, "It was also shown that ring opening does not occur at the pH of the stomach (no loss in bioavailability) but low pH-values have to be avoided during the manufacturing process." (DTX-054 at 20:17–21). Dr. Velada testified that he was aware of this language. (Tr. at 475:13–24). Exeltis argues that this language is contrary to Sandrone, which states that the bioavailability of drospirenone is affected "by rapid degradation due to prolonged contact with gastric fluids with a very low pH." (DTX-374 at 2:8–12; *see also* Tr. at 720:6–10, 721:8–16). Exeltis argues that Huempel does not disclose any data to support the proposition that degradation was only a concern during manufacturing. (D.I. 349 at 23).

Having reviewed the conflicting statements in Huempel and Sandrone, along with the teachings in Davila and Funke, I conclude that the evidence does not rise to the level of teaching away from slow-release drospirenone. *See Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) ("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." (citation omitted)). The evidence is nevertheless probative of a lack of motivation to make slow-release drospirenone. *See Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017) ("[P]rior art need not explicitly 'teach away' to be relevant to the obviousness determination. Implicit in our discussion of the 'degree' of teaching away is an understanding that some references may discourage more than others.").

[12] Androgenic effects are testosterone-like effects. (Tr. at 274:12–18, 275:25–276:7).

b. Differences Between the Prior Art and the Claimed Invention

Lupin argues that the combination of Huempel and Davila renders the asserted claims obvious. (D.I. 335 at 20). The asserted claims include the following seven limitations: (1) a pharmaceutical composition; (2) a 4 mg dose of drospirenone; (3) drospirenone with specific particle sizes; (4) no estrogen; (5) a dissolution profile in which less than 50% of the drospirenone is dissolved in thirty minutes when subjected to the Paddle Method; (6) a particular PK profile; and (7) a 24/4 dosing schedule.[13] Lupin argues that these limitations are taught by one or both of Davila and Huempel. (*Id.*).

Davila teaches a drospirenone particle range from 30 μm to 90 μm. (DTX-049 at [0078]). Huempel teaches a pharmaceutical composition containing 3 mg of drospirenone. (DTX-054 at 9:13–19 (describing Yasmin® and Yaz®)). Exeltis does not contest these facts in its post-trial briefing. (*See generally* D.I. 349 at 19–33). Davila also teaches a pharmaceutical composition containing 2 mg to 4 mg of drospirenone. Claim 5, for instance, recites that "drospirenone is present in an amount of from about 2 mg to about 4 mg." (DTX-049 at claim 5). The specification similarly states,

> The pharmaceutical compositions of the invention preferably comprise[] drospirenone or a pharmaceutically acceptable salt or ester thereof, in an amount corresponding to a daily dosage of from about 2 mg to about 4 mg, more preferably from about 2.5 mg to about 3.5 mg. Optionally, the compositions of the invention include ethinyl estradiol.

(*Id.* at [0019]). Exeltis argues that Davila teaches "nothing about 3 vs. 4 mg or removing estrogen from combination products." (D.I. 349 at 31). Although I agree that Davila does not explicitly describe POPs with 4 mg of drospirenone, the language in the specification and claims is broad enough to include a 4 mg dose of a rapidly-dissolving drospirenone POP within the

[13] Some asserted claims contain only a subset of these limitations.

scope of the claims. *See CIAS, Inc. v. All. Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'").

Exeltis contends that Davila and Huempel do not disclose the asserted claims' PK limitations (applicable only to claim 21 of the '632 patent, claim 29 of the '122 patent, claim 7 of the '249 patent, and claim 19 of the '487 patent), dosing schedule (only applicable to the '249 patent), or drospirenone in a POP (applicable to all asserted claims).

First, Exeltis argues that Huempel does not teach the claimed T_{max} range of 2.2 to 6 hours. (D.I. 349 at 25). Lupin conceded this point in its briefing. (D.I. 335 at 22 ("Huempel discloses all the functionally-claimed pharmacokinetic elements, with the sole exception of the claimed T_{max} range of 2.2 to 6 hours.")).[14]

Second, Exeltis argues that Huempel and Anttila[15] do not teach a 24/4 dosing schedule for a POP, while Davila does not disclose a 24/4 dosing regimen at all. (D.I. 349 at 27). Anttila and Huempel teach non-continuous, i.e., 24/4 or 21/7, regimens in the context of COCs only. They do not teach a non-continuous dosing regimen for a POP. (*See* DTX-048 at Lupin_Slynd_0027296 ("A new low-dose COC . . . has been developed that comprises a regimen with 24 active pills and 4 inert pills (24/4) regimen."); DTX-048 at Lupin_Slynd_0027297 ("The present study was undertaken to compare the bleeding pattern, cycle control, contraceptive efficacy and safety of [drospirenone] 3mg/EE 20 mcg 24/4 COC regimen with a low-dose 21/7 preparation containing desogestrel (DSG) 150 mcg and EE 20 mcg."); DTX-054 at 8:8–11

[14] Huempel discloses a T_{max} value of 1.7 hours and a T_{max} value of 10 hours. (DTX-054 at 22:24–29, fig.4).

[15] Lupin contends that claim 7 of the '249 patent is invalid as obvious over Huempel in view of Davila and in further view of Anttila. (D.I. 275-1 at 7 of 25).

