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

ASTRAZENECA AB and
ASTRAZENECA PHARMACEUTICALS LP,

Plaintiffs,

v. **CIVIL ACTION NO. 1:18CV193**
(Judge Keeley)

MYLAN PHARMACEUTICALS INC. and
KINDEVA DRUG DELIVERY L.P.,

Defendants.

c/w 1:19CV203

MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

In this patent infringement action, the plaintiffs, AstraZeneca AB and AstraZeneca Pharmaceuticals LP (collectively, "AstraZeneca"), and the defendants, Mylan Pharmaceuticals Inc. and Kindeva Drug Delivery L.P.[1] (collectively, "Mylan"), dispute whether claims 2 and 3 of United States Patent No. 10,166,247 ("the '247 patent") are valid and enforceable. Following a three-day bench trial, pursuant to Federal Rule of Civil Procedure 52(a), and based on the following findings of fact and conclusions of law, the Court **HOLDS** that Mylan has demonstrated by clear and convincing evidence that claims 2 and 3 of the '247 patent are invalid for lack of enablement and lack of written description.

[1] Although AstraZeneca originally included 3M Company as a defendant in this action, the parties stipulated to its dismissal because it had transferred all activities related to Mylan's generic Symbicort® program to Kindeva Drug Delivery L.P. (Dkt. No. 386).

ASTRAZENECA AB, ET AL. V. MYLAN PHARMS INC., ET AL. 1:18CV193
C/W 1:19CV203

MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

I. BACKGROUND

The asserted claims are associated with Symbicort®, AstraZeneca's New Drug Application ("NDA") product approved by the FDA as a treatment of asthma and as a maintenance treatment of chronic obstructive pulmonary disease ("COPD") (Dkt. Nos. 285 at 3-4; 286 at 3-4).[2] After Mylan filed Abbreviated New Drug Application ("ANDA") No. 211699 seeking to engage in the commercial manufacture, use, or sale of generic versions of the two dosage forms of Symbicort® prior to the expiration of the patents at issue, AstraZeneca filed this lawsuit (Dkt. No. 286 at 2).

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

[2] All docket numbers refer to Civil Action Number 1:18CV193 unless otherwise indicated.

("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)). Upon receiving a 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)).

Pursuant to the Hatch-Waxman Act, on October 12, 2018, AstraZeneca filed this action alleging that Mylan infringed United States Patent Nos. 7,759,328 ("the '328 patent"); 8,143,239 ("the '239 patent"); 8,575,137 ("the '137 patent"); and 7,967,011 ("the '011 patent") (1:19CV203, Dkt. No. 1). Thereafter, AstraZeneca amended its complaint to delete its claims related to the '011 patent and to add claims related to the '247 patent (Dkt. Nos. 89, 91).

A. Claim Construction

Shortly before trial in 2020, the parties disputed the meaning of the term "0.001% w/w PVP," which appeared in several of the asserted claims and related to the concentration of polyvinylpyrrolidone ("PVP") in the claimed invention (Dkt. No.

317). AstraZeneca argued that "0.001%" should have its plain meaning, "0.001%, expressed using one significant digit" (Dkt. No. 292 at 5), while Mylan contended that, because AstraZeneca had abandoned its proposed construction of "0.001%" during prosecution of the patents-in-suit, "0.001%" meant "that precise number, with only minor variations" (Dkt. No. 288 at 4). The Court adopted AstraZeneca's construction (Dkt. No. 317).

B. 2020 Bench Trial

Following the Court's construction, the parties agreed to dismiss their claims related to the '247 patent (Dkt. No. 349). They also stipulated that Mylan's ANDA infringed the '328, '239, and '137 patents ("the Previously Tried Patents"). Id. Therefore, the only dispute remaining at trial was whether certain claims of the Previously Tried Patents were invalid as obvious pursuant to 35 U.S.C. § 113 (Dkt. Nos. 285 at 4-5; 286 at 4-5; 390).[3] After a five-day bench trial, the Court by a Memorandum Opinion and Order entered on March 2, 2021, concluded that the asserted claims were not obvious and entered judgment in favor of AstraZeneca (Dkt. No. 431).

[3] Specifically, the parties disputed the validity of claims 9, 10, 13, and 14 of the '328 patent; claims 12, 13, 18, and 19 of the '239 patent; and claims 10 and 19 of the '137 patent ("the Previously Tried Claims").

C. Appeal

On appeal, the Federal Circuit affirmed the Court's determination of nonobviousness but vacated its claim construction. In AstraZeneca AB v. Mylan Pharms. Inc., 19 F.4th 1325 (Fed. Cir. 2021), it held that the term "0.001% w/w PVP" meant "that precise number with only minor variations, i.e., 0.00065% to 0.00104%" and remanded the case for this Court to consider whether Mylan's ANDA infringed the patents-in-suit under that construction. Id. at 1329-30, 1338. It also denied AstraZeneca's request for panel rehearing or rehearing en banc (Dkt. No. 496).

D. Remand

On remand, the parties moved to vacate their earlier stipulations related to infringement of the Previously Tried Patents and the dismissal of the '247 patent (Dkt. Nos. 503, 512). They then entered new stipulations based on the Federal Circuit's claim construction (Dkt. No. 539). Specifically, they agreed that Mylan's ANDA infringes claims 1, 2, 3, 5, 6, 7, 10, 11, and 12 of the '247 patent, but does not infringe the Previously Tried Patents or claim 4 of the '247 patent. Id. at 4-5. At trial, AstraZeneca asserted only claims 2 and 3 of the '247 patent, which Mylan argued

were invalid under 35 U.S.C. § 112 for lack of enablement, lack of written description, or indefiniteness.

II. FINDINGS OF FACT

In its March 2, 2021 Memorandum Opinion and Order holding that the Previously Tried Claims were not obvious, the Court made findings of fact related to asthma, COPD, several prior art references, AstraZeneca's development of Symbicort®, and the relevant prosecution history of the patents-in-suit. It incorporates those findings here.

A. Symbicort® and Suspension pMDIs

To review, the asserted claims relate to AstraZeneca's Symbicort® product, which was approved by the FDA on July 21, 2006, to treat asthma and COPD (Dkt. No. 564 at 2-3). The Symbicort® formulation consists of two active ingredients (budesonide and formoterol fumarate dihydrate ("FFD")) and two excipients (PVP with a nominal K-value of 25 ("PVP K25") and polyethylene glycol with an average molecular weight of 1000 ("PEG 1000")), suspended in the propellant 1,1,1,2,3,3,3-heptafluoropropane ("HFA 227"). Id. at 2.

AstraZeneca sells Symbicort® in two dosage strengths, a low-strength dose delivering 80 micrograms of budesonide and 4.5

micrograms of FFD, and a high-strength dose delivering 160 micrograms of budesonide and 4.5 micrograms of FFD (Dkt. No. 591 at 8-9). In both dosages, the concentration of PVP K25 is 0.001% and the concentration of PEG 1000 is 0.3% (Trial Trans. 1463:1-7 (Stein)).

Symbicort® is administered through a pressurized metered dose inhaler ("pMDI"), one of several delivery systems available to administer inhaled medications (Dkt. No. 431 at 7-8). The pMDI delivery system contains gas that is liquified under pressure. Id. at 9. Unlike other delivery systems, the pressurized gas performs all the work needed to get the medication into the patient's lungs. Id. A pMDI does not require a deep breath for the patient to receive an adequate dose and is especially useful in treating certain types of patients, such as those experiencing a respiratory attack, young children, elderly individuals, and those with neurological impairments. Id. at 8-9. To use a pMDI, patients shake the inhaler, place it in their mouth, and press a button to actuate it while breathing in. Id. at 9-10. A metering chamber in the inhaler controls the dose a patient receives. Id. at 9.

In suspension formulations such as Symbicort® the active ingredients are suspended in a liquid while remaining in their

solid form (Trial Trans. 979:22-980:2). Because they are not dissolved into the liquid, over time the active ingredients will cluster together, or flocculate, and then either float to the top or sink to the bottom of the liquid. Id. at 980:3-5, 980:21-981:7. In the Symbicort® formulation, where the active ingredients are less dense than the HFA 227 in which they are suspended, when at rest, they "cream," or rise to the top. Id. at 1321:1-6 (Young).

To effectively treat patients, the pMDI must deliver a consistent and reproducible dose of the inhaled drug into the patient's lower airways (Dkt. No. 431 at 8, 10). Given the tendency of the active ingredients to flocculate, suspension formulations pose a unique challenge in this regard. If the clusters of active ingredients cling together at the top or bottom of the suspension, the patient will not receive a proper dose of the active ingredients and will receive different doses over the life of the inhaler (Trial Trans. 980:21-982:21; 1322:22-1323:21 (Young)).

