**No. 2021-2121**

**IN THE**

# United States Court of Appeals

**FOR THE FEDERAL CIRCUIT**

MYLAN PHARMACEUTICALS INC.,

*Appellant*,

v.

MERCK SHARP & DOHME CORP.,

*Appellee*.

On Appeal from the Patent Trial and Appeal Board
No. IPR2020-00040

## RESPONSE BRIEF OF APPELLEE MERCK SHARP & DOHME CORP.

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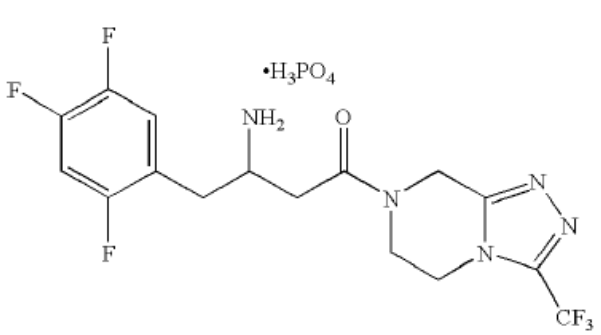
## REPRESENTATIVE PATENT CLAIMS

### U.S. Patent No. 7,326,708
### Claims 1-4

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

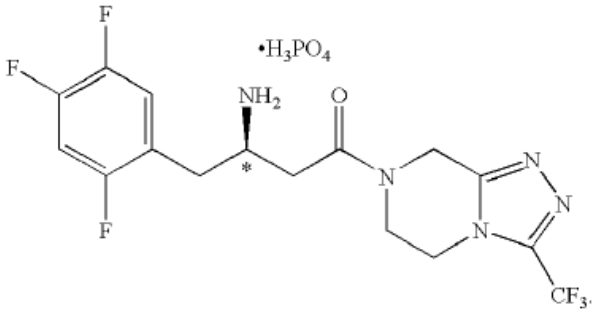



(I)

or a hydrate thereof.

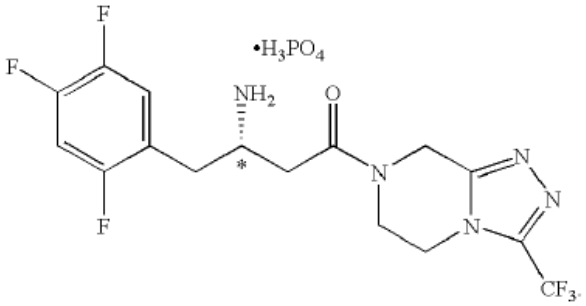
2. The salt of claim 1 of structural formula II having the (R)-configuration at the chiral center marked with an *

(II)




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

(III)




4. The salt of claim 2 characterized in being a crystalline monohydrate.

# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2021-2121

**Short Case Caption** Mylan Pharmaceuticals Inc. v. Merck Sharp & Dohme Corp.

**Filing Party/Entity** Merck Sharp & Dohme Corp.

**Instructions:** Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 01/28/2022

Signature: /s/ Jeffrey A. Lamken

Name: Jeffrey A. Lamken

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☐ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☐ None/Not Applicable |
| Merck Sharp & Dohme Corp. | None | Merck & Co., Inc. |
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☐ Additional pages attached

**4. Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

| | | |
|---|---|---|
| Williams & Connolly LLP | Alexander S. Zolan | Sarahi Uribe |
| Anthony Sheh | Jingyuan Luo | Vanessa O. Omoroghomwan |
| Elise M. Baumgarten | Jihad Komis | Jessamyn S. Berniker |

**5. Related Cases.** Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☐ None/Not Applicable ☐ Additional pages attached

| | | |
|---|---|---|
| Merck Sharp & Dohme Corp. v. Mylan Pharmaceuticals Inc., No. 1:19-cv-00101 (N.D. W. Va.) | | |
| In re Sitagliptin Phosphate ('708 & '921) Patent Litigation, MDL No. 19-2902-RGA (D. Del.) | | |
| | | |

**6. Organizational Victims and Bankruptcy Cases**. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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## CASES

**STATUTES**

## STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, Appellee states:

a. No other appeal in or from this action was previously before this or any other appellate court.

b. The following cases are pending and may be directly affected by this Court's decision: *Merck Sharp & Dohme Corp. v. Mylan Pharmaceuticals Inc.*, No. 1-19-cv-00101 (N.D. W. Va.); *In re Sitagliptin Phosphate ('708 & '921) Patent Litigation*, MDL No. 19-2902-RGA (D. Del.).

## INTRODUCTION

This case concerns a series of breakthroughs for treating type-2 diabetes. In the early 2000s, Merck Sharp & Dohme Corp. invented a genus of compounds called dipeptidyl peptidase-IV ("DP-IV") inhibitors, which help diabetics regulate blood sugar without the side effects of prior-art treatments. Of the millions of compounds within that genus, one—sitagliptin—proved particularly promising. Through further research, Merck developed the inventions claimed in its '708 patent—a sitagliptin dihydrogen-phosphate salt with a 1:1 stoichiometry, and a crystalline monohydrate form of that salt. That invention—1:1 sitagliptin DHP—is used in Merck's Januvia® and Janumet® medications.

Mylan Pharmaceuticals Inc. petitioned for *inter partes* review of the '708 patent. While Mylan says it presented "a classic case of anticipation and obviousness," Mylan.Br.2, its arguments were hardly standard. In classic anticipation cases, the challenger produces a prior-art reference that "not only disclose[s] all elements of the claim within the four corners of the document, but . . . also disclose[s] those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Here, each challenged claim recites a 1:1 sitagliptin DHP salt. It was undisputed that Mylan's reference—Merck's international patent application WO '498, which disclosed the genus of DP-IV inhibitors—did ***not*** expressly disclose 1:1 sitagliptin DHP.

Mylan's theory singled out sitagliptin from a list encompassing numerous DP-IV inhibitors in WO '498; pieced it together with general statements regarding the use of multiple acids to form pharmaceutical salts; and argued to the Patent Trial and Appeal Board that skilled artisans would "at once envisage" a resulting sitagliptin phosphate salt. But the Board found that, even if one ignored WO '498's other disclosures and narrowed the genus of salts WO '498 disclosed to the combinations resulting from one list of DP-IV inhibitors and another list of acid counterions, that yielded ***957*** combinations in the varied potential stoichiometries of those salts—many of which may not even exist in this unpredictable field. The notion that skilled artisans would "at once envisage" a sitagliptin phosphate salt from among those 957 hypothetical salts—much less envision all of them at once, as precedent requires—was fanciful.

As for the 1:1 stoichiometry, Mylan argued inherency, stating that a salt would form in a 1-to-1 ratio of sitagliptin to phosphoric acid "every time" they react. But Mylan's theory cratered when Merck ***actually made*** sitagliptin phosphate salts in 3:2 and 2:1 stoichiometries. Mylan shifted to an alternate theory, insisting WO '498's example 7 inherently disclosed 1:1 sitagliptin DHP. The Board rejected that, too. Among other reasons, example 7 involved a ***hydrochloride*** salt, not a ***phosphate*** salt. And the evidence showed the two are quite different.

Mylan's obviousness arguments fared no better. Mylan invoked WO '498 and Bastin and Brittain, two general references that never mention sitagliptin. But Merck had reduced 1:1 sitagliptin DHP to practice before WO '498 published, eliminating it as a reference for all but two claims (3 and 4). As for claim 3, reciting 1:1 sitagliptin DHP in the (S)-configuration, and claim 4, reciting a crystalline monohydrate, Mylan failed to show skilled artisans would be motivated to combine those elements or have a reasonable expectation of success. Merck's evidence showed they would not.

The Board's opinion is thorough and record-intensive. To prevail now, Mylan must establish that the Board's findings are not supported by "substantial evidence." *In re Chudik*, 851 F.3d 1365, 1371 (Fed. Cir. 2017). But the Board's findings are amply supported by expert testimony, *see* Appx2589-2766; Appx2409-2532, including admissions by Mylan's expert. Rather than address the overwhelming evidence the Board invoked, Mylan re-argues its case de novo. For example:

- Mylan argues "[t]his is not a case in which the skilled artisan would have to envisage a limitation from a broad or undefined class." Mylan.Br.34. But Mylan never addresses the Board's finding that the class includes at least 957 theoretical salts that might or might not exist. Appx29.

- Mylan accuses the Board of "ignoring" issues on which the Board made detailed findings. *Compare* Mylan.Br.48 (accusing Board of "ignoring this presumption of enablement"), *with* Appx49-51 (Board explaining why "[e]ven if that presumption were appropriate here, we find it overcome").

- Mylan presents arguments not made below. While Mylan argued below that 1:1 stoichiometry was "inherent," *see* Appx36-41, it now argues that skilled artisans "could easily envisage" that stoichiometry, Mylan.Br.29. Even if that argument had been preserved—it was not—it radically misapprehends anticipation law.

The Board's comprehensive decision properly rejected Mylan's arguments. The Court should affirm.

## STATEMENT OF THE ISSUES

1. Whether substantial evidence supports the Board's finding that Mylan failed to prove WO '498 anticipates claims 1-3, 17, 19, and 21-23 of the '708 patent.

2. Whether substantial evidence supports the Board's finding that the '708 patent antedates WO '498.

3. Whether substantial evidence supports the Board's findings that Mylan failed to prove claims 3 and 4 of the '708 patent obvious.

## STATEMENT

### I. MERCK'S SERIES OF BREAKTHROUGHS IN TREATING TYPE-2 DIABETES

#### A. Merck Discloses Its Invention of a Class of DP-IV Inhibitors in WO '498 and the '871 Patent

##### 1. *Merck Invents a Genus of DP-IV Inhibitors*

Persons with type-2 diabetes have a resistance to insulin, the hormone that regulates blood sugar. Appx368. Their inability to regulate blood-sugar levels can lead to heart disease, strokes, kidney failure, and blindness. *Id.* Longstanding diabetes treatments had serious side effects. Appx368-369. Some can overcorrect,

causing blood-sugar levels to drop dangerously. Appx369. Others can cause nausea, diarrhea, and even liver toxicity. *Id.*

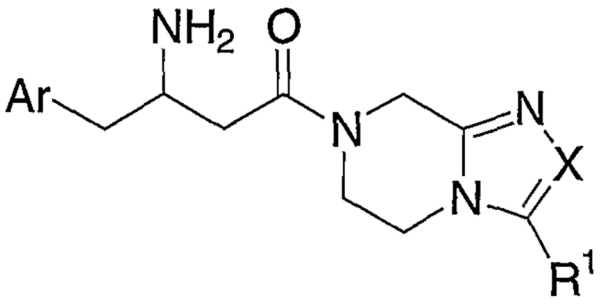
In the early 2000s, Merck invented a class of compounds that treat type-2 diabetes by inhibiting production of the DP-IV enzyme. DP-IV inactivates hormones that would otherwise stimulate insulin production when patients consume food. Appx370. Merck's DP-IV inhibitors allow those hormones to function unimpeded, stimulating insulin production. Appx368-370. Because DP-IV inhibitors act only when the patient eats, they reduce the risk of dangerously low blood sugar. Appx369-370.

2. *Merck Discloses a Genus of DP-IV Inhibitors in WO '498 and the '871 Patent*

Merck sought patent protection for the genus of DP-IV inhibitors it invented. In July 2002, Merck simultaneously filed application WO 03/004498 with the World Intellectual Property Organization, Appx367, and a corresponding application with the U.S. Patent and Trademark Office, Appx504. WO '498 published on January 16, 2003, Appx367, and U.S. Patent No. 6,699,871 issued on March 2, 2004, Appx504. WO '498 and the '871 patent are Mylan's primary prior-art references in this case.[1]

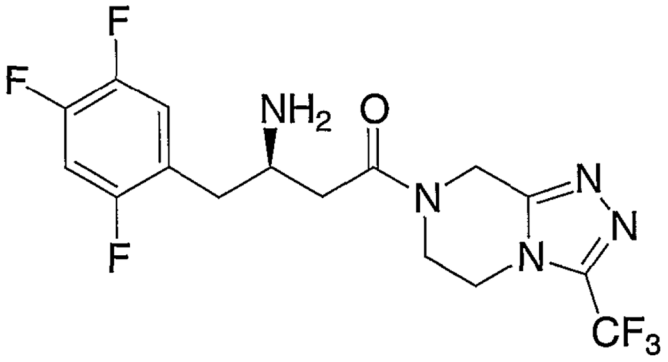
[1] Mylan acknowledges that "WO '498 and the '871 Patent are identical in relevant part." Mylan.Br.1. The Board likewise treated them as identical. Appx42. For convenience, Merck refers to WO '498 to encompass both.

