Merck Sharp & Dohme, LLC v. Mylan Pharmaceuticals Inc. et al Doc. 204

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

MERCK SHARP & DOHME LLC,

Plaintiff,

v. **CIVIL ACTION NO. 1:19CV101**
(Judge Keeley)

MYLAN PHARMACEUTICALS INC.,

Defendant.

****SEALED****

MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

I. INTRODUCTION

In this patent infringement action, the plaintiff, Merck Sharp & Dohme LLC ("Merck"), and the defendant, Mylan Pharmaceuticals Inc. ("Mylan"),[1] dispute whether Mylan has infringed claim 3 of Merck's U.S. Patent No. 7,326,708 ("the '708 patent") and claim 1 of Merck's U.S. Patent No. 8,414,921 ("the '921 patent"). They also dispute whether claims 1, 2, 3, and 19 of '708 patent are valid and enforceable.

The '708 patent and the '921 patent ("the patents-in-suit") are associated with Januvia® and Janumet®, Merck's New Drug Application ("NDA") products approved by the Food and Drug Administration ("FDA") and directed to the dihydrogenphosphate

[1] Although Merck originally included Mylan Inc. as a defendant in this action, the parties previously stipulated to its dismissal from this civil action (Dkt. No. 43).

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salt of the compound known as sitagliptin for the treatment of type 2 diabetes. Mylan seeks to market two Abbreviated New Drug Applications products ("the ANDA products") that are the bioequivalent to Januvia® and Janumet® prior to the expiration of the patents-in-suit.

The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (otherwise known as the "Hatch-Waxman Act"), seeks to encourage "pioneering research and development of new drugs," as well as the "production of low-cost, generic copies of those drugs." Eli Lilly & Co. v. Teva Pharm. USA, Inc., 557 F.3d 1346, 1348 (Fed. Cir. 2009). To that end, a manufacturer may obtain FDA approval to market a generic drug by making a certification regarding patents listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") as covering the NDA drug, and certifying that those patents are "invalid or will not be infringed by the manufacture, use, or sale of the new generic drug for which the ANDA is submitted" ("paragraph IV certification"). Id. (citing 21 U.S.C. § 355(j)(2)(A)(vii)(IV)). Following an applicant's paragraph IV certification, a patentee may sue the applicant for patent infringement within 45 days, thus delaying FDA approval of the ANDA. Id. (citing 21 U.S.C. § 355(j)(5)(B)(iii)).

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MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

In this case, where Merck has sued Mylan under the Hatch-Waxman Act for infringement of the patents-in-suit, the Court is tasked with deciding the following: (1) do Mylan's ANDA products infringe claim 3 of the '708 patent or claim 1 of the '921 patent; (2) are claims 1, 2, 3, and 19 of the '708 patent invalid under the judicially created obviousness-type double patenting doctrine; and (3) are claims 1, 2, 3, and 19 of the '708 patent invalid under 35 U.S.C. § 112 for lack of written description or enablement. Following a five-day bench trial, the parties submitted their memoranda of law, and the case is ripe for the Court's decision.

II. BACKGROUND

A. The Parties, Jurisdiction, and Venue

Merck Sharp & Dohme Corporation, a corporation organized under the laws of the State of New Jersey, with its principal place of business at One Merck Drive, Whitehouse Station, New Jersey 08889, commenced this action on May 2, 2019 (Dkt. No. 123 at 1). Due to a later transfer of ownership, however, the Court granted Merck's unopposed motion to substitute Merck Sharp & Dohme, LLC as the plaintiff in this civil action (Dkt. No. 190).[2] Merck Sharp & Dohme LLC is organized under the laws of the State of New Jersey,

[2] Effective May 1, 2022, Merck Sharp & Dohme Corporation merged into Merck Sharp & Dohme, LLC, with the latter emerging as the surviving entity (Dkt. No. 189).

with its principal place of business at 126 East Lincoln Avenue, P.O. Box 20000, Rahway, New Jersey 07065. Id. at 6. Mylan is a company organized under the laws of the State of West Virginia with its principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. Id. The Court has subject matter and personal jurisdiction, and venue in this District is proper.

B. Factual and Procedural Background

The Court begins its analysis with a review of the chemical compound known as sitagliptin, how and why pharmaceutical salts are formed, Merck's synthesis and development of the dihydrogenphosphate salt of sitagliptin, the asserted claims of the patents-in-suit, other relevant patents and patent applications, and the parties' prior art references.

1. Sitagliptin

The patents-in-suit relate to the basic compound known as "sitagliptin," 4-oxo-4-[3-trifluorom-ethyl)-5,6-dihyrdo[1,2,4] triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, belonging to a class of compounds that act as dipeptidyl peptidase-IV ("DPP-IV") inhibitors (Dkt. No. 123 at 2; JTX 001.0001; JTX 002.0002; Trial Trans. 55:5-11, 309:7-9 (Buckton)). DPP-IV is an enzyme produced by the human body to raise glucose, or blood sugar (Trial Trans. 55:5-11). Sitagliptin inhibits production of the DPP-IV enzyme to improve glycemic control in

adults with type 2 diabetes (Dkt. No. 123 at 2; Trial Trans. 268:9-13). Sitagliptin has one chiral center, or one carbon atom around which the molecule can orient itself (Trial Trans. 281:7-16 (Buckton); 535:21-23 (Shupe); 689:2-5 (Cockcroft)). Because it has one chiral center, sitagliptin has two isomers, or configurations, the (R)-configuration and the (S)-configuration. Id.

2. Salt Formation

The patents-in-suit relate to a particular salt form of sitagliptin synthesized by Merck. Pharmaceutical salts are formed by reacting an active compound with a counterpart acid or base. When a basic compound is combined with a counterpart acid, a salt forms when the acid donates a hydrogen ion to the base. Id. at 9:22-10:5. If the acid used in this reaction is polyprotic, or capable of donating multiple hydrogen ions, salts in different ratios or stoichiometries may form. Id. at 820:7-24 (Myerson).

But whether a salt will form is highly unpredictable (Trial Trans. 837:22-838:17, 840:4-841:3, 883:17-884:9 (Myerson); Dkt. No. 104-1 at 55, 58). Also unpredictable are what pharmaceutical properties any resulting salt might display (Trial Trans. 110:13-15 (Hansen); 344:18-22 (Buckton); 927:16-22 (Myerson); 740:3-6 (Wenslow)).

After selecting a chemical compound for development, pharmaceutical manufacturers may create one or more salt forms of

the compound in the hope that one such salt will possess pharmaceutical properties suitable for manufacturing, such as increased solubility, increased stability, and block-like morphology. Id. at 92:3-6 (Hansen); 287:10-19 (Buckton); 743:5-11 (Wenslow). To find salt forms of a basic compound, the manufacturer conducts a "salt screen" in which it pairs various acids and solvents with the single basic compound to determine whether a resulting salt, if any, possesses better pharmaceutical properties than the free form of the basic compound. Id. at 109:20-110:6, 113:5-14 (Hansen); 293:14-19 (Buckton); 951:11-15 (Myerson).

3. Merck's Development of the Dihydrogenphosphate Salt of Sitagliptin

In 2001, Merck set out to market the first DPP-IV inhibitor for the treatment of type 2 diabetes. Id. at 94:17-23 (Hansen). While several DPP-IV inhibitors were known in the literature, none had been approved by the FDA to treat non-insulin dependent diabetes. Id. at 94:17-18 (Hansen); 757:18-23, 773:4-7 (MacMillan)). Merck classified two lead compounds for development in its DPP-IV project, L221869 and L224715. Id. at 95:8-13 (Hansen). Compound L224715 is now known as sitagliptin. Id. at 95:24-25 (Hansen).[3]

[3] Merck first synthesized the sitagliptin free base compound in early 2001. Id. at 96:11-13 (Hansen).

To begin, Dr. Leigh Schulz conducted a preliminary assessment of the pharmaceutical properties of sitagliptin free base. Id. at 98:18-21, 99:7-25 (Hansen). According to that assessment, sitagliptin presented several hurdles to pharmaceutical development. Id. at 102:2-14, 103:10-104:4, 104:15-105:11 (Hansen). Although it had "great" solubility, it also had needle-like morphology (which is not preferred for the production of pharmaceutical tablets) and exhibited degradation and deamination (indicating instability in both solution and bulk powder). Id. As a consequence, Merck prioritized finding a salt form of sitagliptin in the hope that it would exhibit superior properties. Id. at 106:20-107:7 (Hansen).

Next, Vicky Vydra conducted a salt screen by reacting the sitagliptin free base with eleven different acids in a variety of solutions to determine if any salts would form. Id. at 110:16-25, 114:1-3, 115:10-11 (Hansen); 715:7-8 (Vydra). If a salt formed, she used x-ray powder diffraction ("XRPD") to characterize the salt as either crystalline or amorphous.[4] Id. at 115:3-11 (Hansen); 721:19-23 (Vydra).

[4] In a crystalline salt, the molecules are arranged in a repeating pattern that does not exist in an amorphous salt (Trial. Trans. 114:9-11 (Hansen); 277:7-10 (Buckton)).

During Vydra's salt screen, a salt was produced from the reaction of sitagliptin with five acids, including phosphoric acid, sulfuric acid, tartaric acid, benzene sulphonic acid, and toluene sulphonic acid. Id. at 115:5-9 (Hansen); 722:5-14 (Vydra). Vydra included hydrochloric acid in this screen, but despite the fact that another Merck employee had previously formed a hydrochloride ("HCL") salt of sitagliptin, no salt formed. Id. at 108:4-14, 114:15-115:4 (Hansen).

Thereafter, Dr. Karl Hansen performed "scaleup reactions" in which he generated larger quantities of the known sitagliptin salts to determine their viability for further development. Id. at 116:8-17 (Hansen). He replicated the phosphate salt of sitagliptin but because it appeared to be amorphous, he prioritized other salts. Id. at 117:4-19 (Hansen). After recommending the besylate and tartrate salts for further development, he returned to the phosphate salt. Id. at 122:10-17 (Hansen).

Following "a number of trial and error" experiments, Dr. Hansen synthesized a crystalline phosphate salt of sitagliptin, the dihydrogenphosphate ("DHP") salt, which he also recommended for development. Id. at 122:10-17 (Hansen). Because phosphoric acid can donate up to three protons and sitagliptin can receive up to two protons, salts from this reaction may form in different stoichiometries. Id. at 820:8-9, 821:11-13, 821:17-20, 879:4-7

(Myerson); 157:11-13 (Hansen). In the DHP salt of sitagliptin formed by Dr. Hansen, phosphoric acid and sitagliptin exist in a 1-to-1 ratio (Dkt. No. 104-1 at 3). Later, Dr. Hansen also synthesized an HCL salt of sitagliptin after "a lot of experimentation" but he did not recommend it for development due to its instability and needle-like morphology (Trial Trans. 116:25-117:3, 128:12-24 (Hansen)).

These salts recommended by Dr. Hansen were referred back to Dr. Schulz to undergo a preliminary assessment. Id. at 118:20-119:1 (Hansen). Her assessment allowed Merck's DPP-IV team to compare the pharmaceutical properties of each salt. Ultimately, that comparison established that the DHP salt was superior to the besylate and tartrate salts because it had good solubility, was the most stable, and eliminated several of the hurdles the other salts presented. Id. at 118:20-119:1, 120:11-22 (Hansen). And, unlike the besylate and tartrate salts, the DHP salt showed no signs of degradation in a bulk powder. Id. at 120:25-122:8, 124:13-126:5 (Hansen). It also presented the lowest risk of liquifying at a higher humidity; appeared to only have one polymorph, or distinct crystalline structure; and exhibited a "flake-like" morphology, rather than the "needles and rods" morphology known to inhibit production. Id. Surprised to discover this unique set of favorable

properties,[5] the members of Merck's DPP-IV team selected the DHP salt for continued development. Id. at 129:2-5 (Hansen).

Initially, the DPP-IV team believed the DHP salt existed in one form only, an anhydrous crystalline polymorph that did not contain water in the crystal lattice. Id. at 126:7-10; 129:10-13 (Hansen); 278:23-25 (Buckton). But later the team discovered several other anhydrous forms, id., and in April 2003 Stephen Cypes unexpectedly synthesized a hydrated form of the DHP salt. Id. at 129:18-130:1 (Hansen). Before this, Merck's DPP-IV team had believed no hydrated DHP salt could exist.[6] Id. at 132:18-133:10 (Hansen).

Merck's DPP-IV team then determined that the newly discovered, crystalline monohydrate[7] form of the DHP salt possessed exceptional pharmaceutical properties, superior even to the properties of its anhydrous forms. Id. Its morphology was more

[5] In an email to other members of the DPP-IV team discussing the properties of DHP salt of sitagliptin, Ivan Santos, the head of Merck's physical measurements team stated: "I too recommend the phosphate salt. Given the data we have to date, we have a simple solid-state system, good solubility and stability, a workable morphology. This is incredible. Not often do we see these." (PTX 082.0001; Trial Trans. 126:19-22 (Hansen)).

[6] Prior to Cypes's synthesis of the crystalline monohydrate, Dr. Hansen had unsuccessfully attempted to create a hydrated form of the DHP salt. Id. at 132:18-25, 133:10. Determining whether hydrated forms of the salt could be synthesized was important to Merck because hydrated salt forms could have presented additional hurdles its development program. Id.

[7] In the crystalline monohydrate form, water and the DHP salt exist in a 1-to-1 ratio in the crystal lattice.

suitable to manufacturing and it had only one polymorph. Id. at 133:12-134:22 (Hansen). Notably, as of 2021, the crystalline monohydrate remains the only known hydrate of the DHP salt of sitagliptin. Id. at 134:23-135:1 (Hansen).

Based on all this, Merck's DPP-IV team chose to commercialize the crystalline monohydrate form of the DHP salt of sitagliptin. Id. at 136:12-14, 147:17-148:10 (Hansen). After clinical studies indicated that it could be effective in the treatment of diabetes, this salt became the active ingredient in the first FDA approved DPP-IV inhibitor to treat diabetes, Merck's Januvia® product. Id. at 97:15-98:5 (Hansen). It also became the active ingredient in Merck's Janumet® product, which combines sitagliptin with metformin to treat diabetes and hypertension. Id. at 180:23-181:1 (Alani).

4. The Asserted Claims

The '708 patent covers the 1-to-1 DHP salt of sitagliptin and methods of use. The '921 patent describes pharmaceutical compositions of the 1-to-1 DHP salt of sitagliptin in combination with metformin.

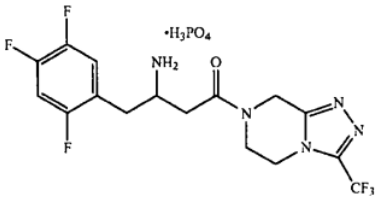
a. The '708 Patent

The '708 patent, filed on June 23, 2004, is titled "Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitor" (JTX 001.0001). It lists Stephen Cypes, Alex Chen, Russell Ferlita, Karl Hansen,

Ivan Lee, Vicky Vydra, and Robert Wenslow, Jr. as inventors and Merck as the assignee. Id. Issued on February 5, 2008, the patent, with pediatric exclusivity, expires on March 24, 2027[8] (Dkt. No. 123 at 2-3). The asserted claims are as follows:

1. A dihydrogenphosphate salt of 4-oxo-4-[3-trifluorom-ethyl)-5,6-dihyrdo [1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine of structural formula I:

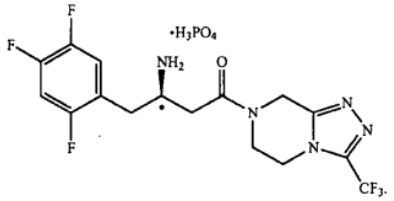
(I)



or a hydrate thereof.

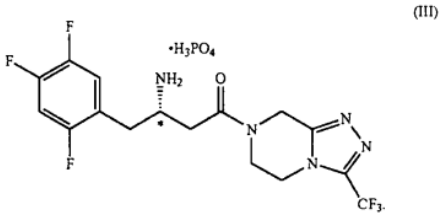
2. The salt of claim 1 of structural formula II having the (R)-configuration at the chiral center marked with an *

(II)



3. The salt of claim 1 of structural formula III having the (S)-configuration at the chiral center marked with an *

[8] Without pediatric exclusivity, the '708 patent expires on November 24, 2026 (Dkt. No. 123 at 3).



> 19. A method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim 2 or a hydrate thereof.