To avoid this problem, it is essential that these clusters break apart and the active ingredients redisperse throughout the liquid when the patient shakes the inhaler prior to actuation. Id. at 981:8-17; 1322:22-1324:3 (Young). Certain excipients and

surfactants, such as PVP, facilitate this redispersion. Id. at 982:22-983:16.

B. Mylan's ANDA Products

Mylan submitted ANDA No. 211699 to the FDA seeking approval to manufacture generic versions of Symbicort® prior to the expiration of the '247 patent (Dkt. No. 564 at 2-3). During the pendency of this case, Mylan received FDA approval to launch its ANDA products (Dkt. No. 591 at 8).

Mylan's ANDA products contain the same five ingredients as Symbicort®, budesonide, FFD, PVP K25, PEG 1000, and HFA 227 (Dkt. No. 564 at 2-3), and the same concentrations of budesonide, FFD, and PEG 1000, suspended in HFA 227 (Trial Trans. 1463:6-15 (Stein)). Moreover, Mylan will sell its ANDA products in the same two strengths to deliver the same doses of the active ingredients. Id. at 1438:4-12 (Stein). But Symbicort® and Mylan's ANDA products contain different concentrations of PVP K25.[4] Id. at 1438:16-22, 1463:3-5 (Stein).

[4] For this reason, the parties stipulated that Mylan's ANDA products do not infringe the Previously Tried Claims (Dkt. No. 539; Trial Trans. 597:15-18).

C. The '247 Patent

The '247 patent, filed on February 8, 2017 and issued on January 1, 2019, is titled "Composition for Inhalation" (JTX 2022.0001). It lists Nayna Govind and Maria Marlow as inventors and AstraZeneca as the assignee. Id. The relevant claims of the patent are as follows:

> 1. A stable pharmaceutical composition comprising formoterol, budesonide or an epimer thereof, 1,1,1-2,3,3,3-heptafluoropropane (HFA 227), polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG).
>
> 2. The composition according to claim 1 wherein the PVP is present from about 0.0005 to about 0.05% w/w and the PEG is present from about 0.05 to about 0.35% w/w.
>
> 3. The pharmaceutical composition according to claim 1 in which the PVP is PVP K25.

Id. at .0023.

The '247 patent is listed in the FDA's Orange Book for Symbicort®, and the parties agree that Symbicort® is an embodiment of the asserted claims (Dkt. No. 564 at 2-3). Mylan contends that claims 2 and 3 of the '247 patent are invalid under § 112.[5]

[5] For the first time at trial, the parties offered opposing definitions of the term "stable pharmaceutical composition," as used in claim 1 of the '247 patent. AstraZeneca contended that stability in this context referred only to short-term physical stability related to the redispersion of the active ingredients within a suspension formulation after flocculation. Mylan, however, asserted that stability encompassed not only short-term physical stability, but also

The '247 patent teaches that "[s]tability is one of the most important factors which determines whether a compound or a mixture of compounds can be developed into a therapeutically useful pharmaceutical product" (JTX 2022.0019). It "found that certain HFA formulations comprising formoterol and budesonide together with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) exhibit excellent physical suspension stability." Id. It then provides three routine methods for measuring redispersion in a suspension formulation. These include (1) photographic analysis or visual inspection, (2) optical suspension characterization ("OSCAR"), and (3) Turbiscan. JTX 2022.0019-21; see also Trial Trans. 1070:13-15, 1072:16-19 (Pritchard); 1365:19-23 (Young).

D. Methods for Testing Physical Suspension Stability

The '247 patent teaches that visual inspection is a qualitative method of measuring dispersion over time (JTX 2022.0020). During this analysis, a person of ordinary skill in the art (a "POSA") places the suspension in a clear bottle, shakes it, and then digitally photographs it at set intervals. Id. at .0021; see also Trial Trans. 1074:3-14 (Pritchard). For example,

chemical stability and long-term stability. The parties ultimately agreed that the Court need not resolve this dispute to reach a decision on the merits of this case (Trial Trans. 1651:10-13, 1654:4-1655:11), and the Court does not do so.

the inventors of the '247 patent photographed suspensions at 0, 15, 30, and 60 seconds, and at 2, 5, and 10 minutes (JTX 2022.0021). A POSA next rates the suspension in these photographs "in increments of 1-5 at 20% intervals to express the degree of dispersion: i.e., 0 [is] fully suspended and 5 fully creamed." Id. This method allows for comparison across formulations. Id.

While visual inspection is a qualitative method, the OSCAR and Turbiscan testing methods are semi-qualitative. OSCAR and Turbiscan both measure the dispersion of a suspension over time using light (JTX 2022.0019-20).

OSCAR "utilizes changes in light transmission over time to characterize a preagitated suspension formulation." Id. at .0020; see also Trial Trans. 1329:11-14 (Young). To perform this test, a formulation is placed in a transparent bottle with probes fixed at high and low positions on both sides of the bottle.[6] JTX 2022.0020; see also Trial Trans. 1070:5-12 (Pritchard); 1329:19-25 (Young). The probes direct light through the suspension and measure the amount capable of passing through. JTX 2022.0020; see also Trial Trans. 1070:5-12 (Pritchard); 1330:2-6 (Young). When the suspension is dispersed, the amount of light transmitted between

[6] Figure 1 of the '247 patent depicts the OSCAR setup. See JTX 2022.0003-05.

the probes is low; as the suspension creams the amount of light transmitted will increase (Trial Trans. 1070:5-12 (Pritchard); 1330:7-10 (Young)).

In the '247 patent, OSCAR testing measures how quickly light transmission increases, or how quickly a formulation creams. Id. at 1070:7-8 (Pritchard). According to the inventors, "low light transmission is indicative of stable suspensions with low flocculation characteristics" (JTX 2022.0020), while unstable formulations have high light transmission rates (Trial Trans. 1332:7-14 (Young)).

The Turbiscan test operates in a manner similar to the OSCAR test except that one set of light sensors is placed at the center of the canister. Id. at 1072:10-15 (Pritchard); 1355:16-21 (Young). Like OSCAR testing, Turbiscan testing measures the amount of light transmitted through the suspension. Id. at 1071:25-1072:7 (Pritchard). In addition, it measures the amount of backscattered, or reflected, light. Id.

E. Previously Tried Patents and Claims

The Previously Tried Patents share a specification with the '247 patent (Dkt. Nos. 563-12 at 11; 563-13 at 2). Claim 1 of

the '328 patent is representative of the Previously Tried Claims and recites:

> 1. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 2 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

(JTX 2000.0021).

F. Prior Art

1. Mistry

Mistry is the lead inventor on related foreign and United States patents and patent applications titled "Pressurized aerosol compositions," directed primarily to polymers that work in HFA propellants to stabilize pMDI suspension formulations (JTX 2381.0001-02). The invention claimed in Mistry is:

> a pressurized aerosol composition . . . that comprises a liquefied hydrofluoroalkane, a medicinal product in powder form dispersible therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes repeating structural units, the units being selected from units that contain an amide and units that contain an ester of a carboxylic acid.

Id. at .0002-3.

Relevant to the patents-in-suit, Mistry disclosed polymers soluble in HFA propellants. Id. at .0002. It particularly preferred

a polymer containing 1-ethylenepyrrolidin-2-one, i.e., PVP. Id. at .0003. Mistry found that PVP in a "wide variety of molecular weights" provided acceptable suspensions. Id. PVP is usually characterized by its K value, "where K is determined from measurements of viscosity using the Fikentscher equation." Id. Mistry particularly preferred polymers with K values from 10 to 150, with a specific preference for 15 to 120. Id. "The particular K values and ranges that may be mentioned include 10-14, 15-18, 29-32, 88-100 and 115-125." Id. "The amount of polymer in the composition will depend on the active ingredient that is to be dispersed, its concentration and the particular polymer selected; however, in general the amount of polymer is from 0.00001 to 10% w/w, preferably 0.0001 to 5% w/w and especially 0.001 to 1% w/w." Id. at .0004.

Mistry also disclosed the possibility of using an additional excipient with the chosen polymer in an HFA propellant and stated a preference for PEG. Id. It particularly preferred a PEG with an average molecular weight from 200 to 3000, or more preferably with an average molecular weight from 400 to 2000. Id. "In general, a concentration from 0.01 to 4% w/w and more preferably 0.1 to 2% w/w is preferred." Id. at .0004-05.