WO '498 is "directed to compounds" of its formula I:




Appx371. WO '498's claim 1, Appx417, covers "millions of compounds within" that formula, Appx2630.

This case concerns one of the millions of DP-IV inhibitors within the genus WO '498 disclosed—"sitagliptin." Sitagliptin is one of 33 compounds depicted in WO '498's claim 15:




Appx422.

WO '498's claims 1 and 15 generically encompass "pharmaceutically acceptable salts" of the DP-IV inhibitors. Appx418; Appx427. WO '498 defines "pharmaceutically acceptable salts" as "salts prepared from pharmaceutically acceptable non-toxic bases or acids." Appx376. It notes that "[s]alts in the solid form may exist

in more than one crystal structure, and may also be in the form of hydrates." *Id.* When the DP-IV inhibitor is basic, salts "may be prepared from pharmaceutically acceptable non-toxic acids." Appx377. WO '498 lists 26 "[s]uch acids." *Id.* Eight—citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids—are described as "[p]articularly preferred." *Id.*

The challenged claims of the '708 patent in this case recite sitagliptin ***phosphate*** salts with a ***1:1 stoichiometry***—*i.e.*, a 1-to-1 ratio of sitagliptin to phosphoric acid. *See* pp. 11-13, *infra*. The only salts WO '498 discloses of ***any*** exemplified compounds, however, are ***hydrochloride*** salts. *See* pp. 17-18, *infra*. Example 7 discloses a process for making a sitagliptin ***hydrochloride*** salt. Appx413.

### B. Merck Develops 1:1 Sitagliptin DHP and a Crystalline Monohydrate Thereof

#### 1. *Merck's Experiments Produce a Promising 1:1 Sitagliptin DHP Salt*

By the time WO '498 published in January 2003, Merck had made advances ***not*** disclosed in that reference. From the millions of DP-IV inhibitors, Merck had identified one, sitagliptin, as particularly promising. And it had reduced to practice a salt for administration to humans—a sitagliptin phosphate salt with a 1:1 stoichiometry ("1:1 sitagliptin DHP").

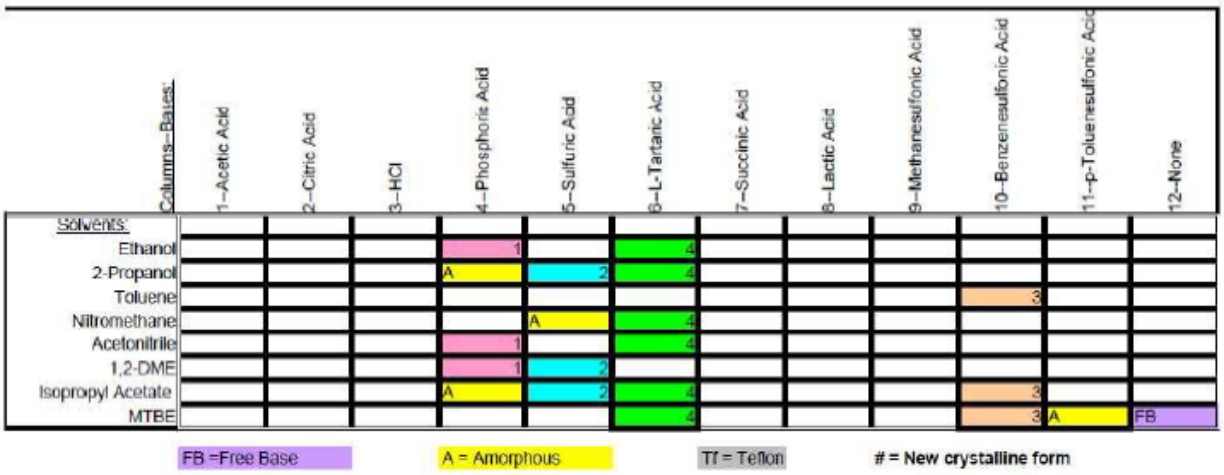
By the end of 2001, Merck had selected sitagliptin for clinical development. Appx3530; Appx4063-4064.[2] Merck's project team initially focused on the free-base, Appx4068, but it exhibited poor stability, degrading in solution and bulk form, Appx4071-4074.

Merck researched developing a "crystalline salt of sitagliptin," hoping to create one with favorable characteristics for a commercial drug. Appx1094; *see* Apx1069; Appx4074. Pharmaceutical salts are formed by reacting the "free" form of an active compound with an acid or base. Appx2603. Because sitagliptin is "weakly basic," Appx2609, it would need to react with an acid to form a salt, Appx2603.

Developing pharmaceutical salts, however, "require[s] an empirical R&D process that is unpredictable and fraught with trial and error." Appx2603. "'No 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.'" Appx2603-2604 (quoting Appx2038). Even if a salt forms, its properties "may not be desirable for use in a drug product." Appx3533.

[2] Mylan erroneously states that "WO '498 'describes' sitagliptin as a potent DP-IV inhibitor." Mylan.Br.13. Mylan's expert admitted that WO '498 reported "no data" "specifically attributable to sitagliptin." Appx2373-2374(188:6-189:8).

In December 2001, Merck's Vicky Vydra (one of the '708 patent's inventors) attempted to form sitagliptin salts. Appx1070. Vydra's experiments involved creating solutions of sitagliptin and each of 11 different acids, and adding eight different recrystallization solvents to those solutions in a well plate. Appx3531; Appx1080. Only 15 of the 88 combinations in Vydra's experiments produced crystalline salts:




Appx1083; Appx3532.

Experimenting with sitagliptin and phosphoric acid, Vydra produced a dihydrogenphosphate salt with a 1:1 stoichiometry. Appx1072; Appx2606. Merck's subsequent experimentation with that salt revealed "favorable properties." Appx4081. It had a "flake" or "plate" shape, beneficial for "pharmaceutical processability." Appx4076. It was "non-hygroscopic," meaning it did not absorb water. Appx4077. And it had "high solution stability," which ensured "stab[ility] during pharmaceutical processing." Appx4078-4081. In February 2002, Merck selected 1:1 sitagliptin DHP for development. Appx4081-4082.

But 1:1 sitagliptin DHP was not perfect. It sometimes changed structure under thermal or mechanical pressure. Appx3141-3143; Appx3534-3538. Merck "made concerted efforts in 2002 . . . to identify all polymorphs of" 1:1 sitagliptin DHP. Appx3547. Merck "spent over a year experimenting with and developing ***anhydrous*** forms of" the salt—forms without water in their crystalline structure. Appx3546 (emphasis added). Despite "deliberate[ ]" efforts to "synthesize a ***hydrate*** form"—a salt with water in its structure—Merck "did not obtain" one. Appx3546-3547 (emphasis added).

2. *Merck Unexpectedly Discovers a Crystalline Monohydrate with Superior Characteristics*

After WO '498 published in January 2003, Appx367, Merck discovered a new form of 1:1 sitagliptin DHP. Pursuing more efficient routes to produce ***anhydrous*** 1:1 sitagliptin DHP, Stephen Cypes (another of the '708 patent's inventors) experimented with an unusual solvent—isoamyl alcohol. Appx3404-3407. In "a surprising and unexpected" development, that produced a crystalline ***monohydrate*** of 1:1 sitagliptin DHP. Appx3407.

Despite having run more than a year of screens to identify all polymorphs of 1:1 sitagliptin DHP, Merck had never identified any hydrates. Appx3404; Appx3547. Dr. Hansen (another inventor on the '708 patent) had made "deliberate[ ]" attempts to "synthesize a hydrate form," but failed. Appx3546-3547. Cypes's

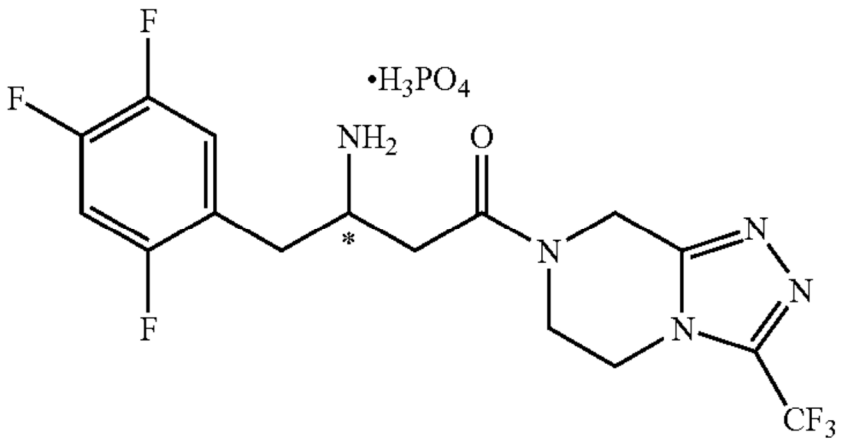
experiments were not designed to produce a hydrate—its appearance was serendipity. *See* Appx3406.

The monohydrate proved superior to anhydrous 1:1 sitagliptin DHP. Appx3148. It did not change forms in response to humidity, shear, or pressure. Appx3148-3149. It had a "well-defined rod-like" shape and larger size, was non-hygroscopic, was less "sticky," did not discolor, and exhibited improved chemical stability. Appx4085-4091; Appx3146-3151. Even though Merck was scheduled to produce clinical supplies for human studies in just two months, it shifted its development efforts to the monohydrate. Appx3146.

### C. Merck Receives the '708 Patent for 1:1 Sitagliptin DHP and Its Crystalline Monohydrate

In June 2003, Merck sought patent protection for 1:1 sitagliptin DHP and the crystalline monohydrate. Appx78. It was awarded U.S. Patent No. 7,326,708 on February 5, 2008. Appx78-93.

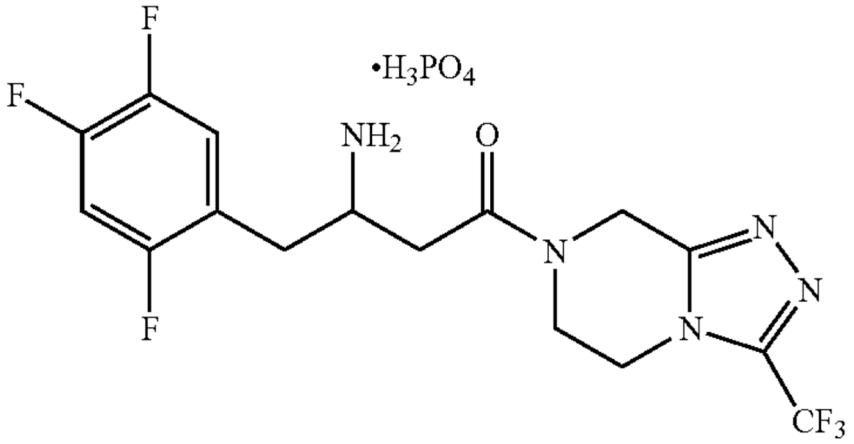
The '708 patent states that "[t]he present invention relates to a particular salt of a [DP]-IV inhibitor"—the 1:1 "dihydrogenphosphate salt" of sitagliptin. Appx84(1:13-18). Formula I discloses 1:1 sitagliptin DHP:




Appx84. The specification states that the "dihydrogenphosphate salt of the present invention is comprised of one molar equivalent of mono-protonated [sitagliptin] . . . and one molar equivalent of the dihydrogenphosphate . . . anion." Appx85(3:46-52). "This novel salt and crystalline hydrates thereof are useful for the treatment" of "Type 2 diabetes." Appx84(1:18-22). The specification teaches skilled artisans how to crystallize the 1:1 sitagliptin DHP monohydrate. Appx86-90(6:57-13:21).

The '708 patent observes that WO '498 "describes a class of . . . potent inhibitors of DP-IV," Appx84(1:49-52); it discloses sitagliptin, and "[p]harmaceutically acceptable salts of this compound are generically encompassed within [its] scope," Appx84(1:53-57). But the '708 patent explains that "there is no specific disclosure" in WO '498 "of the newly discovered" 1:1 sitagliptin DHP. Appx84(1:58-62). The "salt of the present invention exhibits pharmaceutic advantages over the free base and the previously disclosed hydrochloride salt" in WO '498, such as "enhanced chemical and physical stability." Appx85(4:19-28).

Claim 1 of the '708 patent recites 1:1 sitagliptin DHP (below), "or a hydrate thereof":




Appx91(15:64-16:14). Claim 2 recites "[t]he salt of claim 1" in "the (R)-configuration." Appx91(16:16-30). Claim 3 recites "[t]he salt of claim 1" in "the (S)-configuration." Appx91(16:32-46). The (R)- and (S)-configurations differ in that the $NH_2$ substituents form mirror images called "enantiomers." Appx2425-2427(¶¶43-49). Claim 4 recites "[t]he salt of claim 2 characterized in being a crystalline monohydrate." Appx91(16:47-48). As relevant here, claims 17, 19, and 21-23 also require the salt of claim 2, among other limitations. Appx92(17:21-24, 17:29-32, 17:37-18:12).

