IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,

Plaintiff,

v.

MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC.,

Defendants.

Civil Action No. 22-228-RGA
(Consolidated)

TRIAL OPINION

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October 15, 2024

ANDREWS, U.S. DISTRICT JUDGE:

Exelixis, Inc. brought this patent infringement action under 35 U.S.C. §§ 271(a)–(c) and/or (e)(2) and pursuant to the Hatch-Waxman Act codified at 21 U.S.C. § 355 against MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc. ("MSN"). (D.I. 1 ¶¶ 1–2, D.I. 124 ¶ 1). I held a four-day bench trial from October 23 to October 26, 2023.

The asserted patents fall into two groups. The first group consists only of U.S. Patent No. 11,298,349 (the "'349 patent"). Exelixis asserted Claim 3 of the '349 patent. The parties dispute whether MSN infringed Claim 3 of the '349 patent. (D.I. 124 ¶ 6). The parties dispute whether Claim 3 of the '349 patent is invalid as obvious. (*Id.*).

The second group consists of U.S. Patent Nos. 11,091,439 (the "'439 patent"), 11,091,440 (the "'440 patent"), and 11,098,015 (the "'015 patent"). This group is called the Malate Salt Patents; they share an identical specification. (*Id.* ¶ 33). The claims at issue are Claim 4 of the '439 patent, Claim 3 of the '440 patent, and Claim 2 of the '015 patent. (*Id.* ¶ 6). MSN stipulated to the infringement of the asserted claims of the Malate Salt Patents. (D.I. 23). The parties dispute whether the asserted claims of the Malate Salt Patents are invalid for lack of written description and obviousness-type double patenting.

For the following reasons, I find Claim 3 of the '349 patent not infringed and not invalid. I find the asserted claims of the Malate Salt Patents not invalid.

I. BACKGROUND

MSN submitted Abbreviated New Drug Application ("ANDA") No. 213878 to the U.S. Food and Drug Administration ("FDA"), seeking approval to manufacture and sell a generic version of Cabometyx, a cancer drug made by Exelixis (the "MSN ANDA Product"). (D.I. 1 ¶ 1).

Exelixis brought a complaint, alleging MSN infringed the Malate Salt Patents. (D.I. 1 ¶¶ 28–56). Exelixis had filed a separate action against MSN, alleging infringement of the '349 patent. (D.I. 34)[1]. The two actions are consolidated into the present case. (*Id.*).

The asserted Malate Salt Patent claims require a cabozantinib malate salt that is crystalline. ('439 patent at 32:22–24, 32:28–36; '440 patent at 32:16–21; '015 patent at 32:11–16). The '349 patent is directed to a pharmaceutical composition of cabozantinib (L)-malate that includes certain classes of excipients and is free of a harmful genotoxic impurity. ('349 patent at 34:30–51).

Exelixis sells Cabometyx and Cometriq. Cabometyx is indicated for the treatment of kidney cancer, liver cancer, and differentiated thyroid cancer. (D.I. 124-1 at 9 of 314). Exelixis markets capsules comprising cabozantinib (S)-malate[2] in the United States under the trade name Cometriq. (*Id.*). Cometriq is indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer. (*Id.* at 10 of 314). The active pharmaceutical ingredient ("API") in Cabometyx and Cometriq is the (L)-malate salt of cabozantinib. (*Id.* at 7–8 of 314).

The Malate Salt Patents and the '349 patent have been listed in connection with Cabometyx in the FDA's Orange Book. (*Id.* at 10 of 314).[3]

II. LEGAL STANDARD

A. Infringement

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any

[1] The complaint for the '349 patent is filed in case number 22-945. The complaint was filed before the actions were consolidated into the present case.

[2] Dr. Shah testified that (S)-malate and (L)-malate are the same type of salt. The (S) and (L) refer to different naming conventions. (Tr. 589:9–13).

patented invention during the term of the patent." 35 U.S.C. § 271(a). Determining infringement is a two-step analysis. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *Id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *Id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). The patent owner bears the burden of proving infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab'ys Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

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

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To prevail on a claim of induced infringement, the plaintiff must show (1) "that there has been direct infringement," and (2) "that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018) (cleaned up). In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted

claim]." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018).

B. Written Description

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

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

C. 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) (internal citations and quotation marks omitted). "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 (internal citation and quotation marks omitted).

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

D. Obviousness-Type Double Patenting

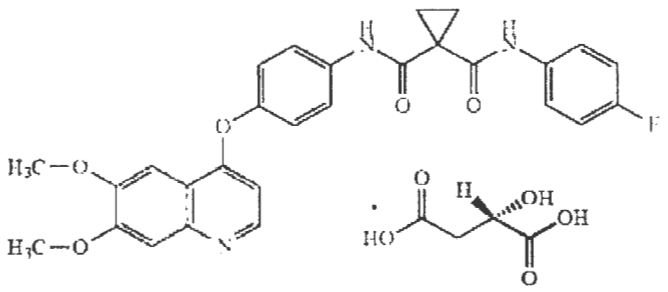
Generally, an obviousness-type double patenting analysis entails two steps. First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences. *Georgia–Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999). Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct. *Id.* at 1327. A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obviousness-type double patenting. *In re Berg*, 140 F.3d 1428, 1431 (Fed. Cir. 1998). A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim. *Eli Lilly & Co. v. Barr Lab'ys, Inc.*, 251 F.3d 955, 968

(Fed. Cir. 2001). Objective indicia (that is, secondary considerations) of non-obviousness must be considered in an obviousness-type double patenting analysis. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1381 (Fed. Cir. 2012).

III. INFRINGEMENT

A. The Asserted Claim

The parties dispute whether MSN's ANDA Products infringe Claim 3 of the '349 patent. Claim 3 recites:

> A pharmaceutical composition for oral administration comprising Compound IB;
>
> IB
>
> 
>
> one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and;
>
> wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.

('349 patent at 34:30–51).[4]

B. Findings of Fact

1. A glidant is a material that improves the flow of a drug powder mixture. (Tr. 60:2–4, 82:9–11, 230:16–19).[5]

[4] The parties refer to "6,7-dimethoxy-quinoline-4-ol" as the "1-1 impurity." I will also refer to it as such.

[5] "Tr." refers to the trial transcript. (D.I. 161, 162, 163, 164). It is consecutively paginated.

2. A diluent can affect the flow properties of a mixture. (Tr. 194:21–195:6, 227:10–228:3).

3. An excipient can have multiple functions. (Tr. 77:3–8, 179:25–180:4, 247:12–13). An excipient can be both a glidant and a diluent. (Tr. 77:3–8, 93:2–6, 247:12–22).

4. Neither the claims nor the specification of the '349 patent state that a glidant must improve flow through specific mechanisms. ('349 patent; Tr. 116:17–25).

5. Remington and Swarbrick are two authorities on pharmaceutical compositions cited in the '349 patent specification. ('349 patent at 20:40–49). Remington defines glidant as "a substance that improves the flow characteristics of a powder mixture." (PTX-572A at 13 of 48). Swarbrick states that "glidant excipients improve the flow characteristics of tablet granulations (and capsule powder blends)." (PTX-394 at 26 of 69).

6. The cabozantinib (L)-malate API exhibits poor flow properties. (Tr. 60:16–24, 89:5–16; DTX-215 at 34 of 116).

7. GRASTAR is a starch derivative known as granulated corn starch. (Tr. 86:5–11, 96:6–7).

8. Glidants are typically added after wet granulation, during the pre-lubrication step. (Tr. 83:5–84:3, 228:19–23). MSN adds GRASTAR in its ANDA products during the pre-lubrication step, just prior to compression. (Tr. 86:12–16). Exelixis adds a glidant during the pre-lubrication step after wet granulation in manufacturing Cabometyx. (Tr. 609:15–21, 610:10–23). MSN adds GRASTAR in its manufacturing process at the same step that glidants are typically added. (Tr. 104:10–17, DTX-215 at 97–98 of 116).

9. Disintegrants, fillers, and other ingredients can also be added at the pre-lubrication stage of manufacturing. (Tr. 142:9–22, 228:14–229:10).

10. MSN adds GRASTAR at a concentration of 9.71% of the total drug mixture. (Tr. 105:18–21, 201:21–22). The scientific literature discloses that the typical concentration range for a starch glidant is between 1 and 10.0%. (Tr. 97:24–98:7, 232:24–233:11). 9.71% is also consistent with what the scientific literature reports for potential use of granulated corn starch as a filler in pharmaceutical compositions. (Tr. 201:21–202:4, DTX-275 at 754, 790 of 945).

11. MSN submitted a Pharmaceutical Development Report ("PDR") to the FDA. (DTX-215). In the Initial Risk Assessment portion of the PDR, MSN includes a table of different drug substances. (DTX-215 at 36 of 116). MSN states "Granulated Corn Starch is used as a diluent in minimal concentration and it enhances the flowability of the granules." (*Id.*). This type of table is usually prepared after the core formulation is identified. (Tr. 91:9–25). This assessment is usually performed before formulation development starts to direct and prioritize evaluating a formulation. (Tr. 227:2–9).

12. To justify its manufacturing process selection, MSN told the FDA in its PDR that the process of choice was wet granulation over direct compression after stating it is evident the API exhibits poor flow properties. (DTX-215 at 34 of 116).

13. In the Formula Optimization Section of PDR, MSN states, "The level of Granulated [C]orn Starch plays an important role in flow characteristics." (DTX-215 at 58 of 116).

14. In MSN's Justification for Microbial Method Validation, MSN wrote "Starch are used in pharmaceutical industry for a wide variety of reasons, such as an excipient in tablet and capsule as a diluent, as a glidant or as binder." (PTX-724 at 2 of 3, Tr. 101:3–7).

15. GRASTAR's manufacturer conducted testing on GRASTAR which showed that GRASTAR has better flowability than Japanese Corn Starch. (Tr. 119:25–120:15). The testing showed that GRASTAR improved flowability of fenofibrate, another drug substance, more than Japanese Corn Starch did. (Tr. 119:15–121:23). GRASTAR's manufacturer says that GRASTAR has excellent oral disintegration properties, and lists filler as one of the functions of GRASTAR. (Tr. 164:1–18). The manufacturer does not identify GRASTAR as a glidant in any literature. (Tr. 164:16–18).

16. MSN told the FDA that GRASTAR improves flow. (FOF ¶¶ 12–15).

17. The changes to MSN's excipients during formulation development, including the substitution of maize starch B with GRASTAR, were focused on the disintegration and dissolution properties of its tablets. (Tr. 210:1–211:16, 212:1–5).

18. Whether GRASTAR acts as a glidant in a particular pharmaceutical composition depends on the pharmaceutical composition. Dr. Koleng concedes that both unmodified and pregelatinized starches can serve as fillers in pharmaceutical formulations without also being glidants. (Tr. 155:7–156:15). Dr. Nithiyanandam testified that whether GRASTAR will actually improve flow depends on the specific formulation in which GRASTAR is used. (Tr. 61:17–62:9).

19. The literature identifies that granulated corn starch is a commonly used glidant. (Tr. 95:13–96:7).

20. Swarbrick identifies starch and its derivatives as commonly used glidants (Tr. 95:13–96:7). Granulated corn starch is a starch derivative. (*Id.*).

21. The Lachman reference states that starch and starch 1500, which is pregelatinized corn starch, are "commonly used glidants." (PTX-553A at 197–98 of 611; Tr. 96:11–97:19). Dr. Koleng testified that granulated corn starch is pregelatinized corn starch. (Tr. 97:11–19).

22. MSN's lab notebook data that purportedly shows GRASTAR does not improve flow is unreliable. (DTX-196). The Hausner Ratio and Carr Index for the GRASTAR batch were incorrectly calculated from the recorded bulk density and "tapped density."[6] (Tr. 139:1–141:9). It is unclear if the error was in the recorded bulk density and tapped density or the calculated Hausner Ratio and Carr Index. (Tr. 107:12–18).

23. MSN's ANDA does not infringe Claim 3 of the '349 patent.

C. Conclusions of Law

1. Definition of Glidant

The parties agree that MSN's ANDA Products meet all the claim limitations of Claim 3 other than "comprising . . . one or more glidants." (D.I. 149-1 ¶¶ 65–70; '349 patent at 34:30–51). The only disputed issue, therefore, is whether MSN's ANDA Products include a glidant such that MSN's ANDA Products infringe Claim 3 of the '349 patent.

The parties dispute the definition of a glidant. Exelixis defines glidant as "a material that improves the flow of a drug powder mixture." (D.I. 167 at 5). MSN defines glidant as a material that improves flow of a powder blend through five specific mechanisms: "(1) coating/adherence; (2) adsorbing fine particles; (3) reducing electrostatic forces; (4) adsorbing environmental gases; and (5) reducing van der Waals forces." (D.I. 173 at 4). These are the only two definitions the parties proposed.

The parties did not ask me to construe glidant, or any term in the '349 patent. (D.I. 53). Therefore, "glidant" is given its plain and ordinary meaning. "[T]he 'ordinary meaning' of a

[6] "Tapped density" is not defined in the trial record. (D.I. 183 at 1). After I issued an oral order asking the parties if "tapped density" was defined in the record, MSN asked me to take judicial notice of the US Pharmacopeia's definitions of "tapped density" and "bulk density." (D.I. 184 at 1). I decline to do so. It is in my discretion whether to reopen the record. *Zenith Radio Corp. v. Hazeltine Rsch.*, 401 U.S. 321, 331 (1971). The definitions may be subject to "reasonable dispute" and, indeed, Exelixis has opposed MSN's request. FED. R. EVID. 201(b); (D.I. 185 at 1). The definitions are not material to this case or my decision. For these reasons, I exercise my discretion to decline to reopen the record and take judicial notice of the definitions.

claim term is its meaning to the ordinary artisan after reading the entire patent." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1321 (Fed. Cir. 2005). "[I]ntrinsic evidence is the most significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

I agree with Exelixis that a glidant is "a material that improves the flow of a drug powder mixture." As Exelixis argues, neither the claims nor specification of the '349 patent state that a glidant must improve flow through specific mechanisms. Dr. Koleng testified that after reviewing the patent, he could not find any "mechanism requirement" for something to be a glidant. (Tr. 116:17–19). Dr. Koleng further testified that neither Claim 3 of the '349 patent nor its specification references a particular mechanism for a glidant. (Tr. 116:20–25). The intrinsic evidence supports that the definition of a glidant does not need to include the mechanism of action.