JTX 001.0014-15. Claims 4 through 16 of the '708 patent, no longer at issue in this case,[9] relate to the crystalline monohydrate form of the 1-to-1 DHP salt of sitagliptin. Id. Merck alleges that Mylan's ANDA products will infringe claim 3 of the '708 patent. Mylan alleges that claims 1, 2, 3, and 19 of the '708 patent are invalid and unenforceable.

b. The '921 Patent

The '921 patent, filed on December 16, 2005, is titled "Pharmaceutical Compositions of Combinations of Dipeptidyl Peptidase-4 Inhibitors with Metformin" (Dkt. No. 123 at 3-4; JTX 002.0001). It lists Ashkan Kamali, Laman Alani, Kyle Fliszar, Soumojeet Ghosh, and Monica Tijerina as inventors and Merck as the assignee (JTX 002.0001). Issued on April 13, 2013, the patent,

[9] Prior to trial, Merck withdrew its allegation that Mylan's ANDA products infringe claims 4-16 of the '708 patent (Dkt. No. 152).

with pediatric exclusivity, expires on January 21, 2029 (Dkt. No. 123 at 4).[10] The following claim is asserted:

> 1. A pharmaceutical composition comprising:
> (a) about 3 to 20% by weight of sitagliptin, or a pharmaceutically acceptable salt thereof;
> (b) about 25 to 94% by weight of metformin hydrochloride;
> (c) about 0.1 to 10% by weight of a lubricant;
> (d) about 0 to 35% by weight of a binding agent;
> (e) about 0.5 to 1% by weight of a surfactant; and
> (f) about 5 to 15% by weight of a diluent.

(JTX 002.0007). Merck alleges that Mylan's ANDA products will infringe each element of this claim.

5. Claim Construction

On August 8, 2019, the United States Judicial Panel on Multidistrict Litigation granted Merck's request to centralize pretrial proceedings in this case with Merck's thirteen other lawsuits against generic manufacturers related to its Januvia® and Janumet® products then pending in the District of Delaware (Dkt. No. 49). In that litigation, Judge Richard Andrews construed several terms in the claims at issue before this Court. See generally, In re Sitagliptin Phosphate ('708 & '921) Pat. Litig., 2020 WL 6743022, at *3 (D. Del. Nov. 17, 2020).[11]

[10] Without pediatric exclusivity, the '921 patent expires on July 21, 2028 (Dkt. No. 123 at 4).

[11] Because Mylan had instigated an inter partes review of the '708 patent, it did not propose constructions of the disputed terms or join in the other defendants' proposed constructions. In re Sitagliptin, 2020 WL 6743022 at n.1.

As proposed by Merck, Judge Andrews construed the term "the salt of claim 1 [or 2]" in claims 2 and 3 of the '708 patent to include hydrates of the molecules described. Id. at *4. He construed the term "crystalline monohydrate" used in claims 4 and 24 of the '708 patent as "a repeating unit cell incorporating a 1:1 ratio of water to a dihydrogenphosphate salt of sitagliptin." Id. at *3. He also construed the term "surfactant" in claim 1 of the '921 patent as a "surfactant that works as a wetting agent to increase the dissolution of sitagliptin." Id. at *8, *11.

Judge Andrews rejected the generics' suggestion to limit the term "sitagliptin" in claim 1 of the '921 patent to "the dihydrogenphosphate salt of sitagliptin in the form of a monohydrate." Id. at *11-12. He was unpersuaded that Merck had thus limited the scope of the term during prosecution where it cited to the unexpected results of the specific crystalline monohydrate form of the DHP salt. Id. He found that this single comment in the prosecution history did not "rise to the level of clear and unmistakable disavowal." Id. at *12.

6. Related Patents and Applications

a. U.S. Patent Number 6,699,871

U.S. Patent Number 6,699,871 ("the '871 patent"), filed on July 5, 2002, is titled "Beta-Amino Heterocyclic Dipeptidyl Peptidase Inhibitors for the Treatment or Prevention of Diabetes"

(DTX 2054.0001). It lists Scott Edmonson, Michael Fisher, Dooseop Kim, Malcolm Maccoss, Emma Parmee, Anne Weber, and Jinyou Xu as inventors and Merck as the assignee. Id. Issued on March 2, 2004, with pediatric exclusivity, the patent expires on January 26, 2023 (Dkt. No. 123 at 9-10).[12]

The '871 patent is directed to DPP-IV inhibitors "which are useful in the treatment or prevention of diseases in which the [DPP-IV] enzyme is involved, such as diabetes and particularly type 2 diabetes" (DTX 2054.0001). It is also directed to "pharmaceutical compositions comprising of these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases." Id. This patent discloses thirty-three (33) DPP-IV inhibiting compounds, including sitagliptin. Id. at .0019-21.

Claims 17 and 20 of the '871 patent are relevant to the issues in this case. Claim 17 depicts the sitagliptin compound in its (R)-configuration "or a pharmaceutically acceptable salt thereof." Id. at .0022. Claim 20 covers "[a] pharmaceutical composition which comprises an inert carrier and a compound of claim 17." Id.

The '871 patent specification defines "pharmaceutically acceptable salts" as those "prepared from pharmaceutically

[12] Without pediatric exclusivity, the '871 patent expires on July 26, 2022 (Dkt. No. 123 at 10).

acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids." Id. at .0004. The specification also states that "[w]hen the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids." Id. It then provides a list of twenty-six (26) acceptable acids and a list of eight (8) preferred acids, both of which include phosphoric acid. Id. at .0004-05.

The specification also provides that each of the claimed compounds has one chiral center that can produce two isomers "and it is intended that all of the possible optical isomers . . . are included within the ambit of this invention." Id. at .0004. Example 7 of the '871 patent depicts an HCL salt of sitagliptin, id. at .0018, but the '871 patent does not describe or exemplify any phosphate salt of sitagliptin, or any other compound.

b. W/O 03/004498

W/O 03/004498 ("WO '498") is an international patent application filed by Merck prior to the patents-at-issue and is directed to DPP-IV inhibitors "which are useful in the treatment or prevention of diseases in which the [DPP-IV] enzyme is involved, such as diabetes and particularly type 2 diabetes" (DTX 036.0004). The specifications of the '871 patent and WO '498 are substantively identical (Trial Trans. 327:25-328:2 (Buckton)).

c. Patent Application Publication No. 2006/0287528

Patent Application Publication No. 2006/0287528 ("the '528 publication"), filed on September 3, 2003, is titled "Novel Crystalline Forms of a Phosphoric Acid Salt of a Dipeptidyl Peptidase Inhibitor" and lists Robert Wenslow, Joseph Armstrong III, Alex Chen, Stephen Cypes, Russell Ferlita, Karl Hansen, Christopher Lindemann, and Evangelia Spartalis as inventors (DTX 2198.0001). On March 18, 2008, the USPTO issued a Notice of Abandonment of the '528 publication (Dkt. No. 123 at 9-11).

d. Common Ownership

Each inventor of the '708 patent, the '871 patent, and WO '498 assigned their inventions, patent applications, and patents to Merck. Id. at 17. Thus, the subject matter of the '708 patent, the '871 patent, and WO '498 were commonly owned by Merck at the time of the inventions claimed in the '708 patent. Id.

7. Inter Partes Review

On May 7, 2021, the United States Patent Trial and Appeal Board ("PTAB") adjudicated Mylan's petition for inter partes review of claims 1, 2, 3, 4, 19, 21, 22, and 23 of the '708 patent (Dkt. No. 104-1). In this proceeding, Mylan raised anticipation and obviousness challenges to the asserted claims pursuant to 35 U.S.C. § 102 and § 103, respectively. Id. at 4-5.

The PTAB concluded that WO '498 did not expressly or inherently disclose the 1-to-1 DHP salt of sitagliptin used in Merck's Januvia® and Janumet® products. Id. at 41. And because no other prior art disclosed that phosphoric acid and sitagliptin could form non-1-to-1 salts, the PTAB concluded that Mylan's anticipation challenges based on WO '498 and the '871 patent failed. Id. at 41-43.

And because Merck had reduced to practice the subject matter of claims 1, 2, 17, 19, 21, 22, and 23 before WO '498 was published, and given that both the '708 patent and WO '498 were commonly owned by Merck, the PTAB concluded that WO '498 could not be used as a prior art reference under § 102(a). Id. at 69. As to claims 3 and 4 of the '708 patent that remained subject to Mylan's obviousness challenge, the PTAB determined that neither of these claims was obvious in view of the prior art. Id.

8. Mylan's Accused ANDA Products

Mylan submitted ANDA No. 202473 to the FDA seeking approval to manufacture a generic version of Merck's Januvia® product prior to the expiration of the '708 patent (Dkt. No. 123 at 11). It also submitted ANDA No. 202478 to the FDA seeking approval to manufacture a generic version of Merck's Janumet® product prior to the expiration of the patents-in-suit. Id.

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One of the active pharmaceutical ingredients ("APIs") in Mylan's ANDA products [redacted]

Mylan's Janumet® ANDA product is [redacted]

[redacted]

[redacted]

9. Prior Art

a. Berge

Berge, a journal article published in 1977, teaches that salt formation is crucial to the pharmaceutical industry because it alters the properties of a new drug entity and allows the most suitable form of the drug to be developed (DTX 006.0004-05). But Berge warns that choosing the most suitable salt form is a "very difficult task, since each imparts unique properties to the parent compound" and there are numerous available salt forms. Id. at .0001-02. Further, salt formation is highly unpredictable and "there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." Id. at .0001.

Various salt forms of the same compound have different physical, chemical, and thermodynamic properties. Id. at .0001-02. Due to this unpredictability, "[s]alt-forming agents are often chosen empirically. Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists primarily on a practical basis: cost of raw materials, ease of crystallization, and percent yield. Other basic considerations include stability,

hygroscopicity, and flowability of the resulting bulk drug." Id. at .0001.

Berge also discloses a list of FDA approved salts of basic drugs. Chloric, hydrochloric, and dihydrochloric acids were the most frequently used acids, appearing in 47.66% of the salts of basic drugs. Id. at .0004. Phosphoric and diphosphoric acids were the fourth most frequently used acids, found in 3.16% of the salts of basic drugs. Id.

b. Gould

Gould, a journal article published in 1986, discusses salt selection for basic drugs and describes the ideal salt as "chemically stable, non-hygroscopic, not [the] cause [of] processing problems, and . . . quick[] [dissolving] from solid dosage forms" (DTX 012.0005). It also teaches that, based on its availability and pharmaceutical properties, hydrochloride salts are "by far the most frequent (~40%) choice" of all the available acids. Id. at .0005.

According to Gould, "there is clear precedent, and an overwhelming argument on many grounds to immediately process to the hydrochloride salt and evaluate other forms only if problems with the hydrochloride emerge." Id. Such problems may include a reduced dissolution rate in gastric fluid, a very low pH in aqueous solution, excessive hygroscopicity, and reduced stability. Id. at

.0005-06. Ultimately, Gould instructs that "progression of a hydrochloride salt should be a first move," but if issues arise other acids should be considered based on trends reported in the literature. Id. at .0006, .0015.

c. Bighley

Bighley, the Encyclopedia of Pharmaceutical Technology, published in 1996, updates Berge's list of FDA approved salts of basic drugs (DTX 007.0003-05). Although twice as many salts existed, hydrochloric acid remained the most frequently chosen acid, appearing in approximately 48% of salts. Id. at .0003-04. The second and third most frequent chosen acids were sulfate and bromide, appearing in 5.85% and 3.79% of salts, respectively. Id. at .0004-05. Citrate, malleate, mesylate, tartrate, and phosphate were the next most frequently chosen acids, appearing in a similar percentage of salts. Id. Specifically, phosphoric acid, the eighth most frequently chosen acid, appeared in 2.48% of salts. Id.

Bighley also provides a "decision tree to create a prototype thought process whereby a suitable salt form can be chosen in an efficient and timely manner with few false starts and the minimum expenditure of resources." Id. at .0029-30. Pursuant to this tree, the chemist first determines if a salt form is needed, or if the compound is viable per se. Id. at .0030-31. Second, the chemist prepares the hydrochloric salt. Id. at .0034. At this step, Bighley

teaches that "the range of anions available for salt formation depends on the pK_a of the conjugate acid relative to the basicity of the drug itself. There should be at least one unit of separation between the pK_a of the basic drug and that of the anion."[14] Id. Accordingly, hydrochloric acid is popular because, with a pK_a of -6, it is a very strong acid and can form a salt with most basic drugs. Id. Third, the chemist studies the physical properties of the hydrochloride salt to determine if it presents any known hurdles to development.[15] Id. at .0034-35. Fourth, the chemist prepares other mineral acid salts which are typically used to reduce hygroscopicity and acidity where necessary. Id. at .0035. Fifth, the chemist characterizes the chemical stability of the prepared salts. Id. at .0035-36. Sixth, the chemist prepares organic salts which can be used to resolve specific problems, such as high acidity, drug-excipient interactions, or low water solubility. Id. at .0036. Seventh, the chemist tests absorption to determine if a salt form with a greater aqueous solubility is needed. Id. at .0036-37. Finally, the chemist selects the salt

[14] The pK_a value is a measurement of the acidity of a molecule whereby lower values indicate that the compound is a strong acid and higher values indicate that the compound is a strong base (Trial Trans. 157:2-4 (Hansen); 284:18-21 (Buckton)).

[15] The known risks of using hydrochloric acid to create pharmaceutical salts included the common ion effect, hygroscopicity, powder handling problems, and corrosion of machinery. Id. at .0034-35.

form most suitable for commercialization based on its aggregate properties. Id. at .0037.

Bighley teaches that efficiency in salt selection is imperative because the decision "lies fairly and squarely on the critical path of the drug's development schedule." Id. at .0037. Accordingly, the chemist should narrow down the potential acids, then select and prepare "only several salt form[s] for experimentation" based on the known pharmaceutical properties of the basic compound. Id. Salt selection then "becomes a compromise situation, balancing the desirable attributes vs. the undesirable ones and making the decision process transparent to all." Id.

d. Bastin

Bastin, a journal article published in 2000, discusses salt selection and procedures for optimizing new drug entities (DTX 005.0001). It reiterates that the benefit of salt selection is that it allows scientists to develop a dosage form with the best pharmaceutical properties, including solubility, melting point, hygroscopicity, chemical stability, dissolution rate, solution pH, and crystal form. Id. Bastin teaches that, after a chemist has identified a lead compound for development, "[i]nvariably, the first information generated for each candidate is the calculated pK_a value." Id.

> Knowledge of the pK_a value enables potential salt forming agents (counter[-]ions) to be selected, for each candidate, based on lists that are available in the literature. For the formation of a stable salt, it is widely accepted that there should be a minimum difference of about 3 units between the pK_a value of the [compound] and that of its counter[-]ion, especially when the drug substance is a particularly weak acid or base. Occasionally, exceptions may be found where a salt has an acceptable stability, despite there being a smaller difference in the pK_a values.

Id. at .0001-02. Having identified potential salt forms, the chemist then compares the properties of each and proposes "a single salt for further study, although . . . it is occasionally found that the overall properties of the free acid/base are much better than any of the salts." Id. at .0004.

According to Bastin, if the salt is being created to enhance aqueous solubility of weak basic drug substances, organic acids such as hydrochloride, sulphate, or phosphate should be considered. Id. at .0002. Hydrochloric acid is "the first choice for weakly basic drugs" because it can "nearly always" form a salt. Id. But it has potential disadvantages, such as high acidity in formulations, high risk of corrosion, suboptimal solubility, and poor stability if the drug is hygroscopic. Id. Bastin includes three examples of salt screens with basic compounds. Id. at .0004-06. In each example, the chemist either chose not to include phosphoric acid in the salt screen, or a phosphoric salt did not form. Id.

e. Aulton

Aulton teaches the importance of determining the pK_a value of a new drug entity (DTX 235). "[I]f nothing else is measured, the solubility and the pK_a must be determined. These control all future work. . . The pK_a allows the informed use of pH to maintain solubility and to choose salts should they be required to achieve good bioavailability from the solid state . . . and improve stability . . . and powder properties." Id. at .0008.

f. Stahl

Stahl, a textbook titled the Handbook of Pharmaceutical Salts: Properties, Selection, and Use published in 2002, teaches that half of all drug entities are administered as salts. Accordingly, finding an appropriate salt form of a drug molecule is an "essential step in drug development" (DTX 021.0001). Due to the important and often irreversible nature of salt selection in pharmaceutical development, "a rational strategy should be followed in order to guide the selection processing in an economic way." Id. at .0010.