("Numerous analogues have been developed since the first so-called one-phase preparations consisting of a fixed daily dose of a progestin and an estrogen for 21 days followed by a 7 days drug-free interval."); DTX-054 at 9:16–18 ("Just recently, the EE reduced version YAZ® (DRSP 3 mg plus EE 0.02 mg taken for 24 days followed by a 4 days drug-free interval) was granted FDA approval.")). Davila does not teach a non-continuous dosing regimen for a POP either. The Davila specification states that some embodiments of the invention have a 21/7 dosing schedule. (*See* DTX-049 at [0070]–[0072]). The only claim describing a 21/7 dosing schedule, however, recites a pharmaceutical kit comprising daily dosage units that comprise both drospirenone and ethinyl estradiol, an estrogen. (DTX-049 at claim 20). Viewing Davila as a whole, I do not think that the patent teaches the administration of a drospirenone POP in a 21/7 dosing schedule.

Third, Exeltis argues that the prior art does not teach the use of drospirenone in a POP. (D.I. 349 at 28). I agree that Huempel does not teach the use of a drospirenone POP, as Huempel is directed to the use of a new estrogen in a COC. (*See, e.g.*, DTX-054 at 18:5–28 (describing "[t]echnical problems of the invention")). The Davila specification, however, repeatedly states that the invention "optionally" includes ethinyl estradiol. (*See* DTX-049 at [0007]–[0010], [0016], [0019], [0043], [0059]). Two of the examples (Example 1 and Example 2) describe a POP, as neither example's list of ingredients includes ethinyl estradiol. (*Id.* at [0074]–[0077]). Relatedly, many of the claims are broad enough to include both a POP and a COC. (*See, e.g.*, *id.* at claims 1, 3, 5). Thus, although Davila does not expressly claim drospirenone POPs, its claims are broad enough to include such pills.

In sum, I conclude that Davila, Huempel, and Anttila do not teach a drospirenone POP with a non-continuous dosing schedule, nor do they teach a drospirenone POP with the claimed

PK parameters. The Davila claims are broad enough to include a 4 mg dosage of a drospirenone POP, but the patent teaches a rapidly-dissolving composition, which is contrary to the asserted claims.

c. Motivation to Modify the Prior Art

"For a patent to be obvious, 'some kind of motivation must be shown . . . why a person of ordinary skill would have thought of either combining two or more references or modifying one to achieve the patented method.'" *Shire*, 802 F.3d at 1306 (quoting *Innogenetics, N.V. v. Abbott Laby's*, 512 F.3d 1363, 1374 (Fed. Cir. 2008)). A POSA's "[m]otivation to combine may be found in many different places and forms." *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1197 (Fed. Cir. 2014) (quoting *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013)). "[C]ase law does not require that a particular combination must 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).

i. Motivation to Make Estrogen-Free Drospirenone Tablets in the Claimed Dosage Ranges

Lupin argues that a POSA would have been motivated to make drospirenone POPs in 2010. (D.I. 335 at 21). Although the FDA approved POPs for contraceptive use more than fifty years ago (Tr. at 62:21–24, 269:20–24), a drospirenone POP was not developed prior to SLYND® (Tr. at 297:2–5, 519:7–16). Lupin is correct in arguing that the prior art did not need to describe drospirenone as the preferred progestin. Lupin has nevertheless failed to show that drospirenone POPs were a "suitable option from which the prior art did not teach away." *Bayer Pharma AG v. Watson Lab'ys, Inc.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017) (citation omitted). Even if drospirenone had some superior properties compared to other progestins, such as a lack of androgenic effects, drospirenone was associated with VTE and a tendency to cause

hyperkalemia. POPs as a whole were disfavored because they caused unpredictable bleeding, had a continuous dosing schedule, and had a strict missed pill window. The evidence shows that women preferred COCs and only turned to POPs as a "last ditch" option if they could not take COCs due to blood clotting or other health concerns. (Tr. at 57:24–58:8, 603:18–604:6). This evidence does not suggest that a POSA would have been motivated to make a drospirenone POP.

Lupin's reliance on Davila does not show a motivation to make slow-release drospirenone POPs. Lupin's expert, Dr. Amiji, did not explain why a POSA would combine conflicting examples in Davila to find a motivation to make a drospirenone POP. On the one hand, Examples 1 and 2 in Davila teach a drospirenone-only formulation. (Tr. at 356:2–357:6, 414:4–18). The examples describe the use of a surfactant (Polysorbate 80) in the preparation of the examples, and the resulting examples have a rapid dissolution profile. (DTX-049 at [0074]–[0077], [0081]). The asserted claims, by contrast, have a slow dissolution profile. Example 3 of Davila, described as a "comparative" example, and in contrast to Examples 1 and 2, teaches a formulation with estrogen. Example 3 does not describe the use of a surfactant, and it describes a slower dissolution rate. (Tr. at 357:7–14, 359:2–360:1, 414:4–9). Example 3 falls outside the scope of the Davila claims (Tr. at 413:1–6), and Dr. Amiji did not explain why a POSA would combine an example that does not reflect the Davila invention with examples that do (Tr. at 414:4–18).

Lupin's citations to Huempel and Heil 892 do not show the relevant motivation either. Huempel, rather than teach a POP, teaches that a new estrogen may be used. Heil 892, meanwhile, describes drospirenone-only formulations for the treatment of endometriosis and cancer. (Tr. at 403:8–404:16; DTX-139 at [0011]–[0012]). Although Heil 892 mentions using drospirenone for contraception, it does so in the context of COCs. (*See* DTX-139 at [0002]–

[0005]). These references do not provide motivation for a POSA to make a drospirenone POP as of the priority date.