Exelixis also cites extrinsic evidence to support its definition. The Remington and Swarbrick references define a glidant as a substance or excipient that improves flow of a powder mixture or tablet granulations. (Tr. 231:14–232:20). Neither reference states that an excipient is a glidant only if it functions through specified mechanisms. Furthermore, Dr. Donovan, Dr. Koleng, and Mr. Nithiyanandam all testified that a glidant is a chemical that improves the flow characteristics of a powder blend. (Tr. 82:9–11, 230:16–19, 60:2–4).

MSN presents only extrinsic evidence to support its contention that the definition of a glidant includes a mechanism of action. But extrinsic evidence is disfavored when intrinsic evidence is available. *Phillips*, 415 F.3d at 1317. ("[W]hile extrinsic evidence can shed useful light on the relevant art, we have explained that it is less significant than the intrinsic record in determining the legally operative meaning of claim language." (internal citations and quotations

omitted)). I do not understand the Lachman reference to disclose that a glidant must use a particular mechanism. The Lachman reference states only that "the mechanisms of action of a glidant have been hypothesized," then list several mechanisms. (PTX-553 at 136 of 611). The only reference MSN cites that indicates glidants function through specific mechanisms is the Swarbrick reference, which states, "Glidant excipients are usually added to improve flowability of powder blends and granulations through one or more of several proposed physical mechanisms [listing mechanisms]." (PTX-394 at 33–34 of 69). But Swarbrick earlier defines glidant without reference to mechanisms. (*Id.* at 26 of 69). Swarbrick's characterization of the mechanisms as "proposed" indicates that these mechanisms might not be the complete list of how a glidant works. MSN's extrinsic evidence does not persuade me that the definition of a glidant should include specific mechanisms of action.

MSN argues that a POSA would not find every material that improves flow to be a glidant. (D.I. 173 at 15). Dr. Donovan testified that a POSA would not consider every excipient that has any positive impact on powder flow to be a glidant. (Tr. 198:24–199:3, 254:19–255:2). But in defining glidant, I must consider the extrinsic evidence in the context of the intrinsic evidence. *Phillips*, 415 F.3d at 1319. Because the patent does not limit the definition of a glidant to certain mechanisms, the intrinsic evidence suggests the definition of glidant is broader than the definition MSN argues the extrinsic evidence advances. "[E]xtrinsic evidence . . . may not be used to vary, contradict, expand, or limit the claim language from how it is defined, even implicitly, in the specification." *Dow Chem. Co. v. Sumitomo Chem. Co.*, 257 F.3d 1364, 1373 (Fed. Cir. 2001). I am not persuaded by Dr. Donovan's testimony because the intrinsic evidence never mentions that glidants use particular mechanisms. I agree with Dr. Koleng, who testified that any material that improves flow is a glidant. (Tr. 128:21–24).

MSN argues that a diluent can affect the flow properties of a mixture. I agree, but I do not think the argument helps MSN. An excipient can have multiple functions. (Tr. 77:3–8, 179:25–180:4, 247:12–13). For example, an excipient can be both a glidant and a diluent. (Tr. 77:3–8, 93:2–6, 247:12–22). If an excipient is a diluent, that does not mean it is not also a glidant.

MSN argues that defining glidant as any material that improves flow is too broad because then "at least half—if not all" excipients that are added to a poorly flowing mixture would be a glidant. (D.I. 173 at 17). MSN does not cite to any evidence in the record in support of the "at least half—if not all" argument. (*Id.*). I therefore disregard this argument.

I define glidant as "a material that improves the flow of a drug powder mixture."

2. Direct Infringement

With this definition of glidant in mind, I now turn to the evidence presented regarding whether the ANDA product has a glidant. The dispute concerns GRASTAR, which is added to the ANDA product at the pre-lubrication step. (FOF ¶ 8). Exelixis argues GRASTAR is a glidant, whereas MSN argues GRASTAR is a diluent, not a glidant. (D.I 167 at 6, D.I. 173 at 11–12). Because an excipient can be both a glidant and a diluent, I do not consider persuasive MSN's arguments that GRASTAR is a diluent. And since I have defined glidant as "a material that improves the flow of a drug powder mixture," I focus my analysis on arguments relating to whether GRASTAR improves flow of the drug powder mixture.

MSN presented data from a laboratory notebook that purportedly shows that GRASTAR does not improve flow. (D.I. 173 at 8). MSN argues that therefore, GRASTAR is not a glidant. (*Id.*). The experiment in the laboratory notebook tested which of two different formulations of the cabozantinib API had better flow. (DTX-196 at 46, 84 of 175). The two formulations were the same, except that one formulation (Batch 252/023) included 30 mg/unit of GRASTAR and

the other (Batch 252/044) included 30 mg/unit of unmodified corn starch. (Tr. 134:11–21, 135:19–136:6, 210:1–21). The notebook contained experimentally determined values for bulk density and tapped density for each batch. (Tr. 135:15–137:1). From the bulk density and tapped density, the Hausner Ratio and Carr Index, two numerical values that characterize powder flow, were calculated. (*Id.*). I disregard this data because, for two reasons, I find it unreliable.

First, there was an error in the laboratory notebook that makes the data unreliable. Dr. Koleng testified that the Hausner Ratio and Carr Index for the GRASTAR batch were incorrectly calculated from the recorded bulk density and tapped density. (Tr. 139:1–141:4). The parties agree that the correctly calculated Hausner Ratio and Carr Index, from the recorded bulk density and tapped density, would indicate that GRASTAR decreases flow. (Tr. 139:19–140:9; D.I. 173 at 10). MSN would have me disregard the computational error and use the correctly calculated Hausner ratio and Carr Index to conclude that GRASTAR does not improve the flow of the cabozantinib API. I agree, however, with Exelixis that the error puts into question the validity of the whole experiment. It is unclear whether the recorded bulk density and tapped density are correct, or whether the Hausner Ratio and Carr Index were correct but the bulk and tapped density were recorded incorrectly. While MSN assumes the recorded densities are correct, neither party introduced evidence of the origin of the error. Dr. Koleng disregarded the totality of the laboratory notebook because he found "[t]he source of th[e] disparity could not be identified within the context of the documents provided." (Tr. 107:16–18). I agree that the lab notebook should not be taken into consideration. *See Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 2018 WL 6011697, at *9 (D. Del. Nov. 15, 2018) (giving little weight to a set of results because the laboratory notebook documenting the test offered insufficient detail); *In re Johnson & Johnson Talcum Powder Prod. Mktg., Sales Pracs. & Prod. Litig.*, 509 F. Supp. 3d 116, 147

(D.N.J. 2020) (stating that computation errors in a lab notebook may impact the weight that a factfinder gives to the lab notebook).

Second, I do not think the lab notebook shows what it sets out to show: that GRASTAR does not improve flow and therefore is not a glidant. At trial, I asked counsel for MSN what is shown by comparing the flow of two formulations with two purported glidants. (Tr. 1046:3–7). I thought then, as I do now, that the relevant testing would have been comparing the flow properties of a formulation with GRASTAR and a formulation without GRASTAR. (Tr. 1046:15–17). The only information to take away from the lab notebook, if I accept the corrected Hausner ratio and Carr Index, is that corn starch improves flow more than GRASTAR does. (Tr. 1046:3–7). But this does not eliminate the possibility that GRASTAR is also a glidant, albeit a worse one than unmodified corn starch.

MSN argues that Dr. Koleng relied on the MSN lab notebook to opine that GRASTAR is a glidant when he thought the batch with GRASTAR had a lower Hausner Ratio and Carr Index, thus indicating GRASTAR improved flow. (D.I. 173 at 11). MSN argues that Dr. Koleng cannot now disregard the lab notebook data he was willing to use when it supported his conclusion that GRASTAR is a glidant. (*Id.*). But Dr. Koleng was relying on the lab notebook only at the time when he thought the underlying data was accurate. (Tr. 135:1–18). When notified that there were errors, Dr. Koleng disregarded the lab notebook. (Tr. 107:16–18).

Exelixis presents two arguments for why GRASTAR is a glidant. First, Exelixis argues that GRASTAR is a glidant because it is added at the same time and concentration (9.71%) that a glidant would be added in manufacturing. (D.I. 167 at 7–8). GRASTAR is added at the pre-lubrication step. (*Id.*). The literature confirms that this is the step when glidants are added and is the same step when Exelixis adds its glidant in its manufacturing process. (Tr. 83:23–84:3). But

Dr. Donovan and Dr. Koleng testified that other excipients, such as disintegrants and fillers, can also be added at the pre-lubrication step. (Tr. 142:9–22, 228:14–229:10). Dr. Donovan testified that a concentration of GRASTAR of 9.71% is consistent with the use of GRASTAR as a filler. (Tr. 201:21–202:4). Because MSN has shown that other excipients could be added at the pre-lubrication step and at a concentration of 9.71%, this evidence does not show that GRASTAR is a glidant.

Second, Exelixis cites several statements that GRASTAR improves flow to argue it is a glidant.

- Exelixis argues that because MSN told the FDA that GRASTAR improves flow, it is a glidant. (D.I. 167 at 8). Specifically, MSN told the FDA in its Initial Risk Assessment that granulated corn starch enhances the flowability of the granules. MSN argues that this statement is out of context. (*Id.* at 9). Dr. Donovan testified that the Initial Risk Assessment is usually performed before formulation development starts to direct and prioritize evaluating a formulation. (Tr. 227:2–9). Therefore, MSN argues, there is no experimental evidence that GRASTAR improved flow in the final formulation. (D.I. 173 at 7). Dr. Nithiyanandam testified that this was written based on the scientific literature before formulation development trials started. (Tr. 61:17–62:2). Dr. Nithiyanandam also testified that whether GRASTAR will actually improve flow depends on the specific formulation in which GRASTAR is used. (Tr. 62:4–9). I am persuaded by Dr. Nithiyanandam's testimony and agree that MSN's statement to the FDA does not establish that GRASTAR improves flow in MSN's formulation.

- MSN told the FDA that the level of granulated corn starch plays an important role in flow characteristics. (D.I. 167 at 8–9). Dr. Nithiyanandam testified that the context of this statement was testing dissolution profiles of cabozantinib tablets with different weight percentages of granulated corn starch. (Tr. 63:15–64:5). Dr. Nithiyanandam explained that the statement was based more on the dissolution profile of granulated corn starch rather than the flow properties of granulated corn starch. (*Id.*). Dr. Donovan explained that no flow testing was conducted in support of the statement. (Tr. 214:25–215:8). I am persuaded that the statement does not establish that GRASTAR improves flow in MSN's formulation.
- Exelixis cites Swarbrick and Lachman as identifying granulated corn starch as a commonly used glidant. (D.I. 167 at 11).
- Exelixis points to testing by GRASTAR's manufacturer. (D.I. 167 at 10). The manufacturer concluded that GRASTAR has better flowability than Japanese corn starch when both were tested using fenofibrate as the drug substance. (*Id.*).
- Dr. Donovan testified that GRASTAR would "be expected, even before experiments, to potentially enhance the flowability of the granules." (Tr. 237:7–9).
- Dr. Donovan testified that GRASTAR "had good flow properties so it would be expected that the addition of GRASTAR could improve the flow properties." (Tr. 217:21–23).

The statements show that GRASTAR can be used as a glidant, because they show that GRASTAR does improve flow in some contexts. For example, GRASTAR improves the flow of fenofibrate. (Tr. 120:12–15). And I am persuaded that the literature explains that GRASTAR is a

commonly used glidant. But there is no evidence that GRASTAR improves the flow of the API in this formulation. A glidant is "a material that improves the flow of a drug powder mixture." But if GRASTAR is not improving the flow of this powder mixture, then it is not acting as a glidant in MSN's ANDA Product. Whether GRASTAR acts as a glidant in a particular pharmaceutical composition depends on the pharmaceutical composition.

The statements Exelixis cites, including the statements made to the FDA, do not pertain to MSN's pharmaceutical composition. The only evidence somewhat relating to MSN's pharmaceutical composition is that Dr. Donovan testified that GRASTAR would "be expected, even before experiments, to *potentially* enhance the flowability of the granules." (Tr. 237:7–9) (emphasis added).

Exelixis argues that it does not need to present direct evidence of testing to prove infringement. (D.I. 178 at 5). I take Exelixis to be arguing that Exelixis does not need to present experimental evidence that GRASTAR improved flow in MSN's ANDA product. Exelixis cites to *C R Bard Inc. v. AngioDynamics, Inc.*, 979 F.3d 1372, 1379 (Fed. Cir. 2020). I find *Bard* instructive. There, the Federal Circuit held that, on a motion for judgment as a matter of law, the plaintiff did not need to test the defendant's product to show that it infringed but could rely on the defendant's "statements to the FDA regarding the product's capabilities." *Id.* at 1378–79. The Federal Circuit held that "statements regarding the capabilities of [the defendant's] own product constituted substantial evidence of those capabilities." *Id.* at 1379. To be sure, the standard for JMOL, substantial evidence, is harder to meet than the preponderance standard for infringement. But here, the evidence is slight. MSN did not present statements to the FDA regarding its product's capabilities. I cannot find that Exelixis met its burden based on Dr. Donovan's one equivocal statement about "potential" enhancement.

Exelixis has not met its burden to show there is a glidant in MSN's ANDA products, because it did not show by a preponderance of the evidence that GRASTAR is improving flow in MSN's ANDA products. I find MSN did not directly infringe the '349 patent.

3. Induced Infringement

Because I have found that Exelixis did not prove direct infringement of the '349 patent, it follows that Exelixis did not prove any indirect infringement of the '349 patent. *See Meyer Intell. Props. Ltd. v. Bodum, Inc.*, 690 F.3d 1354, 1366 (Fed. Cir. 2012) ("It is well-established that a finding of direct infringement is a prerequisite to a finding of inducement.").