## II. PROCEDURAL HISTORY

### A. The Board Institutes *Inter Partes* Review Based on Mylan's Assertion That WO '498 Inherently Discloses 1:1 Sitagliptin DHP

After Merck sued Mylan for infringement, Appx1637-1647, Mylan petitioned for *inter partes* review, seeking cancellation of claims 1-4, 17, 19, and 21-23 of the

'708 patent. Appx177-261. Mylan's challenges relied on Merck's own prior art—WO '498 and the '871 patent. *See* Appx201.

For claims 1-3, 17, 19, and 21-23, Mylan argued anticipation. To anticipate, prior-art references ordinarily must "disclose all elements of the claim within the four corners of the document, . . . 'arranged as in the claim.'" *Net MoneyIN*, 545 F.3d at 1369. Mylan did not contend that WO '498 expressly disclosed 1:1 sitagliptin DHP. For the claims' requirement of a 1:1 stoichiometry—a 1-to-1 ratio of sitagliptin to phosphoric acid—Mylan urged inherency. A limitation is inherently disclosed "only if it is necessarily present, not merely probably or possibly present, in the prior art." *Guangdong Alison Hi-Tech Co. v. ITC*, 936 F.3d 1353, 1364 (Fed. Cir. 2019) (quotation marks omitted). Citing the declaration of its expert, Dr. Chorghade, Mylan asserted that sitagliptin "can ***only*** be mono-pronated at the primary amine," such that a 1:1 salt forms "every time" sitagliptin and phosphoric acid react. Appx207-209 & n.8.

Mylan, moreover, did not urge that WO '498 expressly disclosed sitagliptin DHP (in any stoichiometry, 1:1 or otherwise). To establish that, Mylan urged that skilled artisans would "'"at once envisage"'" a sitagliptin phosphate salt by piecing together disclosures in WO '498. Appx210 (quoting *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012)). Mylan argued that WO '498 disclosed sitagliptin among 33 compounds in claim 15; that it generically

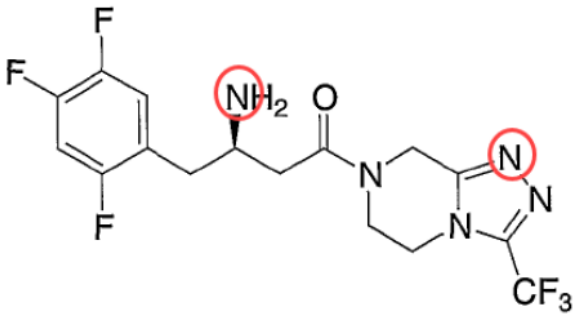
claimed "pharmaceutically acceptable salts"; and that WO '498 elsewhere listed phosphoric acid as one of eight "particularly preferred" acids that might be considered for reaction with basic compounds (sitagliptin is weakly basic). Appx206-207. Those lists of potential constituents, it argued, "collapse to form a single comprehensive list, which provides the complete list of compounds and their accompanying 'pharmaceutically acceptable salts'—one of which is sitagliptin phosphate." Appx212. Mylan also asserted obviousness challenges. Appx235-252.

Opposing institution, Merck explained (among other things) that Mylan had no "evidence or analysis" proving the 1:1 stoichiometry was inherent. Appx1052-1060; *see* Appx1010. Dr. Chorghade's declaration was "devoid of any explanation, evidence, or even a citation supporting his conclusory opinion." Appx1056. On obviousness, Merck argued that Mylan's primary reference—WO '498—could not be used for all but two claims because Merck reduced 1:1 sitagliptin DHP to practice before the reference's publication date. Appx1039.

While instituting review, Appx1740, the Board questioned Mylan's assertion that WO '498 inherently discloses "the 1:1 stoichiometry of the phosphoric acid salt of sitagliptin," calling it "light on analysis," Appx1789. But Mylan provided some "expert testimony in support of its position." Appx1789-1790. The Board left that issue for "final determination" at "trial." Appx1791. The Board "left to trial" other issues as well. Appx1795.

### B. Merck Disproves Inherency

In ensuing proceedings, Mylan's inherency argument about 1:1 stoichiometry failed spectacularly. Appx207-209 & n.8. Merck's expert, Dr. Matzger, identified other stoichiometries when reacting sitagliptin with phosphoric acid. Phosphoric acid is polyprotic, meaning it is potentially capable of donating three protons. Appx2652-2653. And sitagliptin has two sites where it can accept a proton—at the primary amine, and the triazole ring (both circled in red below):




Appx2649-2650. Thus, those compounds can form salts with stoichiometries of 1:1 (one sitagliptin molecule with one phosphoric acid molecule), 1:2 (one sitagliptin molecule and two phosphoric acid molecules), 2:1 (two sitagliptin molecules accepting protons from one molecule of phosphoric acid) and 3:2 (three sitagliptin molecules accepting protons from two molecules of phosphoric acid). Appx2649-2658.

The art confirmed that. A Merck international patent application from 2012 disclosed sitagliptin phosphate salts with 1:2 and 2:1 stoichiometries. Appx2154, 2164. Mylan's Dr. Chorghade admitted the reference disclosed a non-1:1 sitagliptin phosphate salt. Appx2369-2370 (172:12-173:2). And Dr. Matzger described experi-

ments where he ***actually made*** 3:2 and 2:1 salts. *See* Appx2666-2719. Those experiments proved that "the reaction of phosphoric acid with sitagliptin" does not "necessarily or inherently result[] in a 1:1" sitagliptin DHP salt, as Mylan contended. Appx2664.

Dr. Chorghade conceded that his declaration's assertion that the 1:1 salt forms "every time" sitagliptin and phosphoric acid react was unsupported. Appx304. He could not offer "test data because [he did] not have any." Appx2369(169:9-14). He "ha[d] not researched any literature" before issuing his opinion. Appx2369(172:1-7).

### C. The Board's Final Written Decision Rejects Mylan's Challenges to the '708 Patent

The Board's final written decision rejected Mylan's challenges. Appx1-76.

#### 1. *The Board Rejects Mylan's Anticipation Arguments*

The Board found that Mylan failed to prove claims 1-3, 17, 19, and 21-23 anticipated by WO '498. It was "undisputed that a 1:1 sitagliptin DHP salt" recited in the challenged claims "is not ***expressly*** disclosed in WO '498." Appx27. WO '498 did not disclose ***any phosphate salt*** of ***any*** exemplary DP-IV inhibitor. Appx17. WO '498 disclosed ***hydrochloride*** salts, including a sitagliptin hydrochloride salt in example 7. Appx27-28. But hydrochloric acid and phosphoric acid "are different." Appx28. The Board credited Dr. Matzger's testimony that skilled artisans "would not simply conclude that whatever applies for hydrochloric acid"

also applies for phosphoric acid. *Id.* Among other things, phosphoric acid can create more stoichiometries because it has three protons to donate, whereas hydrochloric acid only has one. *Id.* As to 1:1 stoichiometry, the Board rejected Mylan's inherency argument. Appx41.

The Board Rejects Mylan's "Envisage" Theories. The Board found that Mylan's "'list(s)' and 'envisage' theories do not make up for the absence of express disclosure of the claimed 1:1 sitagliptin DHP salt on this record." Appx29. Under this Court's "envisaging" precedent, "disclosure of a ***limited number of combination*** possibilities" may in some circumstances effectively disclose each of the individual "combinations" themselves. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274 (Fed. Cir. 2017) (emphasis added). The Board set aside for the moment that WO '498's formula I encompassed millions of potential compounds. Appx29. "Even accepting" Mylan's position that WO '498 could be reduced to a "'list' of 33 example active compounds" and another "'list' of eight preferred acids . . . to form potential salts, . . . there is no 'list' that identifies ***expressly*** all the phosphate salts in any, much less all, the potential stoichiometric ratios." *Id.* That distinguished the precedent Mylan cited "where the relevant subject matter was listed expressly." *Id.*

The Board rejected Mylan's theory that skilled artisans would "envisage" sitagliptin DHP by combining a list of thirty-three DP-IV inhibitors in the claims

with a list of eight preferred acids elsewhere in the patent application. The Board found "the evidence is undisputed that making salts like those disclosed in the '708 patent . . . is an unpredictable endeavor." Appx34. Skilled artisans would not necessarily envisage salts simply by combining constituents on unrelated lists.

Moreover, to anticipate under an "envisaging" theory, a reference must expressly disclose ***all*** of the challenged claim's limitations. *Nidec*, 851 F.3d at 1274-75. The Board found that combining Mylan's lists would not account for the claims' "1:1 stoichiometry." Appx29-30 & n.19. The Board explained that, "[w]ith no express disclosure of all limitations of the 1:1 sitagliptin DHP salt in WO '498, [Mylan] cannot fill gaps by arguing a POSA would 'envisage' what is missing." Appx30 (citing *Nidec*, 851 F.3d at 1274-75). Yet "[t]his gap-filling is precisely what [Mylan] attempts to do." Appx30 n.19.

Finally, under this Court's "envisaging" precedent, Mylan was required to prove skilled artisans "would 'at once envisage'" not just the claimed species, but "'***each member*** of th[e] limited class' of phosphate salts allegedly disclosed in WO '498." Appx33 (quoting *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006)) (emphasis added). The Board found it unnecessary to address Merck's contention that Mylan improperly used hindsight to narrow the class to combinations based on just two lists, as opposed to WO '498's entire disclosure. *See* Appx1891-1892. "[E]ven if it were appropriate to limit the genus" to

33 example compounds, not the "millions within formula I," and even if it were appropriate to focus on combining those with the "8 preferred acids," not the patent's "open-ended list of twenty-six acids," it was "uncontested" that (after "accounting for varied stoichiometry") that would yield "'957 salts'" that only "might exist." Appx29. Mylan's combination did not amount to an "express listing of all these 950-plus hypothetical salts, much less the specific 1:1 sitagliptin DHP as claimed." Appx29-30.

The Board explained that, "even if the law did not foreclose [Mylan's] 'envisaging' theory," its evidence was "weak." Appx31. Even Mylan's Dr. Chorghade had "not opine[d] that a POSA would 'at once envisage' the 1:1 sitagliptin DHP salt." *Id.* He merely said he "agree[d]" with Merck's expert, Dr. Matzger, that—by looking at example 7's 1:1 ***hydrochloride*** salt—one "'can imagine'" a 1:1 phosphate salt. *Id.* But the Board found that Dr. Chorghade took that statement out of "context," and that it "tells a different story." Appx31-32. Dr. Matzger had opined that 1:1 sitagliptin DHP "'does not' come to mind based on WO '498"; that hypothetically imagining something is not the same as understanding from the disclosure that a particular salt actually exists; and that Dr. Matzger had "unequivocal[ly] and repeated[ly]" testified that, based on the unpredictability of salt formation, it was impossible for skilled artisans to "at once envisage all the possible salts." Appx32.

Dr. Matzger's "isolated 'imagine' testimony" thus offered Mylan no support. Appx32-33.

The Board then found that Mylan's "envisaging theory fails for yet another reason." Appx33. While the law requires skilled artisans to "at once envisage ***each member***" of the class disclosed in WO '498, *Eli Lilly*, 471 F.3d at 1376 (emphasis added), Mylan's own Dr. Chorghade "did not even 'at once envisage' each" of the phosphate salts—a small "sub-class" of the genus based on two lists Mylan combined from WO '498, Appx33. Dr. Chorghade initially "testified that sitagliptin forms the 1:1 salt with phosphoric acid 'every time,'" but the evidence "show[ed]" that other phosphate salts of sitagliptin "do exist," including "1:2, 2:1, and 3:2" salts. *Id.* Mylan's theory that skilled artisans would "at once envisage" each member of a supposedly "limited class" of phosphate salts from WO '498 was fatally "undermined" by its "own (initial) position, and its own expert's testimony," which failed to envisage salts of various stoichiometries within that class. *Id.*

The Board Rejects Mylan's Inherency Arguments. On inherency, the Board found that Merck disproved Mylan's original assertion that "sitagliptin can only be mono-protonated and will form the 1:1 DHP salt every time." Appx35. The Board found that "the evidence—confirmed experimentally and reported in the technical literature—undeniably shows that non-1:1 sitagliptin phosphate salts do exist" and are created using "conventional salt-screening techniques." Appx41.