2. Carling

Carling is the lead inventor on United States Patent No. 5,674,860, titled "Combination of Bronchodilator and a Steroidal Anti-Inflammatory Respiratory Disorders" (JTX 2373.0001). Issued on October 7, 1997, Carling discloses a method of treating asthma with a novel combination of budesonide and formoterol, or a physiologically acceptable salt or solvate of formoterol. Id.

> The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 6 to 100 [micrograms] with a preferred dose 6-48 [micrograms] and the suitable daily dose for budesonide is 50 to 4800 [micrograms] with a preferred dose of 100-1600 [micrograms]. The particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate severe asthma etc).

Id. at .0003.

III. INVALIDITY OF THE '247 PATENT

According to Mylan, claims 2 and 3 of the '247 patent are invalid under 35 U.S.C. § 112 for lack of enablement, lack of written description, and indefiniteness. Because each of the asserted claims is presumed to be valid, see 35 U.S.C. § 282; Novo Nordisk A/S v. Caraco Pharm. Lab'ys, Ltd., 719 F.3d 1346, 1352 (Fed. Cir. 2013), Mylan 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 Corp. v. I4i Ltd. P'ship, 564 U.S. 91, 102 (2011) ("[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)).

A. Person of Ordinary Skill in the Art

Determining who constitutes a person of ordinary skill in the art is a factual question. See ALZA Corp. v. Andrx Pharm., LLC, 603 F.3d 935, 940 (Fed. Cir. 2010). In its March 2, 2021 Memorandum Opinion and Order, the Court determined that a POSA would have an advanced degree such as a master's degree or Ph.D. in a pharmaceutical science, several years of experience in the field of aerosol pharmaceutical development, and the ability to collaborate with others, including experts in the field of chemistry or chemical engineering (Dkt. No. 431 at 29). Consistent

with the parties' arguments on remand, the Court again applies this definition to assess the validity of the asserted claims.

B. Enablement

1. The Parties' Contentions

Mylan contends that the asserted claims are not enabled because their breadth is not supported by the specification's narrow disclosures (Dkt. No. 591 at 15-29). More specifically, it argues the asserted claims cover the "tens of thousands or millions of combinations of different doses of budesonide, different doses of formoterol and all of its salts, and different PVP and PEG grades and concentrations" (Dkt. No. 595 at 13), while the specification only teaches a POSA how to make a limited subset of this claim, namely, how to reproduce Symbicort®, and Symbicort®-like products. Id. at 7. Mylan argues that undue experimentation would be required to find any other formulation that satisfies the asserted claims' structural and functional limitations because any change to a single ingredient impacts the whole formulation and a POSA would have to create and test each distinct formulation to determine if it is stable (Dkt. No. 591 at 17).

In support of its argument, Mylan points out that the asserted claims are significantly broader than the Previously Tried Claims.

Id. at 17-19. While those Claims required FFD, a specific salt form of formoterol; precise concentrations of both active ingredients; and precise grades and concentrations of PVP and PEG, the asserted claims replace these exacting limitations with the generic requirement that the combination of budesonide, formoterol, PVP, PEG, and HFA 227 be "stable." Id. And while the shared specification might have supported the Previously Tried Claims, it adds nothing to enable the extended scope of the asserted claims. Id.

Mylan's expert, Dr. John Pritchard, opined that the asserted claims are not enabled because their breadth vastly exceeds the teachings of the specification (Trial Trans. 1044:3-18 (Pritchard)). Due to the unpredictability of the art and lack of prior art to inform a POSA about the interactions between the ingredients, a POSA would have to test an "astronomical" number of formulations "in order to understand whether [she] could actually achieve stable formulations across this enormous range of different components, grades, and concentrations." Id. at 1044:11-18 (Pritchard).

AstraZeneca contends that Mylan's enablement challenge fails because it has not identified any specific embodiment of the

asserted claims that is not enabled by the specification (Dkt. No. 593 at 28-29). It also contends that no undue experimentation would be required for a POSA to practice the full scope of the invention because the specification teaches her to make numerous stable formulations. Id. at 29-30. According to AstraZeneca, a POSA would not deviate from the specification's stated preferences to go in search of new stable formulations and any additional screening she might undertake would be routine (Dkt. No. 601 at 27-28).

AstraZeneca's expert, Dr. Paul Young, opined that upon reading the '247 patent specification, a POSA could create stable formulations throughout the scope of asserted claims 2 and 3 without undue experimentation because it gives a "guidebook" for creating stable formulations as well as methods for evaluating stability (Trial Trans. 1286:25-1287:12 (Young)).

2. Legal Standard

"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 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, 603 F.3d at 939. Enablement is a question of law, based on underlying factual findings. See Alcon Research Ltd. v. Barr Lab'ys, Inc., 745 F.3d 1180, 1188 (Fed. Cir. 2014).

"To be enabling, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." MagSil Corp. v. Hitachi Glob. Storage Techs., Inc., 687 F.3d 1377, 1380 (Fed. Cir. 2012). "Thus, a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage." Id. at 1381. 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 the patentee must "ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." Sitrick v. Dreamworks, LLC, 516 F.3d 993, 999 (Fed. Cir. 2008) (citing Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc., 166 F.3d 1190, 1195–96 (Fed. Cir. 1999)). Enabling "an embodiment, or even several embodiments, is not always sufficient." Amgen Inc. v. Sanofi, Aventisub LLC, 2019 WL 4058927, at *6 (D. Del. Aug. 28, 2019) (collecting cases).

To determine whether the asserted claims have been sufficiently enabled to avoid undue experimentation, courts consider the so-called "Wands factors:"

> (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).

3. The Asserted Claims are Structurally and Functionally Defined

At the outset of its enablement analysis, the Court must address whether the asserted claims are defined by their structure, function, or both. Mylan contends they are defined by both (Dkt. No. 591 at 17), while AstraZeneca argues they are defined by their structure alone (Dkt. No. 601 at 21-25).

Undoubtedly, the asserted claims contain structural limitations. Claim 1 requires a formulation comprised of five ingredients: formoterol, budesonide, PVP, PEG, and HFA 227 (JTX 2022.0023). Dependent claim 2 also requires the formulation to have a PVP concentration "from about 0.0005 to about 0.05% w/w" and PEG concentration "from about 0.05 to about 0.35% w/w." Id. And dependent claim 3 specifies that the formulation must contain

PVP K25.[7] Id. The parties agree that a POSA could quickly identify which formulations meet these structural limitations by containing each of the five ingredients within the parameters of claims 2 and 3.

But the asserted claims also contain an important behavioral limitation, that the formulation be "stable." Id. This is a considerable change from the Previously Tried Claims which imposed even more specific structural limitations upon the formulation by requiring particular grades or concentrations of each of the five ingredients. See e.g., JTX 2000.0021. In demanding a certain behavior from the resulting formulation, the asserted claims impose a functional limitation. That the asserted claims are defined by both structural and functional limitations is relevant to the Court's analysis because "use of broad functional claim limitations raises the bar for enablement." Amgen, 987 F.3d at 1087.

4. Mylan Is Not Required to Identify a Concrete Embodiment

AstraZeneca urges the Court to dispose of Mylan's enablement challenge without reaching its merits (Dkt. No. 593 at 28-29). It contends that Mylan has not met the threshold requirement of

[7] Notably, claim 3 depends only from claim 1.

identifying formulations covered by the asserted claims but not enabled by the '247 patent specification. Id.

AstraZeneca is correct that

> [c]onducting the Wands analysis has routinely involved concrete identification of at least some embodiment or embodiments asserted not to be enabled—including what particular products or processes are or may be within the claim, so that breadth is shown concretely and not just as an abstract possibility, and how much experimentation a skilled artisan would have to undertake to make and use those products or processes.

McRO, 959 F.3d at 1100. But where the claims contain both structural and functional requirements "undue experimentation can include undue experimentation in identifying, from among the many concretely identified compounds that meet the structural requirements, the compounds that satisfy the functional requirement." Id. (collecting cases). This issue lies at the heart of the parties' dispute.

Both agree that a POSA could readily determine whether a formulation contains each of the five generic ingredients. At trial, Mylan gave examples of hypothetical formulations comprised of the five generic ingredients that are not disclosed in the specification. But AstraZeneca takes issue with the fact that Mylan did not establish which, if any, of these hypothetical formulations also would be stable (Dkt. No. 593 at 28-29). Mylan counters that

undue experimentation would be required for a POSA to identify from among the huge number of formulations that could be created from the five generic ingredients the smaller set of formulations that would be stable (Dkt. No. 595 at 10-11).

Because the asserted claims contain both structural and functional requirements, undue experimentation may be proven on this basis. McRO, 959 F.3d at 1100. Therefore, despite AstraZeneca's contention otherwise, the Court concludes that this is not a case in which Mylan must, as a prerequisite, concretely identify an embodiment that is claimed but not enabled.