Lupin further argues that a POSA would have been motivated to make drospirenone POPs at the claimed dosages. (D.I. 335 at 21). Exeltis argues that the evidence does not show a motivation to increase the dosage from 3 mg in a COC to 4 mg in a POP. (D.I. 349 at 30).

Although Davila does not expressly claim a 4 mg dose of a drospirenone POP, the language in the claims is broad enough to cover a 4 mg dose of a rapidly-dissolving drospirenone POP. Davila thus shows some motivation for making a 4 mg dose of a drospirenone formulation. Dr. Gersh's testimony is consistent with a motivation to use a 4 mg dosage. (*See* Tr. at 275:25–276:7 ("So you don't have to worry about lowering the dose and you even have the option, you could even raise the dose because you have no androgenic effect.")).

Thus, I conclude that a POSA would have been motivated to make drospirenone formulations in a 4 mg dosage, but would not have been motivated to make a slow-release drospirenone POP.

ii. Motivation to Develop a Product with the Claimed Pharmacokinetics

Lupin argues that a POSA had practical and commercial reasons to design around the Schering references, which claimed drospirenone-only products with a rapid-release rate and/or products with micronized drospirenone. (D.I. 335 at 24 (citing *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1339 (Fed. Cir. 2018))). Lupin contends it follows that a POSA would focus on slower-release and non-micronized drospirenone. (*Id.*).

Lupin's reliance on *Acorda* is unpersuasive. The Federal Circuit in *Acorda* considered blocking patents in the context of objective indicia, not in relation to a motivation to combine. The evidence nevertheless shows some support for Exeltis's desire to design around the Schering

references. (*See* DTX-364 at 2 (stating "[d]o not use micronized drospirenone" and "[d]issolution <70% in 30 minutes")). On its own, however, a motivation to design around the Schering references does not amount to a motivation to develop a product with the claimed T_{max} of 2.2 to 6 hours.

Lupin argues that a POSA would have been motivated to combine Davila and Huempel to make a drospirenone POP with the claimed PK profile. (D.I. 335 at 22). Lupin argues that drospirenone's pharmacokinetics were known and predictable as of the priority date. (*Id.*). While Huempel does not disclose a T_{max} range of 2.2 to 6 hours, it discloses T_{max} values of 1.7 hours and 10 hours. (DTX-054 at figs.2 & 4; Tr. at 418:1–7). Lupin argues the claimed T_{max} range corresponds to the transit time of a tablet in the small intestine, where drug absorption is at a maximum. (Tr. at 426:22–427:21). Lupin argues that this time period would have provided motivation to a POSA concerned about bioavailability in the stomach. (D.I. 335 at 24). Lupin thus argues that an intermediate T_{max} would have been obvious to try, and that a POSA would have arrived at the claimed range by routine experimentation. (*Id.* at 23–24).

Huempel does not support Lupin's argument. Besides the fact that Huempel discusses COCs, not POPs (Tr. at 691:13–18, 692:14–21), nothing in Huempel suggests that the disclosures of a 1.7-hour T_{max} and a 10-hour T_{max} form a range. Whereas the asserted claims disclose slow-release drospirenone, the 1.7-hour T_{max} in Huempel refers to an immediate release. The 10-hour T_{max} refers to a "modified" release but is based on a simulation. (Tr. at 417:14–418:16, 424:3–13). Huempel further states, "This invention is to the combination of the unexpected pharmacokinetic profile of 8-Prenyinaringenin with a modified release formulation, which enables release of the drug at an almost constant rate for 8–10 hours." (DTX-054 at 21:29–22:4). In other words, Huempel suggests that the T_{max} value would be closer to 8 or 10

hours. Dr. Amiji testified that a POSA would have tried a T_{max} range of 2.2 to 6 hours. (Tr. at 426:22–427:21). I do not credit this testimony, as it is inconsistent with the teachings of Huempel. I agree with Exeltis that taking the 1.7-hour and 10-hour T_{max} values from Huempel and saying they motivate the claimed PK profile requires hindsight. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig*., 676 F.3d at 1073 (stating that "hindsight analysis is inappropriate because obviousness must be assessed at the time the invention was made").

iii. Motivation to Use the Claimed Particle Sizes to Achieve the Claimed PK and Dissolution Profiles

Lupin argues that modifying particle size would have been an obvious way to achieve the claimed PK parameters. (D.I. 335 at 26). Lupin contends that a connection between particle size, dissolution rate, and the PK profile of drospirenone was known as of the priority date. (*Id.* at 25–26). Particle size was known to determine dissolution, which in turn was known to determine the PK profile. (Tr. at 385:8–386:20).

In its post-trial briefing, Exeltis does not address the motivation to use particle size to achieve the claimed dissolution and PK profiles.[16] I therefore credit Lupin's argument and find it would have been obvious to use particle size to achieve the claimed dissolution and PK profiles.

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> As the party without the burden, Exeltis need not address every limitation. Instead, we focus on those that are the most important defects in Lupin's case, of which there are many—the dissolution rate limitation (present in every claim), the pharmacokinetic profile limitation ('632 claim 21; '487 claim 19; '122 claim 29, '249 claim 7), the no estrogen limitation (present in every claim), and the 24/4 dosing regimen ('249 claim 7). Lupin fails to show with clear and convincing evidence that the Asserted Claims—in part or on the whole—are obvious.