IV. INVALIDITY

The parties dispute whether Claim 3 of the '349 patent is invalid for obviousness.

The parties dispute whether the asserted claims of the Malate Salt Patents are invalid for written description and obviousness-type double patenting. The Malate Salt Patents share a common specification. (D.I. 124 ¶ 33). The three asserted claims of the Malate Salt Patents (and the claims from which they depend) are reproduced below:

1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is crystalline.

('439 patent at 32:22–24).

3. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is the (L)-malate salt or (D)-malate salt.

('439 patent at 32:29–32).

4. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (L)-malate salt.

('439 patent at 32:33–36).

3. A pharmaceutical composition comprising the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or (D)-malate salt and wherein said salt is crystalline; and a pharmaceutically acceptable excipient.

('440 patent at 32:16–21).

1. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, and wherein said salt is crystalline.

('015 patent at 32:5–10).

2. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, said salt is crystalline, and said cancer is kidney cancer.

('015 patent at 32:11–16).

V. WRITTEN DESCRIPTION

MSN argues that the Malate Salt Patents are invalid for lack of written description. (D.I. 169 at 5). Exelixis argues that the Malate Salt Patents have adequate written description. (D.I. 175 at 4).

A. Findings of Fact

1. Crystalline is used as an adjective to describe that the cabozantinib (L)-malate has a "regular repeating underlying arrangement of molecules." (Tr. 537:22–25).

2. Solid matter can exist as amorphous or crystalline material. (Tr. 846:4–19). Amorphous material is not crystalline. (Tr. 535:16–19, 846:4–19, 853:7–15). A POSA could distinguish between crystalline and amorphous cabozantinib. (Tr. 542:10–25, 846:4–19, 856:6–24, 866:10–867:3).

3. A salt cannot be crystalline without existing in a specific crystalline form (Tr. 440:21–22, 560:13–19).

4. "[A]ll crystalline cabozantinib (L)-malate salts fall within [the] scope" of the asserted claims. (Tr. 558:5–6).

5. The maximum potential size of any pure polymorph genus is fourteen forms. (Tr. 547:2–5).

6. There are three identified species in the genus of crystalline cabozantinib (L)-malate. These are Exelixis' N-1 and N-2 and MSN's form S. (Tr. 455:5:24). There may be up to seven additional identified species in the genus of crystalline cabozantinib (L)-malate salts. These are Mylan's M-2, M-3, and M-4 and Cipla's C-2, C-3, C-4, and C-5. (Tr. 455:5–456:12). There may be one identified primarily-amorphous species of cabozantinib (L)-malate: Mylan's form M-1. (Tr. 865:6–866:1).

7. The specification discloses structural features shared by all crystalline cabozantinib (L)-malate, including chemical name, formula, and structure. ('439 patent at Abstract, 1:26–39, 2:58–3:12, 5:25–6:67; Tr. 866:10–867:3). The specification disclosed two methods of preparation for crystalline cabozantinib (L)-malate, namely, methods of preparing the N-1 and N-2 form. ('439 patent at 18:59–23:60, Tr. 539:10–25).

8. The Malate Salt Patent inventors did not invent any crystalline form of cabozantinib (L)-malate other than Forms N-1 and N-2. (Tr. 902:11–18).

9. The word "form" does not appear in the asserted claims of the Malate Salt Patents. (Tr. 854:22–25).

10. MSN has not proved by clear and convincing evidence that the Malate Salt Patents lack sufficient written description.

B. Legal Conclusions

1. Genus

As an initial matter, the parties dispute whether the Malate Salt Patents claim a genus of crystalline cabozantinib (L)-malate. MSN contends they do. (D.I. 169 at 4–5). Exelixis argues that the Malate Salt Patents do not claim a genus of crystalline cabozantinib (L)-malate. (D.I. 175 at 1). The parties dispute the size of the genus. Exelixis contends the genus consists of three species, whereas MSN argues the genus is eleven species.[7] (D.I. 169 at 8; D.I. 175 at 4–5).

[7] I do not determine the size of the genus because, as explained in the analysis, it does not need to be resolved.

Exelixis presents three arguments for why the claims do not claim a genus of polymorphic forms of crystalline cabozantinib (L)-malate. First, Exelixis argues that "crystalline" is used as an adjective to describe that the cabozantinib (L)-malate has a "regular repeating underlying arrangement of molecules." (Tr. 537:22–25; D.I. 175 at 10–11). Exelixis does not explain why the use of crystalline as an adjective means the patents do not claim the genus of crystalline cabozantinib (L)-malate. I therefore reject this argument.

Second, Exelixis argues that because the word "form" is not used in the asserted claims, "crystalline" refers to the property of crystallinity, not to specific polymorphic forms. (D.I. 175 at 11). But a salt cannot be crystalline without existing in a specific crystalline form. (Tr. 440:21–22, 560:13–19). The two go hand-in-hand. The claims may not use the word form, but this does not change that using the term "crystalline" means what is claimed is all the "particular polymorph[s]" or "repeating pattern[s]" of the cabozantinib (L)-malate. (Tr. 852:6–7). I therefore reject this argument.

Third, Exelixis argues that because the specification states that N-1 and N-2 are separate disclosures, the Malate Salt Patents do not claim a genus of crystalline polymorphic forms. (D.I. 175 at 11–12, Tr. 851:21–852:16). But what is claimed by a patent reciting "crystalline cabozantinib (L)-malate [i.e., Compound (I)]" if not the genus of crystalline cabozantinib (L)-malate? (Tr. 851:21–852:16). Exelixis does not ask me to limit the claims directed to crystalline cabozantinib (L)-malate to only forms N-1 and N-2. That Exelixis characterizes N-1 and N-2 as separate disclosures does not change that crystalline cabozantinib (L)-malate is the genus.

A genus claim is a "claim[] covering a class of entities characterized by a common property." Jeffrey A. Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 BERKELEY TECH. L.J. 1141, 1168 (2008). Dr. Steed testified that "all crystalline cabozantinib

(L)-malate salts fall within [the] scope" of the asserted claims. (Tr. 558:5–6). I agree. The claims at issue are genus claims, covering the genus of cabozantinb (L)-malate salts that are characterized by the common property of being crystalline.

2. Analysis

I turn to the question of whether the asserted claims have adequate written description. The parties agree that Exelixis possessed at least two species in the genus of crystalline cabozantinib L malate: N-1 and N-2. (D.I. 169 at 1). N-1 and N-2 are the only forms disclosed in the specification. (Tr. 902:11–18).

Exelixis can satisfy the written description requirement in one of two ways. First, forms N-1 and N-2 could be a "representative number of species falling within the scope of the genus." *Ariad*, 598 F.3d at 1350. Second, the specification could disclose "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." *Id.* (internal citations and quotations omitted). I find that Exelixis satisfies the written description requirement the second way.

I agree with Exelixis that *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725 (Fed. Cir. 2014) [hereinafter *GSK*] is instructive. In *GSK*, the Federal Circuit held that the claims to solvates of dutasteride were adequately described by the patent. *Id.* at 729. The court held, "Describing a complex of dutasteride and solvent molecules is an identification of structural features commonly possessed by members of the genus that distinguish them from others, allowing one of skill in the art to visualize or recognize the identity of the members of the genus." *Id.* at 730 (cleaned up). The Federal Circuit explained that dutasteride was the key structural component of the solvate complex, and that the description was further narrowed by the requirement that the structure must result from one or any of three processes: reaction,

precipitation, or crystallization. *Id.* Critical to the Federal Circuit's finding was that "the claim term at issue, 'solvate,' is not functional." *Id.* at 731. The written description for "solvate" thus did not need to meet the more rigorous requirements for written description in support of functional claim language. *Id.*

Here, the claims are directed to crystalline cabozantinib (L)-malate salts. Disclosing the chemical name and formula of cabozantinib (L)-malate, as well as that the structure is crystalline, is "an identification of structural features commonly possessed by members of the genus." *Id.* at 730. The specification also discloses processes used to make the invention. The specification discloses general methods of forming a crystalline salt. ('439 patent at 17:10–18:57). And the specification discloses two methods of preparation for crystalline cabozantinib (L)-malate, namely, methods of preparing the N-1 and N-2 form. ('439 patent at 18:59–23:60, Tr. 539:16–25).

As in *GSK*, the limitation at issue here is structural, not functional. Neither party disputes that crystalline is a structural limitation. Although there are different crystalline polymorphs of cabozantinib (L)-malate, the claims "involve[] no performance property . . . and hence raises no issue of insufficient structural, creation-process, or other descriptions to support such a property." *GSK*, 744 F.3d at 729–30.

Merck is another example in which a court found claims with no functional limitations to be adequately described. *Merck Sharp & Dohme, LLC v. Mylan Pharms. Inc.*, 2022 WL 22855168 (N.D. W.Va. Oct. 26, 2022). "[T]he asserted claims cover[ed] a genus of all forms of the 1-to-1 DHP salt of sitagliptin, including hydrates." *Id.* at *36. At issue was whether Merck possessed the genus of all hydrates of the 1-to-1 DHP salt of sitagliptin, because Merck only possessed and disclosed one species along with its chemical formula and structure. *Id.* However,

the court found there was adequate written description because the "key structural feature of th[e] genus is its unique chemical formula, or structure." *Id.* The court concluded it "need not address whether Merck also disclosed a representative number of species" since it found adequate written description satisfied by Merck disclosing the key features of the genus. *Id.* at *37.

Here too, the key feature of the genus is the chemical formula and structure of crystalline cabozantinib (L)-malate. All crystalline cabozantinib malate share the same chemical name and formula. (Tr. 558:24–559:3). A POSA would be able to identify whether the structure of a polymorph is crystalline. (Tr. 542:10–25, 846:4–19, 856:6–24, 866:10–867:3). And a POSA could distinguish between crystalline and amorphous cabozantinib. (Tr. 542:10–25, 846:4–19, 856:6–24, 866:10–867:3). This evidence was sufficient for the court in *Merck* to find adequate written description, and I find it is sufficient here.[8] Since this evidence is sufficient to satisfy written description, I need not determine the size of the genus and whether Exelixis disclosed a representative number of species.

MSN argues that N-1 and N-2 have different crystal structures and physico-chemical properties than the other reported forms. (D.I. 169 at 8). MSN contends that crystalline forms generally have "different densities, melting points, solubilities, hygroscopicity, vapor pressure, and stability." (*Id.*). MSN argues that the properties of one crystalline form cannot be used to

[8] The *Merck* court cited expert testimony at trial to explain why the key feature of the genus was the chemical formula or structure. *Merck*, 2022 WL 22855168, at *36. The court cited testimony that "every form of the DHP salt of sitagliptin, whether hydrous or anhydrous, shares the common chemical formula disclosed in the . . . patent." *Id.* The court further cited expert testimony, "Based on this chemical structure, a POSA using routine techniques would be able to recognize any form of the 1-to-1 DHP salt of sitagliptin and distinguish it from other compounds." *Id.*

predict the properties of a different form. (*Id.*). MSN contends that the properties of the known crystalline forms of cabozantinib (L)-malate differ. (*Id.*). MSN argues that these differences mean N-1 and N-2 are not representative of the genus, and thus Exelixis cannot meet the written description requirement by disclosing common structural features that are shared by N-1, N-2, and the rest of the genus. (*Id.* at 8–9).

The problem with MSN's argument is that MSN does not explain why these differences in physico-chemical properties and structure mean N-1 and N-2 are so different from other forms that they are unrepresentative. For example, in *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1291 (Fed. Cir. 2014), the patents in question were directed to human antibodies that help treat psoriasis and rheumatoid arthritis by binding to a particular type of antigen. The Federal Circuit held that the jury heard ample evidence to conclude that the patents were invalid for lack of written description because they "only describe one type of structurally similar anti-bodies and . . . those antibodies are not representative of the full variety or scope of the genus." *Id.* at 1300. Defendant's invention fell within the scope of the claimed genus but shared only a "50% sequence similarity" with the claimed antibodies. *Id.* In finding that the claimed antibodies are not representative of the genus, the Federal Circuit cited expert testimony that "antibodies with 80% sequence similarity [to the disclosed antibody] could bind to completely different antigens," highlighting the "significant structural differences" of the antibodies and "unpredictability of the field of invention." *Id.* Here, MSN baldly asserts there are differences between N-1, N-2, and the rest of the genus without giving me a framework to evaluate such differences. I reject this argument.

MSN also cites three cases in which the Federal Circuit found inadequate written description for genus claims and argues that the claims here are analogous. (D.I. 169 at 4, 6, 11). I now explain why the three cases are not applicable.

First, MSN cites *ICU Medical, Inc. v. Alaris Medical Systems, Inc.*, 558 F.3d 1368 (Fed. Cir. 2009). In *ICU*, the asserted claims were directed to "medical valves used in the transmission of fluids to or from a medical patient." *Id.* at 1372. The Federal Circuit held that because the specification described only medical valves with spikes, a POSA would not understand the inventor to have invented a "spikeless" medical valve. *Id.* at 1378. MSN argues that there is inadequate written description because a POSA would not know from the specification "what other forms of crystalline cabozantinib (L)-malate existed, how to make those forms, what the crystal structure of such other forms might be, or what properties each unknown form would have." (D.I. 169 at 7).

As I have discussed above with regard to the *GSK* and *Merck* cases, I do not think that what MSN alleges a POSA would not know from the specification establishes lack of written description. Furthermore, *ICU* is inapposite because in that case the spike limitation was functional. *ICU*, 558 F.3d at 1375–76. The district court construed it in relevant part as "having a pointed tip for piercing the seal," and the Federal Circuit affirmed this construction. *Id.* at 1376. Functional claim limitations require more disclosure to meet the written description requirement.[9] That is not the case here, because there are no functional limitations. A POSA

[9] *See, e.g., AbbVie*, 759 F.3d at 1301 ("Functionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus.").

would understand the inventor to have invented all malate salts of cabozantinib that are crystalline and have the disclosed chemical name and formula.