The Court turns next to address the merits of Mylan's enablement challenge.

5. Wands Analysis

The '247 patent claims any stable formulation of five ingredients and discloses between thirty (30) and forty (40) different stable formulations (Trial Trans. 1063:13-1064:12, 1159:18-1160:10 (Pritchard); 1276:17-21 (Young)). It is undisputed that upon reading the patent a POSA could replicate these embodiments. But that alone does not dictate the enablement inquiry. Rather, the Court must determine whether a POSA could

practice the full scope of the claimed invention based on the specification's disclosures and data.

Hence, the question is whether the examples in the '247 patent, all relating to the same grades, concentrations, and salt forms of the five generic ingredients, teach a POSA to practice the full scope of the claimed invention. In other words, could a POSA, upon reading the specification, create additional embodiments that satisfy the structural and functional requirements of the asserted claims without undue experimentation.

a. The Breadth of the Claims

Both parties emphasize the importance of the breadth of the claims on the Court's enablement inquiry. Mylan contends that the asserted claims are extraordinarily broad because they require only a stable combination of generic ingredients (Dkt. No. 591 at 17-18). AstraZeneca argues the asserted claims are narrow given their structural requirements and the specification's disclosures (Dkt. No. 593 at 29-32).

i. Mylan's Position

According to Mylan, the asserted claims encompass millions of unique candidate formulations (Dkt. No. 591 at 18-21). To demonstrate this broad scope, Dr. Pritchard replicated a

demonstrative exhibit used by AstraZeneca in its closing argument during the 2020 bench trial. Compare Attachment A (AstraZeneca's 2020 demonstrative exhibit) with Attachment B (Dr. Pritchard's 2022 demonstrative exhibit).

In 2020, Mylan asserted that the Previously Tried Claims were obvious because a POSA, guided by the prior art, could have arrived at the covered formulations through routine experimentation (Dkt. No. 431 at 30). AstraZeneca rebutted this contention, arguing that the prior art would not have motivated a POSA to make each of the choices necessary to arrive at the claimed formulations. Id. at 30-31.

In support, it prepared a demonstrative exhibit illustrating each of these choices and surmising that "had a POSA relied on Mistry's disclosures alone, the sheer number of potential formulations would have exceeded 2,560,000" (Dkt. No. 431-2). AstraZeneca further asserted that "testing these formulations to determine whether or not the combination was viable would have taken an 'eternity.'" (Dkt. No. 431 at 38). Citing to this demonstrative exhibit, the Court agreed with AstraZeneca when it found that Mylan had overlooked the unpredictability associated with altering ingredients in the formulation and discounted the

fact that experimentation would be required to evaluate formulations made from other grades of the polymers disclosed by Mistry. Id. at 33-39.

Relying on the prior art, inferences previously drawn by AstraZeneca, and disclosures in the '247 patent, in this case, Dr. Pritchard modified AstraZeneca's 2020 demonstrative exhibit to account for the differences between the Previously Tried Claims and the asserted claims. See Attachments B, C, and D; Trial Trans. 1046:21-24, 1050:14-18 (Pritchard). And based on Carling's teachings about the recommended daily doses for the active ingredients he determined that a POSA would consider five (5) different doses of formoterol and seven (7) different doses of budesonide. Id. at 1052:10-1054:25 (Pritchard). From disclosures in the '247 patent, he determined that a POSA could use twenty-four (24) different salt forms of formoterol, id. at 1055:1-15 (Pritchard), but only one (1) propellant, HFA 227. Id. at 1046:16-19, 1052:1-4, 1056:4-5 (Pritchard). And from Mistry's teachings he found that there were eight (8) pharmaceutically acceptable grades of both PVP and PEG that a POSA could use in the formulation. Id. at 1056:1-8, 1058:10-17 (Pritchard).

Dr. Pritchard expanded the range of PVP and PEG concentrations a POSA could consider based on examples of stable formulations disclosed in the '247 patent. Id. at 1056:13-1057:8 (Pritchard). During the 2020 bench trial, AstraZeneca had asserted that a POSA could use PVP in a concentration between 1% and 0.001% and PEG in a concentration between 2% and 0.1%. Id. But the '247 patent demonstrates that stable formulations can be formed from lower concentrations of these ingredients, specifically, with 0.0001% PVP and 0.01% PEG. Id. Thus, as to PVP, he determined that a POSA could use a concentration between 1.0000% and 0.0001%. Id. at 1056:9-12 (Pritchard). As to PEG, he determined that a POSA could use a concentration between 2.00% and 0.01%. Id. at 1057:3-10 (Pritchard).

He also used an increased level of precision when determining how many different concentrations of these ingredients a POSA could consider. In 2020, relying on Mistry's teachings, AstraZeneca had varied PVP down to the third decimal and PEG to the first decimal, resulting in 1,000 possible concentrations of PVP and 200 possible concentrations of PEG. Id. at 1056:9-1058:9 (Pritchard). But in addressing the Court's claim construction on appeal, the Federal Circuit determined that the specification taught that changes in

the PVP concentration down to the fourth decimal point impacted the stability of the formulation. So based on this finding, Dr. Pritchard determined there were 10,000 possible PVP concentrations and 200 concentrations of PEG that a POSA could consider.[8]

Given the number of ways in which the five generic ingredients could vary within a formulation, Dr. Pritchard opined that an "astronomical" number of candidate formulations would satisfy the structural limitations of the asserted claims and that a POSA would have to individually create and test them all to assess stability. Id. at 1058:23-1059:3 (Pritchard). Even when limiting his analysis to account for the additional structural limitations of the asserted claims, he reached the same conclusion. Id. at 1059:4-1061:6 (Pritchard); see also Attachments C and D. Specifically, he testified that the asserted claims encompass more than 2,500,000 million formulations, the number of candidate formulations that, during the 2020 bench trial, AstraZeneca had argued would take an eternity to test[9] (Trial Trans. 1059:4-1061:6 (Pritchard)).

[8] Dr. Pritchard also testified that he would have reached the same conclusion had he used AstraZeneca's concentration ranges and intervals for PVP and PEG (Trial Trans. 1057:11-1058:9 (Pritchard)).

[9] Dr. Pritchard repeatedly testified he was not offering a definitive number of candidate formulations that satisfied the structural limitations of the asserted claims. Rather, his methodology was intended only to "illustrate . . . the range of possibilities that fall within the claim" (Trial Trans. 1051:5-8 (Pritchard)). In his opinion, there are several areas in which the asserted claims could be even broader. For example, he limited his methodology to include

On cross-examination, Dr. Pritchard testified that even if a POSA were to limit her experimentation to one (1) dose of formoterol, four (4) doses of budesonide, eight (8) pharmaceutically acceptable grades of PVP, and eight (8) pharmaceutically acceptable grades of PEG, and if she tested only the concentrations of PVP and PEG described in claim 2, she would still have to create and test "20-odd-thousand" candidate formulations to determine which satisfied the functional requirement of the asserted claims. Id. at 1162:18-1163:14 (Pritchard).

In summary, based on Dr. Pritchard's opinions, Mylan argues that "at an absolute minimum, there are tens of thousands of formulations for synthesis and screening, and in reality[,] there are millions" (Trial Trans. 1677:17-19).

ii. AstraZeneca's Position

AstraZeneca contends that Mylan's argument overstates the breadth of the claims and that the asserted claims are narrowed by their structural limitations, as well as by the specification's

only the grades of PVP and PEG known to be pharmaceutically acceptable, although not required by the '247 patent, because these are the grades to which a POSA would naturally be drawn. Id. at 1050:25-1051:4 (Pritchard). Likewise, although the '247 patent does not specify a dosage range for either active ingredient, he limited his analysis to the doses a POSA might consider to those believed to be safe and effective for patients. Id. at 1053:12-1054:3 (Pritchard).

stated preferences for certain ingredients, grades, and concentrations (Dkt. No. 593 at 30; Trial Trans. 1718:16-25). Its expert, Dr. Young, explained that the '247 patent states preferences for (1) 0.0001% w/w of PVP K25; (2) 0.3% w/w of PEG 1000; (3) the fumarate dihydrate salt of formoterol; and (4) a ratio of formoterol/budesonide that delivers 4.5/40 micrograms, 4.5/80 micrograms, 4.5/160 micrograms, or 4.5/360 micrograms per actuation. Id. at 1197:9-1198:4 (Young). From this, AstraZeneca posits that the breadth of the asserted claims is limited and reasonably enabled by the textual disclosures, examples, and data disclosed in the specification (Dkt. No. 593 at 29-39).