(D.I. 349 at 19).

iv. Motivation to Use 24/4 Dosing

Lupin argues that a 24/4 dosing schedule would have been an obvious way to provide effective contraception. (D.I. 335 at 26). Lupin contends that Davila and Anttila both taught non-continuous dosing schedules, and that the FDA approved a 24/4 dosing schedule for Yaz® prior to the priority date. (*Id.* at 27). Lupin also argues it was known that an effective amount of drospirenone would remain in the blood "following a four-day period of no drug." (*Id.*). Exeltis argues that a POSA would not have been motivated to make a POP with a 24/4 dosing schedule because all POPs before SLYND® had continuous dosing. (D.I. 349 at 31).

The evidence supports Exeltis's position. Lupin has not shown that a POSA would have been motivated to use 24/4 dosing for a POP. As I concluded above, Davila, Huempel, and Anttila all taught non-continuous dosing in the context of COCs, not POPs. The 24/4 dosing schedule for Yaz® is similarly limited to COCs. (Tr. at 282:3–20). Dr. Amiji's testimony—that a POSA would have known an effective amount of drospirenone remains in the blood after four days of a patient not taking the drug (Tr. at 390:14–391:18)—relates to the teachings in Huempel, which focused on COCs. As of 2010, however, all POPs were administered continuously. (Tr. at 291:12–293:23). Only COCs were administered effectively with a non-continuous dosing regimen (Tr. at 605:16–21, 606:15–18), and Dr. Shoupe testified that a COC's dosing regimen would not tell a POSA much about the dosing regimen of a POP that used the same progestin as the COC (Tr. at 618:17–21). Lupin has not proven otherwise.

I have concluded that a POSA would have been motivated to make drospirenone formulations in the claimed dosage ranges, and it would have been motivated to use the claimed particle sizes to achieve the claimed PK and dissolution profiles. A POSA would not, however,

have been motivated to make slow-release drospirenone POPs, to make a product with the claimed PK profile, or to use 24/4 dosing. On this basis alone, I would have to conclude that the asserted claims are not obvious in light of Davila, Huempel, and Anttila.

d. Reasonable Expectation of Success

In the interest of completeness, I consider whether there was a reasonable expectation of success. Even if a POSA had the motivation to combine prior art to achieve the claimed invention, Lupin has not shown that a POSA would have a reasonable expectation of doing so. For an invention to be found obvious, a POSA must have, in addition to a motivation to modify the prior art, a "reasonable expectation of success" in "achiev[ing] the claimed invention." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012) (citation omitted). "Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) (citations omitted); *see also Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021) (noting that obviousness does not require a showing that "a skilled artisan would have precisely predicted" the claimed dosage of a drug, merely a showing of "a reasonable expectation of success in achieving the specific invention claimed").

Lupin makes few references to a reasonable expectation of success in its briefing. (*See* D.I. 335 at 17 ("There is no real factual dispute that a POSA would have been able to develop a product meeting the claimed limitations with a reasonable expectation of success had the POSA been motivated to do so."), *id.* at 21 ("As a threshold matter, the undisputed evidence shows that a POSA would have been motivated to make DRSP POP tablets, free of estrogen, at the claimed dosages with a reasonable expectation of success."), *id.* at 22 ("A POSA would have been motivated to combine Davila and Huempel to develop a DRSP POP with the claimed

pharmacokinetics with a reasonable expectation of success.")). Lupin argues that Exeltis achieved its targeted dissolution and PK profiles on its first try. (Tr. at 551:24–552:23 ("The first clinical trial was successful.")). I think Lupin's arguments about a reasonable expectation of success are too conclusory to prove obviousness even if Lupin had shown that a POSA would have been motivated to achieve all limitations of the asserted claims.

e. Objective Indicia of Nonobviousness

Even if Exeltis asserted no objective indicia of nonobviousness, I would find that Lupin has failed to prove by clear and convincing evidence that the asserted claims are obvious. Nevertheless, I address the parties' arguments about objective indicia. Exeltis offers evidence of five objective indicia of nonobviousness: unexpected results, a long-felt but unmet need, skepticism, industry praise, and commercial success. (*See* D.I. 334 at 9–18). Consideration of the proffered objective indicia offers further support for the nonobviousness of the asserted claims.[17]

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.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, then the probative value of each secondary 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

[17] Generally speaking, the parties address the objective indicia as though they are equally applicable (or non-applicable) to all the asserted claims.

of the secondary consideration. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). That burden stays always with the patent challenger. *Id.* at 1359–60.

i. Unexpected Results

"In considering unexpected results, courts ask whether 'the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.'" *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019) (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)). These results support a conclusion of nonobviousness where "[t]he unexpected properties of the claimed formulation, even if inherent in that formulation, differ in kind from the prior art." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015).

As an initial matter, Lupin argues that Exeltis's objective indicia arguments should not be given weight because Exeltis did not compare SLYND® to the closest prior art, Cerazette®. (D.I. 351 at 14). Exeltis argues that Lupin "frames its objective indicia analysis through the wrong lens." (D.I. 355 at 10). Exeltis contends that Lupin simultaneously ignored Cerazette® for its own obviousness analysis and insisted that Cerazette® be considered in the objective indicia analysis. (*Id.* at 10–11).