Second, MSN cites *In re Entresto (Sacubitril/Valsartan) Patent Litigation*, 2023 WL 4405464 (D. Del. July 7, 2023), *appeal docketed*, No. 23-2218 (Fed. Cir.) (scheduled for oral argument on November 13, 2024). The asserted claims covered "valsartan and sacubitril as a physical combination and as a complex." *Id.* at *17. Because complexes were unknown to a POSA as of the priority date, I found that the inventors could not have possessed complexes of valsartan and sacubitril and held the claims invalid for lack of written description. *Id.* at *22. MSN analogizes to *Entresto* to argue that here, the POSA could not have predicted that there were other forms of cabozantinib (L)-malate in the genus, nor could a POSA predict what polymorph would be obtained before testing. (D.I. 169 at 9–11).

Entresto is distinguishable. I do not think *Entresto* stands for the proposition that a POSA must be able to predict every species in the genus, as MSN argues. In *Entresto*, a POSA would not have known that complexes existed. Here, a POSA would know polymorphic forms of crystalline cabozantinib (L)-malate existed—because Exelixis disclosed two such forms, N-1 and N-2, in the specification. ('439 patent at 18:59–23:60). A POSA must be able to "visualize or recognize the identity of the members of the genus." *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). A POSA would recognize members of the genus by their chemical name and crystalline structure, features that are common to all species in the genus.

Third, MSN cites *Allergan USA, Inc. v. MSN Laboratories Private Limited,* 694 F. Supp. 3d 511 (D. Del. 2023). That case is no longer good law; after the briefing in this case, it was

reversed by the Federal Circuit. *Allergan USA, Inc. v. MSN Lab'ys Priv. Ltd.*, 111 F.4th 1358 (Fed. Cir. 2024). I therefore do not address MSN's arguments based on *Allergan*.

For the reasons stated above, MSN has not met its burden to show by clear and convincing evidence that Exelixis has not adequately described the asserted claims. The asserted claims of the Malate Salt Patents are not invalid for lack of written description.

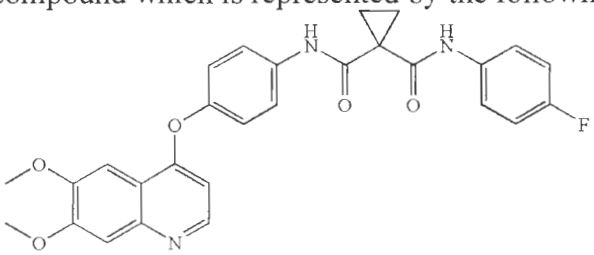
VI. OBVIOUSNESS-TYPE DOUBLE PATENTING

A. Findings of Fact

1. U.S. Patent No. 7,579,473 ("the '473 patent") issued on August 25, 2009, and is assigned to Exelixis. (DTX-013; Tr. 468:6–11). It expires in 2026. (Tr. 468:23–24).

2. Claim 5 of the '473 patent is:

   The compound which is represented by the following structure:

   or a pharmaceutically acceptable salt thereof.

3. Crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (Tr. 469:24–470:1, 831:9–12, 926:21–927:9).

4. Half of all drug products have APIs in salt form. (Tr. 432:25–433:2). The prior art taught salt formation was a way to improve properties of the API. (Tr. 432:2–433:2). A POSA would want to pursue a salt of cabozantinib (L)-malate to improve its solubility. (Tr. 501:4–6).

5. A POSA would be motivated to form a crystalline salt. (Tr. 441:15–23). A POSA would be motivated to form a salt of cabozantinib.

6. By 2009, salt screening was a known technique used to identify potential salt forms of a drug substance. (Tr. 827:11–16).

7. The pKa of a compound is an inherent property of the compound. (Tr. 436:20–21). It indicates how strong its propensity is to form a salt. (Tr. 436:15–21).

8. A POSA would determine the pKa of the cabozantinib base. It would take a couple weeks to determine the pKa of a base. (Tr. 838:2–24).

9. A POSA would use the decision tree outlined in the Bighley reference to conduct the salt screen. (Tr. 813:7–814:16). A POSA would start by testing hydrochloric acid, then turn to inorganic acids, and then turn to strong organic acids. (Tr. 814:3–817:13). A POSA would not try organic acids unless the inorganic acids did not form an acceptable salt. (Tr. 816:18–817:3).

10. A POSA would use Tong's Rule of 2 to narrow the list of counterions. Tong teaches that to form a salt, the "pKa of the acid should be at least 2 pH units lower than the pKa of the compound," which ensures that the counterion is strong enough to transfer a hydrogen ion to the base, resulting in the formation of a salt. (DTX-243; Tr. 437:3–12). Dr. Trout agreed this "Rule of 2" was a "well-known rule of thumb." (Tr. 931:20–25). Pharmorphix, a company that conducted a salt screen for Exelixis, reported that Pharmorphix used the Rule of 2. (Tr. 622:2–624:21).

11. A POSA would not be motivated to use malic acid as a counterion. (FOF ¶¶ 9–10).

12. A POSA would not have a reasonable expectation of success in forming a crystalline salt of cabozantinib (L)-malate. There is no way of predicting whether a crystalline salt will form. (Tr. 884:1–19).

13. It was unexpected that crystalline cabozantinib (L)-malate displayed the best properties out of all the salts Exelixis evaluated. (Tr. 889:1–10).

14. It was unexpected that crystalline cabozantinib (L)-malate dissolved faster than amorphous cabozantinib (L)-malate. (Tr. 889:11–16, 891:1–9; PTX-225 at 5–8 of 9).

15. It was unexpected that crystalline cabozantinib (L)-malate displayed a fast dissolution profile given its low water solubility. (Tr. 891:1–19).

B. Legal Conclusions

MSN argues that Claim 4 of the '439 patent is invalid for obviousness-type double patenting of Claim 5 of the '473 patent. (D.I. 169 at 12). Claim 5 of the '473 patent covers the cabozantinib compound and "pharmaceutically acceptable salts thereof." ('473 patent at 412:24–51). Claim 4 of the '439 patent covers the crystalline cabozantinib (L)-malate salt. ('439 patent at 32:33–36).

1. Step One

The first step of the obviousness-type double patenting analysis is to construe the asserted claims of the earlier and later-issued patents and determine whether there are differences. *Eli Lilly & Co. v. Barr Lab'ys, Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001).

Here, the issue to be resolved at step one is whether a POSA would have recognized that crystalline cabozantinib (L)-malate is a pharmaceutically acceptable salt of the cabozantinib compound. MSN argues that a POSA would recognize that crystalline cabozantinib (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (D.I. 169 at 12). MSN cites Dr. Steed, Dr. Koleng, and Dr. Trout's testimony that crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (D.I. 169 at 15–16, 34–35).

Exelixis contends that neither the specification of the Malate Salt Patents nor the specification of the '473 patent mention malic acid. (D.I. 175 at 21–22). Exelixis argues that a POSA would not know that crystalline cabozantinib (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (D.I. 175 at 22–23).

I think Exelixis' arguments are more appropriate for step two of the obviousness-type double patenting analysis. The issue under step one is whether there are differences between Claim 4 of the '439 patent and Claim 5 of the '473 patent. *See AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1378 (Fed. Cir. 2014) (assuming that the difference under step one of the obviousness-type double patenting analysis is that the asserted claim of the later-issued patent is directed to a species of the reference patent's genus claim). Claim 5 of the '473 patent is very broad. It encompasses the genus of all pharmaceutically acceptable salts of cabozantinib. I credit Dr. Steed, Dr. Koleng, and Dr. Trout's testimony that crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. (Tr.

469:24–470:1, 831:9–12, 926:21–927:9). Therefore, Claim 4 of the '439 patent is directed to a species of the '473 patent's genus claim: crystalline cabozantinib (L)-malate.

But the obviousness-type double patenting inquiry does not end here. "[O]bviousness is not demonstrated merely by showing that an earlier expiring patent dominates a later expiring patent. . . . It is well-settled that a narrow species can be non-obvious and patent eligible despite a patent on its genus." *Mathilda*, 764 F.3d at 1379. If the later expiring patent is an "obvious variation" of the earlier expiring patent, it is invalid for obviousness-type double patenting. *Id.*

I now analyze whether crystalline cabozantinib (L)-malate is "merely an obvious variation" of cabozantinib and its pharmaceutically acceptable salts. *Id.*

2. Step Two

a. Motivation to make a salt of cabozantinib

MSN argues that a POSA would be motivated to make a salt of cabozantinib. MSN argues that the '473 patent claims the salt form of cabozantinib. (D.I. 169 at 14). Dr. Steed testified that half of all drug products have APIs in salt form, and that the prior art taught salt formation was a way to improve properties of the API. (Tr. 432:2–433:2). These properties include solubility and dissolution rate. (*Id.*).

Exelixis disputes that a POSA would be motivated to form a salt. (D.I. 175 at 23–24). Exelixis contends that MSN must show there is some reason for a POSA to develop a salt when the POSA already had the free base. (*Id.* at 24). Exelixis cites to *Merck* for the proposition, "The mere fact that reference claim 17 covers [the sitagliptin free base and] pharmaceutically acceptable salts of sitagliptin would not, in and of itself, have motivated a POSA to abandon the free base form of sitagliptin to go in search of an acid-addition salt of this compound." *Merck*, 2022 WL 22855168, at *26. Dr. Steed testified that if there were no problems with the free base,

then a POSA would pursue the free base as a first formulation option. (Tr. 500:24–501:1). But Dr. Steed also testified that here, there was a solubility issue with the free base, which would be reason to pursue a salt. (Tr. 501:4–6).

Exelixis argues that there were no problems with the free base reported in the prior art, so a POSA would have no reason to make a cabozantinib salt. (D.I. 175 at 24–25). Dr. Trout testified that there was no information disclosed in the prior art about reasons to form a salt of cabozantinib. (Tr. 874:20–23). Dr. Trout testified that a POSA would have considered cabozantinib's permeability as driving its bioavailability, rather than trying to solve the solubility issue to improve bioavailability. (Tr. 877:11–23).

MSN has shown that a POSA would have been motivated to form a salt of cabozantinib. I find persuasive that a POSA would have wanted to form a salt to increase the solubility, dissolution rate, and other properties of the cabozantinib API. (Tr. 432:2–433:2). This is sufficient reason for a POSA to try to formulate a salt of cabozantinib even though the POSA already had the free base. "Our precedent, however, does not require that the motivation be the best option, only that it be a suitable option from which the prior art did not teach away." *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014). I find a POSA would be motivated to form a salt of cabozantinib. *See Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 929–30 (Fed. Cir. 2024) ("A motivation may be found explicitly or implicitly in . . . the background knowledge, creativity, and common sense of the person of ordinary skill." (internal quotations and citation omitted)).

b. Motivation to use malic acid

MSN outlines the path a POSA would have taken to use malic acid to form cabozantinib (L)-malate. (D.I. 169 at 14–17). MSN contends that a POSA would have started the process of

forming a salt of cabozantinib by testing 15–20 counterions in a salt screen. (Tr. 434:15–25, 470:19–23). MSN argues a POSA would be motivated to select malic acid as one counterion to use in the salt screen. (D.I. 169 at 15).

MSN contends that a POSA would have started with a list of counterions from the prior art. (*Id.*). This list includes fifty counterions, including malic acid. (Tr. 435:6–24). MSN argues a POSA would have narrowed the list to nine by using Tong's Rule of 2[10] and using only counterions that are generally recognized as safe for administration to humans ("GRAS"). (D.I. 169 at 15; Tr. 475:14–476:1, Tr. 837:15–21, Tr. 932:14–933:1). MSN contends that the nine counterions a POSA would test includes malic acid. (D.I. 169 at 16).

Exelixis disputes MSN's outline of how a POSA would be motivated to use malic acid on several grounds.

Exelixis contends that a POSA would use the Rule of 3, not Tong's Rule of 2, to select counterions to use in the salt screen. (D.I. 175 at 30–31). MSN presented evidence that a POSA would know of the Rule of 2 as a rule of thumb, and that the Rule of 2 has been used by a company Exelixis hired to conduct its salt screen. (Tr. 622:2–624:21). "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (cleaned up). That the Rule of 3 existed in the prior art does not mean a POSA would not use Tong's Rule of 2. I find a POSA would use the Rule of 2 as part of choosing a suitable counterion.

[10] Tong's Rule of 2 is that a counterion selected for salt screening should have a pKa at least two units lower than the base. (Tr. 437:3–9).

Exelixis argues that a POSA would not consider a counterion's GRAS status. (D.I. 175 at 30–31). Dr. Koleng testified that GRAS is "related to food additives of the pure materials," and is "really not directly applicable to pharmaceuticals." (Tr. 818:13–819:5). Dr. Koleng testified that the safety and toxicity of the salt, not just the counterion, is qualified as GRAS, and that the corresponding acids of the most common counterions used in salt screens are not GRAS. (Tr. 818:20–819:5). I find Dr. Koleng's testimony persuasive. I do not think a POSA would use a potential counterion's GRAS status to narrow the list of counterions to test in a salt screen. MSN counters, "The Handbook of Pharmaceutical Salts explicitly provides a 'List of Salt Formers' with 'acids and bases regarded as innocuous' in which GRAS status is given." (D.I. 177 at 20, PTX-610 at 336 of 376). But the table lists many qualities of the salt formers, including ones that MSN has not argued a POSA would consider. (PTX-610 at 336 of 376). That the table also lists GRAS status does not convince me a POSA would narrow the list of counterions by excluding any counterion that is not GRAS.

MSN argues that, instead of the method Exelixis proposes a POSA would use to conduct the salt screen, a POSA would use the decision tree outlined in the Bighley prior art reference. (Tr. 813:7–814:16). Dr. Koleng testified that Bighley teaches that a skilled artisan would start a salt screen with hydrochloric acid, because it is a strong acid and very common. (Tr. 814:17–25). After hydrochloric acid, a POSA would turn to inorganic acids because they are strong acids, and, after that, to strong organic acids. (Tr. 815:1–817:13). Dr. Koleng listed the five most common organic acids, and malic acid was not among them. (Tr. 818:2–12).