The Board rejected Mylan's new argument at trial that skilled artisans would have understood WO '498's example 7 to inherently disclose a process for making 1:1 sitagliptin DHP. Appx35-36. Mylan based that argument on experiments Dr. Leonard Chyall had performed. Appx35. But those experiments, the Board found, did ***not*** adhere to example 7's process. There was no evidence Dr. Chyall was trying to reproduce example 7, and his process involved over "half-a-dozen" changes from example 7. Appx38. Most notably, he used ***phosphoric*** acid, where example 7 "is ***explicitly*** a process for preparing a ***hydrocholoride*** salt." Appx37 (second emphasis added). "One could run [example 7's] process 10,000 times and it would never produce any phosphate salt of sitagliptin." *Id.* Since example 7 "must necessarily be changed to produce any phosphate salt," the Board concluded that it does not inherently disclose any phosphate salt, much less one with 1:1 stoichiometry. *Id.*

2. *The Board Rejects Mylan's Obviousness Arguments for Claims 1-2, 17, 19, and 21-23*

Although "[a]ll of [Mylan's] obviousness grounds rely on WO '498," Appx43, the Board found that WO '498 could not be used as prior art in challenging claims 1-2, 17, 19, and 21-23. It was "not dispute[d]" that Merck reduced the subject matter of those claims—1:1 sitagliptin DHP—to practice before WO '498's January 16, 2003, publication date. Appx43-45. Consequently, WO '498 was not § 102(a) prior art, but "only a § 102(e) reference." Appx52. And "[b]ased on Merck's undisputed ownership . . . of the claimed subject matter and WO '498, that reference is

excluded from consideration for obviousness purposes under pre-AIA § 103(c)(1)." *Id.* That eliminated Mylan's obviousness challenge to everything but "claims 3 and 4." *Id.*

Mylan had raised only "a relatively discrete counterargument." Appx45. Mylan insisted that, to establish antedation, Merck must have reduced "***hydrates*** of the 1:1 sitagliptin DHP salt" to practice before WO '498 published. Appx45-46. The parties agreed, however, that Merck only needed to reduce to practice as much of "'the claimed invention'" as "'the reference shows.'" Appx47 (quoting *In re Clarke*, 356 F.2d 987, 991 (C.C.P.A. 1966)). The Board found that, whatever WO '498's other disclosures, "there is no ***hydrate*** of that salt shown anywhere in the reference." Appx48. Accordingly, there was no requirement that ***hydrates*** have been reduced to practice.

Mylan's Dr. Chorghade opined that skilled artisans would understand WO '498's "sole mention of 'hydrates'"—which states only that they "'may exist'"—to mean 1:1 sitagliptin DHP actually "exists as a crystalline hydrate." Appx48 (quoting Appx376). The Board rejected "[t]hat conclusory opinion." *Id.* It credited the testimony of Merck's expert that skilled artisans "would not have understood the sentence as applying to sitagliptin phosphate salts in particular." Appx48-49. Moreover, WO '498 posits that hydrates "'may' exist," not "that any such hydrates ***do***

exist." Appx49. The "evidence" showed that whether any salt "is even capable of forming as a hydrate is highly unpredictable." *Id.*

A "prior art reference," moreover, "must be enabling." *Impax Lab'ys, Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006). Mylan argued only "that WO '498 is presumptively enabling for the hydrated forms of the various salts." Appx49. The Board found that, "[e]ven if that presumption were appropriate here, we would find it overcome based on a complete absence of examples or guidance in WO '498 about making such hydrates, and the substantial unpredictability concerning whether a hydrate of any specific salt will even form." *Id.* Merck "explain[ed] persuasively," through expert testimony and "literature of record," that skilled artisans "would not have known or predicted whether particular salts, especially the 1:1 sitagliptin DHP, could crystallize at all, form a hydrate, or form a monohydrate." Appx49-50. Mylan's expert "agreed that the art was unpredictable on precisely this point." Appx50. And Merck provided "additional testimony and documentation showing that its actual discovery of a hydrate of 1:1 sitagliptin DHP . . . was unforeseen and arose only after substantial work with other salt forms." Appx51.

The "evidence shows that Merck reduced to practice at least as much (indeed, more) of the claimed subject matter versus what is shown in WO '498." Appx52. WO '498 thus was "excluded from consideration for obviousness purposes" for

claims 1-2, 17, 19, and 21-23. *Id.* Without that reference, Mylan's "challenge to those claims fails." *Id.*

3. *The Board Finds Claim 3 Not Proved Obvious*

The Board rejected Mylan's obviousness challenge to claim 3—which recites 1:1 sitagliptin DHP in the (S)-configuration (the enantiomer to claim 2's (R)-configuration). Appx55.

First, neither of Mylan's references—WO '498 and Bastin—provided skilled artisans reason to create ***any*** sitagliptin phosphate salt, rather than the hydrochloride salt in WO '498's example 7. Appx56. Bastin noted that "[h]ydrochloride salts often have been the first choice for weakly basic drugs," but described some "potential disadvantages." Appx496. Bastin did note that phosphoric acid was one of numerous potential alternative counterions. *Id.* But the Board found that hydrochloric acid and phosphoric acid are not "interchangeable." Appx56. It found that no shortcomings of the sitagliptin hydrochloride salt had been reported, and there were "numerous reasons" why skilled artisans would not "have reasonably believed" a phosphate salt superior. *Id.* The Board credited Dr. Matzger's testimony that phosphates had known disadvantages, including "reduce[d] solubility and stability versus hydrochloric salts." *Id.* Nor did Mylan "identify where the recited 1:1 ratio is necessarily satisfied upon the combination of WO '498 and Bastin." Appx55.

Second, the Board found that, even "assuming" one looked past those issues, "that still would not produce the claimed subject matter," because it "would, at best, make a 1:1 (R)-sitagliptin DHP," rather than "the (S)-enantiomer" in claim 3. Appx56-57. Mylan offered "no expected or even theoretical benefit to making" the (S)-configuration. Appx58. And evidence "that forming such salts is highly unpredictable" bolstered the conclusion that skilled artisans would not have had "a motivation to make, with reasonable expectation of success, 1:1 (S)-sitagliptin DHP." *Id.*

4. *The Board Finds Claim 4 Not Proved Obvious*

The Board rejected Mylan's argument that the "'crystalline monohydrate'" of 1:1 sitagliptin DHP, recited in claim 4, was obvious in light of WO '498, Bastin, and Brittain. Appx58-69.

Mylan "fail[ed] to provide a persuasive motivation for making the crystalline monohydrate." Appx63. Mylan's petition "provide[d] no rationale." Appx61. Its expert "offered no motivation (persuasive or otherwise) in his declaration and admitted that he gave no opinion on why a POSA would have preferred a hydrate of sitagliptin." *Id.* And when "asked at the oral hearing to identify" a reason to make the monohydrate, Mylan "was unable to do so." Appx62. "On the other hand," Merck's expert, Dr. Myerson, "testifie[d] persuasively" that there were numerous reasons skilled artisans "would have sought to avoid hydrates." Appx63. Mylan did

not attempt to "address the numerous downsides of hydrates that are reported in the literature." Appx62.

While lack of motivation to combine was "alone" sufficient reason to "reject[] [Mylan's] obviousness challenge," Mylan also failed to show skilled artisans would have "a reasonable expectation of success." Appx63. Dr. Myerson "testifie[d] persuasively" that whether any particular compound can be crystallized is unpredictable, and that no means existed to predict formation of hydrates. *Id.* Dr. Chorghade conceded as much. *Id.* The Board rejected his "conclusory opinion" that skilled artisans would expect sitagliptin DHP to exist as a crystalline hydrate, Appx64, which rested on WO '498's generic statement that hydrates "may exist," Appx376.

Mylan invoked Brittain's teachings that "approximately one-third of the pharmaceutical actives are capable of forming crystalline hydrates," half of which are monohydrates. Appx59 (quoting Appx441). But the Board found that Brittain "undermines" Mylan's argument. Appx64. Brittain's disclosure that "only about ***one-sixth***" of studied active compounds "could form a monohydrate" showed that the "probability was low." Appx65. That was "unpersuasive in showing a POSA's reasonable expectation of success." *Id.*

The crystalline monohydrate's "unexpected properties" further "undermin[ed]" Mylan's challenge. Appx67. Mylan did "***not*** contest" that the monohydrate's advantages were "surprising or unexpected." *Id.* It complained that Merck

compared the monohydrate to WO '498's sitagliptin hydrochloride salt as the closest prior art, rather than comparing it to 1:1 sitagliptin DHP. *See* Appx2759. But the Board explained that sitagliptin DHP was not in the prior art, and that "'unexpected results are shown in comparison to what was known, not what was unknown.'" Appx68 (quoting *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017)). And "even assuming a 1:1 sitagliptin DHP salt was identified in WO '498," Merck proved that the hydrate "unexpectedly" overcame the anhydrous salt's "undesirable form conversion." *Id.* Merck thus "provide[d] a more robust and persuasive comparison than it was even required to make." *Id.*

## SUMMARY OF ARGUMENT

I.A. The Board properly rejected Mylan's argument that WO '498 anticipates claims 1-3, 17, 19, and 21-23. The Board found that, particularly given the unpredictability of the art, skilled artisans would not "at once envisage" the genus of DP-IV-inhibitor salts WO '498 discloses—at least 957 theoretical salts, many of which might not exist. Mylan's expert did not testify that skilled artisans would at once envisage each; Mylan's own expert did not; and the Board reasonably credited Merck's evidence that they would not. Mylan ignores those findings, never attempting to show they are unsupported by substantial evidence.

Mylan argues that the Board should have asked only whether skilled artisans could at once envisage 1:1 sitagliptin DHP from among the four possible stoichi-

ometries of a sitagliptin phosphate salt. That argument is waived. Regardless, Mylan improperly uses hindsight to narrow the genus, rather than accounting for the breadth of WO '498's disclosures as precedent requires.

B. Mylan now urges that WO '498 anticipates because it gives skilled artisans "everything they need to know" to eventually "arrive at" 1:1 sitagliptin DHP. But that is not the same as "at once envisaging." It also improperly focuses on whether skilled artisans might eventually find the particular embodiment claimed in the '708 patent, as opposed to envisaging each member of the genus WO '498 discloses. It also improperly relies on "envisaging" to supply the 1:1 stoichiometry limitation, which WO '498 does not disclose.

Mylan's theory also fails because, as the Board found, WO '498 does not disclose sitagliptin phosphate salts generally, or the 1:1 stoichiometry for a sitagliptin phosphate salt. Mylan's expert failed to testify that he would envisage 1:1 sitagliptin DHP based on WO '498, and the Board credited Merck's evidence that skilled artisans would not envisage that salt. Mylan's new argument that WO '498's example 7—which discloses a 1:1 sitagliptin ***hydrochloride*** salt—would "help a skilled artisan envision" 1:1 sitagliptin DHP, is waived, defies the "at once envisage" standard, and ignores the Board's findings that skilled artisans would not find example 7 relevant to a sitagliptin ***phosphate*** salt.

II. A-B. The Board properly rejected Mylan's obviousness challenge (all claims but 3 and 4) because the '708 patent antedates WO '498. There was no dispute Merck reduced 1:1 sitagliptin DHP to practice before WO '498 published, eliminating WO '498 as a prior-art reference. Mylan's argument that Merck had to reduce the ***crystalline monohydrate*** form to practice fails. Substantial evidence supports the Board's findings that WO '498 neither discloses nor enables the crystalline monohydrate.

III. A. The Board correctly found that Mylan failed to prove claim 3—the (S)-configuration of 1:1 sitagliptin DHP—obvious. Mylan failed to show skilled artisans would be motivated to make 1:1 sitagliptin DHP, much less the (S)-configuration. Nor had Mylan shown a reasonable expectation of success, particularly given undisputed evidence that salt formation is unpredictable. The Board's conclusions are supported by substantial evidence.

B. Mylan failed to prove claim 4—1:1 sitagliptin DHP in crystalline monohydrate form—obvious. Mylan provided no reason why skilled artisans would be motivated to make the crystalline monohydrate. The Board found, based on the undisputed evidence, that skilled artisans would have avoided hydrates.

Substantial evidence likewise supported the Board's finding of no reasonable expectation of success. The experts agreed that hydrate formation is unpredictable. Mylan argues that skilled artisans would have expected to succeed based on evidence

that one-sixth of studied active compounds can form a monohydrate. The Board properly rejected that argument, as it actually proved likelihood of success was low.

## ARGUMENT

The Board's thorough opinion evaluated and comprehensively rejected each of Mylan's challenges to the '708 patent on multiple grounds. Mylan fails to show that any aspect of the Board's well-reasoned decision was unsupported by substantial evidence.