"To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Here, the evidence shows that Exeltis considered Cerazette®. Drs. Perrin and Colli both testified that they compared SLYND® to Cerazette®, and Exeltis conducted a clinical trial comparing the two products. (*See* Tr. at 486:13–487:1, 509:11–20, 575:1–578:16; PTX-078 (July 2019 paper by

Exeltis's employees reporting on the clinical trial). That Lupin submitted evidence of another study—Foidart—to undermine the findings in Exeltis's study does not show that Exeltis ignored Cerazette®. I thus turn to the remainder of Exeltis's unexpected results argument.

First, Exeltis has not shown that SLYND®'s bleeding profile was unexpectedly superior to Cerazette®'s. On the one hand, the evidence suggests that a POSA would have expected SLYND® to have drawbacks because SLYND® has a higher dose of progestin than other POPs, and progestins have poor bleeding control. (Tr. at 484:21–485:22, 608:14–22; PTX-195.0004). Exeltis contends that Phase III clinical trials surprisingly showed that SLYND® had a better bleeding profile than Cerazette®. A low percentage of patients discontinued SLYND® due to irregular bleeding (Tr. at 575:19–576:14, 612:18–613:9; PTX-096.0005), which percentage was about half the discontinuation rate of Cerazette®. (Tr. at 486:13–487:1; *see also* PTX-078).

The Foidart paper, on which Lupin relies, acknowledges that SLYND® had a 4% "discontinuation rate owing to bleeding complaints" compared to Cerazette®'s 7% discontinuation rate. (DTX-140 at 4).[18] Foidart, however, states that the discontinuation rate due to bleeding-related adverse events was not reported in the U.S. trial for SLYND® because the trial "had a high overall dropout rate of 65% with 27% of participants lost to follow-up." (*Id.*).

Foidart states that the decline in unscheduled bleeding during Phase III clinical trials "may be facilitated by a substantial dropout rate occurring from 2178 participants in cycle 1 to 726 in cycle 12." (*Id.* at 3). Foidart continues, "A comparative, randomized, 9-month trial with

[18] Exeltis's expert, Mr. Segers, also testified that patients who take SLYND® continue taking it. (Tr. at 661:2–23).

a 75 µg DSG POP[19] in a continuous 28-day treatment regimen suggested limited differences in the bleeding profiles for the 2 products." (*Id.*).

The Barbieri study is consistent with Foidart's findings. Barbieri, which states that roughly 50% of norethindrone[20] POP users have "bleeding between periods, spotting, and/or prolonged bleeding," concludes that "[a] similar frequency of unscheduled uterine bleeding has been reported with drospirenone POP." (DTX-326 at 11; *see also* Tr. at 786:23–787:20). Evidence of the FDA writing to Exeltis about "false or misleading claims" regarding SLYND®'s bleeding profile further casts into doubt that SLYND had a better bleeding profile than Cerazette®. (DTX-410 at 1–3; Tr. at 580:22–584:15). The FDA wrote that one of Exeltis's posts, which stated, "Offer your patients estrogen-free birth control with periods on a schedule," was misleading, in part because "the majority of patients [did] not experienc[e] scheduled bleeding . . . during treatment with Slynd and the large proportion of patients still experienc[ed] breakthrough bleeding." (DTX-410 at 2–3). The FDA thus concluded that Exeltis's post was "not supported by the data." (*Id.* at 3). Exeltis's attempt to downplay the FDA's letter as "just . . . a statement made in marketing materials" (D.I. 355 at 13) is unpersuasive.

Viewing the evidence as a whole, Foidart, Barbieri, and the FDA communications undermine Exeltis's argument that SLYND® had a superior bleeding profile than Cerazette®. I think Exeltis has failed to prove by a preponderance of the evidence that SLYND®'s bleeding profile was unexpectedly superior.

Second, Exeltis has not shown it was unexpected that "removing estrogen from the combination product would result in preserving the missed-pill window and non-continuous

[19] DSG is desogestrel. DSG POP is Cerazette®.

[20] Norethindrone is a first-generation progestin. (Tr. at 273:1–6).

dosing regimen." (D.I. 355 at 13). On the one hand, the evidence shows that as of 2010, efficacy depended on continuous daily dosing, so other POPs did not have a pill-free dosing window. (PTX-195.0004; *see also* Tr. at 606:6–10, 609:14–20). Cerazette® had a twelve-hour missed pill window, while POPs in the United States had a missed pill window of roughly three hours. (Tr. at 292:11–18, 293:7–20, 606:11–14). COCs with the same progestin as these POPs had twenty-four-hour missed pill windows. (Tr. at 292:21–293:3, 293:24–294:5). On the other hand, Lupin's argument about the inherent characteristics of drospirenone is persuasive. Lupin argues that a twenty-four-hour missed pill window was enabled because drospirenone did not have androgenic effects[21] and therefore allowed for a higher daily dose. (Tr. at 274:8–276:7, 640:16–19). Lupin also argues that a 24/4 dosing regimen was not unexpected because drospirenone was known to remain in the blood after a four-day period of a patient not taking the drug. (Tr. at 391:1–18). Lupin's evidence shows support for a longer missed pill window and a non-continuous dosing schedule.

Third, Exeltis has shown that the lack of VTE cases for SLYND®, compared to other contraceptives, was unexpected in 2010. Lupin argues that SLYND®'s lack of VTE risk was predictable. The evidence shows that industry concerns about blood clots have changed from 2010 to the present day. In 2010, progestins were associated with blood clots. (Tr. at 607:1–20, 610:25–611:14). Lupin's argument—that VTE concerns are belied by the existence of drospirenone COCs—is unpersuasive, as COCs with drospirenone had black box warnings on their labels for serious cardiovascular side effects. (Tr. at 578:20–579:16, 614:18–615:16; PTX-431.0006). Because SLYND® has 4 mg of drospirenone instead of 3 mg, the FDA was worried that the VTE risk for SLYND® would be even higher. (Tr. at 513:10–18, 565:13–566:10; PTX-

[21] Dr. Gersh actually testified that SLYND® has antiandrogenic effects. (Tr. at 279:4–17).