Based on Dr. Koleng's testimony, I do not think a POSA would be motivated to select malic acid to test during the salt screen. First, I am persuaded that a POSA would not test every acid in the list of acids to try. Dr. Koleng testified that, consistent with the Bighley reference, a

POSA would follow a hierarchical approach to pick a salt "in an efficient and timely manner with few false starts and the minimum expenditure of resources." (Tr. 814:3–16). Dr. Koleng also testified that a POSA would not try organic acids unless the inorganic acids did not form an acceptable salt. (Tr. 816:18–817:3). I find persuasive that, to save resources, a POSA would not try every salt on the list.

Malic acid would be far down on the list of acids a POSA would consider trying. I do not think a POSA would consider GRAS status. Dr. Steed concluded that a POSA, relying on an excerpt of Bighley, would consider organic acids, but I find more persuasive Dr. Koleng's testimony that the excerpt related to a specific issue for injectable drugs. (Tr. 816:2–17). The drugs at issue here are oral dosage forms, not injectable drugs. (Tr. 816:13–17). Therefore, I do not think a POSA would be motivated to make it far enough down the list of counterions such that the POSA would use malic acid in the salt screen.

MSN argues that a POSA would be motivated to select malic acid because "another FDA-approved tyrosine kinase inhibitor, sunitinib, had been formulated as an (L)-malate salt." (D.I. 169 at 16 n.3, Tr. 471:8–14). But Dr. Koleng testified that because of sunitinib's pKa, it would be considered a stronger base than cabozantinib. (Tr. 823:20–824:18). A POSA would be motivated to consider different counterions to use with sunitinib than with cabozantinib. (*Id.*). I find Dr. Koleng's testimony persuasive, particularly because Exelixis argued that pKa does matter in counterion selection, as per Tong's Rule of 2. (D.I. 175 at 27–28). I do not think that the formation of sunitinib as an (L)-malate salt would make a POSA consider malic acid in a salt screen of cabozantinib.

MSN contends that Exelixis is improperly arguing about whether malic acid is the best option, not whether it's a suitable option. (D.I. 177 at 11; *see Par Pharm.*, 773 F.3d at 1197–98).

I disagree. Because a POSA would follow a hierarchical approach in testing counterions, a POSA would not reach far enough down the list to test malic acid. The question is not whether malic acid is a possible alternative, but whether a POSA would consider it when there were so many more promising alternatives. I find a POSA would not. A POSA would not be motivated to use malic acid to form a salt of cabozantinib.

c. Motivation to form a crystalline salt

Exelixis does not dispute that a POSA would have been motivated to form a crystalline salt. Dr. Steed testified that a crystalline salt is preferred over an amorphous salt because crystalline salts are usually more stable and less hygroscopic. (Tr. 441:15–18). Dr. Steed also testified that prior art shows that drugs in crystalline forms are preferred. (Tr. 441:19–23). I find a POSA would have been motivated to form a crystalline salt.

d. Reasonable expectation of success

MSN argues that a POSA would have a reasonable expectation of forming a crystalline malate salt using a salt screen. (D.I. 169 at 14). Dr. Steed testified that a POSA would expect a solid salt to form after following Tong's Rule of 2. (Tr. 437:3–438:14).

MSN presents no evidence for whether a POSA would have a reasonable expectation of success of forming a *crystalline* salt. MSN cites Dr. Steed's testimony that most salts can be crystallized to argue that a POSA would have a reasonable expectation of success of forming a crystalline salt. (D.I. 169 at 16–17). The testimony MSN cites is:

> Q. Will a POSA be able to crystallize out of solution all of the pharmaceutical salts that are formed during a salt screen?
> A. Not all of them, no. But typically they would be able to isolate a solid, most of them, if only by evaporating off the solvent and then characterize what the result was.
> Q. Could you explain what the typical last step of a salt screen is?

> A. Yes. In whatever solids arise from that crystallization attempts, then the person of skill would use routine analytical techniques to characterize the outcome, characterize the residual solids.
> Q. And what are the typical properties that will be characterized for each salt that's prepared in a screen?
> A. So typically it's crystallinity using x-ray powder diffraction. The sort of properties I alluded to earlier; hygroscopicity, melting point, it's—whether it's a solvate or not, those sorts of things.
> Q. And you mentioned one of the properties of a salt is its crystallinity. Can you explain the different—what that is?
> A. Yes. So the outcome of the salt screen, if it's a solid it might be either amorphous or crystalline. If it's a crystalline solid, then there will be a regular repeating array of the molecules that give rise to the crystal structure.

(Tr. 438:8–439:16) (cleaned up). I do not think Dr. Steed's testimony that a salt can be crystallized out of solution is the same as the salt being crystalline. Dr. Steed refers to crystallizing a salt out of solution as "isolat[ing] a solid." (Tr. 438:8–12). Dr. Steed explains that a POSA would characterize the residual solid as crystalline or amorphous. (Tr. 439:9–16). I understand Dr. Steed to be testifying that crystallizing a salt out of solution refers to getting a solid out of solution, which is later characterized as crystalline or amorphous. The testimony was not that a POSA would reasonably expect the solid to be crystalline.

MSN cites Dr. Steed's testimony that a POSA would be motivated to prepare a crystalline form of cabozantinib (L)-malate because more than 90% of pharmaceuticals are in crystalline form. (Tr. 478:19–479:1). But this testimony does not establish that 90% of salts formed through a salt screen are crystalline, nor that a POSA would have a reasonable likelihood of success in obtaining a crystalline salt. MSN cites no other testimony regarding the likelihood of forming a crystalline salt. Exelixis cites Dr. Trout's testimony that there is no way of predicting whether a crystalline salt will form. (Tr. 884:10–19). I find MSN did not meet its burden to show by clear and convincing evidence that a POSA would have a reasonable expectation of success in obtaining a crystalline salt from doing a salt screen with cabozantinib and malic acid.

A POSA would not be motivated to use malic acid to form a salt. A POSA would not have a reasonable likelihood of success in obtaining a crystalline salt using malic acid. Therefore, I find the asserted claims of the Malate Salt Patents are non-obvious.

e. Unexpected Results

Exelixis offers evidence of unexpected results for the Malate Salt Patents. (D.I. 175 at 38–39). Exelixis discusses three examples of unexpected results and incorporates by reference the discussion of commercial success and long-felt need from its obviousness argument for the '349 patent.[11] (*Id.*, D.I. 175 at 38 n.14).

I have already found that the asserted claims of the Malate Salt Patents are non-obvious. Exelixis does not prove by a preponderance of the evidence that there are secondary considerations of non-obviousness for the Malate Salt Patents. Exelixis has proven by a preponderance of the evidence that there were unexpected results, but that finding is obviated given that there is no nexus between the Malate Salt Patents and the secondary considerations. *See infra* VII.B.2.f.v.

Exelixis argues there were three unexpected results. First, Exelixis argues it was unexpected that crystalline cabozantinib (L)-malate displayed the best properties out of all the salts Exelixis evaluated. (D.I. 175 at 38, Tr. 889:1–10). Second, Exelixis argues it was unexpected crystalline cabozantinib (L)-malate dissolved faster than amorphous cabozantinib (L)-malate. (D.I. 175 at 38–39; Tr. 889:11–16, 891:1–9; PTX-225 at 5–8 of 9). Third, Exelixis

[11] I likewise incorporate by reference my later discussion of commercial success and long-felt need. *See infra* VII.B.2.f.i, iii–v. For the reasons set forth there, I find that Exelixis has not proven by a preponderance of the evidence that Cabometyx met a long-felt but unmet need. Exelixis has proven by preponderance of the evidence that Cabometyx was a commercial success but failed to prove a nexus between commercial success, or any other secondary consideration, and the Malate Salt Patents.

argues it was unexpected that crystalline cabozantinib (L)-malate displayed a fast dissolution profile given its low water solubility. (D.I. 175 at 39, Tr. 891:1–19).

MSN argues that the results argued by Exelixis are not unexpected results, because for a result to be unexpected, it must be unexpected compared to the reference patent. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991). MSN contends that the reference patent is the '473 patent, and crystalline cabozantinib (L)-malate is within the scope of the patent. (D.I. 177 at 22). Therefore, MSN argues that any property of crystalline cabozantinib (L)-malate is a "latent property" within the scope of the reference claim, rather than an unexpected result. *See In re Pasteur*, 2023 WL 8609987, at *4 (Fed. Cir. Dec. 13, 2023) ("[T]he fact that performing [the] prior art method would produce a result . . . is . . . mere recognition of a latent property in an obvious method of treating pain with the same peptide." (internal quotations and citation omitted)).

AbbVie sheds light on how to consider unexpected results in the context of an obviousness-type double patenting analysis. The Federal Circuit held, "To determine whether the [asserted] patent is directed to a species that yielded unexpected results, we must necessarily look to the [reference] patent's disclosures to assess what results were expected at the time the [reference] patent application was filed." *AbbVie*, 764 F.3d at 1380. Because the study the plaintiff used to show unexpected results in the asserted patent was the same study the reference patent relied on to show utility, the Federal Circuit held that there were no unexpected results. *Id.*

AbbVie teaches that it is not the case that any result of the species claim is a latent property of the reference genus claim. Rather, the reference claim must teach the alleged unexpected result for it to be a latent property. Nothing in the specification of the '473 patent

teaches that crystalline cabozantinib (L)-malate displays the best properties, that crystalline cabozantinib (L)-malate dissolves faster than its amorphous counterpart, or that crystalline cabozantinib (L)-malate displays a relatively fast dissolution profile. I reject MSN's argument that there can be no unexpected results of crystalline cabozantinib (L)-malate.

MSN contends that any result cannot be unexpected, because a POSA would not have any "expectation of what the 'suite of properties' for any salt will be before it is formed." (D.I. 177 at 22). MSN cites Dr. Koleng's testimony that there is no way to guarantee a salt would form in a salt screen or what the properties of the salt would be. (Tr. 828:3–12). MSN also cites Dr. Trout's testimony that there is no way to predict the pharmaceutical properties of a salt before it is made and characterized. (Tr. 889:1–6). I do not take this testimony to mean that a POSA would have no expectation of what properties cabozantinib (L)-malate would have. Dr. Trout went on to testify that it was unexpected cabozantinib (L)-malate had the best suite of properties given "potential issues with the low acidity, the high molecular weight, the tendency to form pseudodimerism and also the fact that it has two acid groups." (Tr. 889:7–10). I understand the testimony to reflect that the exact pharmaceutical properties, and thus the efficacy, of a salt cannot be predicted, but that a POSA can have expectations of pharmaceutical properties and efficacy based on other properties of the salt.

MSN argues that the crystalline cabozantinib (L)-malate does not dissolve unexpectedly fast, but that it is the amorphous cabozantinib (L)-malate that dissolves unexpectedly slowly. (D.I. 169 at 35). Dr. Trout testified that not only is it surprising the crystalline cabozantinib (L)-malate dissolved faster than the amorphous cabozantinib malate, but that the crystalline cabozantinib (L)-malate dissolving fully in fifteen minutes, given its low solubility, was unexpected. (Tr. 891:3–9). Against this backdrop, the testimony MSN cites does not persuade

me that the crystalline form did not have unexpected results. Dr. Steed testified that the solubility of the amorphous cabozantinib (L)-malate was anomalous, explaining that its slow dissolution was surprising because it is hygroscopic and forms clumps.[12] (Tr. 485:5–19). I find persuasive Dr. Trout's reasoning that the crystalline form dissolving faster than the amorphous form is surprising given its low solubility. (Tr. 891:3–9). There is no reason both results cannot be surprising. It can be unexpected that the crystalline form dissolves more quickly than the amorphous form while also being surprising that the amorphous form dissolves more slowly than expected. Therefore, the Exelixis study showing that amorphous cabozantinib (L)-malate dissolves slowly (Tr. 640:18–641:6) does not prevent me from finding that it was unexpected that crystalline cabozantinib (L)-malate dissolves quickly.

Exelixis has shown by a preponderance of the evidence that the crystalline cabozantinib (L)-malate displayed unexpected results. But, Exelixis has not shown a nexus between the unexpected results and the Malate Salt Patents. *See infra* VII.B.2.f.v.

f. Claim 3 of the '440 patent and Claim 2 of the '015 patent

MSN argues that Claim 3 of the '440 patent and Claim 2 of the '015 patent are not patentably distinct from Claim 5 of the '473 patent. (D.I. 169 at 18).

Claim 3 of the '440 patent recites:

> 3. A pharmaceutical composition comprising the [cabozantinib] malate salt, wherein said salt is the (L)-malate salt or (D)-malate salt, and wherein said salt is crystalline; and a pharmaceutically acceptable excipient.

('440 patent at 32:16–21).

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[12] The transcript is confusing. In one sentence, Dr. Steed says, "So [amorphous cabozantinib (L)-malate] dissolves very quickly." (Tr. 485:15–16). In the next sentence, Dr. Steed says, "[Amorphous cabozantinib (L)-malate] dissolves unexpectedly slowly." (*Id.* 485:18). I understand Dr. Steed to be saying that, given its properties, he would expect amorphous cabozantinib (L)-malate to dissolve quickly and it is surprising that it in fact dissolves slowly.

MSN contends that the only added limitation and difference between Claim 3 of the '440 patent and Claim 5 of the '473 patent is that the '440 patent requires the crystalline cabozantinib (L)-malate to be in "a pharmaceutical composition." (D.I. 169 at 18).

MSN cites Dr. Steed's testimony to argue that it would have been obvious for a POSA make a pharmaceutical composition of cabozantinib. (*Id.*). Dr. Steed testified that the application that led to the '473 patent, U.S. Patent Pub. No. 2007/0054928 (the "'928 application"), "teaches administration of the compounds of the invention or their pharmaceutically acceptable salts which would include the malate salt in appropriate pharmaceutical compositions." (DTX 180; Tr. 481:3–6). Dr. Steed testified that the '928 application does not identify "any specific pharmaceutical compositions with cabozantinib or how to make one." (Tr. 481:7–11). Dr. Steed testified that a POSA would have been able to use the POSA's general knowledge and the prior art to make a pharmaceutical composition of cabozantinib. (Tr. 481:12–20).