It also counters Dr. Pritchard's testimony in several other respects. First, it contends he disregarded how a POSA would actually practice the invention. Id. at 8, 28, 34-36. Dr. Young testified that a POSA would have been motivated by the specification's disclosures to make formulations within the stated preferences (Trial Trans. 1276:12-15 (Young)). In other words, using common sense, a POSA would "focus on the actual invention disclosed by the patent," and would practice the optimal invention disclosed in the specification instead of searching for other stable candidate formulations. Id.; see also Dkt. No. 593 at 8.

Dr. Young also opined that a POSA's experimentation with the active ingredients would be narrowed by her desire to reformulate the Symbicort® Turbohaler DPI as a pMDI while maintaining its proven dosing and efficacy (Dkt. No. 593 at 36-37).[10]

Second, AstraZeneca contends that Dr. Pritchard ignored the teachings in the specification in favor of the prior art. Id. at 34. It asserts that he should have used the preferred grades and concentrations disclosed in the patent rather than the teachings of Mistry or Carling to determine how many unique formulations might satisfy the structural limitations of the asserted claims. Id.; see also Trial Trans. 1166:14-1167-21 (Pritchard).

iii. The Asserted Claims Are Extraordinarily Broad

Despite AstraZeneca's attempts to persuade otherwise, the asserted claims are extraordinarily broad. As has been discussed, in drafting the '247 patent the inventors replaced the narrow structural limitations from the Previously Tried Patents with broad structural limitations combined with a functional limitation. In doing so, it claimed a huge number of potentially

[10] The Symbicort® Turbohaler DPI is a breath-actuated inhaler that delivers a dry powder formulation comprised of budesonide and formoterol into a patient's lungs (Dkt. No. 431 at 8). The Symbicort® Turbohaler DPI predated the Symbicort® pMDI and, during the 2020 bench trial, the parties agreed that a POSA would have been motivated to adapt Symbicort® from a DPI to a PMDI. Id. at 33.

stable formulations. Claim 1 encompasses any stable formulation from the combination of any grade and concentration of PVP, any grade and concentration of PEG, any dose of budesonide, any dose of formoterol, and any salt form of formoterol. The additional structural limitations of the asserted claims do little to narrow claim 1's breadth. While claim 2 identifies concentration ranges of PVP and PEG, it does not limit the grade of these ingredients or any other aspect of the formulation. Similarly, claim 3 merely limits the grade of PVP in the formulation.

AstraZeneca attempts to narrow the breadth of the claims based on how a POSA would actually practice the invention, but Wands instructs that, when analyzing the breadth of the claims factor, a court should "consider[] the scope of the claims as written, not just the subset of the claim that a POSA might practice." Idenix Pharms. LLC v. Gilead Scis. Inc., 941 F.3d 1149, 1162 (Fed. Cir. 2019). Thus, in assessing the scope of the claims here, the Court must consider the "number of possible candidates falling within the claimed genus." Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc., 928 F.3d 1340, 1346 (Fed. Cir. 2019); see also Wyeth & Cordis Corp. v. Abbott Lab'ys, 720 F.3d 1380, 1385 (Fed. Cir. 2013).

Even if a POSA preferred to practice only the stable embodiments disclosed in the specification, the asserted claims encompass far more candidate formulations. During the 2020 bench trial, AstraZeneca argued that any alteration of an ingredient in the formulation resulted in a new formulation that required independent study.

Using this same logic, during the 2022 bench trial, Dr. Pritchard demonstrated how the asserted claims encompass millions of unique candidate formulations. Even accepting the limitations offered by AstraZeneca, he testified that the asserted claims encompass at least "20-odd-thousand" candidate formulations (Trial Trans. 1162:18-1163:14 (Pritchard)). Although Dr. Young never offered his own opinion as to how many formulations might fall within the scope of the asserted claims, he confirmed that stable formulations likely exist outside of the specification's stated preferences and disclosed examples. Id. at 1280:8-12, 1382:6-1383:1 (Young).

After considering the evidence and the parties' arguments, the Court finds that the asserted claim broadly encompass tens of thousands, if not millions, of candidate formulations. As such, the breadth of the claims factor weighs against enablement.

b. State of the Prior Art

In its Memorandum Opinion following the 2020 bench trial, the Court extensively discussed the state of the prior art at the time of the invention. After considering all of the evidence, it found there was a "dearth of prior art that taught towards a formulation with all of the claimed components" of the Previously Tried Claims (Dkt. No. 431 at 34). Given this lack of guidance, it concluded that "it [was] unclear what would have prompted (or even enabled) a POSA at the priority date to select and combine all the elements of the claimed invention." Id. In reaching this conclusion, the Court rejected Dr. Pritchard's opinion that a POSA relying on the prior art could, through routine experimentation, have created stable formulations covered by the Previously Tried Claims and credited Dr. Young's testimony that nothing in the prior art would have motivated a POSA to combine budesonide, formoterol, PVP, PEG, and HFA 227 in a suspension formulation. Id. at 35-39.

The parties have not disputed these findings on remand. Notably, during the 2022 bench trial, Dr. Young reiterated his opinion that, prior to reading the shared specification, a POSA would not have known how to create any stable suspension

formulation containing budesonide, formoterol, PVP, and PEG (Trial Trans. 1379:15-23 (Young)).

The prior art did offer some guidance regarding the five generic ingredients, however. Carling taught that asthma could be treated with a combination of budesonide and formoterol and recommended daily doses of these active ingredients (JTX 2373.0001-03). Mistry taught (1) that HFA 227 could be used to stabilize pMDI suspension formulations; (2) that PVP and PEG were soluble in HFA propellants; and (3) that the amount of PVP in a formulation would depend on the active ingredient to be dispersed and its concentration (JTX 2381.0002-05). Mistry also recommended several preferred grades and concentrations of PVP and PEG. Id. at .0003.

Nonetheless, these sources provided no guidance as to how the five generic ingredients would interact in suspension formulations or how a POSA might combine them to achieve stable formulations. Thus, they provided little aid to a POSA attempting to create stable formulations encompassed by the asserted claims. From this, the Court concludes that the state of the prior art also weighs against enablement.

c. Nature of the Invention and Unpredictability of the Art

The evidence of record establishes that pMDI suspension formulations are complex, multi-dimensional systems. During the 2020 bench trial, Dr. Young testified that "pMDI suspension formulations are very complex chemical systems that interact in interrelated and unpredictable ways" (Trial Trans. 1380:4-19 (Young)). He also stated that, given the lack of prior art, a POSA could not predict how the five ingredients would react in a formulation. Id. at 707:6-709:2, 1382:1-5 (Young).

Likewise, Dr. Nayna Govind, a named inventor of the '247 patent, testified that the interactions between the ingredients were crucial to the stability of the formulation. Id. at 541:7-18 (Govind), 1066:22-1067:13 (Pritchard). She also stated that altering the concentration or grade of any ingredient impacted the stability of the whole formulation and, as such, a POSA had to study each ingredient in isolation. Id. at 946:9-24; 1066:22-1067:13 (Pritchard). She further explained that, because there was "no magic formula" for predicting how the ingredients would react, a POSA had to create each candidate formulation to evaluate its stability. Id. at 514:1-15, 563:6-25 (Govind); 1066:22-1067:13 (Pritchard).

MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

In its Memorandum Opinion following the 2020 bench trial, the Court recognized the unpredictability of the art at the time of the invention, particularly noting that experimentation would have been required for a POSA to determine the properties of formulations using different grades of PVP or PEG (Dkt. No. 431 at 37). The Federal Circuit agreed, finding that the intrinsic record taught a POSA that changes in the PVP concentration down to the fourth decimal place impacted the stability of the formulation. See AstraZeneca, 19 F.4th at 1327.

Pointing to the same testimony on remand, Mylan now argues that a POSA seeking to practice the full scope of the asserted claims would be dealing with complex formulations in a highly unpredictable art (Dkt. No. 591 at 22-23); see also Trial Trans. 1065:22-1066:9 (Pritchard). But AstraZeneca focuses on the level of predictability in the art following the publication of the '247 patent (Dkt. No. 301 32-33). Nevertheless, Dr. Young did concede that, at the time of the invention, "identifying stable formulations of budesonide, formoterol, PVP, PEG, and HFA 227 was completely unpredictable" (Trial Trans. 1382:11-14 (Young)).