027 at SLYND_0400922–23; PTX-027A.0003–04). Although a POSA today would understand that a drospirenone POP does not cause blood clots because estrogen, not drospirenone, is associated with blood clots, Exeltis has shown that in 2010, drospirenone had a reputation for increasing clotting risk. Ultimately, SLYND®'s Phase III clinical trials did not report any cases of VTE. (Tr. at 570:15–571:10, 578:20–579:1, 610:25–611:5).[22]

Fourth, Exeltis has shown that SLYND® was unexpectedly effective in a larger portion of women than COCs or other POPs. Lupin argues the use of Yaz® shows that the efficacy of drospirenone in high-BMI women was already known. To support this proposition, however, Lupin cites to evidence that does not mention BMI. (D.I. 352 ¶ 64). The only proposed finding of fact that mentions the words "BMI" or "obese" is conclusory and unsupported by any evidence. (*See id.* ¶ 70). Exeltis, on the other hand, points to evidence that oral contraceptives, prior to SLYND®, had a limitation of use due to potentially reduced efficacy in high-BMI women. (Tr. at 571:20–25, 573:9–19). Phase III clinical trials, meanwhile, showed no difference in efficacy between high-BMI women and other women. (Tr. at 571:13–19, 572:13–573:8; PTX-463.0003). Exeltis has shown that this was unexpected.

Thus, in sum, Exeltis has shown unexpected results by a preponderance of the evidence with respect to SLYND®'s lack of cardiovascular risks and its efficacy in women with high BMI.

ii. Long-Felt but Unmet Need

Exeltis argues that many patients, especially ones with cardiovascular risk factors, did not have a suitable option for oral contraceptives in 2010. (D.I. 334 at 11). Even though Exeltis has not shown that SLYND® provided a better bleeding profile than Cerazette®, Exeltis has

[22] In its briefing, Lupin argues that Exeltis has not shown that the small patient population in the clinical trial was sufficient to detect a rare event like VTE. (D.I. 351 at 18). Lupin does not point to any evidence to suggest that the population was too small to be reliable.

established that SLYND® filled the need for "a safe and effective drug with . . . a 24/4 dosing regimen, and a forgiving missed-pill window." (*Id.*). POPs prior to SLYND® did not compete clinically with COCs. (PTX-195.0004; Tr. at 485:3–22, 603:18–604:6, 605:22–24, 606:11–22, 615:17–616:3). Lupin's argument that there is little difference between a twelve-hour missed pill window and a twenty-four-hour missed pill window is contradicted by evidence of patients discontinuing SLYND® at lower rates than Cerazette®. *See Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 964 (Fed. Cir. 2023) ("[T]he district court did not err in determining that, before apremilast, there was a long-felt need for a psoriasis treatment that was suitable for oral administration to a patient without the risks and barriers to adherence that were common with other psoriasis treatments."). I thus conclude that Exeltis has shown a long-felt but unmet need by a preponderance of the evidence.

iii. Skepticism

"Evidence of industry skepticism weighs in favor of non-obviousness. If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016).

Exeltis argues that in April 2011, the FDA did not believe that a 4 mg dose of drospirenone was the optimal or lowest effective dose due to the risk of VTE and hyperkalemia. (Tr. at 513:10–18, 607:1–608:13; PTX-027 at SLYND_0400922). Exeltis contends that even after the data showed SLYND® had a "lower systemic exposure" of drospirenone compared to Yaz®, the FDA stated that any reports of VTE would create a "major review issue." (D.I. 334 at 12). Lupin argues that the FDA was not skeptical about SLYND®'s safety or effectiveness. Lupin argues the FDA instead recommended additional evaluation of higher dosages and

justification for using a 24/4 dosing regimen because SLYND® was filed as a section 505(b)(2) application that relied on the clinical trials of a 3 mg drospirenone product. (D.I. 351 at 19). Lupin argues this does not rise to the level of industry skepticism. (*Id.*). I agree. *Cf. Purdue Pharma L.P. v. Accord Healthcare Inc.*, 669 F. Supp. 3d 286, 306 (D. Del. 2023) (concluding that plaintiffs who only cited to the inventor and the FDA had failed to show industry skepticism), *appeal docketed*, No. 2023-1953 (Fed. Cir. May 30, 2023).

Because I have concluded that the evidence does not rise to the level of teaching away from slow-release drospirenone, Exeltis cannot show industry skepticism based on teaching away. The fact that Exeltis's research and development team put experimental activities on hold for one month until receipt of PK results (Tr. at 467:16–469:19; PTX-234.0004–05) is not evidence of pre-invention *industry* skepticism. *Cf. SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1377 (Fed. Cir. 2013) ("[T]he record shows that even Defendants' engineers were highly skeptical of the claimed invention, at one point describing it as a 'whopper in terms of technical challenge.'").

iv. Industry Praise

Exeltis argues, "SLYND® proved skeptics wrong, demonstrating that slow dissolving drospirenone results in an effective drug with significant clinical benefits." (D.I. 334 at 13). Lupin argues that Exeltis did not present any evidence of industry praise in its opening brief. (D.I. 351 at 19). It is true that Exeltis cites to proposed findings of fact that have no relation to industry praise (D.I. 334 at 13 (citing D.I. 336 ¶¶ 87, 132)), but other proposed findings of fact address the industry's response under the heading "The Industry Praised SLYND® After Launch" (D.I. 336 ¶¶ 108–11). I will not reject the argument because it relies upon the equivalent of a typo.