But Stahl also teaches that "[n]o predictive procedure to determine whether a particular acidic or basic drug would form a salt with a particular counter-ion has been reported in the literature." Id. at .0062. Earlier research had suggested that salt formation depends on the acid's pK_a value being at least two

pH units lower than the pK_a value of the basic drug. Id. at .0062-63. According to Stahl, however, while pK_a could be a valuable guideline, "a more predictive method for assessing the feasibility of salt formation would be necessary to minimize trials and errors in the salt-selection program." Id. at .0063. Stahl asserts that the pH-solubility relationship is more critical in determining which salt, if any, can be synthesized for a particular basic drug. Id. at .0063-65. Later Stahl recommends that "for the formulation of a stable salt, there should be a minimum difference of . . . three units between the pK_a value of the ionizable group and a possible counter-ion." Id. at .0091.

Stahl next discloses notable pharmaceutical properties of various acids used to form salts of basic drugs. Id. at 0.0136-38. Hydrochloric acid, the most widely used acid due to its tendency to form salts, carries the risk of corroding stainless-steel equipment and being unstable long-term in very weak bases. Id. at. 0136, .0169. Phosphoric acid tends to form thermally stable salts that can be used to enhance water solubility, but it carries the risk of forming hydrates. Id. at .0137, .0182.

Stahl also updates the list of FDA approved salts of basic drugs reported in Berge and Bighley. Id. at 021.0210. Stahl organizes the acids by pK_a value and discloses that the pK_a value

of phosphoric acid's first, second, and third protons are 1.96, 7.12, and 12.32, respectively. Id. at .0215-16.

Finally, Stahl teaches that a compound's pharmaceutical properties may vary from one polymorph to another. Id. at .0007. It also teaches that polymorphs can be characterized using routine techniques. Id.

g. Davies

Davies, a journal article published in 2001, discusses the impact of changing the salt forms of a compound. Specifically, it teaches that "different salts of the same active drug are distinct products with their own chemical and biological profiles that underlie differences in their clinical efficacy and safety" (PTX 113.0001). But there is "no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity . . . ," or the way that it is "handled by the body." Id.

h. Remington

Remington, a textbook titled The Science and Practice of Pharmacy and published in 2006, teaches that pharmacists must understand the degree of permissible error in weighing and measuring ingredients (PTX 650.0015). It also describes the types of balances that may be used in measuring operations and teaches that they "must be used within a degree of error that can be

tolerated in prescription compounding and in pharmaceutical manufacturing. The USP allows a maximum error of 5% in a single weighing operation." Id. at .0015-19.

Remington further teaches that, when measured quantities are written, "the numbers should contain only those digits that are significant within the precision of the instrument." Id. at .0022 (emphasis in original). It also defines significant digits as those with practical meaning based on the precision of the weighing instrument. Id.

i. United States Pharmacopeia and National Formulary

"The United States Pharmacopeia and the National Formulary are recognized as official compendia and are referenced in various statutes for a basis for determining the strength, quality, purity, packaging, and labeling of drugs and related articles" (PTX 651.0007). The USP-NF teaches how to compare measured values to a stated limit to determine conformance. Id. at .0012. "The observed or calculated values usually will contain more significant figures than there are in the stated limit and an observed or calculated result is to be rounded off to the number of places that is in agreement with the [stated] limit. . . ." Id.

j. Handbook of Pharmaceutical Excipients

The Handbook of Pharmaceutical Excipients, a textbook published in 2003, provides monographs of common pharmaceutical

excipients (PTX 594.0004-05). It teaches that pregelatinized starch ("PGS"), "is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and disintegrant" and may be used in dry-compression or wet granulation manufacturing processes. Id. at .0025. And it also provides that PGS typically "contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch." Id.

k. The Handbook of Pharmaceutical Granulation Technology

The Handbook of Pharmaceutical Granulation Technology, a textbook published in 2005, teaches that PGS "is a modified starch used in tablet formulations as a binder, diluent, and disintegrant. It is obtained by chemically and mechanically processing the starch to rupture all or part of the starch granules" (DTX 2136). It further specifies that Starch 1500, a form of PGS, "contain[s] 20% maximum cold-water soluble fraction, which makes it useful for wet granulation. The water-soluble fraction acts as a binder, while the remaining fraction facilitates the tablet disintegration process." Id. at .0016.

l. Multifunctional Excipients

Multifunctional Excipients, a journal article published in 2006, "presents a case history of a pharmaceutical manufacturer that replaced a polymer binder, a super disintegrant and a portion

of a standard filler with a multifunctional partially pregelatinized starch . . . and achieved remarkable results" (PTX 552.0001). It teaches that Starch 1500 outperformed the individual ingredients and had an estimated cost savings of 60%. Id. "One key reason is that Starch 1500 performs multiple functions within a wet granulation formulation, as a binder, disintegrant, filler and lubricant, eliminating the need for a multitude of costly excipients and additional processing steps." Id.

m. Pharmaceutical Powder Compaction Technology

Pharmaceutical Powder Compaction Technology, a textbook published in 2011, teaches that native starches consist of two polysaccharides, amylopectin and amylose (PTX 585.0026). "Amylose is a linear polymer and represents approximately 27% by weight, while amylopectin has a branched structure and represents about 73% by weight." Id.

n. Bernstein

Bernstein, a journal published in 1993, examines polymorph forms and teaches that "[v]irtually all compounds are polymorphic and the number of polymorphs of a material depends on the amount of time and money spent in research on that compound" (PTX 213.0002).

o. Vippagunta

Vippagunta, journal published in 2001, discusses recent advances in predicting and characterizing polymorphs (DTX 047). It teaches that predicting hydrate formation is "complex and difficult" and, because each solid compound responds different, generalizations about hydration formation cannot be made. Id. at .0016. Nevertheless, once hydrates are formed, a POSA could characterize them with one of several common methods. Id.

III. DISCUSSION OF FACTS AND LAW

A. Person of Ordinary Skill in the Art

Determining who constitutes a person of ordinary skill in the art ("POSA") is a factual question. See ALZA Corp. v. Andrx Pharm., LLC, 603 F.3d 935, 940 (Fed. Cir. 2010). To determine the level of ordinary skill in the art, courts consider the following non-exhaustive factors: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." Daiichi Sankyo Co., Ltd. v. Apotex, Inc., 501 F.3d 1254, 1256 (Fed. Cir. 2007).

1. The '708 Patent

The parties offer similar definitions of a POSA to whom the '708 patent is directed, and experts for both parties testified

that adopting the other party's definition of a POSA would not alter their opinions (Trial Trans. 546:17-20 (Myerson); 687:25-688:13 (Cockcroft); 757:6-8 (MacMillan)).

According to Mylan, a POSA would (1) have a doctoral degree in pharmaceutical sciences, a field of chemistry relating to crystals in drug delivery, or some other related field; (2) have two years of experience working with solid state materials for pharmaceuticals, including their characterization in relation to the development of pharmaceutical formulations; and (3) work in a multidisciplinary team and interact with individuals possessing specialized skills, such as a clinician (Trial Trans. 273:1-14 (Buckton)). A POSA could have a lower education level with a commensurate increase in years of relevant work experience. Id.

Merck similarly asserts that a POSA would (1) have a doctoral degree in chemistry, chemical engineering, or a related field; (2) have two years of laboratory experience working with pharmaceutical solids, including polymorph forms; (3) be familiar with "a variety of issues relevant to developing pharmaceutical solids, including, among other things, analytical characterization techniques and pharmaceutical formulations;" and (4) have a medical degree and experience in treating patients with type 2 diabetes. Id. at 545:1-13 (Myerson). A POSA could have a lower

education level with a commensurate increase in years of relevant work experience. Id.

Merck's requirement that a POSA also have a medical degree is the only meaningful difference between the parties' definitions. But at trial Merck's expert clarified that an individual without a medical degree still would satisfy its definition of a POSA by working as part of a team with a medical doctor having knowledge of type 2 diabetes. Id. at 545:17-546:2 (Myerson).

Based on the parties' definitions and the evidence introduced at trial, the Court finds that a POSA should (1) have a doctoral degree in chemistry, chemical engineering, pharmaceutical sciences, or another related field; (2) have at least two years of experience working with pharmaceutical solids, including polymorph forms and characterization; (3) be familiar with issues that arise in the development of pharmaceutical solids; and (4) work as part of a multidisciplinary team and have access to a clinician or medical doctor with experience treating type 2 diabetes. A POSA may have a lower education level so long as she has have a commensurate increase in years of relevant experience.

2. The '921 Patent

The parties offer similar definitions of a POSA to whom the '921 patent is directed, and their experts' opinions would not change if the Court adopted the other party's definition Id. at

572:8-14. According to Mylan, a POSA would (1) have a doctoral degree in chemistry, biochemistry, medical chemistry, pharmacy, pharmaceutics, or a related discipline, and two years of relevant experience in drug development; (2) be familiar with oral dosage forms and excipients; (3) understand that the drug product development process is multidisciplinary; and (4) draw upon their own skill set as well as the specialized skills of their colleagues to solve problems. Id. at 572:13-573:2 (Crowley). A POSA could have a lower education level with a commensurate increase in years of relevant work experience. Id.

Merck submits that a POSA would have (1) a doctoral degree in pharmaceutical science, chemical engineering, or a related field; (2) work experience in developing or analyzing solid oral pharmaceutical dosage forms, or a related field; and (3) a medical degree or other clinical experience in treating patients with type 2 diabetes (DTX 2114.0017). A POSA could have a lower education level with a commensurate increase in years of relevant work experience. Id.

Because the slight differences in the parties' definitions do not impact their experts' opinions, the Court determines that a POSA should have (1) a doctoral degree in pharmaceutical science, chemical engineering, chemistry, biochemistry, or a related field; (2) experience in drug development of solid oral pharmaceutical

dosage forms; (3) access to a multidisciplinary team that includes an individual with a medical degree or other clinical experience in treating patients with type 2 diabetes. A POSA may have a lower education level so long as she has a commensurate increase in years of relevant experience.

B. Infringement of the Patents-in-Suit

Merck contends that Mylan's Janumet® ANDA Products infringe claim 3 of the '708 patent and claim 1 of the '921 patent.

1. Legal Standard

"[W]hoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). "The patentee bears the burden of proving infringement by a preponderance of the evidence." Creative Compounds, LLC v. Starmark Lab'ys, 651 F.3d 1303, 1314 (Fed. Cir. 2011) (quoting SRI Int'l v. Matsushita Elec. Corp., 775 F.2d 1107, 1123 (Fed. Cir. 1985)). "An infringement analysis entails two steps. The first step is determining the meaning and scope of the patent claims asserted to be infringed. The second step is comparing the properly construed claims to the device accused of infringing." Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc) (citation omitted). The first step is a question of law, id.

at 979, while the second step is a question of fact. Spectrum Pharms., Inc. v. Sandoz Inc., 802 F.3d 1326, 1337 (Fed. Cir. 2015).

2. Mylan's ANDA Products Infringe Claim 3 of the '708 Patent

a. The Parties' Contentions

The parties dispute whether Mylan has infringed claim 3 of the '708 patent, which covers the DHP salt of sitagliptin in the (S)-configuration (JTX 001.0014). Their dispute turns on which of two Federal Circuit precedential cases govern the Court's infringement analysis.

Merck contends that, under Sunovion Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc., 731 F.3d 1271, 1278 (Fed. Cir. 2013), the relevant inquiry is whether Mylan has sought FDA approval to sell a product that may contain any amount of the DHP salt of sitagliptin in the (S)-configuration (Dkt. No. 181 at 2-3). Because Mylan's ANDAs request approval to sell products that

[redacted]

Mylan, on the other hand, asserts that, under Glaxo, Inc. v. Novopharm Ltd., 110 F.3d 1562 (Fed. Cir. 1997), the relevant inquiry is whether it is likely to sell a product that contains the DHP salt of sitagliptin in the (S)-configuration following FDA approval (Dkt. No. 177 at 32-33). And because there is no evidence

that Mylan's generic products contain [redacted] Id. at 32-34.

b. Applicable Law

Under 35 U.S.C. § 271(e)(2), it is an act of infringement to submit an ANDA "'for a drug claimed in a patent or the use of which is claimed in a patent.'" Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1354 (Fed. Cir. 2003) (quoting § 271(e)(2)). This creates "a highly artificial act of infringement that consists of submitting an ANDA . . . containing" a paragraph IV certification that erroneously claims a generic drug will not infringe a patent covering the pioneer drug. See Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 678 (1990). Accordingly, § 271(e)(2) vests the court with jurisdiction to determine "if a particular drug were put on the market, it would infringe the relevant patent." Bristol-Myers Squibb Co. v. Royce Lab'ys, Inc., 69 F.3d 1130, 1135 (Fed. Cir. 1995).

In Glaxo, Inc. v. Novopharm Ltd., the Federal Circuit, applying these principles, held that in suits brought under § 271(e)(2) "[t]he relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product. What is likely to be sold, or, preferably, what will be sold, will ultimately

determine whether infringement exists." 110 F.3d at 1570. It then instructed courts to consider "all of the relevant evidence, including the ANDA" to determine what product the generic would likely sell if its ANDA were approved. Id. at 1570.

The compound at issue in Glaxo was capable of existing in multiple forms and the ANDA stated that the generic product would contain one form of the compound. Id. at 1565-66. But the ANDA did not address whether the product would also contain the particular form of the compound covered by the disputed patent. Significantly, there was no evidence in the ANDA that the generic product contained the claimed form of the compound. Id.

After considering all this, the Federal Circuit concluded that the patentee had not proven by a preponderance of the evidence that the generic would likely market a product containing the claimed form of the compound. The generic's filing of the ANDA therefore did not constitute infringement of the disputed patent. Id. at 1570.

Later, in Sunovion Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc., the Federal Circuit held that in such suits brought under § 271(e)(2) "[w]hat a generic asks for and receives approval to market, if within the scope of a valid claim, is an infringement," even where internal documents suggest that the generic product will not meet the disputed claim limitation in

practice. 731 F.3d at 1279. The disputed patent in Sunovion claimed a compound in its (S)-configuration and specified that the invention was "essentially free" of the (R)-configuration. Id. at 1273-74. The district court construed "essentially free" to mean "less than 0.25%" of the (R)-configuration. Id. at 1274-75. In its ANDA specification, the generic requested FDA approval to market a product containing between 0.0% and 0.6% of the claimed compounds in its (R)-configuration. Id. at 1274-75.

Following the district court's claim construction, the generic submitted a declaration to the district court representing that, if granted FDA approval, it would limit its product to between 0.3% and 0.6% of the (R)-configuration. Id. at 1275. In light of that representation, the district court concluded that the generic product would not infringe the disputed patent. Id.

On appeal, the Federal Circuit affirmed the district court's claim construction but reversed its finding of non-infringement. Id. at 1280. In doing so, it specifically held that the language of the ANDA controlled the infringement analysis. Because the generic had sought FDA approval to sell a product containing an amount of the (R)-configuration that fell within the range claimed in the disputed patent, the ANDA product would infringe the patent regardless of the generic's representations to the court. Id.

In several later decisions, the Federal Circuit has distinguished its infringement analyses in Glaxo and Sunovion. As this Court understands the distinction, Glaxo governs cases where a generic's ANDA is silent with respect to a claim limitation, while Sunovion governs cases where a generic's ANDA defines a compound in such a way that it meets a limitation of an asserted claim. See Ferring B.V. v. Watson Lab'ys, Inc.-Fla., 764 F.3d 1382 (Fed. Cir. 2014) (applying Glaxo to the generic's first ANDA because, unlike the disputed patent, it did not include a dissolution rate of an essential ingredient, but applying Sunovion to the generic's second ANDA, which did specify a dissolution rate).

In Par Pharmaceuticals, Inc. v. Hospira, Inc., 835 F. App'x 578 (Fed. Cir. 2017), a case discussed in detail by the parties, the disputed patent included a claim limitation of "about 0.01 to 0.4 mg/mL" of a compound. The district court found that the generic infringed this limitation because its ANDA (1) identified the claimed compound as a potential impurity in the generic product, and (2) permitted the claimed compound to be present in an amount within the claimed range. Id. at 582-83.