I find that MSN has not met its burden of proving by clear and convincing evidence that it would be obvious for a POSA to make a pharmaceutical composition of crystalline cabozantinib (L)-malate. First, MSN has not shown it is obvious for a POSA to make a crystalline cabozantinib (L)-malate salt. But even if MSN had shown it is obvious for a POSA to make crystalline cabozantinib (L)-malate, Dr. Steed's conclusory testimony is not clear and convincing evidence that it would be obvious for a POSA to make a pharmaceutical composition. As MSN argues, Dr. Steed admitted that the '928 application does not disclose "any specific pharmaceutical compositions with cabozantinib or how to make one." (Tr. 481:7–11). Dr. Steed does not explain what a POSA's general knowledge would be that would allow a POSA to turn the salt into a pharmaceutical composition. Dr. Steed does not explain what steps

the POSA would take to create a composition, and whether the steps would be supported by a POSA's general knowledge or prior art. Nor does any other expert.

I turn to evaluating whether Claim 2 of the '015 patent is invalid for obviousness-type double patenting.

Claim 2 of the '015 patent recites:

> 2. A method of treating cancer, comprising administering to a subject in need thereof [cabozantinib] malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, said salt is crystalline, and said cancer is kidney cancer.

('015 patent at 32:11–16).

MSN contends that the only added limitation and difference between Claim 2 of the '015 patent and Claim 5 of the '473 patent is that the '015 patent requires the additional limitation of administering crystalline cabozantinib (L)-malate as "a method of treating cancer . . . wherein said cancer is kidney cancer." (D.I. 169 at 18).

MSN argues that the '928 application discloses the additional limitation. (*Id.*). Dr. Steed testified that the '928 application discloses treating kidney cancer with cabozantinib and it would be obvious for a POSA to use crystalline cabozantinib (L)-malate to treat kidney cancer. (Tr. 482:9–483:20).

I find that MSN has not its burden of proving by clear and convincing evidence that it would be obvious for a POSA to treat kidney cancer with the malate salt of cabozantinib. As with the '440 patent, MSN assumes that a POSA could use crystalline cabozantinib (L)-malate as a starting point. However, this assumption fails because MSN has not shown it is obvious for a POSA to make a crystalline cabozantinib (L)-malate salt. Even if I had found MSN had shown a POSA would know how to make crystalline cabozantinib (L)-malate, MSN has not offered clear and convincing evidence that it would be obvious for a POSA to use crystalline cabozantinib (L)-malate to treat kidney cancer. Dr. Steed's testimony, the only testimony MSN cites on this

issue, is highly conclusory. Dr. Steed admitted that the '928 application does not "identify any specific methods or other properties of kidney cancer treatment resulting from administering any of the claimed compounds to a patient." (Tr. 483:4–9). No expert provided testimony on what method the POSA would use to treat kidney cancer, or how a POSA would go about identifying a successful method.

I find that MSN has not proved by clear and convincing evidence that Claim 3 of the '440 patent and Claim 2 of the '015 patent are invalid for obviousness-type double patenting.

VII. OBVIOUSNESS

A. Findings of Fact

1. Asserted Claim 3 of the '349 patent recites a formulation of cabozantinib (L)-malate that includes a filler, lubricant, disintegrant, and glidant, and is "essentially free" of the 6,7-dimethoxy-quinoline-4-ol impurity (the "1-1 impurity," *see supra* n.4), where "essentially free" is defined as 200 ppm or less. ('349 patent at 8:15–20, 30:4–51). The '349 patent issued on April 12, 2022, and claims priority to a provisional application filed on February 10, 2011. ('349 patent).

2. There are three routes by which the 1-1 impurity could become present in cabozantinib (L)-malate API—due to the 1-1 impurity being a starting material and carrying through to the final API, due to the formation of the impurity as a degradation product, or due to the formation of the impurity as a byproduct. (Tr. 264:23–265:6, 690:7–13, 657:18–658:1).

3. A POSA would know the 1-1 starting material is potentially genotoxic because it is a quinoline. (Tr. 300:9–21, 304:1–13, 769:3–770:4).

4. A POSA would heed FDA guidance on how to deal with genotoxic impurities. A POSA would be motivated to identify the 1-1 starting material as genotoxic. (Tr. 301:8–10, 302:4–8, 303:5–15).

5. The Brown process, or the A-2 process, is disclosed in Example 1 of Exelixis' 2010 International Patent Application No. WO 2010/083414 to Brown (the "Brown Publication"). (Tr. 606:6–15; DTX-291 at ¶ 0098–00114). It describes how to synthesize cabozantinib (L)-malate API. (Tr. 267:4–268:10). It is a five step process with two side steps. (Tr. 677:11–19, 678:4–13; DTX-291 at ¶ 0098–00114). The A-2 process is an optimized version of an earlier-developed A-1 process. (Tr. 602:4–11).

6. There were four experimental batches prepared of the cabozantinib (L)-malate API. Three were prepared by the contract manufacturer Regis and one was prepared by the contract manufacturer Girindus. (Tr. 603:13–16, 783:7–15).

7. The Regis batches did not follow the Brown experimental process. Regis stated there were some "processing and reagent changes" to the synthetic route they had planned to follow to prepare the batches. (PTX-10 at 9 of 37). Dr. Lepore did not know what those changes were. (Tr. 336:17–338:19).

8. A 1-1 impurity can form as a degradation product during the Brown process. (Tr. 569:16–25, 600:8–601:4, 671:2–20). The so-called "1-3" intermediate material in the A-1 process was found to decompose to form large amounts of the 1-1 impurity. (Tr. 600:19–601:4, 693:3–13, 698:16–18; PTX-35 at 9 of 16). The same decomposition problem occurred in the A-2 process. (Tr. 694:5–12).

9. MSN has not shown by clear and convincing evidence that if the Brown process is followed, it will result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity. (FOF ¶ 8).

10. A POSA would not be motivated to minimize the 1-1 impurity after the Brown process because a POSA would expect that there is, at most, de minimis impurity left at the end of the Brown process. Each step of the Brown process purifies the API. (Tr. 668:16–669:14, 708:23–709:19).

11. Recrystallization of the cabozantinib (L)-malate API is the "first thing" a POSA would have attempted to purify the API if a POSA would have been motivated to minimize the 1-1 impurity after the Brown process. (Tr. 307:23–308:9). Many prior art examples show that recrystallization purifies an API of an impurity. (Tr. 310:11–311:3).

12. A POSA would not be motivated to add a recrystallization step at the end of the Brown process to remove the impurity because a POSA would expect that there is, at most, de minimis impurity left at the end of the Brown process. (Tr. 737:5–15).

13. Recrystallization would not have worked to purify the API of the 1-1 impurity because the impurity would be embedded in the crystalline lattice of the API. (Tr. 735:7–23, 736:13–22). Recrystallization could also produce more 1-1 impurity through "decomposition." (Tr. 737:5–15).

14. A POSA would not be motivated to obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity. (FOF ¶¶ 11–13).

15. Manufacturing exposes an API to heat, humidity, and excipients, which can cause degradation and thereby lead to increased impurity levels. (Tr. 414:13–24, 689:17–690:6).

16. A POSA would be motivated to ensure that cabozantinib (L)-malate is formulated as a tablet or capsule that includes a filler, lubricant, disintegrant, and glidant. (Tr. 392:15–394:19).

17. It was not unexpected that cabozantinib (L)-malate could be formulated and stay essentially free of the 1-1 impurity. A POSA would have expected that cabozantinib (L)-malate that is essentially free of the 1-1 impurity could be formulated into a capsule or tablet that is essentially free of the 1-1 impurity. (Tr. 399:18–400:19). The API Exelixis used had very low levels of the 1-1 impurity. (Tr. 612:7–8).

18. The '473 patent is a blocking patent. It issued in 2009. (Tr. 403:17–21). Its published parent application, the '140 publication, would have some discouraging effect similar to that of a weak blocking patent once it was published in August 2005. The '473 patent covered cabozantinib and its pharmaceutically acceptable salts and the '140 publication covered uses of cabozantinib. ('473 patent 411:10–412:57; DTX-192).

19. From August 2005 to the end of the patent term of the '473 patent there would have been some blocking effect. (Tr. 403:9–404:1, 485:23–487:2, 1016:11–14).

20. A POSA would be discouraged from developing technology covered by the '140 publication because the application might be granted and the POSA would then infringe its issued claims. (Tr. 486:20–487:2).

21. There was no successful challenge to the '473 patent or development of others in the 2009 to 2011 time frame. (D.I. 1018:9–11). Competitors would have concerns of losing the invention race to Exelixis and its partners, there was no evidence of a good licensing opportunity due to Exelixis' exclusive collaborations with GSK and BMS, and there was low economic opportunity for others in light of the blocking patent. (Tr. 1018:1–1019:7).

22. In 2019, CIPLA filed an international patent application related to its work investigating cabozantinib. (DTX-121).

23. The purity and stability of the crystalline cabozantinib (L)-malate drives at least part of the commercial success of the drug. (957:22–958:13, 959:4–960:10).

24. There is a nexus between the asserted claims of the '349 patent and the secondary considerations. (FOF ¶ 23; '349 patent at 34:50–51).

25. Cabometyx and Cometriq embody the asserted claims of the '349 patent. (Tr. 422:7–9, 688:12–15).

26. There is no nexus between the Malate Salt Patents and the secondary considerations. (Tr. 894:22–895:2, 1020:13–1022:13).

27. Cabometyx is commercially successful. (Tr. 979:5–6).

28. Cabometyx had $4.9 billion in sales in four years, and a 39% market share within seven years of its launch. (Tr. 981:14–982:8, 985:8–22). Cabometyx is the market leader for second-line therapy as well as therapies capable of use as a monotherapy or combined therapy. (Tr. 982:20–985:5).

29. Cabozantinib offered only an incremental improvement over existing therapies. (Tr. 996:8–11).

30. Doctors prescribe treatments other than cabozantinib for first-line treatments, and there are other treatments used for second-line treatment. (Tr. 965:22–966:4, 1002:13–20).

31. Cabozantinib does not fulfill the long-felt but unmet need for a safe and effective cancer treatment. (FOF ¶¶ 29–30).

B. Conclusions of Law

At issue is the "essentially free" limitation of Claim 3 of the '349 patent. MSN argues that Claim 3 of the '349 patent is invalid because making a cabozantinib (L)-malate API essentially free of the 1-1 impurity would be obvious to a POSA. (D.I. 169 at 20, 26). MSN presents two arguments. First, that the Brown process inherently discloses a cabozantinib (L)-malate API essentially free of the 1-1 impurity. (D.I. 169 at 20). Second, in the alternative, that it would have been obvious for a POSA to modify the Brown process to obtain a formulation of cabozantinib (L)-malate essentially free of the 1-1 impurity. (D.I. 169 at 26).

1. Inherency

MSN argues that the Brown prior art reference inherently discloses a cabozantinib (L)-malate API essentially free of the 1-1 impurity. (D.I. 169 at 20).

In the context of obviousness, proving a claim element is inherent in a prior art reference must meet a high bar. "[T]he concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the natural result of the combination of prior art elements." *Par Pharm.*, 773 F.3d at 1195 (internal quotations and citation omitted).

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not

> sufficient. . . . If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

In re Oelrich, 666 F.2d 578, 581 (Fed. Cir. 1981).

MSN did not meet its burden of proving inherency by clear and convincing evidence. MSN failed to offer clear and convincing evidence that if the Brown process is followed, it will inherently result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity. The Federal Circuit has found inherency in an obviousness argument when there is both expert testimony of the underlying scientific principles and experimental data showing that the prior art reference inherently discloses the claimed limitation. *See Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1330 (Fed. Cir. 2020); *see also Par Pharm., Inc. v. TWi Pharms., Inc.*, 120 F. Supp. 3d 468, 474 (D. Md.), *aff'd without opinion*, 624 F. App'x 756 (Fed. Cir. 2015). Here, there is neither clear and convincing experimental data nor expert testimony about the underlying scientific principles.

MSN's experimental data does not meet the clear and convincing standard. There were four batches of the cabozantinib (L)-malate API prepared: three by Regis and one by Girindus.[13] It is undisputed that the three Regis batches all had lower than 100 ppm of the 1-1 impurity and thus met the "essentially free" limitation. (D.I. 169 at 22–23, D.I. 175 at 46). However, I find MSN did not show by clear and convincing evidence that the Regis batches followed the Brown

[13] There is testimony that the batch produced by Girindus had the highest levels of the 1-1 impurity, ranging as high as 411 or 600 parts per million ("ppm") using HPLC/UV testing. (Tr. 603:5–23, 785:2–10, 789:12–790:3). MSN argues I should disregard the data from the Girindus batch because it does not follow the Brown process. Exelixis argues I should consider the Girindus data and find against inherency. I do not consider evidence of the Girindus batch because even without it, I still find that Brown does not inherently disclose the "essentially free" limitation.

process. Dr. Lepore testified that the Brown process and Regis process were the same. (Tr. 271:20–275:21, 364:3–365:13). Dr. Lepore walked through the steps of the Brown process and the Regis process and explained that they are virtually identical. (Tr. 271:20–275:21, 364:3–365:13). The document Dr. Lepore relied on for opining on the "synthetic scheme for how Regis went about synthesizing the API, step-by-step reaction by reaction" is a regulatory document Exelixis prepared and submitted to the FDA. (Tr. 271:7–272:3, DTX-38). But in another document Exelixis submitted to the FDA, Regis stated there were some "processing and reagent changes" to the synthetic route it had planned to follow to prepare the batches. (PTX-10 at 9 of 37). Dr. Lepore testified that he had not seen what the changes were, and that he had to assume Exelixis put all the information required of it into its FDA document. (Tr. 336:17–338:19). Dr. Lepore testified, "I'm assuming that these [changes] are extremely minor things that I wouldn't even call deviation." (Tr. 338:1–3). Because Dr. Lepore did not know what changes Regis made to the Brown process, I do not find persuasive his testimony that the Brown process and Regis process are virtually identical. I cannot find that the Brown process inherently produces a cabozantinib (L)-malate API essentially free of the 1-1 impurity because it is not clear to me that the Regis process followed the Brown process.