To the extent that Exeltis relies on testimony from its own witnesses, such as Drs. Colli and Velada, that is not reliable evidence of industry praise. *See In re Cree, Inc.*, 818 F.3d 694, 702 (Fed. Cir. 2016) (stating that "self-serving statements from researchers about their own work do not have the same reliability" as praise in the industry or praise from a competitor). Dr. Shoupe, however, praised SLYND® prior to her involvement with Exeltis. In 2021, Dr. Shoupe wrote, "This high dose drospirenone oral contraceptive pill provides a progestin-only option with good bleeding control without the restricted daily intake 2–3 h time frame." (PTX-195.0004, .0009). Dr. Shoupe called SLYND®'s 24/4 dosing schedule a "big advantage." (PTX-195.0004). As for the Foidart and Barbieri studies, Lupin is incorrect that the studies only discuss the benefits of drospirenone generally. Foidart discussed drospirenone and estetrol, an estrogen, generally. (DTX-140 at 1–2). Foidart, however, largely focuses on two new contraceptives, one of which is SLYND®. Foidart calls SLYND® a "valuable addition[] to the contraceptive market" and states that "DRSP alone [i.e., SLYND®] offers the advantage of no or a low additional VTE risk like with other POPs." (*Id.* at 10). On the other hand, Foidart states,

> However, DRSP alone [i.e., SLYND®] provides a suboptimal bleeding profile even if somewhat better than other POPs thanks to the 24/4 regimen. Indeed, it is associated with a high level of discontinuation, a higher rate of unscheduled bleeding, and a lower rate of scheduled bleeding than combined products.

(*Id.*). Barbieri similarly makes general statements about drospirenone but also includes a comparison of two specific products: SLYND® and Camila, a norethindrone POP. (DTX-326 at 11). Barbieri concludes, "My assessment is that drospirenone has superior contraceptive properties over norethindrone POP." (*Id.* at 12).

Barbieri and Dr. Shoupe thus show praise for SLYND®, even if Foidart makes negative remarks about the product. I conclude that Exeltis has shown weak evidence of industry praise by a preponderance of the evidence.

v. Commercial Success

"Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art. Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention, probative of whether an invention was non-obvious." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). When others are "legally barred from commercially testing" the ideas of the claimed invention, "[f]inancial success is not significantly probative of that question." *Id.* at 1377. Even when commercial embodiments of the invention enjoy commercial success, the "failure to link that commercial success to the features of [the] invention that were not disclosed in [the prior art] undermines the probative force of the evidence." *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Exeltis argues that SLYND® is a commercial success because it is gaining market share in a market where generic oral contraceptives are significantly cheaper. (D.I. 334 at 13). Within four years of its launch, SLYND® ranked second in sales and prescriptions among oral contraceptives. (*Id.*).

Lupin argues that about a 2% market share does not establish commercial success. (D.I. 351 at 21). Lupin contends that Exeltis's revenue share analysis is "unhelpful" because oral contraceptives are largely generic products that cost less, so a revenue share analysis "will be driven more by price differential and less by volume." (*Id.*). Lupin argues that growth does not show commercial success either. (*Id.*).

SLYND® was the fifteenth entrant into the POP market. After four years, it had a 19% market share. I credit Mr. Segers's testimony that a fifteenth entrant would not expect to get

more than at most a 6% to 7% market share. (Tr. at 652:15–653:10). I believe that SLYND®'s acquisition of a substantial market share exceeded expectations and is evidence of commercial success.

SLYND® has also performed well compared to COCs, as it ranked second in sales and prescriptions among the top twenty oral contraceptives after only being on the market for nearly four years. (Tr. at 594:14–596:8). *See Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1361 (Fed. Cir. 1999) ("Although sales figures coupled with market data provide stronger evidence of commercial success, sales figures alone are also evidence of commercial success."). SLYND® is surpassing COCs in revenue share as well (Tr. at 655:21–656:10), and its market share (as defined by prescriptions) relative to the top oral contraceptive, LO LOESTRIN FE®, has reached nearly 30% (Tr. at 653:24–655:5). I also consider that total prescriptions for SLYND® are increasing at 13% per month, and new prescriptions are increasing by 11% per month. (Tr. at 661:2–23). Exeltis has shown compelling evidence of commercial success. Lupin's arguments are unpersuasive to the extent that Lupin criticizes Exeltis for only considering POPs, as Mr. Segers analyzed SLYND®'s success compared to both POPs and COCs. SLYND®'s cost—$190 compared to LO LOESTRIN FE®, which costs about the same, and generic pills that costs between $2 and about $13—further suggests there is a demand for SLYND® despite its price. (Tr. at 662:25–663:10).

In 2023, SLYND®'s market share among oral contraceptives was 2.1%, and its market share among hormonal contraceptives was 1.9%. (Tr. at 800:18–801:3). I think the more relevant data is for the market that consists of SLYND®'s closest competitors, which is the POP market.