### I. THE BOARD'S FINDINGS THAT WO '498 AND THE '871 PATENT DO NOT ANTICIPATE CLAIMS 1-3, 17, 19, & 21-23 OF THE '708 PATENT ARE SUPPORTED BY OVERWHELMING EVIDENCE

A prior-art reference ordinarily cannot anticipate unless it "not only disclose[s] ***all elements*** of the claim within the four corners of the document, but . . . also disclose[s] those elements '***arranged as in the claim***.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (emphasis added). That standard is not met here. "[I]t is undisputed" that WO '498 and the '871 patent "do[ ] not expressly disclose the specific 1:1 DHP salt of sitagliptin" recited in each challenged claim. Appx3.

Below, Mylan attempted to evade the express-disclosure requirement by combining two narrow exceptions. For limitations other than stoichiometry, Mylan invoked the rule that a prior-art reference need not disclose a species expressly if skilled artisans seeing the reference would "at once envisage each member" of the

class the reference discloses. Mylan's theory required the Board to accept that skilled artisans would combine WO '498's disclosure of 33 DP-IV inhibitors in a claim, Appx421-427, together with an unmatched disclosure of 8 preferred acids 44 pages earlier, Appx377, to "at once envisage" an entire class. But the Board rejected that theory on multiple grounds. Among other things, it found that, in this unpredictable art, skilled artisans would not "at once envisage" the entire genus of salts that might result—a minimum of 957 theoretical salts, many of which would not actually exist. Appx29-30. And for stoichiometry, Mylan urged "inherency." But Merck proved that a 1:1 stoichiometry is ***not*** inherent when reacting sitagliptin and phosphoric acid. Appx35-41.

Mylan scarcely mentions the Board's reasons for rejecting its anticipation challenge. It does not try to show the Board's findings are unsupported by substantial evidence. And Mylan abandons its inherency arguments—the word "inherent" appears only once in its argument, when describing anticipation law. *See* Mylan.Br.24.[3] Mylan instead attempts to re-litigate its case de novo, urging new anticipation theories never submitted to the Board—and never endorsed by this Court. Mylan's arguments defy the standard of review, are procedurally barred, and fail on the merits.

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[3] Mylan thus cannot raise any inherency argument "for the first time in [its] reply brief." *Norman v. United States*, 429 F.3d 1081, 1091 n.5 (Fed. Cir. 2005).

Standard of review: "Anticipation is a question of fact" this Court "review[s] for substantial evidence." *In re Chudik*, 851 F.3d 1365, 1371 (Fed. Cir. 2017). The Court "defer[s] to the fact-finder," and may not "reweigh [the Board's] factual determinations." *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1073 (Fed. Cir. 2017). Even "[w]here two different conclusions may be warranted based on the evidence of record, the Board's decision to favor one conclusion over the other . . . must be sustained by this court as supported by substantial evidence." *In re Bayer Aktiengesellschaft*, 488 F.3d 960, 970 (Fed. Cir. 2007).

### A. The Board's Rejection of Mylan's "At Once Envisage" Theory Is Amply Supported

1. This Court has held that, even when a reference does not expressly disclose a species, its disclosure of a "genus may anticipate a claimed species" if "the genus is ***so small*** that" skilled artisans "would '***at once*** envisage ***each member*** of this limited class.'" *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1285 (Fed. Cir. 2017) (quoting *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1379 (Fed. Cir. 2014)) (emphasis added). The theory is that, where there is a "small recognizable class" defined by "common properties," *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965), disclosing the genus may be equivalent to disclosing "each member," *In re Petering*, 301 F.2d 676, 681-82 (C.C.P.A. 1962). The Board found that standard was not met here. The evidence

showed that skilled artisans could not "at once envisage" the genus of DP-IV-inhibitor salts encompassed by WO '498. Appx27-35.

Mylan's theory was that WO '498 disclosed two "lists"—one depicting 33 DP-IV inhibitors in claim 15, Appx421-427, and another 44 pages earlier that named eight "preferred" acids that might be considered when making salts, Appx377. According to Mylan, the two lists "'collapse to form a single comprehensive list' of all the compounds and salts." Appx20. But the Board found that skilled artisans could not simply "envisage" the salts that would result from combining those lists. The Board found the "evidence is undisputed that making salts . . . is an unpredictable endeavor." Appx34. It thus credited the testimony of Merck's expert, Dr. Matzger, "that a POSA would not and could not at once envisage all the [genus's] possible salts." Appx32. Mylan's expert conceded that the process of forming salts "was mainly trial and error," Appx2355-2356(116:6-117:3), and that skilled artisans would "need to run [a] salt screen to know whether [a] particular combination" of compound and counterion "will form a salt." Appx2353(105:5-15). Consequently, even "hypothetically imagining something," based on combining the items on Mylan's two lists, was not the same as "understanding from the disclosure that a particular salt would exist or could be made." Appx32.

Mylan's Dr. Chorghade, moreover, "d[id] not opine that a POSA would 'at once envisage'" 1:1 sitagliptin DHP. Appx31. And the Board credited Dr. Matz-

ger's testimony "that the claimed 1:1 sitagliptin DHP," specifically, "'does not' come to mind based on WO '498." Appx32. The Board thus found no proof skilled artisans would envision even the claimed 1:1 sitagliptin DHP salt from Mylan's "lists."

Nor did Mylan try to show skilled artisans would "'at once envisage ***each member***'" of the genus WO 498 disclosed, as required for anticipation under an "envisaging" theory. *Wasica*, 853 F.3d at 1285 (emphasis added). Despite having the burden, Mylan never "attempt[ed] to quantify the breadth of compounds and hypothetical salts encompassed by WO '498's disclosures." Appx29. Merck urged that the genus would encompass the millions of DP-IV inhibitors disclosed in formula I, Appx417-418, combined with the myriad acids identified in the specification, Appx377. The Board, however, explained that, "even if it were appropriate to limit the genus" to the 33 example compounds of Mylan's first list, and even if it were appropriate to focus on the "8 preferred acids" of Mylan's second list, it was "uncontested" that, "accounting for varied stoichiometry," that would yield "957 salts" that theoretically "might exist." Appx29.

The evidence was overwhelming that skilled artisans would not at once envisage each of the 957 potential salts of the class (which might or might not exist). The Board found that Mylan did "not show that a POSA would 'at once envisage each member" of the far more limited class of "phosphate salts allegedly disclosed in WO

'498." Appx33. Indeed, Mylan's Dr. Chorghade "did not even 'at once envisage' each member of the sub-class of different ***sitagliptin*** phosphate salts." *Id.* (emphasis added). He initially opined that sitagliptin phosphate salts exist only in a 1:1 stoichiometry, omitting the 1:2, 2:1, and 3:2 salts Merck proved to exist. *Id.* The Board thus found that Mylan's "envisaging theory is . . . undermined by . . . its own expert's testimony." *Id.*

2. Mylan ***does not challenge*** the Board's factual findings on "at once envisaging." Mylan argues that the Board "improperly broaden[ed] the scope of its envisaging analysis by focusing on . . . ***all*** of the salts that might result by combining" its lists. Mylan.Br.36. Mylan says the genus should be limited to the "four possible stoichiometries for sitagliptin and phosphoric acid." Mylan.Br.34. That fails.

Mylan never urged below that the putatively "envisage[d]" genus must be limited to the four possible stoichiometries of a sitagliptin phosphate salt. "[A]ny argument not raised before the Board is waived on appeal." *Microsoft*, 878 F.3d at 1075.

The "at once envisage" exception to express disclosure is limited to genuses "so small" that disclosing the genus is tantamount to disclosing each member. *Wasica*, 853 F.3d at 1285; *see Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 851 F.3d 1270, 1274 (Fed. Cir. 2017) ("disclosure of a limited number of

combination possibilities" can be tantamount to disclosing each). The analysis must consider the full "class of compounds" the "reference discloses." *Impax Lab'ys, Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006). Mylan cannot "create hindsight anticipations" by plucking sitagliptin phosphate salts out of a much broader disclosure and focusing solely on them. *Ruschig*, 343 F.2d at 1250. And as explained below (at 41-43), nothing in WO '498 directed skilled artisans to sitagliptin phosphate salts out of all the combinations that could be derived from Mylan's lists.

Mylan's citation to *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356 (Fed. Cir. 2012), does not "demonstrate[] the Board's error." Mylan.Br.36. In fact, *Wrigley* confirms that the full "number of categories and components" the reference discloses must be considered in the "at once envisage" analysis. 683 F.3d at 1361. *Wrigley* concerned whether combining menthol and WS-23 in gum was anticipated by a prior-art reference that listed WS-23 as one of two preferred "cooling agents" in one list, and menthol as one of the "most suitable" flavoring agents in another, and specifically "envision[ed] using WS-23 and menthol in a single product." *Id.* at 1361. Far from examining two components in isolation, the Court explained that it had to examine "whether the number of categories and components in Shahidi was so large that the combination of WS-23 and menthol would not be immediately apparent." *Id.*

The Board performed the same sort of analysis here. It determined that, given the number of salts that hypothetically could result from Mylan's two lists (many of which may not exist), the absence of emphasis on sitagliptin, the absence of direction to phosphate salts, the utter unpredictability of the art, Mylan's expert's failure to testify that skilled artisans would "at once envisage" even the sub-class of phosphate salts within the 957 theoretical salts that results from combining WO '498's "lists," and Mylan's expert's own failure to envisage all of the sitagliptin phosphate salts that exist, Mylan's case fell far short. Nothing in *Wrigley* requires a contrary result. *See also* pp. 43-44, *infra*.

### B. Mylan's New "Envisaging" Theory Fails

Attempting to sidestep the Board's findings, Mylan relitigates anticipation de novo. But this Court "do[es] not duplicate the efforts of . . . the Board"; nor does it "reweigh factual determinations" on appeal. *Microsoft*, 878 F.3d at 1072-73. Mylan's theory fails regardless.

#### 1. *Mylan's Theory Defies This Court's "At Once Envisage" Precedent*

Mylan purports to invoke this Court's "'at once envisage'" precedent. Mylan.Br.24-25 (quoting *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)). But its argument is that WO '498 anticipates because it supposedly "tell[s] skilled artisans ***everything they need to know in order to arrive***

***at*** the ***claimed 1:1 sitagliptin DHP compound***." Mylan.Br.25 (emphasis added). That falls short of the "at once envisage" requirement for anticipation.

Using hindsight, Mylan improperly focuses on whether skilled artisans could envisage ***1:1 sitagliptin DHP***. *See* Mylan.Br.24-33; Mylan.Br.36. But Mylan elsewhere concedes that skilled artisans must be able to "'at once envisage ***each member***'" of the class the reference discloses. Mylan.Br.19 (quoting *Petering*, 301 F.2d at 681) (emphasis added); *see also Wasica*, 853 F.3d at 1285; *AbbVie*, 764 F.3d at 1379; *ArcelorMittal France v. AK Steel Corp.*, 700 F.3d 1314, 1323 (Fed. Cir. 2012); *Impax*, 468 F.3d at 1383. ***Only then*** is disclosure of a genus tantamount to disclosure of each member. *See* pp. 33-34, *supra*. Mylan uses hindsight to focus on one singled-out species, while ignoring whether skilled artisans would "at once envisage" every member of the genus.

Even with respect to 1:1 sitagliptin DHP, Mylan's argument is ***not*** that skilled artisans would "at once envisage" that salt. *Impax*, 468 F.3d at 1383. Mylan argues that WO '498 "tell[s] skilled artisans everything they need to know" to eventually "arrive at" it. Mylan.Br.25. That would require selectively piecing together disparate disclosures in WO '498 and combining them with general knowledge of chemistry. Mylan asserts that skilled artisans would pluck sitagliptin from the "33 example compounds" in WO '498's claim 15 (Appx421-427), and choose phosphoric acid from its list of eight "particularly preferred" acids (Appx377), to conceive of a

"sitagliptin DHP salt generally." Mylan.Br.25-26. And "once the skilled artisan" makes that selection, Mylan contends, she would ***then*** "inquire about the salt's stoichiometry." Mylan.Br.29. Mylan claims skilled artisans would ***then*** look to example 7, which disclosed a "different" 1:1 sitagliptin ***hydrochloric acid*** salt, and find "no scientific reason to doubt that phosphoric acid would likewise exist in a 1:1 stoichiometry." *Id.*

This Court has rejected such efforts to expand the "at once envisage" standard. In *Ruschig*, the Court explained that the "at once envisage" doctrine recognized in *Petering* was not

> intend[ed] . . . to become a precedent for the mechanistic dissection and recombination of the components of the specific illustrative compounds in every chemical reference containing them, to create hindsight anticipations . . . on the theory that such reconstructed disclosures describe specific compounds within the meaning of section 102.