Hence, because there is substantial evidence that pMDI suspension formulations are complex and unpredictable, this Wands

factor weighs against enablement. Still, the Court must consider AstraZeneca's argument that the specification's disclosures add predictability to the art and it will do so as part of its analysis of the remaining Wands factors.

d. Presence of Working Examples

The '247 patent specification discloses between thirty (30) and forty (40) different examples of stable formulations. Id. at 1063:13-1064:12, 1159:18-1160:10 (Pritchard); 1276:17-21 (Young). It also reports stability data for these formulations using one or more of the three described methods. Id.

But the guidance provided by these examples is not as extensive as the number of formulations evaluated might suggest. Throughout the specification, the inventors studied a distinct combination of ingredients: budesonide, FFD, PVP K25, PEG 1000, and HFA 227. Their testing focused only the stability of this specific combination of ingredients, varying the concentration of individual ingredients.

Notably, the inventors' evaluation concentrated on those formulations described by the preferred embodiments and the Previously Tried Claims. That the inventors included examples to enable the preferred embodiments, however, does not lead to the

conclusion that they enabled the full scope of the claimed invention where the asserted claims are far broader and encompass many more candidate formulations. See Amgen, 2019 WL 4058927, at *6 (collecting cases). Even Dr. Young agreed that there are stable candidate formulations outside of the specification's stated preferences and disclosed examples. Id. at 1280:8-12 (Young).

Claim 2 covers formulations with any dose of one of the twenty-four (24) salts of formoterol, any dose of budesonide, any of the eight (8) pharmaceutically acceptable grades of PVP, and any of the eight (8) pharmaceutically acceptable grades of PEG. Claim 3 covers formulations with any dose of one of the twenty-four (24) salts of formoterol, any dose of budesonide, any concentration of PVP K25, and any concentration of any of the eight (8) pharmaceutically acceptable grades of PEG. In comparison, the examples only studied the interactions between one dose of one formoterol salt (FFD), four doses of budesonide, several concentrations of one grade of PVP (PVP K25), and several concentrations of one grade of PEG (PEG 1000).

Despite containing many examples of stable formulations, all of the disclosed embodiments consist of the same five ingredients and rest in the same, small corner of the claimed genus. The

presence of these working examples weighs in favor of enablement, but their narrow breadth weighs against enablement. Amgen, 987 F.3d at 1087; Idenix, 941 F.3d at 1161 ("Where, as here, working examples are present but are very narrow, despite the wide breadth of the claims at issue, this factor weighs against enablement.") (quotations and citation omitted).

e. Amount of Guidance in the Specification, and Quantity of Experimentation Necessary

AstraZeneca urges the Court to find that the claims are enabled because the patent teaches a POSA how to replicate several formulations known to satisfy the asserted claims and that span the full scope of the preferred embodiments (Dkt. No. 593 at 29-32). The Federal Circuit, however, has cautioned that where, as here, the asserted claims include a functional requirement, the Court's enablement inquiry must consider "the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim." Amgen, 987 F.3d at 1086. The evidence in this case clearly establishes that the guidance offered by the specification does not significantly reduce the amount of experimentation required to create stable formulations across the full scope of the asserted claims.

According to Mylan, even when aided by the specification's guidance, a POSA would have to create and evaluate each of the tens of thousands, or millions, of undisclosed candidate formulations to determine which might meet the asserted claims' functional stability requirement (Dkt. No. 595 at 12-13). Dr. Pritchard opined that the specification provides no method of predicting the interactions between the generic ingredients (Trial Trans. 1062:19-22 (Pritchard)). And given the unpredictability involved in altering the ingredients within the formulation he testified that "the number of tests [a POSA] would have to perform to understand whether a particular combination from that selection exhibits any form of stability is just unimaginable." Id. at 1063:9-12 (Pritchard).

AstraZeneca, on the other hand, asserts that because the patent teaches the best grades and concentrations of the five ingredients, a POSA would not abandon the optimal, disclosed formulations in search of lesser candidate formulations. See Dkt. Nos. 593 at 30; 601 at 19-20; see also Trial Trans. 1307:11-15 (Young). Alternatively, it contends that the specification contains what the prior art lacked because it teaches a POSA how the active ingredients and excipients interact. See Dkt. Nos. 593

at 30; 601 at 19-20; see also Trial Trans. 1253:4-11 (Pritchard). Thus, after reading the specification, she could predict which candidate formulations would be stable, thereby eliminating her need to create and test each (Dkt. Nos. 593 at 30; 601 at 19-20).

In support of its argument, it points to Dr. Young's "monolayer" theory (Dkt. No. 593 at 14-15, 32-33), and his testimony that the specification teaches a POSA that PVP stabilizes a formulation by forming a monolayer around the active ingredients. Id. at 1253:10-11, 1288:2-6 (Young). If the formulation contains too little PVP, the monolayer will not exist, and the active ingredients will not properly redisperse after flocculation. Id. at 1288:7-12 (Young). If the formulation contains too much PVP, the formulation will become unstable. Id. at 1288:13-20 (Young).

According to Dr. Young, although the specification does not explicitly teach a POSA about his monolayer theory, a POSA nevertheless would understand this concept and know that if she increases the amount of an active ingredient in the formulation, she will also have to increase the amount of PVP to maintain the monolayer. Id. at 1300:7-21, 1392:4-16, 1393:11-24 (Young).[11] He

[11] Dr. Pritchard agreed that a POSA would know from the prior art that she would have to adjust the amount of excipient in the formulation based on the amount of active ingredient (Trial Trans. 1175:19-25 (Pritchard)).

opined that the data in the specification demonstrates this theory, and if a POSA were to plot the disclosed data points on a line, a bell curve would emerge. Id. at 1253:4-18 (Young). She could then predict that candidate formulations along this curve would be stable without a need to create and test each. Id. at 1253:21-23 (Young). Based on this theory, AstraZeneca suggests that when moving to different grades of ingredients, a POSA would not have to test every conceivable combination of ingredients but instead could test only the same PVP concentrations used in the patent (Dkt. No. 593 at 33-34).

Unfortunately, however, Dr. Young's monolayer theory provides limited insight into which undisclosed candidate formulations might be stable. His bell curve considers only the impact of varying amounts of PVP in formulations comprised of FFD, budesonide, PVP K25, PEG 1000, and HFA 227. Although this theory might allow a POSA to predict which undisclosed combinations of these five specific ingredients are stable without trial-and-error testing, it adds nothing to the uncertainty involved in using different grades of PVP or PEG, different concentrations of PEG, different salt forms of budesonide, or different doses of either active ingredient. Notably, there is no evidence that Dr. Young's

bell curve would form at the same PVP concentrations using different ingredients. And Dr. Young conceded that, while a POSA would expect a similar bell curve to form if she used different grades of PVP or PEG, testing would be required to find the outer bounds of the range and the optimal amount of the excipient (Trial Trans. 1299:21-23, 1301:24-1302:4, 1307:11-15 (Young)). Consequently, substantial and repetitive testing would be required to study any change to any of the ingredients in the formulation.

AstraZeneca recognizes that the specification does not demonstrate how other grades of PVP or PEG would behave in a suspension formulation with budesonide and formoterol, but it contends the statement in column 1 of the patent, that "certain HFA formulations comprising formoterol and budesonide together with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) exhibit excellent physical suspension stability," JTX 2022.0019, "tells you these five ingredients are going to work without regard to grade" (Trial Trans. 1753:19-21). The evidence of record does not support this contention.

First, the disclosure upon which AstraZeneca relies states that only certain combinations of ingredients will yield stable formulations. See JTX 2022.0019. This indicates that not every

combination of the five ingredients will result in a stable formulation, but the patent is silent as to which grades of PVP and PEG would yield stable formulations.

Second, AstraZeneca's own expert testimony contradicts this contention. Dr. Young testified during both the 2020 and 2022 bench trials that each grade of PVP and PEG is effectively a different excipient that might behave in very different ways (Trial Trans. 669:14-670:2, 703:17-704:19; 1373:6-22, 1383:22-1384:10 (Young)). Specifically, during the 2020 bench trial, he testified that different grades of excipients have completely different properties and "different interactions with the environment that they're in chemically and physically." Id. at 703:21-704:19 (Young). Given these differences, he opined that a POSA could not predict how the different grades might interact in a suspension formulation. Id. at 708:21-709:2 (Young).

Third, Dr. Govind testified during the 2020 bench trial that the grade of PVP and PEG used was crucial to the formulation because different grades may interact with other ingredients in different and unexpected ways. Id. at 541:7-18 (Govind), 1066:22-1067:13 (Pritchard). Further, she explained that, while creating the known formulations, the inventors studied the impact of

changing the grade of an excipient. Id. at 1067:14-16 (Pritchard). They found that ingredients may react quite differently to even adjacent excipient grades. Id. Such interactions therefore could only be discovered by trial-and-error creation of various candidate formulations. Id.