On appeal, the generic argued that the district court's infringement analysis was flawed because, following Glaxo, it should have focused on the composition of the product likely to be

sold and not on the composition of the product theoretically permitted under the language of the ANDA specification. Id. at 585. The Federal Circuit disagreed. It determined that, because the generic's ANDA specification spoke to the amount of the claimed compound the generic product could contain, Sunovion governed the infringement analysis. Id. at 586. Accordingly, it concluded that the generic's ANDA product infringed the disputed patent because the generic had sought FDA approval for a product that could contain an amount of the compound in the claimed range. Id.

c. Mylan Soug[redacted]ts Containing [redacted]

To assess infringement, whether pursuant to Glaxo or Sunovion, the Court must first determine whether Mylan's ANDAs speak to or are silent on the DHP salt of sitagliptin in the (S)-configuration. On this point, several relevant facts are undisputed. [redacted]

[redacted] Merck has never tested Mylan's ANDA products to determine whether they contain the (S)-configuration (Trial Trans. 553:7-11, 560:14-17 (Myerson); 697:14-18 (Cockcroft)).

As in Par, Mylan's ANDAs speak directly to claim 3 because [redacted] It follows from this that Sunovion's analytical framework governs the infringement inquiry in this case.

Mylan's contention that Merck cannot meet its burden on infringement because it has not introduced any evidence to establish that Mylan's ANDA products contain the (S)-configuration is irrelevant. Sunovion instructs the Court to examine whether Mylan has sought FDA approval to market an ANDA product containing any amount of the DHP salt of the (S)-configuration. 731 F.3d at 1279.

Mylan urges the Court to apply Glaxo in this case, arguing its ANDAs are "tantamount to almost silen[t]" regarding the (S)-

configuration (Trial Trans. 1061:16-21; Dkt. No. 182 at 40-41). In support, Mylan denies including the (S)-configuration limitation in its ANDA specifications [redacted] but rather because, under guidelines provided by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use ("ICH"), it was required to include such limitation. [redacted]

The Court is unpersuaded by this argument. Federal Circuit precedent plainly instructs that where an ANDA speaks to a claim limitation Sunovion governs. Par, 835 F. App'x at 586. Par makes clear that Sunovion does not, as Mylan suggests, provide an exception for constructive silence and as here. In Par, as is the case here, the generic added reference to the claimed compound to its ANDA specification "in response to an FDA request for 'adequate information' showing that its ANDA product would comply with ICH Q3D." Id. at 586 (the generic's "specifications [were] updated to demonstrate that its product met the required elemental impurity guidelines").

Although ICH guidelines may require pharmaceutical manufacturers to identify and control impurities in their products, Mylan remained in control of its specification. The

evidence at trial established that the FDA has adopted the ICH's guidelines for drug product development submissions, and that Mylan's [redacted] (Trial Trans. 567:11-17 (Crowley)); 557:12-23 (Myerson)).

Mylan's internal documents also reference [redacted] But nothing in the record suggests that Mylan could not have satisfied the ICH guideline by setting a lower limit for the impurity. Presumably, if Mylan [redacted] it could have set the limitation at 0.0%, or at its "incredibly low" level of detection of 0.02% (Dkt. No. 182 at 38). [redacted]

Applying Sunovion to these facts leads to the conclusion that Mylan requested FDA approval to market products containing the DHP salt of the (S)-configuration. And, based on the language in its ANDAs, if granted FDA approval, Mylan could market a product containing [redacted] Under Sunovion,

[redacted]

these representations in the ANDAs about their scope, not Mylan's internal testing, regulatory requirements, or safeguards against the (S)-configuration), are determinative. Merck thus has proven by a preponderance of the evidence that Mylan has infringed claim 3 of the '708 patent.

3. Mylan's Janumet® ANDA Product Infringes Claim 1 of the '921 Patent

Merck next alleges that Mylan's Janumet® ANDA product will infringe claim 1 of the '921 patent. The invention in claim 1 is a pharmaceutical composition comprised of sitagliptin, metformin, a lubricant, a binding agent, a surfactant, and a diluent, each within a specific weight range (JTX 002.0007). [redacted]

To establish infringement Merck must prove by a preponderance of the evidence that Mylan's product also satisfies limitations (e) and (f), related to the surfactant and diluent components of the claimed invention. See Enercon GmbH v. Int'l Trade Comm'n, 151 F.3d 1376, 1384 (Fed. Cir. 1998) (direct infringement occurs when "every limitation of the claim is literally met" by the accused

product). As the following discussion establishes, Merck has met its burden.

a. Mylan's Janumet® ANDA Product Literally Infringes Limitation (e)

Limitation (e) provides that the pharmaceutical composition of claim 1 contains "about 0.5 to 1% by weight of a surfactant" (JTX 002.0007). It is undisputed that Mylan's Janumet® ANDA product contains [redacted] a "surfactant" as that term has been construed in this case (Trial Trans. 212:16-214:2 (Little); 574:9-10 (Crowley)).[17] The parties disagree about [redacted]

i. [redacted]

[17] Under Judge Andrews's construction, the term "surfactant" as used in limitation (e) is a "surfactant that works as a wetting agent to increase the dissolution of sitagliptin." In re Sitagliptin, 2020 WL 6743022, at *8, *11.

In determining infringement, the Court is concerned only with the final product Mylan seeks to commercialize. See Ferring, 764 F.3d at 1409 ("The focus that both Ferring and the district court thus gave to infringement by the uncoated cores of Watson's generic product is misplaced. The infringement evaluation is concerned only with the final, coated commercial . . . tablets for which Watson sought and was granted FDA approval to market.").

The evidence at trial established that Mylan seeks to commercialize its Janumet® ANDA product as a [redacted] Infringement thus must be based on [redacted]

Merck asserts that, [redacted] According to Mylan, [redacted] The Court need not resolve the parties' dispute regarding [redacted]

ii. [redacted]met® ANDA Product Contains [redacted] Encompassed by Limitation (e)

Determining if Mylan's Janumet® ANDA product infringes limitation (e) requires the Court to determine what impact the term "about" has on the claimed numeric range. In other words, how far does the term "about" extend the lower end of the "about 0.5 to 1% by weight of a surfactant" range?

At the outset, it is worth noting that resolution of this issue is not a matter of claim construction. "Although defining the outer reaches of 'about' in a claimed range can be a matter of claim construction, when the claims are applied to an accused device, it is a question of technologic fact whether the accused device meets a reasonable meaning of 'about' in the particular circumstances." Par, 835 F. App'x at 584 (citations omitted). So where, as here, the parties have not proposed a narrowing claim construction based on particular intrinsic evidence, the general considerations set forth in Cohesive Technologies, Inc. v. Waters Corporation, 543 F.3d 1351, 1368 (Fed. Cir. 2008), govern the infringement analysis. Id. And pursuant to those considerations, the Court's analysis must focus on whether, as a matter of fact, the [redacted] in Mylan's Janumet® ANDA product comes within the "about 0.5 to 1%" range.

Cohesive instructs that, because the term "about" lacks universal meaning in patent claims, its meaning depends on the technological facts of the particular case. 543 F.3d at 1368. "[A]s part of a numeric range, the use of the word 'about,' avoids a strict numerical boundary to the specified parameter. Its range must be interpreted in its technologic and stylistic context." Id. (quotation omitted). Any extension beyond the claimed range must be limited to what a POSA "would reasonably consider 'about' to encompass." Par, 835 F. App'x at 584 (quoting Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co., 878 F.3d 1336, 1342 (Fed. Cir. 2018). Courts must also consider whether any extension effected by "about" is by a "modest amount, considering the criticality of the numerical limitation to the invention." Id. (quotations omitted). And any extension must be tied to the purpose of the limitation. Cohesive, 543 F.3d at 1368.

Although Merck's expert, Dr. Steven Little, opined that the purpose of the surfactant is to increase the dissolution of sitagliptin (Trial Trans. 283:2-3 (Little)), Mylan, in its briefing, contends that the surfactant in the claimed invention serves several additional purposes (Dkt. No. 177-1 at 13-14).[18]

[18] Specifically, Mylan points to Merck's representations in the prosecution history of the '921 patent that the surfactant not only increased dissolution of sitagliptin, but also "provided more consistent

Judge Andrews resolved this dispute during claim construction, finding that, to overcome the prior art, Merck clearly and unmistakably had disavowed the full scope of the term "surfactant" while prosecuting the '921 patent. In re Sitagliptin, 2020 WL 6743022, at *9. Merck had "limited the functioning of a surfactant to a wetting agent that increases the dissolution of sitagliptin." Id. So it is with this limited purpose in mind that the Court turns to consider whether an extension of the "about 0.5 to 1%" range that would encompass [redacted] is a modest departure.

Applying the Cohesive framework, Merck's expert, Dr. Little opined that a POSA would understand the "about 0.5 to 1%" range to extend downward to at least 0.4% and to include measured values that round to 0.4% (Trial Trans. 216:11-217:6 (Little)). In his view, this extension is a modest departure from the claimed range, gives meaning to the term "about" within the limitation, and aligns with the purpose of the surfactant in the claimed invention. Id. at 238:2-3 (Little).

Mylan's expert, Dr. Michael Crowley, disagreed and opined that a POSA would understand the term "about" in limitation (e) to "capture the errors associated with measurements." Id. at 591:15-18 (Crowley). From examples in the '921 patent, he determined that

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dissolution profiles, and enhanced formulation robustness and stability." Id. (quoting JTX 006.1366, .1378).

the quantity of any ingredient could not vary by more than 3.85%, and so the lower limit of the "about 0.5 to 1%" range extends downward only to 0.475%, or 0.48%. Id.

For several reasons the Court credits the testimony of Dr. Little over that of Dr. Crowley and finds that a POSA would understand the "about 0.5 to 1% by weight of a surfactant" range to encompass values that round to 0.4%. First, Dr. Crowley's "measurement error" approach is not supported by the language of the '921 patent. The inventors chose to express the amount of surfactant through a numeric range rather than an exact value, and to expand that range further through use of the term "about." This language therefore indicates flexibility in the amount of surfactant the inventors believed to be necessary in the claimed invention.

As Dr. Crowley pointed out in his testimony, the prior art does require pharmaceutical weighing instruments to be used within the "maximum error of 5% in a single weighing operation" (PTX 650.0019). But, here, the '921 patent never references weighing or measurement errors in connection with the surfactant or otherwise. There therefore is no evidence that the inventors intended the term "about," in combination with a numeric range, to capture only weighing or measurement errors, as Dr. Crowley contends.

Second, Dr. Crowley considers all ingredients in the claimed invention to be equal. Instead of extending the "about 0.5 to 1% by weight of a surfactant" range in light of the limitation's function within the claimed invention, he calculates his permissible variance from theoretical values of all of the ingredients. But, in doing so, he fails to distinguish the surfactant from any other ingredient and does not consider the purpose and criticality of the surfactant within the claimed invention as Cohesive requires.

The Court also is unpersuaded that a POSA would apply the same variance to each of the ingredients in the claimed invention when these chemical compounds are present in vastly different amounts and have substantially different chemical characteristics.[19] Furthermore, by applying the same permissible variance to all of the claim limitations, Dr. Crowley imposes a strict numerical limit, a result the use of "about" specifically avoids. Cohesive, 543 F.3d at 1368.

Third, Dr. Crowley's method confines the claimed invention to its embodiments. See Phillips v. AWH Corp., 415 F.3d 1303, 1321 (Fed. Cir. 2005) ("[A]lthough the specification often describes

[19] Applying a 3.85% variance to each ingredient in the claimed invention also contradicts the USP-NF's teaching that the amount of API in a tablet may vary between 15% and 25%, (PTX 651.0025).

very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments."). He relies on the examples in the '921 patent to narrow the claimed surfactant range, but in doing so ignores the patent's instruction that its examples are "solely for the purpose of illustration and are not intended to be limitations of the present invention – as many variations thereof are possible without departing from the sprit and scope of the invention" (JTX 002.0005-06).

Indeed, Dr. Crowley's measurement error approach effectively reads the term "about" out of the claim. See Cohesive, 543 F.3d at 1368. Without the term "about," the ordinary rules of rounding would extend the lower end of the "0.5 to 1%" range to 0.45%.[20] See Viskase Corp v. Am. Nat'l Can Co., 261 F.3d 1316, 1320 (Fed. Cir. 2007) (recognizing the "standard scientific convention" of significant figures); see also Trial Trans. 437:1-14 (Little). Thus, Dr. Crowley's extension of the range only to 0.48% makes the range narrower than if it had been written without the term "about."

Dr. Little's approach avoids this result. The Court credits his opinion that, for "about" to have meaning within limitation

[20] The Court notes that in some instances the intrinsic record supports a construction narrower than afforded under the ordinary rules of rounding. See AstraZeneca AB v. Mylan Pharms. Inc., 19 F.4th 1325, 1330 (Fed. Cir. 2021).

(e), it must extend the lower end of the claimed range at least to the next decimal place, or 0.4%. Trial Trans. 227:21-228:10 (Little); see Allergan Inc. v. Sandoz Inc., 796 F.3d 1293, 1311 (2015) ("If 'about 7.3' is to mean anything other than 7.3, it is not clearly erroneous to it to include a value that differs from it by only one decimal place.").

A variance encompassing 0.4% would be a modest departure from the claimed range and within the reasonable expectations of a POSA. As even Dr. Crowley conceded, 0.4% is "extremely close" to 0.5% (Trial Trans. 597:22–598:6 (Crowley)). Although an extension from 0.5% to 0.4% would result in a 20% variance, the use of smaller quantities of ingredients leads to a higher degree of variation in those ingredients. Id. at 173:18-174:15 (Little). Further, the USP-NF permits APIs to vary between 15% and 25% in a compressed tablet (PTX 651.0025).[21] Other courts have found the term "about" to permit even larger variances. See Monsanto, 878 F.3d at 1341-42 ("about 3%" encompassed 4%, a 33% variance); Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Lab'ys, Ltd., 476 F.3d 1321, 1328 (Fed. Cir. 2007) ("about 1:5" encompassed "up to and including 1:7.1," a 42% variance).

[21] While this standard does not discuss acceptable variances in relation to excipients, it informs the Court's understanding of permissible variances of sensitive ingredients in pharmaceutical manufacturing operations.

Such a variance also is supported by the criticality and purpose of the surfactant limitation. Dr. Little explained that the specification is largely silent regarding variability of the surfactant (Trial Trans. 435:4-5 (Little)). It does not indicate that variances in the surfactant could undermine the functionality of the product, or contain any data or testing demonstrating the sensitivity of the surfactant range. Compare Cohesive, 543 F.3d at 1368-1369 (finding surfactant variations highly critical due to teachings in the specification).

Nevertheless, the language of limitation (e) informs a POSA about its criticality. The inventors of the '708 patent opted to articulate the amount of surfactant necessary to their claimed invention as a numeric range, not an exact value. They also chose to qualify that range with the term "about."

Thus, the '921 patent specification indicates that the amount of surfactant in the claimed invention is not highly critical and can serve its intended purpose over a range of quantities (Trial Trans. 232:1-10 (Little)). And, as discussed, the purpose of the surfactant in the claimed invention is to increase the dissolution of sitagliptin. Id. at 238:2-3 (Little). The evidence at trial established that Mylan also [redacted] for this purpose.

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Santanu Chakraborty ("Chakraborty"), the head of product development at Mylan, testified [redacted]

Mylan asserts that its internal testing is irrelevant to the infringement analysis because it occurred post-publication of the '921 patent. At this stage, however, the Court is tasked with determining whether Mylan's accused product infringes the claim limitation as a matter of technological fact. Par, 835 F. App'x at 584. Undoubtedly, this requires an examination of Mylan's Janumet® ANDA product.

Alternatively, Mylan contends that its testing is not informative because it was not performed on the final product and thus may include [redacted] These factors notwithstanding, Mylan's [redacted] allowed it to finalize the [redacted] in its product to accomplish that purpose.

Not only does the record support Dr. Little's opinion that a POSA would understand 0.4% to be a modest departure from the "0.5 to 1%" range, but it also establishes that a POSA would round a measured value to the same degree of precision as a stated value prior to comparison (Trial Trans. 226:16-227:7 (Little)). As Remington teaches, measured values are written to the measuring instrument's degree of precision (PTX 650.0022). For this reason, the USP-NF states that a measured value "usually will contain more significant figures than there are in the stated limit" and provides that the measured value must "be rounded off to the number of places that is in agreement with the limit expression. . . ." (PTX 651.0012).