343 F.2d at 974. Mylan's theory does what *Ruschig* prohibits: It seeks to "dissect[ ] and recombin[e]" various "illustrative" lists of DP-IV inhibitors and acids in WO '498 "to create hindsight anticipations" of 1:1 sitagliptin DHP.

Mylan's theory also requires ***inferring*** limitations found nowhere in WO '498. Mylan spends pages arguing that skilled artisans might ***deduce*** that a ***1:1*** sitagliptin ***phosphate*** salt could exist from example 7's disclosure of a ***1:1*** sitagliptin ***hydrochloride*** salt. Mylan.Br.29-33. But the question is not whether the reference gives skilled artisans "everything" they "would need" to somehow envisage a limi-

tation that is not disclosed. Mylan.Br.33. This Court's envisaging precedent "does not stand for the proposition that a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would 'at once envisage' the missing limitation." *Nidec*, 851 F.3d at 1274; *Galderma Lab'ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 845 (Fed. Cir. 2020). "To anticipate, a reference must do more than 'suggest' the claimed subject matter"—it must actually "disclose" it. *Eli Lilly & Co. v. Los Angeles Biomedical Rsch. Inst.*, 849 F.3d 1073, 1076 (Fed. Cir. 2017).

As the Board explained, such prohibited "gap-filling is precisely what [Mylan] attempts to do." Appx30. WO '498 contains no teaching regarding the stoichiometry of a sitagliptin phosphate salt. Mylan improperly seeks to fill the gap by arguing that skilled artisans could reason their way to "envisage a 1:1 stoichiometry." Mylan.Br.29; *see* pp. 45-46, *infra*. Because Mylan's argument defies the express limits of the "at once envisage" theory, it fails.

2. *Mylan Fails To Prove WO '498 Discloses Any Sitagliptin Phosphate Salt Generally*

Even on its own terms, Mylan's "envisage" theory fails. Mylan asks this Court to find, at the first step of its argument, that WO '498 "disclose[s] the sitagliptin DHP salt generally." Mylan.Br.26. But the Board found—based in part on Mylan's expert's "conce[ssion]"—that "[n]o phosphate salts of sitagliptin . . . are shown in WO '498." Appx27. Mylan states that "[t]he fact that sitagliptin and

phosphoric acid are not explicitly illustrated in combination is of no legal significance." Mylan.Br.26. But that plainly has "legal significance"—the ***legal standard*** for anticipation generally requires that a reference "not only disclose all elements of the claim," but "also disclose those elements 'arranged as in the claim.'" *Net MoneyIN*, 545 F.3d at 1369.

Mylan deems it "more than enough" that WO '498 discloses sitagliptin as one of 33 example compounds in claim 15, and phosphoric acid as one of eight preferred acids 44 pages earlier. Mylan.Br.26. But it cites no evidence suggesting skilled artisans would understand ***that*** as disclosing sitagliptin DHP—particularly where salt-formation is unpredictable. Appx2355-2356(116:6-117:3); Appx2038; Appx2603. Mylan declares, without citation, that WO '498 "instruct[s] the skilled artisan to combine those lists to create the 'pharmaceutically acceptable salts.'" Mylan.Br.26. But Dr. Chorghade conceded that WO '498 does not direct skilled artisans to sitagliptin, in particular, from among the 33 DP-IV inhibitors on the list. Appx2342(61:7-62:9), Appx2373-2374(188:6-189:8). Nor does WO '498 single out phosphoric acid—it discloses no phosphate salt of ***any*** DP-IV inhibitor. Appx27; Appx2629-2631(¶¶72-74); Appx2633-2638(¶¶79-85). Mylan's argument improperly recombines "components of the specific illustrative compounds [of WO '498] with hindsight." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006). The Board properly rejected Mylan's arguments. *See*

Appx27. Mylan nowhere tries to show the Board's findings unsupported by substantial evidence.

Mylan urges that this Court "routinely finds similar disclosures sufficient for anticipation." Mylan.Br.27. But Mylan's authorities—*Wrigley* and *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331 (Fed. Cir. 2016), Mylan.Br.27-28—are nothing like this case. There was no evidence skilled artisans would doubt that the elements disclosed in the references—chewing gum ingredients in *Wrigley*, 683 F.3d at 1360, software features in *Blue Calypso*, 815 F.3d at 1344—could be combined. Here, by contrast, a sitagliptin phosphate salt is not "something that you get just by mixing a little" sitagliptin with "a little" phosphoric acid. *Shire LLC v. Amneal Pharm., LLC*, No. 11 Civ. 3781 (SRC), 2014 WL 2861430, at *15 (D.N.J. June 23, 2014), *aff'd in part, rev'd in part*, 802 F.3d 1301 (Fed. Cir. 2015). It is undisputed that salt formation is unpredictable. *See* p. 19, *supra*. The Board thus credited Merck's evidence that the "hypothetical" possibility of combining the various DP-IV inhibitors with the various acids did not mean skilled artisans would "understand[] from the disclosure that a particular salt would exist or could be made." Appx32. Mylan's assertion that its case is "stronger" than *Wrigley* and *Blue Calypso* because it involves chemical reactions, Mylan.Br.28, is backwards.

Nor was the size of the genus in *Wrigley* and *Blue Calypso* comparable. The reference in *Wrigley* identified three "'particularly preferred cooling agents'" and

twenty-three "flavoring agents," for a total of sixty-nine combinations. 683 F.3d at 1360. *Blue Calypso* involved a software reference disclosing only a "limited number of tools," from which skilled artisans could envisage combining a "direct e-mail" advertising campaign with a "refer-a-friend campaign." 815 F.3d at 1344. By contrast, the Board here found a genus of at least 957 hypothetical salts, many of which would not exist. Appx29. This Court routinely finds much smaller numbers too large for skilled artisans to envisage each combination. *See Ruschig*, 343 F.2d at 974-75 (skilled artisans would not "at once envisage" "four undisclosed specific compounds out of a possible 259"); *Impax*, 545 F.3d at 1383 (skilled artisans would not "at once envisage" species in formula encompassing "hundreds of . . . compounds"). And Mylan's ***own expert*** failed to envisage many of them. *See* p. 21, *supra*.

Finally, *Wrigley* and *Blue Calypso* ***affirmed*** findings of anticipation. *Wrigley*, 683 F.3d at 1362; *Blue Calypso*, 815 F.3d at 1344. Under the substantial-evidence standard, affirmance does not foreclose the possibility that "two different conclusions" may have been supported "based on the evidence of record." *Bayer*, 488 F.3d at 970. Here, the Board found no anticipation, deeming Mylan's evidence to be "weak." Appx31. It is Mylan's burden to prove that no reasonable factfinder could have so found. *Bayer*, 488 F.3d at 970. Mylan does not even try to make that showing. *Wrigley* and *Blue Calypso* cannot save it.

### 3. *Skilled Artisans Would Not "At Once Envisage" a Sitagliptin Phosphate Salt with a 1:1 Stoichiometry*

The Board rejected Mylan's attempt to supply the 1:1 stoichiometry limitation of the claimed sitagliptin DHP salt—missing from WO '498—by arguing "inherency." Appx35-41; *see* pp. 21-22, *supra*. Mylan now abandons those arguments. But it attempts to achieve the same result by arguing that, after skilled artisans envisage the concept of a sitagliptin DHP salt—which they would not, pp. 41-44, *supra*—they would "inquire about the salt's stoichiometry," and then "envisage a 1:1 stoichiometry" "[b]ased upon the teachings of the prior art." Mylan.Br.29. That theory was "not raised before the Board," and so "is waived on appeal." *Microsoft*, 878 F.3d at 1075. It also defies the limits of the "at once envisage" doctrine, which requires artisans to at once see the entire class and excludes efforts to imagine undisclosed elements. *See* pp. 33-34, *supra*.

The argument fails regardless. WO '498 never discusses stoichiometry as such. *See* Appx367-432. Mylan argues that WO '498's example 7 discloses "a sitagliptin salt using ***hydrochloric acid*** . . . that ***has*** a 1:1 stoichiometry." Mylan.Br.29 (emphasis added). From there, Mylan contends the 1:1 limitation in sitagliptin DHP claims is anticipated because "there is ***no scientific reason to doubt*** that ***phosphoric acid*** would likewise exist in a 1:1 stoichiometry." *Id.* Mylan contends that "Merck does not dispute this point." *Id.* But Merck disputed ***exactly*** that point. Merck's expert Dr. Matzger testified—and the Board "credit[ed]"—"that a

POSA would ***not*** simply conclude that whatever applies for hydrochloric acid and sitagliptin also applies to . . . phosphoric acid." Appx28. And Dr. Matzger "unequivocal[ly] and repeated[ly]" testified that, particularly given the field's unpredictability, "a POSA would ***not*** . . . at once envisage . . . the claimed 1:1 DHP salt"—which the Board also credited. Appx32-33 (emphasis added); *see* Appx2641-2646(¶¶91-98). The Board further found that skilled artisans would not understand example 7's disclosure of a 1:1 hydrochloride salt to effectively disclose a 1:1 phosphate salt because "hydrochloric acid has only one proton to donate, whereas phosphoric acid has three," allowing for non-1:1 stoichiometries. *Id.* Mylan cannot prevail by making up a new scientific argument that defies the Board's findings, nor by calling undisputed an issue that Merck directly disputed.

Mylan argues that Dr. Matzger's testimony merely shows that "***other***" stoichiometries were possible, and that he "does not (and cannot) dispute that a skilled artisan would imagine" 1:1 sitagliptin DHP. Mylan.Br.29-30 & n.5. The Board directly addressed the testimony Mylan cites and found that Dr. Matzger's testimony, "in its more complete context, tells a different story." Appx31-32. Dr. Matzger explained that, while skilled artisans could "imagine" that 1:1 sitagliptin DHP ***might*** exist by "exchang[ing] the counterion in their mind," that mental exercise is "different than understanding what could be produced, what would be possible to make." Appx32 (quoting Appx8489-8490(146:21-147:9)). And Dr. Matzger em-

phatically testified that skilled artisans would not envisage 1:1 sitagliptin DHP, specifically, based on WO '498. Appx32-33.

Mylan argues that, because "Example 7 shows a 1:1 salt in the presence of a substantial excess of hydrochloric acid, which is a stronger acid than phosphoric acid . . . it is highly likely that the same result would be obtained with phosphoric acid under similar conditions." Mylan.Br.30. That at best is an obviousness argument, ***not*** anticipation under an "at once envisage" theory. In terms of what WO '498 ***actually*** discloses, the Board found that skilled artisans would not understand example 7's process for making a 1:1 hydrochloride salt to disclose a 1:1 phosphate salt. Appx27-28. It credited Dr. Matzger's testimony that "'[s]ince HCL is monoprotic, the 1:1 stoichiometry of Example 7 is irrelevant to the question whether a polyprotic acid [like phosphoric acid] could form non-1:1 salts with sitagliptin.'" Appx28 (quoting Appx2658 n.39).

Mylan contends that experiments by Dr. Chyall show "that a 1:1 sitagliptin DHP preparation is the ***only*** stoichiometry that forms under conditions similar to those described in WO '498." Mylan.Br.30. The Board found that Dr. Chyall's experiments were ***not*** similar to WO '498's example 7. There was no evidence he was trying to reproduce example 7, and his process involved "at least half-a-dozen" differences from example 7, Appx38—including that he used ***phosphoric*** acid, where example 7 "is ***explicitly*** a process for preparing a ***hydrocholoride*** salt,"

Appx37 (second emphasis added). As the Board explained, an argument that skilled artisans might draw ***inferences*** from a different experiment, with a different acid, is not ***anticipation***. *Id.* (citing *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)).