Thus, the evidence indicates that altering the grade of PVP or PEG will alter how that excipient interacts with the other ingredients. And even if other grades of PVP and PEG could create stable formulations with budesonide and formoterol, a POSA would be required to conduct iterative testing altering a single ingredient at a time to discover which combinations of ingredients might yield a stable formulation.

Moreover, nowhere in the specification do the inventors discuss how a POSA might use different salt forms of formoterol in the formulation while retaining stability. Despite disclosing twenty-four (24) suitable formoterol salts, the specification uses only the FFD salt in each of its examples. Dr. Pritchard testified that excipients bind to different salt forms in different ways, so a POSA cannot assume that different salts of the same molecule will behave similarly in a formulation. Id. at 1055:3-7 (Pritchard). Dr. Young never disputed this point, testifying only

that a POSA practicing the invention would select the salt form shown to be effective, FFD. Id. at 1285:7-20 (Young).

Thus, the guidance provided by the subset of examples included in the specification is limited. It is silent as to how the active ingredients and other grades of excipients might interact. And it provides no guidance regarding how a POSA might change the grades, concentrations, and salt forms of the ingredients in the formulation while retaining stability. Given this lack of guidance and the unpredictability of the art, substantial trial-and-error testing would be required for a POSA to practice the full scope of the claims.

Adding to the amount of testing required is the consensus among the experts and inventors that a POSA would use every method available to them in assessing the stability of candidate formulations. Id. at 1226:23-25, 1238:17-21, 1260:9-15, 1245:4-20, 1255:5, 1260:9-15, 1265:13-20, 1328:13-19, 1361:8-10, 1364:23-1365:18 (Young); 1517:11-1518:13, 1530:21-23 (Govind).[12] Thus, in

[12] Dr. Young initially stated that a POSA might not have to conduct all three tests to determine whether a formulation is stable (Trial Trans. 1226:23-25 (Young)). But he later repeatedly testified that a POSA would "use all three [tests] and then would make the decision based on whether they were stable or not." Id. at 1260:9-15 (Young); see also id. at 1238:17-21, 1245:4-20, 1255:5, 1260:9-15, 1265:13-20, 1328:13-19, 1361:8-10, 1364:23-1365:18, (Young). He further testified that visual inspection can disclose stability issues not detected by OSCAR or Turbiscan. Id. at 1264:23-1265:2 (Young).

practicing the invention, a POSA would need to screen each formulation using all three of the testing methods disclosed in the patent. That she would consider these tests to be routine is irrelevant. Id. at 1119:2-8, 1120:7-9, 1127:5-17 (Pritchard); 1200:15-24, 1217:25-12:18:12, 1217:25-12:18:12 (Young); See also Wyeth, 720 F.3d at 1385-86 (holding that screening tens of thousands of candidate compounds amounted to undue experimentation even if a POSA would routinely use the disclosed testing methods).

In an attempt to undermine Mylan's enablement challenge, AstraZeneca asserts there is no evidence that other ingredients will not create stable formulations. But that misstates the parties' respective burdens in this case. As the drafter of the '247 patent, AstraZeneca bore the burden of including a disclosure that teaches a POSA to make and use the full scope of the invention.

In this case, that would include teaching a POSA how to make stable formulations with other grades of PVP and PEG, as well as other salts of formoterol. Mylan argues that undue experimentation would be required to identify stable formulations from millions of candidate formulations. It is not required to undertake substantial testing to demonstrate which of the potentially millions of undisclosed candidate formulations would satisfy the

asserted claims, or to prove that other grades of PVP or PEG would not produce stable formulation, as AstraZeneca suggests.

To conclude, the asserted claims encompass at least tens of thousands of candidate formulations that must be screened for stability. And obtaining covered embodiments outside of the scope of the disclosed examples would require substantial trial-and-error testing. These facts weigh against enablement. See Amgen, 987 F.3d at 1088 ("We do not hold that the effort required to exhaust a genus is dispositive. It is appropriate, however, to look at the amount of effort needed to obtain embodiments outside the scope of the disclosed examples and guidance."); Idenix, 941 F.3d at 1161 ("A specification that requires a POSA to 'engage in an iterative, trial-and-error process to practice the claimed invention' does not provide an enabling disclosure." (quoting ALZA, 603 F.3d at 941)).

f. Relative Skill of Those in the Art

It is undisputed that there was a high degree of skill in the art at the time of the invention. See supra at § III.A; Dkt. No. 591 at 24-25; Dkt. No. 601 at 33; Trial Trans. 1029:15-1030:1 (Pritchard); Tr. 1193:19-23 (Young). This factor therefore weighs in favor of enablement. See Falko-Gunter Falkner v. Inglis, 448

F.3d 1357, 1365 (Fed. Cir. 2006); Wands, 858 F.2d at 740. But even assuming her expertise in a complex field of science, a POSA still could not predict the stability of formulations without substantial experimentation. The POSA's high degree of skill in the art therefore is outweighed by the unpredictability in the art, the amount of experimentation required, the breadth of the claims, and the limited guidance in the specification.

g. Summary

The Court concludes that, on balance, the Wands factors weigh against enablement. Undue experimentation would be necessary to practice the full scope of the asserted claims. The broad functional claims in an unpredictable field are supported only by a narrow subset of examples. Tens of thousands, if not millions, of candidate formulations satisfy the structural limitations of the asserted claims, but a POSA would be required to create and assess each candidate to determine whether it met the claims' functional stability requirement. By enabling only the patent's preferred embodiments, AstraZeneca enabled far less that it claimed and failed to satisfy the quid pro quo of the patent bargain. See Sitrick, 516 F.3d at 999; MagSil, 687 F.3 at 1380-81. As such, it is not entitled to monopolize an entire class of

formulations without teaching the public how to make formulations representative of its breadth.

By this conclusion, the Court does not intend to imply that AstraZeneca would be required to enable every conceivable embodiment of the invention. See Bayer Healthcare LLC v. Baxalta Inc., 989 F.3d 964, 982 (Fed. Cir. 2021). Nor does it speculate as to how many examples or how much guidance would have been sufficient to enable the full scope of the asserted claims. But it is clear here that even the approximately (40) examples contained in the specification do not enable the full scope of the asserted claims. AstraZeneca opted for broad claims defined both by structure and function, but provided only narrow working examples in a specific subset of the claimed class of formulations. These do not come close to representing the full scope of the asserted claims.

6. Federal Circuit Precedent

The Court's conclusion of nonenablement aligns with Federal Circuit precedent, which repeatedly "has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential

embodiments across the full scope of the claim." PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996).

For example, in Pharmaceutical Resources, Inc. v. Roxane Laboratories, Inc., the Federal Circuit found claims covering stable suspension formulations containing any concentration of hundreds of possible surfactants to be invalid for lack of enablement. 253 F. App'x 26, 29-30 (Fed. Cir. 2007). The intrinsic record stressed the importance of the surfactant to the invention, but the specification provided only three example formulations studying only one surfactant. Id. at 30. Moreover, a POSA could not have predicted stability in advance; thus, trial-and-error experimentation would have been required for a POSA to determine whether candidate formulations were encompassed by the claims. Id. at 29. The court therefore concluded that the inventor had not enabled the full scope of its broad claims considering the minimal guidance in the specification and the highly unpredictable art. Id. at 31.

Wyeth & Cordis Corporation v. Abbott Laboratories also involved claims with structural and functional requirements. 720 F.3d 1380, 1385-86 (Fed. Cir. 2013). There, the Federal Circuit found that the claims lacked enablement due to the amount of

experimentation necessary to determine which compounds of the claimed class also had the required functionality. Id. Although the specification disclosed one compound with the desired functional effects, as well as assays for screening candidate compounds for those properties, it provided no instruction for modifying the compound while retaining its utility. Id. Hence, a POSA would have had to create and screen each of the tens of thousands of candidate compounds to determine which had the desired functional properties. Id.

Likewise, in Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc., the broad claims contained both structural and functional requirements, but the specification provided little guidance as to how a POSA could vary the invention within the scope of the claims while retaining the required functionality. 928 F.3d 1340, 1346-47 (Fed. Cir. 2019). Because the patent's disclosures were not commensurate with the scope of the claims, and the claims involved an unpredictable art, the Federal Circuit concluded that the claims lacked enablement. Id. at 1347-48.

Again, in Idenix Pharmaceuticals LLC v. Gilead Sciences Inc., the Federal Circuit held that "the claims had both structural and functional limitations, and that undue experimentation would have

been required to synthesize and screen the billions of possible compounds because, given a lack of guidance across that full scope, finding functional compounds would be akin to finding a 'needle in a haystack.'" Amgen, 987 F.3d at 1086 (citing Idenix, 941 F.3d at 1160–63, 1165 (Fed. Cir. 2019)).