Laman Alani, an inventor of the '921 patent, demonstrated this principle at trial (Trial Trans. 182:10-22 (Alani)). She testified that a measured value of 0.49% and a stated value of 0.5% are "the same number" because 0.49% must be rounded to a single decimal point before comparison. Id. A POSA therefore reasonably would have considered the "0.5 to 1% by weight of a surfactant" range to encompass measured values that round to 0.4%.

Because a POSA would reasonably have considered the "about 0.5 to 1% by weight of a surfactant" range to encompass 0.4% and those measured values that round to 0.4%, the Court finds that Mylan's Janumet® ANDA product, [redacted]

[redacted] literally infringes limitation (e) of claim 1.

b. Mylan's Janumet® ANDA Product Literally Infringes Limitation (f)

Claim 1 of the '921 patent also requires that the pharmaceutical composition contain "about 5 to 15% by weight of a diluent" (JTX 002.0007). Merck asserts that Mylan's Janumet® ANDA product infringes limitation (f) literally and under the doctrine of equivalents. In assessing these contentions, the Court first must determine if Mylan's Janumet® ANDA product contains a diluent as that term is defined in the '921 patent. If so, the Court must further consider whether it contains "about 5 to 15%" of a diluent as provided in limitation (f). But if Mylan's Janumet® ANDA product does not literally infringe limitation (f), the Court must then consider whether it infringes that limitation under the doctrine of equivalents.

i. [redacted]n's Janumet® ANDA Product [redacted]

It is undisputed that Mylan's Janumet® ANDA product contains

[redacted]

pharmaceutical tablets. Id. at 441:25-442:2 (Little); 653:12-23 (Crowley).

[redacted]

But that the '921 patent does not limit [redacted] in the manner Dr. Crowley contends. Its lists of binders and diluents are exemplary and not exhaustive [redacted] Thus, the specification merely provides a POSA with examples of binders and diluents for use in the claimed invention, but it does not clearly disavow the

full scope of the term "diluent" [redacted]

[redacted]

Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1325 (Fed. Cir. 2002) ("The patentee may demonstrate intent to deviate from the ordinary and accustomed meaning of a claim term by including in the specification expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope.").

Based on the language of the specification, the Court agrees with Dr. Little that a POSA would not have read the '921 patent as restricting the [redacted]

[redacted]

ii. [redacted] is a Diluent in Mylan's Janumet® t

Mylan's internal records recognize [redacted] Thus, Mylan's ANDA clearly indicates that its product contains [redacted] as a diluent.

The ANDA also establishes that Mylan relies on [redacted] to function as a diluent in its product. "It is not necessary that [Mylan] intended the [redacted] to function as a [diluent] if, the district court [can] readily find, the [redacted] actually does so." Par, 835 F. App'x at 585. Dr. Little testified that diluents can be used in pharmaceutical compositions to regulate tablet size and compensate for changes in other ingredients, functions [redacted] performs in Mylan's product (Trial Trans. 211:5-8, 239:21-240:9 (Little)).

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Mylan alters the amount of [redacted]

Mylan cannot refute this evidence. Its expert, Dr. Crowley, conceded that [redacted] Mylan nevertheless insists that Dr. Little's characterization of [redacted] as a diluent is inconsistent with the '921 patent's exemplary lists (Dkt. No. 177-1 at 26-27). As previously discussed, however, the specification does not prohibit [redacted] from serving as a diluent in the claimed invention or in Mylan's Janumet® ANDA product.

[redacted]

Alternatively, Mylan argues that [redacted] cannot serve as both a binder and a diluent in the claimed invention. [redacted] Nothing in the '921 patent prevents a single ingredient, such as [redacted] from satisfying multiple claim limitations. Other courts have reached the same conclusion. See Par, 835 F. App'x at 585-87 (affirming the district court's conclusion that citric acid, a multifunctional excipient, could satisfy two claim limitations).

In sum, the Court concludes from the '921 patent specification, the prior art, and Mylan's identification of and reliance on [redacted] that Mylan's Janumet® ANDA product contains a diluent [redacted]

iii. [redacted] Mylan's Janumet® ANDA Product tation (f)

The Court next must determine whether the amount of [redacted] Mylan's Janumet® ANDA product satisfies the "about 5 to 15%" range in limitation (f).

According to Merck's expert, Dr. Little, Mylan's coated[23] 50/500mg strength Janumet® ANDA product contains [redacted] (Trial Trans. 466:15-467:25, 468:24-469:6 (Little)). Based on this, it was his opinion at trial that Mylan's product literally infringes both the "about 5 to 15% by weight of a diluent" range in limitation (f) and the "about 0 to 35% by weight of a binding agent" range in limitation (d). Id.

In explaining how he arrived at this opinion, Dr. Little testified about his understanding of how Mylan incorporates [redacted]

[23] Dr. Little performed his calculations twice, using the weight of a coated tablet and an uncoated tablet (Trial Trans. 466:15-467:25, 468:24-469:6 (Little)). Because infringement is based on the weight of the binder and diluent in Mylan's final product, see Ferring, 764 F.3d at 1409, the Court considers only his calculations based on the weight of Mylan's coated tablet (Trial Trans. 575:8-12 (Crowley); 495:19-21, 496:24-497:5 (Little)).

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Second, Dr. Little [redacted]

[redacted]

Finally, [redacted], Dr. Little determined that Mylan's Janumet® ANDA product contains [redacted] of a diluent, depending on its strength (Trial Trans. 466:15-467:25, 468:24-469:6 (Little)); see also PTX 762.[26] Both strengths of Mylan's Janumet® ANDA product therefore contain [redacted] of a diluent and literally infringe the "about 5 to 15% by weight of a diluent" range in limitation (f). Id. at 467:18-22, 467:24-468:1 (Little).

Dr. Crowley "vehemently disagree[d]" that a POSA would [redacted] in order to determine the amount serving as a diluent in Mylan's Janumet® ANDA product, Id. at 628:3-10 (Crowley), but he proposed no alternative method. Instead, he applied Dr. Little's calculation and determined that Mylan's 50/500mg and 50/1000mg Janumet® ANDA products [redacted] of a diluent, respectively. Id. at 628:11-25 (Crowley). And, as such, he concluded they do not literally infringe limitation (f). Id.

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[26] Dr. Little prepared PTX 762 to demonstrate his mathematical calculation. See Trial Trans. 459:5-469:6 (Little).

[27] As Dr. Little previously explained, to determine if a measured value meets a numeric range in a claim limitation, a POSA rounds the measured value to the same degree of precision. Id. at 467:7-10 (Little).

Although Drs. Little and Crowley apply the same calculation, they reach different conclusions because they entered different values for two variables. Dr. Little's methodology accounts for [redacted] To account for these variables, he relied on the [redacted] while Dr. Crowley relied on a particular batch of [redacted]

At this point, the parties repeat their Glaxo versus Sunovion arguments. But as both experts derive their input values directly from Mylan's ANDA, the ANDA not silent on this issue and Sunovion again governs the Court's infringement analysis. See supra §

III.B.2.b.; Ferring, 764 F.3d at 1382. For this reason, the Court agrees with Dr. Little that, in order to demonstrate the full scope of what Mylan has requested FDA approval to market, a POSA would input values from [redacted]

Finally, because, per Dr. Little's calculations, Mylan's Janumet® ANDA product literally infringes limitation (f), the Court need not consider whether the product also meets that claim limitation under the doctrine of equivalents.

C. Invalidity of the '708 Patent

According to Mylan, claims 1, 2, 3, and 19 of the '708 patent are invalid under the judicially created doctrine of obviousness-type double patenting, and under 35 U.S.C. § 112 for lack of written description or enablement.

1. Legal Standard

Each of the asserted claims is presumed to be valid. See 35 U.S.C. § 282; Microsoft Corp. v. I4i Ltd. P'ship, 564 U.S. 91, 94 (2011); Novo Nordisk A/S v. Caraco Pharm. Lab'ys, Ltd., 719 F.3d 1346, 1352 (Fed. Cir. 2013). Mylan thus bears the burden of proving invalidity by clear and convincing evidence. See 35 U.S.C. § 282 ("The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity."); Microsoft, 564 U.S. at 102 ("[A] defendant raising an invalidity defense [bears] a heavy burden of persuasion, requiring proof of

the defense by clear and convincing evidence." (citation and quotation marks omitted)). "Clear and convincing evidence places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are highly probable.'" Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting Colorado v. New Mexico, 467 U.S. 310, 316 (1984)).

2. Obviousness-Type Double Patenting

An inventor may obtain only one patent for any single invention. See Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1297 (Fed. Cir. 2012) (citing 35 U.S.C. § 101). The judicially created obviousness-type double patenting doctrine thus precludes an inventor "from obtaining more than one valid patent for either (a) the 'same invention,' or (b) an 'obvious' modification of the same invention." Id. (quoting In re Longi, 759 F.2d 887, 892 (Fed. Cir. 1985). The purpose of this doctrine is to prevent an inventor from unduly extending its monopoly by claiming a slight variation of an earlier patented invention. See Sun Pharm. Indus. Ltd. v. Eli Lilly and Co., 611 F.3d 1381, 1384 (Fed. Cir. 2010); Abbvie v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr., 764 F.3d 1366, 1378-79 (Fed. Cir. 2014).

The obviousness-type double patenting analysis involves two steps: "First, the court construes the claims in the earlier patent and the claims in the later patent and determines the differences.

Second, the court determines whether those differences render the claims patentably distinct." Pfizer, Inc. v. Teva Pharms. USA, Inc., 518 F.3d 1353, 1363 (Fed. Cir. 2008) (quotation and alterations omitted). "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 and Co. v. Barr Lab'ys, Inc., 251 F.3d 955, 968 (Fed. Cir. 2001).

a. The Differences Between the Reference Claims and the Asserted Claims

The Court first considers the differences between the asserted claims and the reference claims. According to Mylan, asserted claims 1, 2, and 3 of the '708 patent are patentably indistinct from reference claim 17 of Merck's earlier-issued '871 patent ("the reference patent"), and asserted claim 19 of the '708 patent is patentably indistinct from reference claim 20 of the '871 patent.

Reference claim 17 covers the sitagliptin free base compound in its (R)-configuration, "or a pharmaceutically acceptable salt thereof" (DTX 2054.0022). Asserted claim 1 covers the 1-to-1 DHP salt of sitagliptin, and asserted claims 2 and 3 cover this salt in its (R)-configuration and (S)-configuration, respectively (JTX 001.0014). The difference between these claims is that asserted claims 1, 2, and 3 cover a particular species of sitagliptin salt

encompassed by the broad genus of sitagliptin salts described in reference claim 17. There is no dispute that the 1-to-1 DHP salt of sitagliptin is a pharmaceutically acceptable salt (Trial Trans 309:19-21 (Buckton); 949:10-12 (Myerson)).

Next, reference claim 20 claims "[a] pharmaceutical composition which comprises an inert carrier and a compound of claim 17" (DTX 2054.0022). Asserted claim 19 recites a "method for the treatment of type 2 diabetes comprising administering to a patient in need of such treatment a therapeutically effective amount of the salt according to claim 2 or a hydrate thereof" (JTX 001.0015). These claims are different because the reference claim covers pharmaceutical compositions containing sitagliptin or any pharmaceutically acceptable sitagliptin salt, whereas the asserted claim covers a method of using the particular 1-to-1 DHP salt of sitagliptin in its (R)-configuration to effectively treat patients with type 2 diabetes.

Notably, reference claims 17 and 20 and asserted claims 1, 2, 3, and 19 are similar in that all "are useful in the treatment or prevention of diseases in which the [DPP-IV] enzyme is involved," particularly type 2 diabetes (DTX 2054.0001, .0019-21; JTX 002.0007).

b. These Differences Render the Asserted Claims Patentably Distinct

In light of these differences, the Court must determine whether the asserted claims are more than "slight variations" of the reference claims. Eli Lilly v. Teva, 689 F.3d at 1340. At this second step, "the law of obviousness-type double patenting looks like the law of obviousness generally" and "is analogous to an obviousness analysis under 35 U.S.C. § 103." Abbvie, 764 F.3d at 1379 (quotations omitted).

"It is well-settled that a narrow species can be non-obvious and patent eligible despite a patent on its genus." Id. (citing Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash., 334 F.3d 1264, 1270 (Fed. Cir. 2003); see also Brigham & Women's Hosp. Inc. v. Teva Pharm. USA. Inc., 761 F. Supp. 2d 210, 224 (D. Del. 2011) ("[A]n earlier patent claiming a large genus of pharmaceutical compounds does not preclude a later patent claiming a species within that genus, so long as the species is novel, useful, and nonobvious.").

In the obviousness-type double patenting context, where claimed chemical compounds are involved, the analysis turns on "whether the later compound would have been an obvious . . . modification of the earlier compound." UCB, Inc. v. Accord Healthcare, Inc., 890 F.3d 1313, 1323 (Fed. Cir. 2018). This type

of challenge "requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success." Eli Lilly v. Teva, 689 F.3d at 1378.[28]

c. Asserted Claims 1 and 2

As it relates to asserted claims 1 and 2, the double patenting inquiry is whether, upon reading reference claim 17, a POSA would have been motivated to create the 1-to-1 DHP salt of sitagliptin in its (R)-configuration with a reasonable expectation of success. UCB, 890 F.3d at 1324.

i. Asserted Claims 1 and 2 Are Not Obvious Considering the '871 Patent Alone

Mylan contends that, even without considering any prior art, reference claim 17, in combination with the definition of "pharmaceutically acceptable salts" in the '871 patent specification, renders the 1-to-1 DHP salt of sitagliptin in its (R)-configuration obvious. Merck disagrees. The parties' dispute centers on the extent to which the Court should consider the '871

[28] Mylan relies on Geneva Pharms., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1378 n.1 (Fed. Cir. 2003), to assert that the obviousness-type double patenting analysis does not require an inquiry into the motivation to modify the prior art (Dkt. No. 175 at 7 n.2). But the Federal Circuit rejected this argument in Otsuka, 678 F.3d at 1298, holding that, as with a § 103 analysis, obviousness-type double patenting requires a determination that a POSA would have had a "motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success." Id.

patent specification in its obviousness-type double patenting analysis.

The '871 patent specification defines "pharmaceutically acceptable salts" as used in reference claim 17 as those salts "prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acid" (DTX 2054.0004). It then teaches that when a compound of the invention is basic, as is the sitagliptin free base, "salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids," and it provides a list of twenty-six (26) exemplary acids. Id. at .0004-05. The specification further instructs that, of the exemplary acids, eight are particularly preferred, including phosphoric acid. Id. at .0005.

According to Mylan, the list of particularly preferred acids in the '871 patent is part of the definition of "pharmaceutically acceptable salts" (Dkt. No. 175 at 7-8). Given that, it contends this definition significantly narrows the genus of the pharmaceutically acceptable sitagliptin salts described in reference claim 17. Id. at 8. And based on this narrowing Mylan's expert, Dr. Graham Buckton, opined that a POSA would have been motivated to combine phosphoric acid with the sitagliptin free

base, and would have reasonably expected the 1-to-1 DHP salt of sitagliptin to form (Trial Trans. 309:15-312:12 (Buckton)).

Merck contends Mylan's reliance on the list of preferred acids in the '871 patent specification is misplaced (Dkt. No. 176 at 23-24). It disputes that the list of exemplary acids in the '871 patent is part of the definition of "pharmaceutically acceptable acids," and contends that the Court ought not consider this list since its obviousness-type double patenting analysis turns on what the reference patent claims, not what it discloses. Id.

Because "[i]t is the claims, not the specification, that define an invention," Ortho, 959 F.2d at 943, the Court agrees with Merck. As the Federal Circuit has explained:

> As a general rule, obviousness-type double patenting determinations turn on a comparison between a patentee's earlier and later claims, with the earlier patent's written description considered only to the extent necessary to construe its claims. This is so because the nonclaim portion of the earlier patent ordinarily does not qualify as prior art against the patentee and because obviousness-type double patenting is concerned with the improper extension of exclusive rights—rights conferred and defined by the claims. The focus of the obviousness-type double patenting doctrine thus rests on preventing a patentee from claiming an obvious variant of what it has previously claimed, not what it has previously disclosed.

Eli Lilly v. Teva, 689 F.3d at 1378-79 (emphasis in original) (citations omitted). In limited instances, the Court may consider the reference patent's specification to the extent necessary to

construe its claims and understand their utility, id. at 1379-80, but this case presents no such circumstance.