Lupin argues that SLYND® is not a commercial success because it lacks profitability. Lupin argues that Dr. McDuff properly conducted a net present value ("NPV") analysis. (D.I. 351 at 21). Exeltis criticizes Lupin for "invent[ing] costs and risks to increase the amount of revenue it says SLYND® must achieve to show profitability." (D.I. 334 at 15). Lupin contends that Exeltis's analysis is flawed because it omits COCs and other hormonal contraceptives from the market analysis.[23]

Mr. Segers testified that Lupin spent $75.2 million to develop SLYND®, but that SLYND®'s revenue exceeds those costs. (Tr. at 663:11–18, 668:5–8). Dr. McDuff offered conflicting testimony, stating that the $75 million cost was too low and did not account for costs Exeltis incurred before 2010. Minutes of a 2008 meeting suggest that Exeltis was already working on a drospirenone-only product at that time. (*See* Tr. at 482:17–483:15, 805:16–806:2; *see also* PTX-133). Dr. McDuff instead considered a development cost of $248 million based on economic literature. (Tr. at 806:7–19). Dr. McDuff concluded that SLYND® is not a commercial success. (Tr. at 807:9–12). As for the risk factor, Lupin argues that its inclusion is standard in a NPV analysis (D.I. 351 at 21), while Exeltis argues that the application of a risk factor fails to account for Exeltis and the FDA having experience with drospirenone prior to 2010 (D.I. 355 at 14).

The parties have presented conflicting testimony regarding the NPV analysis, and neither party cites to any documents or other evidence to support their position. Based on this record, I cannot conclude that the profitability analysis favors Exeltis by a preponderance of the evidence. I nevertheless conclude that Exeltis has shown significant evidence of commercial success based on a combination of market share and sales.

[23] Exeltis disputes this point. (D.I. 355 at 14–15).

vi. Nexus

Lupin argues, "Although nexus can be presumed where a patentee shows the secondary considerations are tied to a product that embodies the asserted claims, that presumption is rebutted on a showing that the secondary considerations resulted from features that were known in the prior art, rather than in the claimed invention." (D.I. 351 at 13 (citing *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1364–65 (Fed. Cir. 2023)). Lupin argues that Exeltis's objective indicia arguments focus on features that were already well-known in 2010, such as the use of drospirenone in a POP and the use of drospirenone doses above 3 mg on a non-continuous dosing schedule. (*Id.* at 13–14).

Exeltis argues that SLYND®'s success is tied to its clinical benefits, which result from the claimed PK and dissolution limitations. (D.I. 334 at 15–18). Lupin argues that the dissolution and PK profiles were not novel, as Davila and Huempel both taught the dissolution limitations and Huempel taught the PK limitations. (D.I. 351 at 14). However, I have already concluded that Davila does not teach the claimed dissolution limitations for a drospirenone POP, and Huempel does not teach the claimed PK limitations.

Lupin's argument that SLYND® does not embody the asserted claims' particle size limitations is unpersuasive. Lupin's expert, Dr. Amiji, opined that the particle size would change after direct compression into a tablet. (Tr. at 792:22–793:4). Lupin did not provide any testing evidence to corroborate that opinion. Dr. Koleng, on the other hand, testified that the particle size for the drospirenone in SLYND® is within the claimed ranges "based on the input API measurement of drospirenone before its tablet." (Tr. at 732:24–733:14, 758:16–759:4; PTX-027H at .0039). Dr. Koleng explained that the particle sizes would not change after the raw

material is formed into a tablet. (Tr. at 758:16–759:4). Absent contrary evidence, I credit Exeltis's data showing that the input API meets the claimed particle sizes.

Lupin's argument that SLYND® is not coextensive with the PK and dissolution limitations fails as well. The evidence shows that the dissolution rate of three SLYND® batches ranged from 16.2% to 47.3% in the first thirty minutes, which reasonably encompasses the claimed range of less than 50%. (PTX-027H.0025). Additionally, the mean C_{max} of three SLYND® batches ranged from 16.89 ng/mL to 22.92 ng/mL, and the mean $AUC_{0h\text{-}tlast}$ of those batches ranged from 441.25 ng*h/mL to 458.21 ng*h/mL. (PTX-027H.0078). These results reasonably encompass the claimed ranges. *See Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) ("Objective evidence of nonobviousness need only be 'reasonably commensurate with the scope of the claims,' and we do not require a patentee to produce objective evidence of nonobviousness for every potential embodiment of the claim.").

Exeltis has thus shown that a presumption of nexus applies. Lupin has failed to rebut that presumption. In sum, Exeltis has shown by a preponderance of the evidence that unexpected results, a long-felt but unmet need, and commercial success support a finding of nonobviousness. Exeltis has also shown weak evidence of industry praise.

IV. CONCLUSION

For the foregoing reasons, I find that Exeltis has proven by a preponderance of the evidence that Lupin infringes claim 14 of the '299 patent, claims 12 and 21 of the '632 patent, claim 29 of the '122 patent, claim 7 of the '249 patent, and claim 19 of the '487 patent. Lupin has failed to prove by clear and convincing evidence that the asserted claims are indefinite. Lupin has also failed to prove by clear and convincing evidence that claim 29 of the '122 patent and claim 7 of the '249 patent are invalid for lack of written description. Lastly, Lupin has failed

to prove by clear and convincing evidence that the six asserted claims are invalid as obvious. Exeltis's evidence regarding objective indicia supports a finding of nonobviousness.

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

Dated: September 4, 2024

/s/ Richard G. Andrews
United States District Judge