Finally, in Amgen Inc. v. Sanofi, Aventisub LLC, the Federal Circuit reached the same result. 987 F.3d 1080 (Fed. Cir. 2021). The claims covered a class of antibodies that bound to one of several residues. Id. at 1084. Millions of antibody candidates were encompassed by the structural limitations of the claims. Id. at 1085, 1088. The specification disclosed several embodiments of the invention, but each of these rested in a small corner of the covered class and a POSA could only discover undisclosed embodiments through "trial-and-error, by making changes to the disclosed antibodies and then screening those antibodies for the desired [functional] properties," or "by discovering the antibodies de novo" through randomization. Id. at 1088. Thus, undue experimentation would have been required to practice the full scope of the invention. Id

These cases establish that when inventors opt for broad claims covering a large number of possible candidates they do so at a

substantial risk and bear the burden of drafting disclosures commensurate in scope with those claims. It is well established that narrow working examples cannot support broad functional claims, especially where the claims contain both structural and functional requirements and a POSA would have to engage in trial-and-error testing to determine which candidates possess the desired functionality. This is the problem with the asserted claims.

Because undue experimentation would be required to identify embodiments outside the examples disclosed in the '247 patent, the Court concludes as a matter of law that Mylan has proven by clear and convincing evidence that the asserted claims are invalid for lack of enablement.

C. Written Description

1. The Parties' Contentions

The parties' arguments on written description mirror their arguments on enablement.

Mylan contends that the asserted claims lack written description because the inventors claimed more than they actually invented and possessed (Dkt. No. 591 at 31). As with enablement, it asserts that the '247 patent's narrow subset of examples

describe only a fraction of the broad, functionally defined genus claimed. Id. at 31-33. Thus, the specification would not have led a POSA to believe that the inventors possessed all stable formulations comprised from the five generic ingredients, or even a variety of stable formulations that represent the full scope of the asserted claims. Id. at 33. Instead, the inventors merely disclosed a research plan for others to explore the contours of the claimed genus (Dkt. No. 591 at 31-33). Mylan therefore argues that AstraZeneca cannot "preemptively claim[] all functionally stable formulations using virtually any combinations and amounts of five generic components" in a highly unpredictable art requiring substantial trial-and-error testing (Dkt. No. 595 at 22).

AstraZeneca argues that the asserted claims are adequately described because the specification "unambiguously identifies that the invention is the novel combination of budesonide, formoterol, HFA 227, PVP, and PEG" and describes exemplary formulations that embody this invention (Dkt. No. 593 at 39). It also asserts that the specification identifies a representative number of species within the claimed genus by including "dozens of distinct claimed formulations with stability data, having varying concentrations of PVP, PEG, and budesonide," and recites the common structural

features of formoterol, budesonide, HFA 227, PVP, and PEG (Dkt. No. 594-1 at 35-36).

2. Legal Standard

A patent's specification must include "a written description of the invention." 35 U.S.C. § 112. This requirement "allows a person of skill in the art to recognize that the patentee invented what is claimed." Synthes USA, LLC v. Spinal Kinetics, Inc., 734 F.3d 1332, 1341 (Fed. Cir. 2013) (citing Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). The written description requirement "is satisfied only if the inventor 'conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrates that by disclosure in the specification of the patent.'" Nuvo Pharm. (Ir.) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc., 923 F.3d 1368, 1376 (Fed. Cir. 2019) (cleaned up) (quoting Centocor Ortho Biotech, Inc. v. Abbott Lab'ys, 636 F.3d 1341, 1348 (Fed. Cir. 2011)).

As with enablement, to adequately describe their invention, the inventors must convey that they possessed the full scope of the claimed invention. See Juno Therapeutics, Inc. V. Kite Pharma, Inc., 10 F.4th 1330, 1336 (Fed. Cir. 2021). "[T]he purpose of the

written description requirement is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.'" AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1299 (Fed. Cir. 2014) (quoting Ariad, 598 F.3d at 1352-53). The level of detail required depends on the nature and scope of the invention and claims as well as the complexity and predictability of the art. Juno, 10 F.4th at 1341.

For genus claims using functional language, the written description "must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus." Id., at 1335. The written description requirement "ensures that when a patent claims a genus by its function or result, the specification recites sufficient materials to accomplish that function—a problem that is particularly acute in the biological arts." Ariad, 598 F.3d at 1352-53. "[A] genus can be sufficiently disclosed by 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." Idenix, 941 F.3d at 1164.

Whether the '247 Patent is 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).

3. The Asserted Claims Lack an Adequate Written Description

The asserted claims lack an adequate written description for much the same reason they lack enablement: the specification does not include sufficient guidance from which a POSA could reasonably conclude that the inventors possessed all that they claimed.

The '247 patent does not disclose species representative of the full scope of the asserted claims. In its written description analysis, the Court must consider the breadth of the genus in comparison to the species described in the patent. See AbbVie, 759 F.3d at 1299. "[A]nalogizing the genus to a plot of land, if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus. He only described a portion of it." Id. at 1300. That is the precisely the issue in this case.

As discussed, the asserted claims cover a class of at least tens of thousands of candidate formulations, but the specification's examples only study formulations comprised of a single formoterol salt, a single formoterol dose, four budesonide doses, a single PVP grade, and a single PEG grade. These disclosed species each lie in the same corner of the genus and are insufficient to support the entire functionally defined genus. Id. at 1300. The specification therefore lacks species representing the genus throughout its scope, especially in light of the dearth of prior art and the unpredictability of the invention.

AstraZeneca counters that because the disclosure in column 1[13] refers to PVP and PEG generally, rather than to PVP K25 and PEG 1000 specifically, a POSA would understand that the inventors possessed other undisclosed, stable formulations using different grades of PVP and PEG. See Dkt. No. 593 at 39; Trial Trans. 1737:12-24. But its own expert contradicted this contention. Dr. Young testified that a POSA could only know if the inventors tested candidate formulations for stability by disclosing data in the

[13] Column 1 states that the inventors had found that "certain HFA formulations comprising formoterol and budesonide together with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) exhibit excellent physical suspension stability." JTX 2022.0019. AstraZeneca points to this as the "most important disclosure in the entire case" (Trial Trans. 1736:24-1737:4).

specification (Trial Trans. 1377:17-21 (Young), 1700:19-1701:8). And because the specification includes no data related to formulations using different grades of PVP or PEG, upon reading the '247 patent a POSA would not know whether the inventors had attempted to create or test any candidate formulations. Thus, there is no evidence in the specification that the inventors possessed any additional stable formulations not disclosed in the specification. See generally JTX 2022. Ariad Pharm. Inc., 598 F.3d at 1352 ("[A]ctual 'possession' or reduction to practice outside of the specification is not enough. . . [I]t is the specification itself that must demonstrate possession.").

Next, the asserted claims contain common structural limitations but there is no correlation between such limitations and the functional stability requirement. Ariad, 598 F.3d at 1350 ("[F]unctional claim language can meet the written description requirement when the art has established a correlation between structure and function."). Even if the specification allows a POSA to recognize candidate formulations that contain each of the five general ingredients, it does nothing to help her visualize which

of these many candidates might also satisfy the functional stability requirement.[14]

For these reasons, the inventors failed to sufficiently disclose the entire genus and claimed more than they described. The Court thus finds by clear and convincing evidence that the asserted claims are invalid for lack of written description.

IV. CONCLUSION

For the reasons discussed, Mylan has carried its burden of proving that the asserted claims are invalid pursuant to 35 U.S.C. § 112 for lack of enablement and lack of written description. Based on these conclusions, the Court finds that it is unnecessary for it to address Mylan's indefiniteness challenge.

It is so **ORDERED.**

The Court **DIRECTS** the Clerk to enter separate judgment orders in favor of the defendants, Mylan Pharmaceuticals Inc., and Kindeva Drug Delivery L.P., in Civil Action Numbers 1:18CV193 and 1:19CV203, and to transmit copies of these Orders to counsel of

[14] Given Dr. Young's bell curve theory, a POSA might be able to visualize stable candidate formulations made from the same specific ingredients studied in the '247 patent: FFD, budesonide, PVP K25, PEG 100, and HFA 227. But, as discussed extensively, a POSA could not apply this information to predict stable formulations created using different grades of excipients or different salt forms of formoterol.

record. The Clerk **SHALL** also close this case and strike it from the Court's active docket.

DATED: November 9, 2022

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