In the first place, the reference patent's list of particularly preferred acids is not needed to construe the term "pharmaceutically acceptable salts." Both Dr. Buckton, and Merck's expert, Dr. Allan Myerson, opined at trial that a POSA would have understood this commonly used term without needing to consult the specification (Trial Trans. 310:25-311:10, 366:8-16 (Buckton); 842:25-843:8 (Myerson)). Even so, the reference patent's definition of this term comports with a POSA's common understanding, id. at 368:1-14 (Buckton), and does not include the list of particularly preferred acids. Id. at 368:15-369:20 (Buckton); 843:25-844:10 (Myerson).

Secondly, the '871 patent specification's list of particularly preferred acids is not needed to determine the utility of reference claim 17. Sun Pharm., 611 F.3d at 1387 ("[W]here a patent features a claim directed to a compound, a court must consider the specification because the disclosed uses of the compound affect the scope of the claim for obviousness-type double patenting purposes."). The reference patent teaches that reference claim 17 is "useful in the treatment or prevention of diseases in which the [DPP-IV] enzyme is involved, such as diabetes and particularly type 2 diabetes" (DTX 2054.0001). But its list of

particularly preferred acids adds nothing to a POSA's understanding of this disclosed utility.

Finally, Mylan's argument that the Court may consider the reference patent's list of particularly preferred acids to interpret the scope of the genus in reference claim 17 is unpersuasive. In support of its argument, Mylan relies on Sun Pharm., where the Federal Circuit stated that "a court considering a claim to a compound must examine the patent's specification to ascertain the coverage of the claim, because a claim to a compound '[s]tanding alone . . . does not adequately disclose the patentable bounds of the invention.'" 611 F.3d at 1387 (citing Geneva, 349 F.3d at 1385).

On first review, Sun Pharm. appears to support Mylan's argument. On closer examination, however, it is clear that what Sun Pharm. permits is examination of the reference patent specification to ascertain the relevant disclosed utility of the compound. As the Federal Circuit later explained, the teachings of Sun Pharm. and its related line of cases apply to the "situation in which an earlier patent claims a compound, disclosing the utility of that compound in the specification, and a later patent claims a method of using that compound for a particular use described in the specification of the earlier patent." Eli Lilly v. Teva, 689 F.3d at 1378-79 (collecting cases). As the issue

addressed in Sun Pharm. is not before the Court, its teachings are not relevant to the analysis here.

As it pertains to its obviousness-type double patenting analysis, the Court concludes that the reference patent's list of particularly preferred acids does not narrow the genus of sitagliptin salts covered by reference claim 17. Mylan consequently must demonstrate by clear and convincing evidence that a POSA would have found her way from the generic pharmaceutically acceptable salt of sitagliptin, as claimed in reference claim 17, to the particular 1-to-1 DHP salt of sitagliptin in its (R)-configuration as claimed in asserted claims 1 and 2.

Based on reference claim 17 and the definition of "pharmaceutically acceptable salts," Mylan has not met this burden. The mere fact that reference claim 17 covers 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. And even if a POSA did pursue a salt form nothing in reference claim 17 would have motivated her to select the specific 1-to-1 DHP salt of sitagliptin from all of the pharmaceutically acceptable salts of sitagliptin. Nor would reference claim 17 have given her a reasonable expectation of success in doing so.

ii. WO '498 Does Not Qualify as a Prior Art Reference

Mylan next contends that asserted claims 1 and 2 would be obvious over WO '498 and other prior art. Merck objects that WO '498 does not qualify as prior art to the '708 patent. The specification of WO '498 is substantively identical to that of the '871 patent (Trial Trans. 327:25-328:2 (Buckton)). Thus, if prior art, the Court may consider all of WO '498's disclosures, including its list of particularly preferred acids and its example of a hydrochloric salt of sitagliptin. See DTX 036.0010-11, .0047.

Despite Mylan's assertions, WO '498 does not qualify as prior art. WO '498 and the '708 patent were commonly owned by Merck at the time of the inventions claimed in the '708 patent (Dkt. No. 123 at 17). Based on this common ownership, prior to trial, the parties stipulated that WO '498 was not available as prior art to prove obviousness under 35 U.S.C. § 103. Id. And because WO '498 is disqualified as an obviousness reference, it is also disqualified as an obviousness-type double patenting prior art reference. See Ex Parte Hrkack, 2011 WL 514313, at *5 (B.P.A.I. Feb, 9, 2011). Mylan therefore cannot rely on WO '498 to support its obviousness-type double patenting challenge.

iii. Asserted Claims 1 and 2 Are Not Obvious Considering the Prior Art

Even without WO '498, Mylan contends that asserted claims 1 and 2 would be obvious over reference claim 17 in light of the remaining prior art. Its expert, Dr. Buckton, testified that a POSA would have been motivated to conduct a salt screen of the sitagliptin free base and to include phosphoric acid in her experiment based on the acid's known pharmaceutical properties and frequency of use in pharmaceutical salts (Dkt. No. 175 at 11-12). He further asserted that a POSA reasonably would have expected the 1-to-1 DHP salt of sitagliptin to form in a reaction between the sitagliptin free base and phosphoric acid based on the difference in their pK_a values. Id. at 12.

Merck's expert, Dr. Myerson, rejected this contention, explaining that the prior art would not have motivated a POSA to modify the broad genus of sitagliptin free base and all pharmaceutically acceptable sitagliptin salts to achieve the 1-to-1 DHP salt of sitagliptin (Dkt. No. 176 at 11-12). In his opinion, a POSA would not have been motivated to (1) abandon the sitagliptin free base; (2) abandon the HCL salt of sitagliptin; or (3) conduct a salt screen, including phosphoric acid, in such experiment. Id. at 12-18. Nor would a POSA have had any expectation of success in synthesizing the 1-to-1 DHP salt of sitagliptin

because the prior art did not teach a method for predicting whether any pharmaceutical salt of sitagliptin would form. Id. at 19-22. And if a pharmaceutical salt had formed, the prior art did not teach a method for predicting its stoichiometry. Id.

After fair consideration of this testimony, the Court concludes that Mylan has not established by clear and convincing evidence that a POSA would have been motivated to modify the reference genus in claim 17 of the '871 patent to achieve the 1-to-1 DHP salt of sitagliptin covered by asserted claims 1 and 2. Nor, in doing so, would she have had a reasonable expectation of success.

(a) No Motivation

There are several reasons why the prior art on which Mylan relies would not have motivated a POSA to modify the reference genus. First, even accepting Dr. Buckton's assertion that a salt screen is a relatively simple experiment, the prior art did not necessarily direct a POSA to conduct such an experiment for the sitagliptin free base. Undoubtedly, the benefits of developing pharmaceutical salts were well known when the '708 patent was published. See DTX 006.0004-05 (teaching salt selection as a means for creating and developing the compound with the best aggregate pharmaceutical properties); DTX 005.0001 (same); DTX 007.0037 (teaching that salt forms might display better pharmaceutical

properties than the neutral form of the same compound). The prior art also taught that salt formation was common with weakly basic compounds, because "it is a relatively simple chemical manipulation which may alter the physiochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure" (DTX 007.0002).

But although a POSA would have understood the benefits of pursuing a salt form of sitagliptin, a weakly basic compound (Trial Trans. 956:13-14 (Myerson)), the prior art did not disclose information that would have been essential to her experiment, such as sitagliptin's solubility or pK_a value (DTX 235.0008; DTX 005.0001-02). Thus, even Dr. Buckton's opinion would require a POSA to conduct other preliminary testing of the sitagliptin compound before conducting a salt screen.

Further, the prior art taught that it is not always necessary for a POSA to seek a salt form of a new chemical compound. See PTX 274 (providing examples of pharmaceutical compounds marketed in non-salt forms); DTX 021.0001 (teaching that 50% drug entities were administered as salts). In fact, although Bighley outlines a methodology for salt selection, its first step directs a POSA to determine whether a salt form is even necessary, or whether the pharmaceutical compound is viable per se (DTX 007.0030-31).

Although Dr. Buckton conceded that the prior art did not disclose the pharmaceutical properties of the sitagliptin free base, it was his opinion that a POSA would have immediately pursued salt forms of this compound (Trial Trans. 282:12-283:14, 293:8-13 (Buckton)). But the evidence at trial indicated that sitagliptin might have been one of the compounds for which a salt form would not be needed. Indeed, the prior art taught that "the vast majority of salts are developed to enhance the aqueous solubility of drug substances" (DTX 005.0002), and there generally is no need for a salt form for "a high-melting water-soluble solid" (DTX 007.0032, .0034). As the sitagliptin free base had good solubility and a high-melting point in its solid form (Trial Trans. 849:2-850:23 (Myerson)), a POSA easily could have determined the sitagliptin free base to be viable and not have pursued a salt form.

Second, had a POSA pursued a salt form of sitagliptin, the prior art would have directed her to the HCL salt. The evidence at trial established that, at the time of the invention, hydrochloric acid was the obvious choice for acid-addition salts of basic compounds. Throughout the relevant time frame, hydrochloric was the most commonly used acid in basic drugs. See DTX 006.0004; DTX 012.0005; DTX 007.0003-05. Gould specifically noted that "there is clear precedent, and an overwhelming argument on many grounds to immediately process to the HCL salt and evaluate other forms only

if problems with the hydrochloride emerge" (DTX 012.0005). Bighley's decision tree also taught a POSA to evaluate an HCL salt before making mineral salts, such as a phosphate salt (DTX 007.0034-35).[29] Moreover, the prior art disclosed no problem with the HCL salt of sitagliptin (Trial Trans. 380:8-381:17 (Buckton); 825:17- 826:5 (Myerson)). Therefore, based on the prior art's preference for hydrochloride salts, a POSA likely would have pursued an HCL salt of sitagliptin before attempting a phosphate salt.

Third, had a POSA conducted a salt screen, it is not clear she would have included phosphoric acid. Typically, she would have begun her screen with approximately ten acids. Id. at 293:14-19 (Buckton); 877:19-878:8 (Myerson). But at the time of the invention there were more than 100 pharmaceutically acceptable acids available from which a POSA could have populated her experiment Id. at 876:24-877:12 (Myerson); see also DTX 007.0004-05. And because neither the properties of the sitagliptin free base nor

[29] Although he conceded that Bighley's decision tree is written sequentially, Dr. Buckton testified that it taught a POSA to create a hydrochloride salt and other mineral salts simultaneously. The Court is unconvinced. The weight of the evidence established that Bighley taught a process for efficiency in salt formation and emphasized that pharmaceutical manufacturers must proceed quickly and should narrow salt forms as soon as possible (DTX 007.0034-37). It therefore instructed a POSA to create a hydrochloride salt and study its viability before turning to the time-consuming process of creating and studying other salt forms. Id.

any problem with this compound were known, the prior art would not have directed a POSA's research or narrowed this world of potential pharmaceutically acceptable acids.

Nevertheless, Dr. Buckton testified that a POSA would have included phosphoric acid in her salt screen simply due to its popularity (Trial Trans. 297:14-22 (Buckton)). In 1996, phosphoric acid was the eighth most commonly used acid in pharmaceutical salts (DTX 007.0004-05), but its popularity had decreased during the relevant time frame. Between 1995 and 2006, the FDA approved 101 salts of basic drugs but phosphoric acid appeared in only 2 of them, one of which was Merck's NDA product (PTX 111.0011).[30]

Moreover, when selecting acids other than hydrochloric acid, the prior art did not teach a POSA to consider an acid's frequency of use but instead instructed her to consider any issues with the basic drug compound and the acids known to target such problems (DTX 005.0002-04). For example, a POSA would have relied on phosphoric acid to increase the solubility of basic drugs (DTX 021.0137, .0182). But, here, where sitagliptin did not have poor solubility, a POSA reasonably could have excluded phosphoric acid from any salt screen. A POSA also may have been dissuaded from

[30] During this same time, hydrochloric acid remained the most frequently chosen acid, appearing in 54 salts of drug entities approved by the FDA (PTX 111.0011).

pursuing a phosphoric salt of sitagliptin because she would have been aware that such salts tend to form hydrates (DTX 021.0137, .0182), and in other instances had proved to be unstable (PTX 35; PTX 155; PTX 219).

Dr. Buckton also opined that a POSA would have included phosphoric acid in her salt screen of sitagliptin based on the difference in their pK_a values[31] (Trial Trans. 314:8-315:2 (Buckton)). But the pK_a of sitagliptin had never been disclosed in the prior art, or in the '871 patent. Id. at 382:15-20 (Buckton); 829:9-17 (Myerson). Dr. Buckton nevertheless contends that a POSA could have synthesized sitagliptin and measured its pK_a. Id.

But even if true and a POSA knew sitagliptin's pK_a, phosphoric acid was just one of many acids within Dr. Buckton's desired pK_a range. Specifically, phosphoric acid was one of sixty-nine (69) pharmaceutically acceptable acids with a pK_a value 2 units greater than that of sitagliptin, and one of fifty-five (55) pharmaceutically acceptable acids with a pK_a 3 units greater than that of sitagliptin (DTX 021.0210, .0215-16). Accordingly, a POSA's knowledge of sitagliptin's pK_a would not have significantly narrowed the world of acids that she could have included in her

[31] As discussed in detail below, it was Dr. Buckton's opinion that a POSA would have expected a salt to form if there was an adequate difference between the pK_a values of the basic drug and acid.

salt screen, and she would have had to select phosphoric acid from the many acids with the same or similar pK_a.

For these reasons, the Court concludes that Mylan has failed to establish that the prior art would have motivated a POSA to modify the reference genus to arrive at the specific species covered by the asserted claims.

(b) No Reasonable Expectation of Success

Mylan also has not sufficiently demonstrated that a POSA would have had a reasonable expectation of success in modifying the reference genus to achieve the claimed 1-to-1 DHP salt of sitagliptin. The prior art recognized the unpredictable nature of salt formation. See DTX 006.0001-02; DTX 007.0002. To overcome this unpredictability, Bighley proposed a method to guide a POSA methodically through salt selection. DTX 007.0002, .0029-30 (proposing a methodology "whereby a suitable salt form can be chosen in an efficient and timely manner with few false states and the minimum expenditure of resources").

Other prior art sources recognized that knowledge of a compound's pK_a could be an important factor in a POSA's salt formation process. Aulton taught that solubility and pK_a control a POSA's work, and that pK_a can aid her selection of salts, if necessary (DTX 235.0008). Bighley instructed that the pK_a value of a compound can determine the range of acids available for salt

formation and that "[t]here should be at least one unit of separation between the pK_a of the basic drug and that of the [acid]" (DTX 007.0034). Likewise, Bastin taught that the pK_a value is one of the first pieces of information that a POSA would need to select acids for a salt screen (DTX 005.0001-02). It also instructed that "there should be a minimum difference of about 3 units between the pK_a value of the [compound] and that of its counter[-]ion." Id. Stahl suggested that a POSA should select acids with a minimum difference of 2 or 3 units (DTX 021.0062-63, .0091).

Dr. Buckton relied heavily on this so-called delta pK_a rule to support his opinion that a POSA would have reasonably expected the 1-to-1 DHP salt of sitagliptin to form. As he explained, the pK_a of sitagliptin is 7.7 and the pK_a of phosphoric acid's first, second, and third protons are 1.96, 7.12, and 12.32, respectively. Accordingly, because the difference between the pK_a value of sitagliptin and the pK_a value of phosphoric acid's first proton is greater than 3 units, a POSA could have predicted that a phosphate salt of sitagliptin would form.

But the prior art did not teach the delta pK_a rule to be as predictive as Dr. Buckton contends. Bastin taught that "knowledge of the pK_a value enables potential salt forming agents (counter[-]ions) to be selected. . . ." (DTX 005.0001-02). And Stahl, after recognizing that a pK_a delta of greater than 3 units can be a

valuable guideline for a POSA in selecting acids for a screen, taught that "[n]o predictive procedure to determine whether a particular acidic or basic drug would form a salt with a particular counter-ion has been reported in the literature" (DTX 021.0062-63, .0091). Thus, even with knowledge of a compound's pK_a "a more predictive method for assessing the feasibility of salt formation would be necessary to minimize trials and errors in the salt-selection program." Id. at .0063. Indeed, the prior art also taught that stable salts can form from reactions with a pK_a differential below 3 units, and, significantly, that art contained examples of experiments in which the pK_a differential exceeded 3 units but no salt formed (0005.0001-02, .0004-06).