Mylan accuses the Board of "fundamental[ly] misapprehend[ing]" Mylan's arguments. Mylan.Br.38. Mylan insists "it simply argued that Example 7 would ***help*** a skilled artisan envision a 1:1 phosphate salt." Mylan.Br.37. In fact, Mylan argued below that example 7 ***inherently*** yielded 1:1 sitagliptin DHP. *See* Appx207-209 n.8 (Petition for Inter Partes Review); Appx7832-7835 (Petitioner's Reply). Mylan's new help-a-skilled-artisan-envision theory is unpreserved. But the theory is unsupported regardless. Mylan variously states that: "the skilled artisan could easily envisage a 1:1 sitagliptin DHP"; "it would be the first thing a skilled artisan would envision"; "the 1:1 stoichiometry" is "among the limited class of stoichiometries that the skilled artisan would envisage"; "a skilled artisan would envisage the 1:1 stoichiometry first"; and, "[e]ven if other more remote stoichiometries were possible, a skilled artisan would still start by envisioning the 1:1 stoichiometry." Mylan.Br.29-32, 40. ***Not one*** of those assertions is followed by citation to evidence. The Board found that Mylan's own expert, Dr. Chorghade, "does not opine that a POSA would 'at once envisage' the 1:1 sitagliptin DHP salt." Appx31. And it credited Merck's evidence "that a POSA would not and could not at once envisage

. . . the claimed 1:1 DHP salt." Appx32-33. Substantial evidence thus supports the Board's finding that Mylan failed to establish that skilled artisans would envisage 1:1 sitagliptin DHP, much less "each member" of at least 957 theoretical salts, as would be required for WO '498 to anticipate. *Wasica*, 853 F.3d at 1285.

## II. THE BOARD PROPERLY REJECTED MYLAN'S OBVIOUSNESS ARGUMENTS BECAUSE THE '708 PATENT ANTEDATES WO '498 (ALL CLAIMS BUT 3 AND 4)

Mylan challenged the '708 patent's claims as obvious over WO '498. The "parties agree[d]," however, "that if the '708 Patent antedates WO '498, the latter cannot be considered in an obviousness analysis." Mylan.Br.41 n.11. A party can antedate a prior-art reference for purposes of pre-AIA § 102(a) by "showing that the invention" was "reduc[ed] to practice" "before the effective date of the reference." *In re Steed*, 802 F.3d 1311, 1320 (Fed. Cir. 2015).[4]

The parties agree that, to show antedation here, Merck must show that it reduced to practice "so much of the claimed invention as the reference"—WO '498—"happens to show." *In re Clarke*, 356 F.2d 987, 991 (C.C.P.A. 1966). It is undisputed that Merck reduced claims 1-2, 17, 19, and 21-23 of the '708 patent—1:1

[4] WO '498 could still be §102(e) prior art. Under pre-AIA §103(c)(1), however, a §102(e) reference cannot be used for obviousness if its "subject matter and the claimed invention were," at the relevant time, "owned by the same person or subject to an obligation of assignment to the same person." 35 U.S.C. §103(c)(1) (2000). Here, "[t]he parties agree that the '708 Patent and WO '498 were commonly owned by Merck." Mylan.Br.41 n.11.

sitagliptin DHP—to practice ***before*** WO '498 published in January 2003. Appx45. The Board thus found that "Merck reduced to practice at least as much (indeed, more) of the claimed subject matter versus what is shown in WO '498." Appx52. WO '498 was therefore "excluded from consideration." *Id.* Without it, Mylan's obviousness challenge "fail[s]." *Id.*

Mylan raises only the "relatively discrete counterargument" that WO '498 discloses the crystalline monohydrate recited in claim 4 of the '708 patent, and that Merck did not reduce that to practice before WO '498 published. Appx45-46; Mylan.Br.42. If Mylan truly thought WO '498 disclosed a crystalline monohydrate, it would have challenged claim 4 as anticipated by WO '498. Its failure to do so speaks volumes. Regardless, the Board found, based on extensive evidence, that WO '498 neither discloses, nor enables, a hydrate of 1:1 sitagliptin DHP. Appx47-52.

Standard of Review: The Board's "findings as to the scope and content of prior art" are "factual determinations" reviewed for "substantial evidence." *Cochlear Bone Anchored Sols. AB v. Oticon Med. AB*, 958 F.3d 1348, 1354 (Fed. Cir. 2020).

### A. Overwhelming Evidence Supports the Board's Finding That WO '498 Does Not Disclose a Monohydrate of 1:1 Sitagliptin DHP

1. The Board found that, apart from whether WO '498 disclosed "1:1 sitagliptin DHP, there is no ***hydrate*** of that salt"—and thus no crystalline mono-

hydrate as recited in claim 4 of the '708 patent—"anywhere in the reference." Appx48. Substantial evidence supports that finding. In 65 pages, WO '498 mentions hydrates once: "Salts in the solid form ***may*** exist in more than one crystal structure, and ***may*** also be in the form of hydrates." Appx48 (emphasis added) (quoting Appx376(32-34)). That statement is not specific to 1:1 sitagliptin DHP or any of the "millions" of salts WO '498 theoretically encompasses. Appx48-49; Appx2630-2633(¶¶73, 77). And WO '498 does not contain a single example of a hydrate, Appx48; Appx2376(197:22-198:13), or mention the word "monohydrate."

Merck's expert, Dr. Myerson, testified that skilled artisans would not have understood WO '498's solitary reference to the possibility of hydrates as disclosing that "every one of the disclosed or exemplified compounds . . . can exist as a hydrate," or that 1:1 sitagliptin DHP would. Appx2492-2493(¶150). Skilled artisans would understand the statement to reflect the "general knowledge" that "for any given salt, a hydrate ***may*** exist, not that a hydrate ***does*** exist." Appx2492-2493(¶150). The Board credited that testimony. Appx48-49. And the Board rejected Dr. Chorghade's contrary testimony as "conclusory." Appx48. It did "not hold up to scrutiny" because, among other reasons, Dr. Chorghade conceded he could not predict hydrate formation "with ***any degree*** of certainty." Appx48-49 (quoting Appx2391(257:18-258:11)). The Board cited "literature of record" confirming that

whether any salt "is even capable of forming as a hydrate is highly unpredictable." Appx49-50.

2. Mylan declares the Board's "conclu[sions]" "[i]ncorrect." Mylan.Br. 46. But Mylan does not address ***any*** of the evidence the Board cited. *See* Mylan.Br.47-49. Because the Board's decision is supported by substantial evidence, it must be upheld—even if another factfinder could reach a different result. *Bayer*, 488 F.3d at 970.

Mylan's arguments are not persuasive regardless. Mylan contends that WO '498 discloses hydrates of 1:1 sitagliptin DHP because the ***claims*** to sitagliptin and "pharmaceutically acceptable salts" are broad enough to cover them. Mylan.Br.43-44. That is backwards: When determining what a claim "teach[es]," the analysis is "confined to what it discloses rather than to what it covers." *Bocciarelli v. Huffman*, 232 F.2d 647, 651 (C.C.P.A. 1956). A reference is not interpreted to disclose everything the claims encompass. *E.g.*, *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014). Mylan would interpret WO '498 to disclose millions of hydrates, most of which do not exist. *See* pp. 19-20, *supra*.[5]

[5] Mylan asserts that the "Orange Book" lists the '871 patent (among others) as covering Januvia and Janumet, drugs that contain 1:1 sitagliptin DHP monohydrate. Mylan.Br.49. The Board rejected that argument, finding that the Orange Book listing did not change WO '498's or the '871 patent's disclosures. Appx30-31 n.20. Moreover, the '871 patent indisputably covers sitagliptin, which Januvia and Janumet contain.

Mylan invokes WO '498's statement that salts, such as hydrates, "may exist," Appx376(9:32-34), asserting that the statement does not "express uncertainty as to whether hydrate forms exist but rather . . . define[s] the term 'pharmaceutically acceptable salts' to ***include*** hydrates," Mylan.Br.46. But the Board credited expert testimony that skilled artisans would not share Mylan's tortured reading. Appx48-49; pp. 23-24, *supra*. While Mylan contends precedent "is replete with examples of patentees using the word 'may' to define a claim term," each example it provides uses the phrase "may ***include***," not "may ***exist***." Mylan.Br.46-47. Regardless, even if the claim term "pharmaceutically acceptable salts" were defined to encompass hydrates, that is not equivalent to ***disclosing*** the ***particular monohydrate*** of 1:1 sitagliptin DHP. *Bocciarelli*, 232 F.2d at 651.

### B. Substantial Evidence Supports the Board's Finding That WO '498 Does Not Enable a Monohydrate of 1:1 Sitagliptin DHP

Even if WO '498 had ***described*** the monohydrate, that would not suffice. "[A] prior art reference must be enabling." *Impax*, 468 F.3d at 1381. The Board's finding that WO '498 does not enable a 1:1 sitagliptin DHP monohydrate is amply supported by the evidence. Appx49.[6]

[6] The Board did not address whether non-enablement of the monohydrate form affected the '871 patent's validity, properly deeming that irrelevant to "this proceeding." Appx30-31 n.20. Regardless, the '871 patent was not required to enable unrecited, after-arising embodiments, like 1:1 sitagliptin DHP monohydrate, which

Mylan presented ***no evidence*** of enablement. It merely "suggest[ed], in a footnote, that WO '498 is presumptively enabling for the hydrated forms of the various salts." Appx49. Mylan now accuses the Board of "ignoring this presumption." Mylan.Br.48. However, as Mylan later concedes, Mylan.Br.49-50, the Board specifically addressed the presumption of enablement, explaining that, "[e]ven if ***that presumption*** were appropriate here, we would ***find it overcome***," Appx49 (emphasis added). Mylan says the Board "failed to point to persuasive evidence" of non-enablement. Mylan.Br.50. But the Board's finding was "based on ***a complete absence of examples or guidance*** in WO '498 about making such hydrates, and the substantial unpredictability concerning whether a hydrate of any specific salt will even form." Appx49 (emphasis added). That evidence is surely persuasive when considering whether the reference's "disclosure[s]" are sufficient to "enable[ ] a person of ordinary skill in the art to carry out the invention." *Impax*, 468 F.3d at 1384.

Mylan's assertions that Merck "did not even try to" overcome the presumption of enablement, Mylan.Br.49, and that the "Board failed to show that a skilled artisan would not be able to produce hydrates with 'routine experimentation,'" Mylan.Br.50, are equally mistaken. The Board spent three pages discussing Merck's evidence of non-enablement. Appx49-51. Merck presented extensive proof that

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belong to "a later existing state of the art." *In re Hogan*, 559 F.2d 595, 606 (C.C.P.A. 1977).

skilled artisans would not have been able to make the monohydrate without undue experimentation—including Merck's own failed efforts. Citing the testimony of the '708 patent's inventors, the Board found that Merck spent "'over a year of development on the 1:1 DHP salt,'" conducting "'extensive experiments,'" and only "'unexpected[ly]'" discovered "the hydrated form" when attempting to scale production of anhydrous forms. Appx51 (quoting Appx3145-3146). The Board credited Dr. Myerson's testimony that the "isoamyl alcohol/water . . . solvent system" that eventually produced the monohydrate was not "'reported in the art,'" and that "a 'POSA would not have arrived at the particular experimental conditions necessary . . . absent undue experimentation.'" Appx51 (quoting Appx2460). Mylan does not even try to show that no "reasonable mind might accept" that evidence "as adequate to support a conclusion" of non-enablement. *Chudik*, 851 F.3d at 1371 (quotation marks omitted).

The Board likewise found that Merck "explain[ed] persuasively," through expert testimony and "literature of record," that skilled artisans "would not have known or predicted whether particular salts, especially the 1:1 sitagliptin DHP, could ***crystallize*** at all, form a ***hydrate***, or form a ***monohydrate***." Appx49-50 (emphasis added). Mylan errs in asserting that any focus on "'unpredictability'" was "a question of obviousness," not "disclos[ure]." Mylan.Br.51. "[P]redictability" is a factor

in assessing enablement, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), required here, *Impax*, 468 F.3d at 1381.

## III. SUBSTANTIAL EVIDENCE SUPPORTS THE BOARD'S FINDINGS THAT CLAIMS 3 AND 4 WERE NOT OBVIOUS

The Board properly rejected Mylan's obviousness challenges to claim 3 (Appx54-58) and claim 4 (Appx58-69) on multiple grounds.

Standard of Review. While obviousness is reviewed de novo as a "question of law," the Board's "underlying factual determinations"—including motivation to combine and reasonable expectation of success—are reviewed for substantial evidence. *Facebook, Inc. v. Windy City Innovations, LLC*, 973 F.3d 1321, 1339 (Fed. Cir. 2020); *see Cochlear*, 958 F.3d at 1354.

### A. No Combination of Prior Art Rendered Claim 3 Obvious

Claim 3 recites 1:1 sitagliptin DHP, but in the (S)-configuration. Appx91-92(15:6-18:39). To prove claim 3 obvious, Mylan needed to show that skilled artisans "would have been motivated to combine or modify" prior art to produce that invention, and that skilled artisans would "have had a reasonable expectation of success in doing so." *Endo Pharms. Inc. v. Actavis LLC*, 922 F.3d 1365, 1373 (Fed. Cir. 2019). It showed neither.

No Motivation To Make Sitagliptin DHP. The Board found that Mylan failed to show skilled artisans would be motivated to combine sitagliptin and phosphoric acid to create 1:1 sitagliptin DHP, even apart from the (S)-configuration. That

threshold failure independently dooms Mylan's obviousness challenge to claim 3—and claims 1-2, 17, 19, and 21-23, apart from WO '498's exclusion as a reference. *See* pp. 49-55, *supra*.

Mylan's expert "conceded" that "[n]o phosphate salts of sitagliptin, or any of the other thirty-two exemplary DP-IV inhibitors, are shown in WO '498, nor are there any details given about making them." Appx27. While WO '498's example 7 discloses a sitagliptin ***hydrochloride*** salt, Appx2735-2738(¶¶214-218), the Board found "numerous reasons why a POSA would not have made all the choices that would be needed to arrive at" a ***phosphate*** salt, Appx56. Dr. Chorghade conceded that "nothing" in WO '498 "suggests there is a problem with the hydrochloride salt of sitagliptin." *Id.* (citing Appx2375(193:11-194:6)). And "literature" in the art showed "phosphates were known to" have drawbacks, including "reduce[d] solubility and stability versus hydrochloride salts." *Id.* (citing Appx2743-2745(¶¶227-229)).

Substantial evidence supports the Board's determination that Bastin—a reference having nothing to do with sitagliptin—did not provide motivation either. Bastin confirmed that "hydrochloride salts have often been the first choice for weakly basic drugs." Appx496. While Bastin acknowledged that hydrochloride salts "may" have "potential disadvantages," and listed "phosphate" as one of numerous other acids that "could be considered," *id.*, that would not have motivated skilled

artisans to make a sitagliptin phosphate salt. Over 42% of pharmaceutical salts are hydrocholoride salts, while only 3.16% are phosphate salts. Appx5451. If mere "potential disadvantages" sufficed to teach away from hydrochloric acid, as Mylan argues, then skilled artisans would not turn to phosphoric acid, which has its own disadvantages. Appx55-56; *Bayer*, 488 F.3d at 970. Nor did the "combination of WO '498 and Bastin" satisfy the 1:1 stoichiometry limitation. Appx55. Mylan had not argued otherwise, instead relying on its disproved inherency argument. Appx55-56.

Mylan argues that references to possible use of phosphoric acid in pharmaceutical salts generally provided motivation to combine. Mylan.Br.52-53. But it fails to acknowledge that the Board rejected those same arguments. Appx55-56. And Mylan makes no effort to show the Board's findings are unsupported by substantial evidence. Insofar as Mylan argues that the 1:1 sitagliptin DHP limitations are obvious because WO '498 "anticipates" them, Mylan.Br.53, that reprises Mylan's failed anticipation arguments, *see* pp. 31-49, *supra*.

No Motivation To Make the (S)-Configuration. The Board found that, even "assuming" one overlooked Mylan's failure on 1:1 sitagliptin DHP, "that still would not produce the claimed subject matter," because it would not account for claim 3's "(S)-enantiomer" limitation. Appx56-57. WO '498 disclosed sitagliptin only in the (R)-configuration. *Id.* Because Mylan offered "no expected or even theoretical

benefit to making" the (S)-configuration, the Board found Mylan failed to establish motivation. Appx58; Appx2762(¶255); Appx2370-2371(176:18-177:7).

Mylan urges that, because WO '498 discloses that the "compounds of the instant invention have one asymmetric center at the beta carbon atom," and thus will "produce two optical isomers," any skilled artisan with "a basic knowledge of organic chemistry . . . could envision" both the (R)- and (S)-configurations. Mylan.Br. 53-54 (quoting Appx375(8:21-27)). Mylan urges that establishes "anticipation," rendering motivation to combine not "pertinent." Mylan.Br.54-55. That reasoning is prohibited: WO '498 does not actually disclose 1:1 sitagliptin DHP in the (S)-configuration, and Mylan cannot rely on the "'at once envisage'" doctrine to supply that "missing limitation." *Nidec*, 851 F.3d at 1274-75; pp. 40-41, *supra*. And Mylan's "at once envisage" theory fails regardless. *See* pp. 31-49, *supra*.

Mylan speculates that, because WO '498 discloses that enantiomers may exist, that "would suggest to a skilled artisan that these configurations could have different benefits." Mylan.Br.55. But WO '498 discloses no such benefits. Mylan's expert identified no reason skilled artisans would make the (S)-configuration. Appx57. The Board's conclusion that WO '498 fails to provide a motivation to make 1:1 (S)-sitagliptin DHP is amply supported. Appx58.

No Reasonable Expectation of Success. Finally, extensive evidence shows "that forming such salts is highly unpredictable." Appx58. "'No predictive proce-

dure'" for any particular salt had been "'reported in the literature,'" and Dr. Chorghade conceded it was a "'trial and error process.'" *Id.* (quoting Appx2038, Appx2355-2356(116:6-117:3)). The Board thus found that skilled artisans would not have had "a motivation to make, with reasonable expectation of success, 1:1 (S)-sitagliptin DHP." *Id.*

Mylan errs in arguing that *Pfizer v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007), renders unpredictability "factually and legally inadequate." Mylan.Br.56. Here, the Board's decision did not turn on unpredictability alone. Mylan bore the burden of proving obviousness. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). The Board identified myriad reasons Mylan failed that burden, any one of which suffices to support the Board's conclusion that Mylan "has not shown . . . that claim 3 would have been obvious," Appx58.

Regardless, Mylan over-reads *Pfizer*. That decision was limited to its "***particularized facts***," 480 F.3d at 1367 (emphasis original)—none present here. *Pfizer* was "not [a] case where the prior art teaches merely" about the "'general approach'" to salt-making. *Id.* at 1366. Pfizer had identified a problem with one salt "[e]arly in development," and created a "list of seven alternative anions" that could potentially resolve it. *Id.* at 1362-64. "[N]umerous other publications" "heavily suggest[ed]" that the anion Pfizer used (benzene sulphonate) would resolve the problem, which Pfizer confirmed with "routine testing." *Id.* at 1367-68. Here, by contrast, nothing

suggested a 1:1 (S)-configuration sitagliptin DHP salt could be made, or provided a reason to make it. Appx56; Appx2375(193:11-194:6); Appx2743-2745(¶¶227-229). This Court has distinguished *Pfizer* for similar reasons. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1089 (Fed. Cir. 2008).

### B. No Combination of Prior Art Rendered Claim 4 Obvious

Claim 4 recites a "crystalline monohydrate" of 1:1 sitagliptin DHP. Appx91(16:47-48). The Board found, however, that claim 4's crystalline monohydrate was not enabled by the prior art. *See* pp. 26-28, *supra*. That independently dooms Mylan's obviousness challenge. *See Raytheon Techs. Corp. v. Gen. Elec. Co.*, 993 F.3d 1374, 1381 (Fed. Cir. 2021). Regardless, ample evidence supports the Board's findings that skilled artisans would not have been motivated to develop a hydrate of any sort, Appx61-63; that they would not have expected success in doing so, Appx63-66; and that secondary considerations confirmed the crystalline monohydrate's non-obviousness, Appx67-69.

No Motivation To Combine. The Board found that Mylan "fail[ed] to provide a persuasive motivation for making the crystalline monohydrate of claim 4." Appx63. Mylan's petition "provide[d] no rationale." Appx61. Its expert, Dr. Chorghade, "offered no motivation (persuasive or otherwise) in his declaration and admitted that he gave no opinion on why a POSA would have preferred a hydrate of

sitagliptin." *Id.* And when "asked at the oral hearing to identify" a reason to make the monohydrate, Mylan "was unable to do so." Appx62.

Merck, by contrast, provided "undisputed evidence" that skilled artisans would have avoided hydrates because of problems such as lower solubility and physical instability. Appx62; *see, e.g.*, Appx4870-4878 ("rate of degradation was 4-fold higher" for "hemihydrate"); Appx4879-4882 ("anhydrous form . . . significantly more water soluble than the trihydrate"); Appx4883-4892 ("solubilities of both anhydrates . . . 1.5-1.6 times that of the dihydrate"). Brittain—Mylan's own obviousness reference—cites "lower solubility" among many "problems" hydrates pose for the "development process." Appx440-441. Dr. Myerson "testifie[d] persuasively" that those problems would have dissuaded skilled artisans from pursuing a hydrate of 1:1 sitagliptin DHP, notwithstanding WO '498's "vague disclosure" that "crystalline forms" of unspecified salts might exist. Appx63; Appx2477-2486(¶¶127-138).

Mylan ignores the Board's findings on motivation to combine and the evidence supporting them. *See* Mylan.Br.59. All Mylan can say is that skilled artisans would have been "motivated to explore hydrate[s]" because, 30 years ago, Brittain described them as the "object of increasing attention." *Id.* That hardly renders the Board's contrary factual findings unsupported. *Bayer*, 488 F.3d at 970.

No Reasonable Expectation of Success. Regardless, Mylan failed to prove skilled artisans would have had "a reasonable expectation of success" in making the crystalline monohydrate. Appx63-66. Undisputed evidence showed that hydrate formation is "highly unpredictable." Appx63; Appx2488-2492 (¶¶146-149). It was "not possible to predict with any reasonable level of confidence the crystal structure of an organic material, much less the existence of polymorphism." Appx2283-2293; *see* Appx2256-2266 ("[I]t is not yet possible to predict when materials will crystallize."); Appx2324 n.2 ("It is well known . . . that it is often difficult to crystallize a newly synthesized compound."). Dr. Chorghade conceded that skilled artisans cannot predict hydrate formation with "any degree of certainty." Appx2391 (257:18-258:11).

Mylan argues that skilled artisans "would have expected to succeed," Mylan.Br.58, based on WO '498's general statement that hydrates of salts "'***may*** exist," Appx377 (9:32-34) (emphasis added). But the Board found Dr. Chorghade's "conclusory opinion" on that point "unpersuasive" given extensive contrary "evidence." Appx64. Mylan now makes the equally conclusory argument that skilled artisans "would expect to succeed" "[b]ecause WO '498 is presumptively enabled." Mylan.Br.58. As explained above (at 53-55), however, the Board found any such presumption "overcome" by actual evidence. Appx49.

Mylan does no better by invoking (at 58) Brittain's teaching that "approximately one-third of the pharmaceutical actives are capable of forming crystalline hydrates," and half of those are monohydrates, Appx59 (quoting Appx441). The Board squarely rejected that "probability-based argument." Appx64. Brittain's disclosure—that "only about ***one-sixth***" of studied active compounds "could form a monohydrate"—demonstrates the "probability" of success was "low." Appx65. Mylan ignores that finding. This Court has affirmed findings that skilled artisans lack a reasonable expectation of success based on probabilities of "30 to 35%," double what Mylan posited. *Grunenthal GmbH v. Alkem Lab'ys Ltd.*, 919 F.3d 1333, 1341-44 (Fed. Cir. 2019).

Objective Indicia of Non-Obviousness. The Board found that the "unexpected properties" of claim 4's crystalline monohydrate "further . . . undermine" Mylan's obviousness challenge. Appx67. Mylan calls that an "afterthought that was not critical to the Board's ruling." Mylan.Br.59. The fact that Mylan's challenge failed twice over before the Board reached that issue hardly renders it an "afterthought." The Board would have to address objective indicia of non-obviousness before finding obviousness. *See Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012). Those "objective criteria help inoculate the obviousness analysis against hindsight." *Id.* at 1378.

Claim 4's crystalline monohydrate undisputedly exhibited unexpected qualities, improving upon WO '498's prior-art compounds, including example 7's sitagliptin hydrochloride salt. Appx67. The Board committed no error in comparing the monohydrate to that compound rather than 1:1 sitagliptin DHP. *Id.* The "only" sitagliptin salt "actually identified in WO '498 is the sitagliptin hydrochloride of Example 7." *Id.* "'Unexpected results,'" it explained, "'are shown in comparison to what was known, not what was unknown.'" Appx68 (quoting *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017)). In response, Mylan reprises its unpersuasive argument that WO '498 "disclose[d] sitagliptin phosphate salt." Mylan.Br.61; *see* pp. 31-49, *supra*.

Regardless, the Board found that, "even assuming a 1:1 sitagliptin DHP salt was identified in WO '498," Merck proved that the crystalline monohydrate "unexpectedly" overcame problems with the anhydrous salt's "undesirable form conversion." Appx68. The Board thus made the very comparison Mylan demands on appeal. That finding is entitled to "proper deference," and this Court will not "reweigh" the evidence. *Microsoft*, 878 F.3d at 1073.

## CONCLUSION

The Board's decision should be affirmed.

January 28, 2022

Respectfully submitted,

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**FORM 19. Certificate of Compliance with Type-Volume Limitations** **Form 19**
**July 2020**

# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

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