MSN's expert testimony about how the underlying science of the Brown process leads to an API essentially free of the 1-1 impurity does not meet the clear and convincing evidence standard. The 1-1 impurity could have formed as a degradation product. MSN cites testimony of various experts who explain that a POSA would not have expected the 1-1 impurity to form as a degradation product.[14] However, what a POSA would have expected is not sufficient to show

[14] Dr. Lepore testified that if a POSA followed the Brown process, the Brown process would always produce an API with less than 200 ppm impurity. (Tr. 299:10–18, 366:14–18). Dr. MacMillan testified that a POSA would not expect any 1-1 impurity to be left at the end of

inherency, given that Exelixis presented evidence that the 1-1 impurity did form as a degradation product during the Brown process. In response, MSN contends, "[T]here is no evidence that Exelixis' work discovered the 1-1 impurity formed in any meaningful amount (and certainly not more than 200 ppm) when the Brown Example 1 process was followed." (D.I. 177 at 17 (cleaned up)). But Dr. Myerson testified that "20[%] of the 1-3 [intermediary] was decomposing to 1-1." (Tr. 693:11–12). And it is MSN's burden, not Exelixis', to show that the Brown process does not form the 1-1 impurity through degradation. I am persuaded by Exelixis' evidence that the 1-1 impurity could have formed as a degradation product during the Brown process. (Tr. 569:16–25, 600:8–601:4, 671:2–20). I do not find that MSN has met its burden of showing by clear and convincing evidence that the Brown process inherently results in a cabozantinib (L)-malate impurity essentially free of the 1-1 impurity.

2. Obviousness

MSN argues that it would have been obvious for a POSA to modify the Brown process to obtain a formulation of cabozantinib (L)-malate essentially free of the 1-1 impurity. (D.I. 169 at 26).

a. Motivation to identify the 1-1 impurity

Dr. Lepore testified that a POSA would have heeded an FDA document providing guidance on how to deal with genotoxic impurities. (Tr. 310:9–302:8). The FDA document advises a POSA to consider the genotoxicity of starting materials. (Tr. 301:8–10). Specifically, it guides the POSA to look at the structure of the starting material to determine if it is toxic. (Tr. 303:5–15). Dr. Lepore testified a POSA would have followed this guidance, used the Ames test

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Brown, because each of the five steps of Brown has a purification component and the reagents added through the process could purge the impurity. (Tr. 668:16–669:14, 677:11–25).

(which is disclosed in the FDA document) to determine that the 1-1 starting material is a quinoline, and known from the prior art that quinolines are often genotoxic. (Tr. 302:5–306:16). Dr. Myerson agreed that a POSA would know that the 1-1 starting material is potentially genotoxic because it is a quinoline. (Tr. 769:5–770:4).

Exelixis argues that a POSA would not be motivated to minimize the 1-1 impurity[15] because a POSA would not know that the 1-1 starting material is genotoxic. (D.I. 175 at 45). No prior art taught that the 1-1 impurity is genotoxic. (Tr. 356:5–8). But Exelixis does not counter MSN's argument that the FDA guidance would ultimately inform a POSA that the 1-1 starting material is genotoxic. I am persuaded that a POSA would know from the FDA guidance that the 1-1 starting material is genotoxic.

b. Motivation to minimize the 1-1 impurity

Dr. Lepore testified that a POSA would know from the FDA guidance that the 1-1 starting material had to be reduced to the extent technically possible due to its genotoxicity. (Tr. 302:9–18, 307:9–19). Thus, MSN argues a POSA would be motivated to minimize the impurity. (D.I. 169 at 26–27).

Exelixis argues that a POSA would not be motivated to minimize the impurity because a skilled artisan would not expect there to be any impurity left in the final product of the Brown process. (*Id.*). Dr. MacMillan testified that a POSA would read Brown and expect there to be very little impurity left after step one, and no impurity at the end of step five, because each step purifies the API. (Tr. 668:16–669:14). Dr. Myerson testified that by the end of step one, 98% of the starting material is used up. (Tr. 708:23–709:19). Dr. Myerson testified that a POSA would

[15] The parties refer to the 1-1 starting material as the genotoxic material that exists at the start of the Brown process. The parties refer to the 1-1 impurity as whatever is left of the starting material at the end of the Brown process. They are the same material.

expect a de minimis quantity of the 1-1 impurity to be left at the end, and that a POSA would not expect the 1-1 impurity to form as a degradation product. (*Id.*).

In response, MSN cites Dr. Myerson's testimony that a POSA would have understood from the FDA guidelines that the 1-1 impurity was genotoxic and would need to be minimized. (Tr. 771:17–772:3). MSN contends that Dr. Lepore testified that the FDA Guidance applies to known starting materials even when the starting material is purged in the process. (D.I 169 at 28). But that was not Dr. Lepore's testimony. Dr. Lepore testified that the FDA guidance applies to starting materials and that the guidance states impurities often come from starting materials and need to be controlled. (Tr. 264:23–265:6, 302:1–7). The testimony MSN cites does not convince me that a POSA would try to minimize the 1-1 impurity. I credit Dr. Myerson's testimony that the POSA would think there is, at most, a de minimis amount of impurity left after the Brown process. (Tr. 708:23–709:19; *see also* Tr. 668:16–669:14). A POSA would believe the POSA had already controlled the impurity and thus followed the FDA guidance by following the Brown process.

Because a POSA would not expect that the 1-1 impurity would be present by the end of the Brown process, the POSA would not be motivated to control for it. (Tr. 708:23–709:19; 669:12–14).

c. Motivation to add a recrystallization step

MSN argues that a POSA would be motivated to add a recrystallization step to purify the 1-1 impurity. (D.I. 169 at 28–29).

Exelixis makes the same arguments as above—that a POSA would not think to purify the cabozantinib API further because a POSA would not think any 1-1 impurity would be left by the end of the Brown process. (D.I. 175 at 52). Since I have found a POSA is not motivated to

minimize the 1-1 impurity, I apply the same reasoning to find a POSA would have no motivation to add a recrystallization step to the Brown process.

d. Motivation to obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity

Claim 3 of the '349 patent requires a formulation of cabozantinib (L)-malate that includes a filler, lubricant, disintegrant, and glidant, and is "essentially free" of the 1-1 impurity. ('349 patent at 34:30–51). For MSN to prove the claim to be obvious, MSN must prove two additional requirements: (1) that a POSA would be motivated to ensure the final formulation is essentially free of the 1-1 impurity and (2) that a POSA would be motivated to ensure the final formulation meets the "compositional limitation" of including a filler, lubricant, disintegrant, and glidant.

The second point is easily disposed of, as the parties do not dispute that the POSA would have such a motivation. The parties agree that a POSA would be motivated to formulate the cabozantinib (L)-malate API as a capsule or tablet and ensure the final formulation meets the "compositional limitation." (D.I. 169 at 30–31, D.I. 175 at 54–55). Dr. Donovan testified that a POSA would be motivated by the Brown prior art, the Lachman reference, and the '081 publication "to formulate a cabozantinib (L)-malate tablet or capsule composition with the claimed excipients." (Tr. 394:1–19). I find that a POSA would be motivated to ensure the formulation is a tablet or capsule that includes a filler, lubricant, disintegrant, and glidant.

The parties dispute whether a POSA would be motivated to ensure the final formulation is essentially free of the 1-1 impurity. MSN argues that all that is needed to have a formulation of cabozantinib (L)-malate that is free of the 1-1 impurity is an API free of the impurity. (D.I. 177 at 14). I understand MSN to be arguing that MSN does not need to prove motivation to ensure that the formulation is free of the 1-1 impurity, because if the cabozantinib API is free of the 1-1 impurity, then the formulation would necessarily be free of the 1-1 impurity. Dr. Donovan

testified that a POSA would expect "to be able to formulate cabozantinib (L)-malate into a capsule that was essentially free of the 1-1 impurity." (Tr. 399:18–400:19). Dr. Donovan explained that the components, namely cabozantinib (L)-malate that is essentially free of the 1-1 impurity and excipients, can simply be premixed and added to a capsule shell. (*Id.*). Dr. Myerson testified that the "key feature" to "reliably manufacture" a tablet or capsule was formulating an API essentially free of the impurity, so that the formulation would be essentially free of the impurity. (Tr. 697:25–698:7).

But I think that MSN has not proved that the API would be free of the impurity. The 1-1 impurity could appear in the API as a degradation product. (Tr. 569:16–25, 600:8–601:4, 671:2–20). A POSA would not know there might be some 1-1 impurity left at the end of the Brown process. Yet, MSN must show a POSA would be motivated to ensure that the formulation is free of the 1-1 impurity.

MSN argues that a POSA would be motivated to control for the 1-1 impurity during formulation due to prior art references that advise a POSA to minimize and be concerned with stability in formulation. But that testimony deals with choosing excipients that would not cause additional impurities to form. (Tr. 385:1–20, 385:21–386:12, 396:10–16). MSN does not explain how a POSA would control the impurity in the API. MSN has not shown that a POSA would be motivated to obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity.

e. Reasonable expectation of formulating a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity

I do not think a POSA would have a reasonable expectation of success that by using recrystallization the POSA would create a formulation essentially free of the 1-1 impurity. I find persuasive Dr. Myerson's testimony that recrystallization would not have worked to purify the 1-1 impurity because the impurity would be embedded in the crystalline lattice of the API.

MSN contends that the first thing a POSA would have tried is recrystallization, and that there are many prior art examples that show recrystallization purifies an API. (D.I. 169 at 29). MSN argues that therefore, a POSA would have a reasonable expectation of success in using recrystallization. (*Id.*). MSN cites *Purdue* for the proposition that "because only routine techniques and commonly possessed training would be required, I find that the POSA would have had a reasonable expectation of success." *Purdue Pharma L.P. v. Accord Healthcare Inc.*, 669 F. Supp. 3d 286, 317 (D. Del. 2023), *appeal docketed*, No. 23-1953 (Fed. Cir. May 30, 2023). *Purdue* does not help MSN's argument. In *Purdue* there was no debate that a POSA would be successful using known techniques—the issue was whether a POSA would be motivated to use the known techniques. *Id.* Here, I find that the known technique of recrystallization would not be expected to be successful. While recrystallization might work for many APIs, Dr. Myerson's testimony is specific to cabozantinib and the 1-1 impurity. Dr. Myerson convincingly explains why in this case, a POSA would not have a reasonable expectation of success in using recrystallization.

f. Secondary considerations/objective indicia of non-obviousness

MSN generally argues secondary considerations in connection with the obviousness challenge to the '349 patent. (D.I. 169 at 31). But it also incorporated by reference its arguments as to commercial success and long-felt but unmet need into its arguments about double patenting of the Malate Salt Patents. (D.I. 169 at 33). Thus, some of what follows addresses not only the '349 patent but also the Malate Salt Patents.

Exelixis offers evidence of three secondary considerations of non-obviousness: commercial success, long-felt but unmet need, and unexpected results. (D.I. 175 at 57–58).

A patentee is not required to present evidence of secondary considerations. *See Prometheus Lab'ys, Inc. v. Roxane Lab'ys, Inc.*, 805 F.3d 1092, 1101–02 (Fed. Cir. 2015). There must be enough evidence, however, for a finding that a given secondary consideration exists by a preponderance of the evidence. *See Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, then the probative value of each secondary consideration will be considered in light of the evidence produced. "It is the fact finders' job to assess the probative value of the evidence presented." *Id.* at 1056. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007). That burden stays always with the patent challenger. *Id.*

I think, even without analysis of secondary consideration, Claim 3 of the '349 patent is non-obvious. Since Exelixis has asserted three secondary considerations, I will take them into account. Exelixis has not proven by a preponderance of the evidence that Cabometyx met a long-felt but unmet need, or that there were unexpected results. Exelixis has proven by preponderance of the evidence that Cabometyx was a commercial success and that there is a nexus between Claim 3 of the '349 patent and the secondary considerations. But, because I find that the '473 patent was a blocking patent to the '349 patent, the commercial success of Cabometyx is not a strong indicator of non-obviousness.

i. Long-felt but unmet need

Exelixis argues there is a long-felt, unmet need for a safe and effective kidney cancer treatment. (D.I. 175 at 58; Tr. 955:2–10). The parties' dispute centers around whether cabozantinib's improvement in patient outcomes is sufficient to meet the long-felt, unmet need. (D.I. 169 at 33–34, D.I. 175 at 48).

This court's discussion of long-felt but unmet need in *Pfizer* is instructive. *Pfizer Inc. v. Mylan Pharms. Inc.*, 71 F. Supp. 3d 458 (D. Del. 2014), *aff'd*, 628 F. App'x 764 (Fed. Cir. 2016) (per curiam). In that case, the court found that the renal cancer drug sunitinib malate met a long-felt but unmet need "for treatments for renal cell carcinoma ('RCC') and pancreatic neuroendocrine tumors ('PNET')." *Id.* at 475. Central to the court's finding was evidence "that sunitinib malate provided greatly improved clinical outcomes for RCC patients, and represented a 'huge paradigm shift' for the treatment of PNET." *Id.*

This court has also found long-felt but unmet need when a new drug helps a portion of patients needing treatment. *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 538 (D. Del. 2016) (finding long-felt but unmet need was fulfilled by an epilepsy drug that was "effective at controlling seizures in a segment of the population who had previously gone without relief from other available [antiepileptic drugs]"), *aff'd*, 890 F.3d 1313 (Fed. Cir. 2018).

I do not think that Exelixis has shown by a preponderance of the evidence that cabozantinib fulfilled a long-felt but unmet need. Dr. George testified that cabozantinib improved patient outcomes for a certain population of patients by "[creating] a treatment option for the first time that extended survival . . . for the majority of patients in the subsequent lines of therapy." (Tr. 949:7–15).

Dr. George did not characterize how much greater patient outcomes were on cabozantinib. He testified only that patients demonstrated "increased overall survival, delayed disease progression, and improved the objective response compared with" other drugs. (Tr. 950:13–19). And Dr. George expressed his understanding that any cancer treatment that would extend the lives of cancer patients beyond previously available therapies would meet a long-felt but unmet need. (961:23–962:2). I interpret Dr. George's testimony to be equating "long-felt but

unmet need" to "improvement." But they are not the same thing. Dr. George's testimony is not sufficient for Exelixis to meet its burden of showing long-felt unmet need by a preponderance of the evidence.

MSN argues that cabozantinib offered only an incremental improvement over existing therapies. (Tr. 996:8–11). I find this argument persuasive. I do not think cabozantinib greatly improved clinical outcomes. Dr. Mega testified that there were other drugs that treated renal cell carcinoma on the market when cabozantinib entered the market. (Tr. 996:22–997:1). And Dr. George admitted that he prescribes treatments other than cabozantinib as a front-line treatment for patients with renal cell carcinoma. (Tr. 965:22–966:4). Dr. Mega testified there are options other than cabozantinib for second-line treatment. (Tr. 1002:13–20). The evidence at trial does not establish that cabozantinib "provided greatly improved clinical outcomes," "represented a 'huge paradigm shift,'" or treated patients "who had previously gone without relief." *See Pfizer*, 71 F. Supp. 3d at 475; *UCB,* 201 F. Supp. 3d at 538. Exelixis has not shown by a preponderance of the evidence that cabozantinib fulfilled a long-felt but unmet need.

ii. Unexpected results

Exelixis argues that it was unexpected that cabozantinib (L)-malate could be formulated and stay essentially free of the 1-1 impurity over time. (D.I. 175 at 59). Exelixis cites Dr. Shah, one of the inventors. Dr. Shah testified that the results of the stability testing were "interesting and surprising" because there was less 1-1 impurity formed than expected given that the impurity "was seen to increase in the presence of moisture, heat, and oxygen." (Tr. 612:1–11).

MSN argues that the only expert testimony offered was that cabozantinib (L)-malate was very stable and that a POSA would not expect the 1-1 impurity to form as a degradation product. (D.I. 169 at 35; D.I. 177 at 22; *see* Tr. 661:9–24, 663:8–11, 722:7–10). However, the testimony

that MSN cites from Dr. MacMillan and Dr. Myerson was related to the degradation occurring while forming the API, not during the formulation of the capsule or tablet or while on the shelf.

MSN argues, citing Dr. Donovan, that it was not unexpected that the formulation was essentially free of the impurity because a POSA would have expected that cabozantinib (L)-malate that is essentially free of the 1-1 impurity could be formulated into a capsule or tablet that is essentially free of the 1-1 impurity. (Tr. 399:18–400:19). Exelixis cites testimony that Dr. Shah and his colleagues did not see as much 1-1 impurity as expected because they "were starting at the very low levels of 1-1 in the API." (Tr. 612:7–8). I therefore find that a POSA would expect that the cabozantinib (L)-malate could be formulated and stay essentially free of the 1-1 impurity. Exelixis has not established unexpected results by a preponderance of the evidence.

iii. Commercial success

Exelixis argues that Cabometyx is commercially successful. (D.I. 175 at 58). In the four years ending in 2020, Exelixis generated $4.9 billion in revenue from the sale of Cabometyx. (Tr. 985:8–22). Cabometyx obtained a 39% market share of the tyrosine kinase inhibitor market. (Tr. 981:14–982:8). It is the market leader for second-line therapy and therapies capable of use as a monotherapy or combined therapy. (Tr. 984:13–985:5).

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (internal quotation marks and citations omitted).

MSN does not dispute Exelixis' data. Instead, MSN argues that Exelixis did not provide any sort of benchmark to evaluate whether the numbers it presents means Cabometyx was successful. (D.I. 169 at 34). MSN argues that Dr. Tate did not determine Cabometyx's profitability because Dr. Tate presented revenue rather than profits or return on investment. (D.I. 177 at 22). But Federal Circuit precedent demonstrates that evidence of sales combined with market share is sufficient to evaluate commercial success. *See, e.g.*, *In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012) ("[T]he more probative evidence of commercial success relates to whether the sales represent a substantial quantity in the market.") (cleaned up); *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1361 (Fed. Cir. 1999) ("[S]ales figures coupled with market data provide stronger evidence of commercial success."); *Alcon Rsch., Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1371 (Fed. Cir. 2012) (holding it was not clearly erroneous that a product was an "outstanding commercial success" based on a "70% market share within two years of its launch" and "nearly $2 billion in sales within ten years").

Cabometyx had a 26% market share in 2020 and a 39% market share in 2023. (Tr. 981:17–982:2). Cabometyx had $4.9 billion in sales in four years. (Tr. 985:11–22). I find Cabometyx is a commercial success.

iv. Blocking patent

MSN argues that the '473 patent and its published parent application, the '140 publication, blocked anyone other than Exelixis from commercializing and developing cabozantinib. (D.I. 169 at 33). The '473 patent covers cabozantinib and its pharmaceutically acceptable salts and the '140 publication covers uses of cabozantinib. ('473 patent 411:10–412:57; DTX 192).

"A patent has been called a 'blocking patent' where practice of a later invention would infringe the earlier patent." *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018). "The existence of such a blocking patent may deter non-owners and non-licensees from investing the resources needed to make, develop, and market such a later, 'blocked' invention, because of the risk of infringement liability and associated monetary or injunctive remedies." *Id.* "If the later invention is eventually patented by an owner or licensee of the blocking patent, that potential deterrent effect is relevant to understanding why others had not made, developed, or marketed that 'blocked' invention and, hence, to evaluating objective indicia of the obviousness of the later patent." *Id.* Where "market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

As the '473 patent covers the cabozantinib and its pharmaceutically acceptable salts, "no one other than [Exelixis] could have practiced the invention of the ['473 patent] without facing liability for patent infringement." *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 2017 WL 1199767, at *38 (D. Del. Mar. 31, 2017), *aff'd in part, dismissed in part*, 903 F.3d 1310 (Fed. Cir. 2018).

There were strong disincentives that would have deterred others from developing cabozantinib. (Tr. 1018:1–1019:7). There were no successful challenges to the '473 patent; no development of cabozantinib by others in the 2009 to 2011 time frame; there would have been concerns of losing the invention race to Exelixis and its partners; no evidence of a good licensing opportunity with the exclusive collaborations of Exelixis with GSK and BMS; and low economic

opportunity for others in light of the blocking patent. (*Id.*). I find that the '473 patent and its published parent application deterred others from developing cabozantinib.

Exelixis raises three arguments for why there is no deterrence because of the '473 patent and '140 publication.

Exelixis cites *Bial-Portela & CA. S.A. v. Alkem Lab'ys Ltd.*, 2022 WL 4244989 (D. Del. Sept. 15, 2022) to argue that the blocking patent does not undermine evidence of commercial success. (D.I. 175 at 59). In *Bial-Portela*, the blocking patent did not obviate commercial success because the blocking patent did not cover the feature of the patent that made it successful. *Bial-Portela*, 2022 WL 4244989, at *14. The blocking patent blocked the compound, but what drove commercial success was the once-daily dosing. *Id.* Exelixis argues that here, the blocking patent may cover the cabozantinib salt, but it is the purity and stability of the cabozantinib (L)-malate, not the cabozantinib salt itself, that drove commercial success. (D.I. 175 at 58–59). I agree that the purity and stability of the crystalline cabozantinib (L)-malate drives at least part of the commercial success of the drug. Exelixis presented expert testimony that it is necessary to control the impurity to have a stable product, that it matters to patients to have a non-genotoxic compound, and that doctors had to stop prescribing drugs after they were found to have genotoxic impurities. (957:22–958:13, 959:4–960:10; *see Bial-Portela*, 2022 WL 4244989, at *14 ("[P]hysicians identifying convenient dosing as a key reason they chose [a product protected by a potential blocking patent] over other options" suggested "that the once-daily dosing was a driver of the commercial success of [the product]")).

Exelixis argues that several generic companies investigated cabozantinib and applied for patents. (D.I. 175 at 58). Exelixis contends that this evidence shows that the '471 patent and '140 publication did not have a deterrent effect. (*Id.*). MSN cites *Galderma Laboratories* in reply for

the proposition, "The mere fact that generic pharmaceutical companies seek approval to market a generic version of a drug, without more, is not evidence of commercial success that speaks to the non-obviousness of patent claims." *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013); (D.I. 177 at 21). *Galderma Labs* is inapposite. Exelixis is not offering evidence that generic companies investigated cabozantinib to show cabozantinib was successful, but to show that the generic companies were not deterred by the blocking patent. But the relevant inquiry is whether the '473 patent caused a deterrent effect, not whether all others were dissuaded from resource investment. MSN has cited evidence that only itself and CIPLA were investigating cabozantinib. (D.I. 169 at 33; DTX-121). That only two groups investigated cabozantinib suggests Exelixis' competitors experienced disincentives in investing resources into this area. I find that the '473 patent deterred investment of resources into making, developing, and marketing the claimed invention.

Exelixis contends that there was no blocking patent for the Malate Salt Patents. (D.I. 175 at 38). The priority date of the Malate Salt Patents is January 16, 2009. (Tr. 428:8–10). The date of the '140 publication is 2005, and the '473 patent issued in 2009. (Tr. 9–21). I understand Exelixis' argument to be that the '140 publication cannot be a "blocking patent." That is true, since something that is not a patent cannot be a blocking patent. It does not follow, however, that the '140 publication is irrelevant. Dr. Steed testified that the '140 publication "would discourage [others] from adopting, of developing the kind of technology that's covered by [the '140 publication] just in case the application was granted and then they would infringe claims." (Tr. 486:24–487:2). Though it does not carry the same deterrent force as the '473 patent, I find that the '140 publication had some deterrent effect. It would be a factor to consider by a company

deciding whether to invest resources in investigating cabozantinib, since it had the potential to reduce the return on the company's investment.

v. Nexus

"For secondary considerations to have probative value, the decision maker must determine whether there is a nexus between the merits of the claimed invention and the secondary considerations." *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42 (Fed. Cir. 1985). "[T]he patented invention 'need not be solely responsible for the commercial success' of the accused products in order for a nexus to exist." *IOENGINE, LLC v. Paypal Holdings, Inc.*, 607 F. Supp. 3d 464, 508 (D. Del. 2002) (*citing Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991)). "Whether or not there is a nexus between the novel features of the patented product and the commercial success must be evaluated in terms of what is driving sales." *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 393 (D.N.J.), *aff'd*, 603 F. App'x 999 (Fed. Cir. 2015).

(a) The '349 patent

I think the purity and stability of the crystalline cabozantinib (L)-malate drives at least part of the commercial success of the drug. (FOF ¶ 23). Claim 3 of the '349 patent recites that the formulation is "essentially free" of the 1-1 impurity. ('349 patent at 34:30–51). Therefore, for the '349 patent, there is a nexus between the stability of the drug and its commercial success.

Exelixis argues that a nexus is presumed because "Cabometyx and Cometriq both embody the asserted claims and are coextensive with it." (D.I. 175 at 59–60).[16] "[I]f the

[16] Exelixis is unclear if it intends its embodiment argument for Cabometyx and Cometriq to apply to the Malate Salt Patents as well. In any event, I do not think the argument applies. The Malate Salt Patents have no purity requirements. Thus, since Cabometyx and Cometriq must be essentially free of the 1-1 impurity, they are not coextensive with the Malate Salt Patents.

marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). Coextensiveness requires that the "patentee demonstrate that the product is essentially the claimed invention." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1374 (Fed. Cir. 2019). Dr. Myerson and Dr. Donovan testified that Cabometyx and Cometriq embody the asserted claims. (Tr. 688:12–15; Tr. 422:7–9).

MSN argues that the asserted claims "are broad enough to cover devices that either do or do not solve the long-felt need," so "the evidence of non-obviousness fails because it is not commensurate in scope with the claims." (D.I. 169 at 32, quoting *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010)) (cleaned up). MSN argues that "an equally viable formulation of cabozantinib (L)-malate that is essentially free of the 1-1 impurity could also be formulated without a glidant, which is outside the scope of the asserted claim." (D.I. 169 at 32). *Therasense* is inapposite. The Federal Circuit in *Therasense* was addressing the issue of whether the claims and the invention were coextensive, and thus whether the claims included a limitation that solved the long-felt need argued by the patent owner, not whether the claims could be designed around. *Therasense*, 593 F.3d at 1336.

MSN has argued that its formulation is outside the scope of the '349 claim, and I have so found. MSN does not dispute that Cabometyx and Cometriq embody Claim 3 of the '349 patent. The purity and stability of the crystalline cabozantinib (L)-malate drives part of the commercial success. Therefore, I find that there is a nexus between Claim 3 of the '349 patent and the secondary considerations.

(b) The Malate Salt Patents

Exelixis argues that there is a "nexus between the claimed inventions of the Crystalline Malate Salt Patents and Cabometyx and Cometriq: crystalline cabozantinib (L)-malate allows the API to be manufactured and developed in a formulation that is stable, safe, and effective for patients." (D.I. 175 at 38).

I do not think that Exelixis has met its burden to show by the preponderance of the evidence that the crystalline cabozantinib (L)-malate allows the API to be manufactured in a formulation that is stable, safe, and effective for patients. Dr. Trout's testimony is insufficient, particularly given that Exelixis made the argument in its briefing that impurities could form in the manufacturing process, after the API is formed. (D.I. 175 at 40). Exelixis cannot have it both ways.

Exelixis has not met its burden to show the requisite nexus between the Malate Salt Patents and the secondary considerations.

I have found a POSA would not be motivated to control for the 1-1 impurity, add a recrystallization step, or obtain a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity. A POSA would not have a reasonable likelihood of success in using recrystallization. Therefore, I find Claim 3 of the '349 patent is non-obvious.

VIII. CONCLUSION

For the foregoing reasons, I find the asserted claim of the'349 patent not infringed and not invalid. I find the asserted claims of the Malate Salt Patents not invalid.

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