Thus, while the delta pK_a rule may inform a POSA's selection of acids for a salt screen, and thereby increase the chance of salt formation, it can neither predict nor guarantee that any salt will form. As Dr. Myerson explained, an increased difference in pK_a values ensures that there is sufficient ionization in the chemical reaction to enable proton transfer and salt formation (Trial Trans. 838:21-839:5 (Myerson)). Nevertheless, a POSA cannot predict whether salt formation will occur unless and until the reaction produces such salt.

His perspective was confirmed by the evidence at trial. Dr. Wenslow, one of the named inventors of the '708 patent, testified

that, while the delta pK_a rule might help a POSA select acids for a salt screen, she must still choose from more than 20 or 30 potential acids. Id. at 737:1-21 (Wenslow). Importantly, because salt formation is "serendipitous," he testified that even those "fluent in salt selection" applying the delta pK_a rule could not reasonably predict whether a salt would form in any given reaction. Id. at 736:10-737:9, 738:20-740:2 (Wenslow). Another named inventor, Dr. Hansen, also testified that, despite his efforts, he had been unable to synthesize a hydrochloric salt of sitagliptin although the difference in pK_a values exceeded 3 units. Id. at 114:15-115:4 (Hansen).

The Court is not persuaded by Dr. Buckton's opinion that, although sitagliptin is polyprotic and capable of forming salts in several different stoichiometries, a POSA reasonably would have expected the specific 1-to-1 stoichiometry of the DHP salt of sitagliptin to form. He testified that, because only the pK_a value of phosphoric acid's first proton would satisfy the delta pK_a rule, a POSA reasonably would have expected any phosphate salt of sitagliptin to be in the 1-to-1 ratio. But, as has been discussed, the prior art taught that a salt may form from a reaction that does not satisfy the delta pK_a rule. Notably, since the filing of the '708 patent, non-1-to-1 DHP salts of sitagliptin have been

synthesized (Dkt. No. 123 at 17-18; Trial Trans. 821:21-822:3, (Myerson)).[32]

To conclude, Mylan has failed to prove by clear and convincing evidence that the prior art would have motivated a POSA to modify the reference genus to achieve the specific 1-to-1 DHP salt of sitagliptin with a reasonable expectation of success. Its obviousness-type double patenting challenge to the validity of asserted claims 1 and 2 therefore fails.

iv. Pfizer v. Apotex Is Not Controlling

Mylan's contention that Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359 (Fed. Cir. 2007), compels a different result (Dkt. No. 175 at 8-10) is unavailing. Two patents were at issue that case. In the first, Pfizer claimed the generic amlodipine compound and disclosed twelve of its pharmaceutically acceptable acid-addition salts. 480 F.3d at 1352-53. Although that patent expressed a preference for the maleate salt of amlodipine, Pfizer later discovered that it was not suitable for commercial development due to its stickiness and degradation. Id. at 1353-54. To find a more suitable salt form, Pfizer isolated the problem within the chemical

[32] Nor does the fact that a POSA would have conducted her salt screen using equimolar proportions of the relevant acid and base (DTX 005.0002), alter the Court's conclusion. The prior art demonstrated that, even when using equimolar proportions of the acid and base, non-1-to-1 salts may form (PTX 154).

structure of the maleate salt and, using prior art teachings, compiled a list of seven other pharmaceutically acceptable acids that could eliminate these manufacturing barriers. After determining the besylate salt of amlodipine to be the best alternative to the amlodipine salt, Pfizer claimed it in a second patent. Id. at 1352-54, 1362. After the district court rejected Apotex's obviousness challenge, the Federal Circuit reversed, emphasizing that its holding was premised on the "particularized facts" of the case. Id. at 1358-59, 1369.

It is on those "particularized facts" that the Court distinguishes Pfizer v. Apotex and concludes it does not control the analysis in this case. In the first place, Pfizer's chemists were motivated to modify its earlier-claimed compound to address a particular need and relied on prior art teachings to select a limited number of acids that would allow them to design around the manufacturing issues they had identified. Here, in contrast, the prior art never disclosed any issue with the sitagliptin free base or any pharmaceutically acceptable salt of sitagliptin that would have driven a POSA's salt selection or narrowed the genus of pharmaceutically acceptable acids that could be used in salt formation.

In Pfizer v. Apotex, moreover, the prior art taught that the besylate salt of amlodipine likely would have solved the issues

that prevented Pfizer from manufacturing the maleate salt of amlodipine. Here, Mylan has offered no prior art reference teaching that the phosphate salt of sitagliptin would be beneficial, or even suggesting that a POSA could have synthesized a phosphate salt of sitagliptin in the first place.

d. Asserted Claim 3 Is Not Obvious Over the '871 Patent or the Prior Art

As to asserted claim 3, the obviousness-type double patenting inquiry is whether reference claim 17 covering the sitagliptin free base in its (R)-configuration, in combination with the prior art, would have motivated a POSA to create the 1-to-1 DHP salt of sitagliptin in its (S)-configuration with a reasonable expectation of success. UCB, 890 F.3d at 1324. Because asserted claim 3 differs from asserted claim 2 only in so far as it relates to the (S)-configuration of the 1-to-1 DHP salt of sitagliptin, the Court's obviousness-type double patenting analysis of asserted claims 1 and 2 also applies to asserted claim 3.

Several undisputed facts are relevant to this inquiry. First, with its one chiral center, sitagliptin has two isomers, its (R) and (S)-configurations (Trial Trans. 316:21-317:13 (Buckton); 957:25-958:2 (Myerson)). Second, a POSA knowing the (R)-configuration of a compound could create the (S)-configuration. Id. at 317:8-13 (Buckton); 958:12-959:8 (Myerson). Third, the (R)-

configuration and the (S)-configuration of the same compound can have different biological properties. Id. at 317:14-16 (Buckton); 959:1-3 (Myerson).

These known facts might have motivated a POSA to modify the 1-to-1 DHP salt of sitagliptin in the (R)-configuration to create the (S)-configuration with a reasonable expectation of success. But they do not overcome the larger problem Mylan has, which is that it has failed to establish that reference claim 17 and the prior art would have motivated a POSA to create any DHP salt of sitagliptin with a reasonable expectation of success.[33] It is for this reason that Mylan's obviousness-type double patenting challenge to asserted claims 1, 2, and 3 fails.

e. Asserted Claim 19 Is Not Obvious Over the '871 Patent or the Prior Art

Finally, the Court must consider whether a POSA, upon reading reference claim 20, would have been motivated to treat type 2 diabetes patients with a therapeutically effective amount of the 1-to-1 DHP salt of sitagliptin in its (R)-configuration. Because asserted claim 20 depends from asserted claims 1 and 2, the Court

[33] Mylan also has asserted that a POSA would have been motivated to create the 1-to-1 DHP salt of sitagliptin in its (S)-configuration because the FDA requires pharmaceutical manufacturers to study all isomers of a compound (Dkt. No. 175 at 13-14). Even if the FDA's directives supplied the requisite motivation, a POSA still would have lacked a reasonable expectation of success in forming any DHP salt of sitagliptin.

incorporates its obviousness-type double patenting analysis of these claims.

i. Pfizer v. Teva Is Not Controlling

According to Mylan, because asserted claim 19 uses a pharmaceutically acceptable salt of sitagliptin to treat diabetes, a utility disclosed in the '871 patent, it is not patentably distinct from reference claim 20. In support of this argument, it relies on Pfizer Inc. v. Teva Pharms. USA, Inc., 518 F.3d 1353 (2008), which involved a compound patent and a method patent. In its compound patent, Pfizer claimed "a pharmaceutical composition containing a therapeutically effective amount of a compound selected from a group of listed compounds, including celecoxib" and disclosed that such pharmaceutical composition would be useful in the treatment of inflammation. Pfizer Inc. v. Teva Pharms. USA, Inc., 482 F. Supp. 2d 390, 476 (D.N.J. 2007). In its later-filed method patent, Pfizer claimed a method of treating inflammation in subjects by administering a therapeutically effective amount of celecoxib. Id. The parties stipulated that the term "therapeutically effective amount" carried the same meaning in both patents. Id. at 477.

After Teva challenged several claims of Pfizer's method patent on obviousness-type double patenting grounds, the district court concluded that the asserted method claims were patentably

indistinct from the reference compound claims because the asserted claims merely covered a method of using the identical composition claimed in the reference patent for the identical use disclosed in the reference patent. The Federal Circuit affirmed this conclusion. Pfizer v. Teva, 518 F.3d at 1363.

Pfizer v. Teva does not compel a conclusion here that asserted claim 19 is patentably indistinct from reference claim 20. Although these claims share a common utility, treating diseases involving the DPP-IV enzyme such as type 2 diabetes, they do not claim identical compounds. Reference claim 20 covers a pharmaceutical composition comprised of an inert carrier and a pharmaceutically acceptable salt of sitagliptin. Asserted claim 19, in contrast, covers the use of 1-to-1 DHP salt of sitagliptin in its (R)-configuration. Thus, this is not a case in which Merck has attempted to claim an identical composition for a previously disclosed identical use.

ii. No Motivation or Reasonable Expectation of Success

Mylan's obviousness-type double patenting challenge to asserted claim 19 fails for the same reason its challenge to asserted claims 1 and 2 fails. A POSA would not have been motivated to select the 1-to-1 DHP salt of sitagliptin in its (R)-configuration from the reference genus. It also fails because

reference claim 20 would not have motivated a POSA to treat patients with a therapeutically effective amount of this salt.

Reference claim 20 covers "pharmaceutical compositions" comprised of sitagliptin or a salt of sitagliptin and an inert carrier (DTX 2054.0022). The '871 patent specification defines the term "composition" as one created by "admixing a compound of the present invention and a pharmaceutically acceptable carrier." Id. at .0005. For such carrier to be "pharmaceutically acceptable" it must be "compatible with the other ingredients of the formulation and not deleterious to the recipient thereof." Id.

According to Mylan, a POSA would have known that the purpose of the pharmaceutical composition described in reference claim 20 is to deliver a therapeutically effective amount to a patient in need (Dkt. No. 175 at 15-16; Trial Trans. 320:5-14 (Buckton)). And because treating patients is the ultimate goal of pharmaceutical compositions, a POSA would have been motivated to administer a pharmaceutically acceptable salt to patients with type 2 diabetes. Id.

At trial, there was overwhelming evidence regarding the unpredictability of pharmaceutical salt properties and, specifically, evidence that a POSA cannot predict the properties of a pharmaceutical salt unless and until she synthesizes and studies it. See DTX 006.0004-05 ("[T]here is no reliable way of

predicting the influence of a particular salt species on the behavior of the parent compound."); PTX 113.0001 ("There is, as yet, no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity . . . ."); Trial Trans. 110:13-15 (Hansen); 740:3-6 (Wenslow); 841:8-13 (Myerson); 995:5-8 (Buckton).

If a POSA could not predict a salt's pharmaceutical properties, she also could not predict the human body's reaction to the compound (PTX 113.0001). Accordingly, the language of reference claim 20 alone would not have motivated a POSA to administer the 1-to-1 DHP salt of sitagliptin in its (R)-configuration to a patient with a reasonable expectation of success.

This is especially true where the prior art did not disclose any information regarding the properties of this salt, and where it was known that changing the salt form of a compound could drastically impact its clinical efficacy and safety. Id. Without additional information related to the 1-to-1 DHP salt of sitagliptin, a POSA could not have known if it was safe, nor would she have been motivated to advance it into clinical development, a prerequisite for administration (Trial Trans. 762:3-765:1, 769:14-770:4 (MacMillan); 837:5-14, 902:10-17 (Myerson)). As Merck's expert, Dr. David MacMillan, opined, administration of the

1-to-1 DHP salt of sitagliptin based on the prior art and the '891 patent would have been "reckless if not dangerous." Id. at 776:13-22 (MacMillan).

Nor could a POSA have determined a therapeutically effective amount of the 1-to-1 DHP salt of sitagliptin in its (R)-configuration with a reasonable expectation of success. According to Dr. MacMillan, only 1 of 1000 compounds that are studied preclinically advance to human clinical trials. Id. at 762:3-19, 765:6-766:12 (MacMillan) (citing PTX 246). And many of the compounds that do advance to clinical study ultimately fail. Id. at 765:6-766:12 (MacMillan).

In opining that a POSA would have had a reasonable expectation of success in administering a therapeutically effective dose of the 1-to-1 DHP salt of sitagliptin in its (R)-configuration to type 2 diabetes patients, Mylan's expert, Dr. Buckton, cited the in vitro data in the reference patent demonstrating that sitagliptin would be effective. But the '871 patent defines a "therapeutically effective amount" much more broadly than does the '708 patent. Compare JTX 001 with DTX 2054.0005; see also Trial Trans. 767:1-16, 779:20-780:17 (MacMillan). And even considering the reference patent's data on sitagliptin's efficacy, Dr. MacMillan testified that it is "extremely common" for drugs with

in vitro potency to fail to show efficacy in treating patients. Id. at 761:7-9 (MacMillan).

Thus, given the lack of necessary information related to the claimed salt in the prior art and the high failure rate of compounds in clinical studies, based on the prior art and the reference patent a POSA would have had a very low expectation of success in treating patients with a therapeutically effective amount of the 1-to-1 DHP salt of sitagliptin in its (R)-configuration. For these reasons, Mylan's obviousness-type double patenting challenge to asserted claim 19 fails.

f. Secondary Considerations

Merck contends that the unexpected properties of the 1-to-1 DHP salt of sitagliptin confirm the non-obviousness of the asserted claims. "The burden of proof never shifts to the patentee to prove validity." Pfizer v. Apotex, 480 F.3d at 1359. But the patentee bears the burden of producing evidence to establish the existence of secondary considerations supporting non-obviousness. See Novo Nordisk, 719 F.3d at 1353. In determining whether Mylan has met its burden of proof on its obviousness-type double patenting challenge, the Court must consider objective indicia of non-obviousness, if such evidence is presented. Eli Lilly v. Teva, 689 F.3d at 1381.

****SEALED****

MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

For a patentee to rely on unexpected results as secondary evidence of non-obviousness, "the results must be shown to be unexpected compared with the closest prior art." Abbott Lab'ys v. Andrx Pharms., Inc., 452 F.3d 1331, 1345 (Fed. Cir. 2006) (citing In re Baxter Travenol Lab'ys, 952 F.2d 388, 392 (Fed. Cir. 1991)). "Unexpected results that are probative of non-obviousness are those that are different in kind and not merely in degree from the results of the prior art." Galderma Lab'ys, L.P. v. Tolmar, Inc., 737 F.3d 731, 739 (Fed. Cir. 2013) (citations omitted).

According to Merck, the 1-to-1 DHP salt of sitagliptin exhibits a suite of unpredictable and unexpectedly superior pharmaceutical properties compared to the next closest prior art, the sitagliptin free base and the HCL salt of sitagliptin (Dkt. No. 176 at 31-32; Trial Trans. 903:3-10 (Myerson)). Mylan, however, asserts that these improved qualities are not probative of non-obviousness because pharmaceutical manufacturers routinely pursue salt formation with the expectation of improving a compound's properties (Dkt. No. 175 at 19-20).

Even so, the prior art taught that a POSA could not predict whether any resulting salt form might exhibit more favorable properties (DTX 005.004). And she could not have expected any single salt form to emerge with all of the desired properties. See DTX 006.0004-05; DTX 005.0001. Rather, she would have expected to

compromise and select the compound exhibiting the best aggregate pharmaceutical properties for development. Id.

In this case, Merck's DPP-IV team had hoped that a salt form of sitagliptin might exhibit more favorable properties, but it could not have anticipated which salt, if any, might do so (PTX 082.0001; Trial Trans. 126:19-22, 129:2-5 (Hansen)). It thus was surprised to learn that the 1-to-1 DHP salt of sitagliptin exhibited each of the desired properties. Id.; see also In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997) ("[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."). These favorable properties were vastly superior to those exhibited by sitagliptin free base and the HCL salt of sitagliptin and thus were differences in kind, not degree.

Both the sitagliptin free base and the HCL salt of sitagliptin were unstable with a needle-like morphology that had led Merck to conclude they could not be developed (PTX 71; Trial Trans. 102:2-14, 103:10-104:4, 104:15-105:11, 106:20-107:7, 116:25-117:3, 128:12-24 (Hansen). The 1-to-1 DHP salt of sitagliptin, on the other hand, was better in every respect. It had a desired particle morphology, low hygroscopicity, good chemical stability in solution, and high thermal stability and was quickly recommended for development (Trial Trans. 120:11-122:8, 124:13-126:5

(Hansen)). Later, Merck's DPP-IV team discovered that the crystalline monohydrate exhibited even more exceptional pharmaceutical properties. Id. at 133:12-134:22 (Hansen). These surprising differences from the closest prior art compounds support the conclusion that the asserted claims are non-obvious.

3. Written description

To satisfy the written description requirement outlined in 35 U.S.C. § 112, a patent's specification must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (quotation omitted). "[T]he 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.

Possession as shown in the disclosure is the hallmark of written description. Id. at 1351. The written-description inquiry therefore entails an "objective inquiry into the four corners of the specification from the perspective of a [skilled artisan]." Biogen Int'l GMBH v. Mylan Pharms. Inc., 18 F.4th 1333, 1342 (Fed. Cir. 2021) (citing Ariad, 598 F.3d at 1351). An inventor sufficiently describes a genus claim if it discloses either "a representative number of species falling within the scope of the

genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." Ariad, 598 F.3d at 1349 (quoting Regents of the Univ. of Ca. v. Eli Lilly & Co., 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)).

Whether the asserted claims of the '708 patent are invalid for lack of written description is a factual question for Mylan to establish by clear and convincing evidence. Rivera v. Int'l Trade Comm'n, 857 F.3d 1315, 1319 (Fed. Cir. 2017). Most of the facts on this point are undisputed. First, asserted claim 1 covers the 1-to-1 DHP salt of sitagliptin "or a hydrate thereof" (JTX 002.0007-08, .0014). Second, at the time of the invention, Merck had created several forms of the DHP salt of sitagliptin (Trial Trans. 126:7-10; 129:10-130:1 (Hansen); 278:23-25 (Buckton)). Third, Merck possessed the crystalline monohydrate form, but no other hydrated forms of the DHP salt of sitagliptin existed. Id. at 937:14-18 (Myerson); 334:9-12 (Buckton). Fourth, to date, the crystalline monohydrate remains the only known hydrate of the DHP salt of sitagliptin. Id. at 134:23-135:1 (Hansen). Fifth, it is possible that other hydrates could be discovered in the future and, if so, those would be covered by the asserted claims (Trial Trans. 937:5-13 (Myerson)).

Mylan contends that the asserted claims of the '708 patent fail for lack of written description because, in claiming all hydrates of the DHP salt of sitagliptin while possessing only the crystalline monohydrate, Merck has attempted to claim more than it invented (Dkt. No. 175 at 38-39). Mylan characterizes Merck's disclosure as no more than a research plan for the discovery of additional hydrates.

Merck argues that it has satisfied the written description requirement by identifying structural features common to the members of the genus and by disclosing a representative number of species (Dkt. No. 176 at 40-41). Conceding that the crystalline monohydrate is the only hydrate described in the '708 patent, it contends nothing additional is required. Id. Having described every known hydrate of the DHP salt of sitagliptin, it is not required to describe every unknown or undiscovered hydrate of the DHP salt of sitagliptin in order to satisfy the written description requirement. Id.

"[A]n adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." Ariad, 598 F.3d at 1350. Here, the asserted claims cover a genus of all forms of the 1-to-1 DHP salt of sitagliptin, including

hydrates. The key structural feature of this genus is its unique chemical formula, or structure. At trial, Dr. Buckton and Dr. Myerson agreed that every form of the DHP salt of sitagliptin, whether hydrous or anhydrous, shares the common chemical formula disclosed in the '708 patent (Trial Trans. 349:3-351:6 (Buckton); 913:2-21 (Myerson)). 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. at 352:13-25 (Buckton); 913:14-914:7 (Myerson). And this would be true even if the form is a hydrate. Id. at 352:20-353:8 (Buckton); 912:2-9, 914:4-21 (Myerson).

It is well settled that Merck is not required to describe "every conceivable and possible future embodiment of [its] invention." Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1344 (Fed. Cir. 2001). And it may adequately describe a broadly claimed invention "without describing all species that [the] claim encompasses." Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003). Thus, Merck need not have actually possessed every species within the genus at the time of filing in order to satisfy the written description requirement.

Further, because the genus in the asserted claims does not contain any functional or performance requirement, this is not a case in which Merck has overstated its invention in an attempt to

preempt the future before it arrives by "merely recit[ing] a description of the problem to be solved while claiming all solutions to it." Ariad, 598 F.3d at 1353 (citing Fiers v. Revel, 984 F.2d 1664, 1171 (Fed. Cir. 1993)).

The Federal Circuit's holding in GlaxoSmithKline LLC v. Banner Pharmacaps, Inc., 744 F.3d 725 (Fed. Cir. 2014), on which both parties rely, supports this conclusion. There, the patent claimed dutasteride and its pharmaceutically acceptable solvates. 744 F.3d at 727-28. The defendant argued that the term "solvates" lacked an adequate description because the patent's specification did not describe a wide enough range of the solvates. Id. The district court rejected this challenge. Id. On appeal the Federal Circuit affirmed, holding that "[d]escribing 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 729 (quotations omitted). The Federal Circuit also noted that the term "solvate" was structural rather than functional, that solvation was well established in the prior art, and that a POSA would have known dutasteride to be prone to solvate formation. Id. at 731.

In a similar vein, the asserted claims here describe a genus consisting of a compound and its hydrates, and members of this genus are described using common structural features. Dr. Buckton and Dr. Myerson agreed that a POSA would be familiar with hydrates and hydrate formation, as well as with the prior art teaching that phosphate salts commonly produced hydrates (Trial Trans. 355:12-356:5 (Buckton); DTX 021.0137, .0182).

Because Mylan has not demonstrated by clear and convincing evidence that a POSA would not be able to use the common structural features disclosed in the '708 patent to identify members of its claimed genus, its argument that the asserted claims are not adequately described fails.[34] Given this conclusion, the Court need not address whether Merck also disclosed a representative number of species to satisfy the written description requirement.

4. Enablement

"To prove that a claim is invalid for lack of enablement, [Mylan] must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the

[34] On June 22, 2022, Mylan notified the Court of the Federal Circuit's precedential opinion in Novartis Pharms. Corp. v. Accord Healthcare, Inc., 38 F.4th 1013, 1016 (Fed. Cir. 2022) (Dkt. No. 191). Aside from reiterating established points of law and the importance of the written description requirement, Novartis primarily addresses negative claim limitations, which are not at issue in this case.

claimed invention without undue experimentation." Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1084 (Fed. Cir. 2021) (quotations omitted). The key word is "undue," not "experimentation." ALZA Corp. v. Andrx Pharms., LLC, 603 F.3d 935, 939 (Fed. Cir. 2010). Id. Enablement does not require the specification to describe "how to make and use every possible variant of the claimed invention," McRO, Inc. v. Bandai Namco Games Am. Inc., 959 F.3d 1091, 1100 (Fed. Cir. 2020), but it must reasonably enable a POSA to practice the full scope of the claimed invention. Trustees of Boston Uni. V. Everlight Electronics Co., LTD, 896 F.3d 1357, 1364 (2018).

To determine whether the asserted claims have been sufficiently enabled to avoid undue experimentation, the parties rely on the so-called "Wands factors," as follows:

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

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

The Court agrees that it must analyze these factors in order to determine if the full scope of the claims at issue have been enabled. Under Mylan's analysis of the Wands factors, because the

'708 patent does not enable the full scope of the invention, the asserted claims are invalid (Dkt. No. 175 at 22-23). Specifically, Mylan argues that Merck has claimed all physical forms of the 1-to-1 DHP salt of sitagliptin without enabling each and every one. Id. Merck, in its analysis of the Wands factors, responds that the specification of the '708 patent teaches a POSA to make every known physical form of the claimed salt without undue experimentation (Dkt. No. 176 at 33-36), and the asserted claims therefore are valid.

At bottom, the parties dispute whether the law of enablement requires the '708 patent specification to enable all possible forms of the 1-to-1 DHP salt of sitagliptin, or only known forms of this salt. As the following discussion of the relevant Wands factors establishes, the '708 patent specification enables the full scope of the asserted claims by enabling every known form of the 1-to-1 DHP salt of sitagliptin.

a. Nature of the Invention and Breadth of the Claims

In order to develop a treatment for type 2 diabetes, Merck selected sitagliptin from a class of DPP-IV inhibitors (Trial Trans. 94:17-23, 95:8-25 (Hansen)). Its '708 patent claims a single salt form of this compound, the 1-to-1 DHP salt of sitagliptin. See JTX 001. The asserted claims cover a genus of all physical forms of this salt (Trial Trans. 336:13-20 (Buckton); 934:2-5,

935:6-8, 937:19-22, 939:18-25, 941:4-7, 961:14-21 (Myerson)). Mylan contends that Merck has advocated for a broad construction of the asserted claims, specifically for the phrase "or a hydrate thereof" (Dkt. No. 175 at 24-26). Merck denies this and argues that Mylan's contention is not supported by the evidence of record. The Court agrees with Merck.

During claim construction before the Delaware district court, the issue arose whether asserted claim 2 of the '708 patent included hydrates of the salt of claim 1. In re Sitagliptin., 2020 WL 6743022, at *3. While claim 1 specifically covered hydrates of the 1-to-1 DHP salt of sitagliptin, claim 2 was silent. Id. at *3-4. Based on this silence, the defendants argued for a construction of claim 2 that excluded hydrates. Id.

After careful review, Judge Andrews declined to adopt this construction and concluded that asserted claim 2 did not exclude hydrates. Had he adopted the construction urged by the defendant generics, claim 4, related to the crystalline monohydrate, would have been invalid for a technical defect inasmuch as it depends from claim 2. Id. This history persuades the Court that, when viewed in the proper context, Merck did not advocate for an overly broad construction of the asserted claims but rather urged that dependent claim 2 covered the same physical forms as independent claim 1, which covers hydrates.

Despite covering all hydrates, anhydrous forms, and amorphous forms of the 1-to-1 DHP salt of sitagliptin, the asserted claims are relatively narrow. They are limited to a single salt form of a single compound, with every physical form sharing a common, identifiable chemical structure.

b. State of the Prior Art

The state of the prior art is a pivotal factor in resolving the parties' enablement dispute. Enablement is determined as of the patent's effective filing date. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986). Therefore, the state of the art at the time of the invention is relevant to the enablement inquiry and not any future state of the art. In re Hogan, 559 F.2d 595, 605-06 (CCPA 1977).

According to Mylan, the '708 patent specification must enable all hydrates of the 1-to-1 DHP salt of sitagliptin. But adopting Mylan's position would require Merck to enable technology that was not available as of the date of filing, or even today.

At trial, the parties' experts agreed that the crystalline monohydrate described in the '708 patent is the only known hydrate of the claimed salt (Trial Trans. 338:11-20 (Buckton); 919:6-16, 937:2-4 (Myerson)). They also agreed that it is possible that additional hydrates might be discovered in the future, although

Dr. Myerson opined that the likelihood of finding another hydrate to be "quite low." Id.; PTX 213.0002.

But such possibility does not invalidate the asserted claim for lack of enablement. "[A] patent document cannot enable technology that arises after the date of application. The law does not expect an applicant to disclose knowledge invented or developed after the filing date. Such disclosure would be impossible." Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1254 (Fed. Cir. 2004) (citing Hogan, 599 F.2d at 605-06).

c. Amount of Direction or Guidance Presented and Quantity of Experimentation Necessary

Throughout its enablement challenge, Mylan frames the genus claimed in the '708 patent as hydrates of the 1-to-1 DHP salt of sitagliptin. And, following on that, Mylan's argues that to enable the full scope of this genus, the patent specification must teach the POSA how to create more than one hydrate of the claimed salt (Dkt. No. 175 at 25).

Despite Mylan's argument, the claimed genus is actually all physical forms of the 1-to-1 DHP salt of sitagliptin. Enablement of this genus requires that the '708 patent disclose invented species commensurate in scope. Amgen Inc. v. Sanofi, Aventisub LLC, 850 F. App'x 794, 797 (Fed. Cir. 2021) (denying rehearing en banc) ("Entitlement to a broad genus claim thus requires disclosure

and enablement of species supportive of the genus that a patentee claims to have invented."). This is not a case in which the '708 patent claims a broad genus but only provides examples of a small number of invented species. Here, Merck had reduced to practice and enabled every known species of the 1-to-1 DHP salt of sitagliptin.

When Merck filed the '708 patent, six physical forms of the claimed salt were known to exist. These included anhydrous forms I, II, III, and IV; a crystalline monohydrate; and a dehydrated monohydrate (Trial Trans. 147:4-9 (Hansen); 920:24-921:7 (Myerson)). The evidence of record establishes that a POSA could have made each of these physical forms from the guidance contained in the '708 patent.

In particular, the '708 patent specification includes procedures for creating the "starting compound" of 1-to-1 DHP salt of sitagliptin. JTX 001.0010-13. It sets forth several detailed methods for synthesizing the crystalline monohydrate. Id. at .0009-10; see also Trial Trans. 138:13-25 (Hansen). And it teaches the POSA how to convert the crystalline monohydrate into the dehydrated monohydrate (JTX 001.0014).

The '708 patent does not expressly disclose the anhydrous forms of the claimed salt but, at trial, Merck's witnesses testified that upon reading the specification a POSA would have

known how to make each of these forms (Trial Trans. 139:23-140:25, 145:2-25 (Hansen); 924:15-22 (Myerson)). Specifically, these witnesses testified that a POSA would understand that altering the water concentration in the crystalline monohydrate examples would produce the anhydrous forms. Id. Mylan's expert did not credibly dispute this.

It is clear from the evidence, and the Court so finds, that the '708 patent teaches a POSA how to reproduce every known form of the 1-to-1 DHP salt of sitagliptin. It describes a number of species commensurate with the scope of the claimed genus, thereby rendering the asserted claims sufficiently enabled.[35] Mylan's complaint, that the specification lacks guidance for synthesizing any hydrates other than the crystalline monohydrate, does not alter this conclusion. No other hydrates are known, and Merck is not required to enable hydrates that might be discovered in the future. Chiron, 363 F.3d at 1254; Hogan, 599 F.2d at 605-06.

d. Predictability of the Art

Finally, it is undisputed that formation of new solid forms and hydrates is unpredictable (Trial Trans. 927:16-22 (Myerson);

[35] Mylan also points to the fact that no phosphate salt of sitagliptin was disclosed in the prior art (Dkt. No. 176 at 22; see also Trial. Trans. 921:13-16, 935:19-23 (Myerson)). But this ignores the fact that enablement is based on the teachings of the specification at issue. In this case, those teachings are significant.

see also PTX 213.0002). Thus, a POSA looking to find hydrates of the 1-to-1 DHP salt of sitagliptin could not have predicted if or when she would be successful (PTX 213.0002; DTX 047). But the prior art taught her how to crystallize and characterize solid forms, including hydrates, if any formed (Trial Trans. 926:12-25 (Myerson); DTX 047; DTX 021.0007).

The unpredictability of finding additional hydrates of the claimed salt is offset by the predictability provided by the patent specification. Following the guidance in the '708 patent a POSA could have reproduced each of the known physical forms of the 1-to-1 DHP salt of sitagliptin without any undue experimentation.

e. Summary

For the reasons discussed, the Wands factors support a finding of enablement. The asserted claims cover all physical forms of the 1-to-1 DHP salt of sitagliptin, and the '708 patent enables every known form of this compound. Thus, no undue experimentation would be required to practice the full scope of the asserted claims. Mylan's challenge on this basis fails.

IV. CONCLUSION

For the reasons discussed:

1. Merck has demonstrated by a preponderance of the evidence that Mylan's ANDA products will infringe claim 3 of the '708 patent;
2. Merck has demonstrated by a preponderance of the evidence that Mylan's ANDA products will infringe claim 1 of the '921 patent;
3. Mylan has not demonstrated by clear and convincing evidence that the asserted claims of the '708 patent are invalid under the obviousness-type double patenting doctrine;
4. Mylan has not demonstrated by clear and convincing evidence that the asserted claims of the '708 patent are invalid for lack of written description; and
5. Mylan has not demonstrated by clear and convincing evidence that the asserted claims of the '708 patent are invalid for lack of enablement.

It is so **ORDERED.**

****SEALED****

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The Clerk is directed to enter a separate judgment order in favor of Merck Sharpe & Dohme LLC, and to transmit copies of both orders to counsel of record.

DATED: September 21, 2022

/s/ Irene M. Keeley
IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE