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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner,

v.

REGENTS OF THE UNIVERSITY OF MICHIGAN AND
UNIVERSITY OF SOUTH FLORIDA,
Patent Owners.

Case IPR2023-01346
U.S. Patent No. 10,633,344

PETITIONER'S REPLY TO PATENT OWNERS' RESPONSE

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I. INTRODUCTION

Patent Owners have not disputed that the challenged claims of U.S. Patent No. 10,633,344 (“’344 patent”) are not entitled to the March 2002 priority date of U.S. Provisional Patent Application No. 60/360,768. Nor have they disputed that the claims are anticipated and obvious if not properly described and enabled in U.S. Patent Application No. 10/378,956 (“’956 application”), filed March 2003.¹ Thus, the only issues in this IPR are whether the ’956 priority application provides written description and enablement support. It provides neither, let alone both.

Put simply, the ’344 patent inventors claimed far more than they invented. The challenged claims indisputably cover an “almost infinite” number of possible co-crystals (Ex. 1002, ¶¶74, 118; Petition at 12; Ex. 1072, ¶ 8), yet the ’956 application discloses nothing more than a bare-bones research plan for trial-and-error experimentation. Such experimentation was required because in March 2003, it was not possible to predict whether co-crystals would even form, let alone co-crystals meeting the claim limitations. *See* §§ III.A, VI.A.4; Petition at 27-29. Given the breadth of the claims, the amount of trial-and-error work was certainly undue even if, as Patent Owners allege, the person of ordinary skill in the art (“POSA”) had knowledge of hydrogen bonding principles and high-throughput

¹ The ’956 application and ’344 patent specifications are the same. Ex. 1072, ¶6.

screening (“HTS”). Consistent with the statements and conclusions of two separate patent examiners who examined similar claims in applications related to the ’956 application (*see* Petition at 17-26, 31-32), the challenged claims lack written description and enablement. Patent Owners did not address these related applications, thus waiving any argument about them. Paper 9 at 9 (“[A]ny arguments not raised in the response may be deemed waived.”).

II. THE CHALLENGED CLAIMS AND ’956 APPLICATION

The challenged claims are directed to a pharmaceutical composition comprising a co-crystal having certain specified non-covalent bonds between at least one API and at least one solid co-former. Ex. 1001, claims 10, 11, 18. Beyond specifying that the API must have a carboxamide, carbonyl, or amine first chemical functionality (claims 10, 11) or carboxamide (claim 18), and the supramolecular synthons must comprise certain hydrogen bonds, the challenged claims do not otherwise limit the structure of the co-crystal or its API and co-former components. Ex. 1002, ¶¶69-74. The API(s) can be any “biologically active moiety having a therapeutic effect on a human or animal” (Ex. 1001, 9:27-34; Ex. 1002, ¶¶55, 123), a large genus that includes molecules of all shapes and sizes having a carboxamide, amine, or carbonyl, regardless of the molecule’s complexity or the number of additional functional groups. Ex. 1072, ¶19; Ex. 1002, ¶¶55, 70. Likewise, the genus of possible co-formers is large; the co-former(s) can be any

solid API, GRAS compound, or food additive, without restrictions on the number of functional groups. Ex. 1001, 3:35-37; Ex. 1002, ¶¶72, 117 (explaining there are “thousands” of possible co-formers); Ex. 1072, ¶ 19.

Patent Owners have not contested that: (i) as of March 2003 there were over 50 possible known carboxamide-containing APIs and thousands of possible co-formers; (ii) the claimed co-crystals, which can comprise more than one API and/or co-former, can also include additional components like solvent molecules; and (iii) the challenged claims are exceedingly broad (“almost infinite”), with “limitless” “possible structural variations.” Petition at 1, 22; Ex. 1002, ¶¶74, 116-118.

In stark contrast to the challenged claims’ exceptionally broad scope, the ’956 disclosure is very limited. Patent Owners admit that only nine examples fall within claims 10 and 18, and only three of these nine fall within claim 11. Ex. 1072, ¶14; Ex. 2014, Appendix C. These few examples do not reflect the full scope of the claims, encompassing at a minimum over 50 known carboxamide-containing APIs, thousands of co-formers, and 27 solvents, which could have been combined in countless ways. Ex. 1072, ¶¶14-15, 19-21. There also are no examples of co-crystals with multiple APIs and/or co-formers, and Dr. Ward admits there are no co-crystals with a “carbonyl” or “amine,” two of the three recited first chemical functionalities in claims 10 and 11. Ex. 1072, ¶15; Ex. 2014, Appendix C (omitting

carbonyl and amine). There are likewise no common structural features disclosed that establish the inventors had possession of the full scope of combinations of API(s) and co-former(s) encompassed by the claims. *See* § V.

The '956 application also fails to enable the full scope of claimed co-crystals. *See* § VI. Patent Owners admitted during prosecution that, prior to their invention, co-crystallization was not predictable and could be achieved only with trial-and-error experimentation. Ex. 1017 at pp. 4071-72. Apart from disclosing a handful of new co-crystals in the examples, the '956 application did not change the state of the art. Figure 24 is nothing more than a high-level research plan that requires trial-and-error experimentation to implement, even when combined with the disclosures in the remainder of the specification and knowledge of hydrogen bonding principles and HTS. Ex. 1072, ¶¶16-22; *infra* § VI.A.2.

III. PATENT OWNERS' "BACKGROUND" KNOWLEDGE DOES NOT REMEDY THE '956 APPLICATION'S DEFICIENCIES

To compensate for the '956 application's lack of disclosure and enablement support, Patent Owners attempt to rely on the POSA's knowledge of hydrogen bonding principles, HTS, and information about the APIs' and "suitable" co-formers' solubilities obtained through the POSA's own "pre-formulation" testing (Paper 19 ("POR") at 8-9), none of which the '956 application discloses. These unsupported arguments over-sell what a POSA could have done with such

potential knowledge, and resorting to such external information also confirms the '956 application's disclosures are insufficient.

A. Hydrogen Bonding Principles

As of March 2003, and even today, it was not possible to predict whether a co-crystal of any set of components would form, and if it did form, whether that co-crystal would fall within the challenged claims. Ex. 1002, ¶¶120-125; Ex. 1072, ¶¶22, 114-119. Knowledge of hydrogen bonding principles does not change this outcome. Ex. 1072, ¶¶58-68.

As a preliminary matter, Dr. Rogers did not perform the “wrong analysis” by requiring prediction of the specific three-dimensional crystal structure of any co-crystal. *Contra* POR at 20-21, 24. Rather, Dr. Rogers correctly recognized that the claimed co-crystals require the specifically recited non-covalent interactions (unlike Patent Owners, *see, e.g.*, POR at 21 and Ex. 2014, ¶75, referencing predicting whether “a co-crystal will form at all”). Dr. Rogers's comments about the inability to predict whether particular co-crystals will form plainly refers to the inability to predict whether co-crystals with the claimed non-covalent interactions will form, consistent with his opinion that a POSA could not have predicted whether *any* two or more components will form a co-crystal. Ex. 1072, ¶¶117-119.

For their hydrogen bonding arguments, Patent Owners allege that a 1990 paper by Dr. Etter (Ex. 2005) disclosed three “rules” that allow for prospective

prediction of co-crystal formation. POR at 7-8, 17. But the '956 application nowhere discusses Etter's "rules" or how to apply them to predict co-crystal formation,² Patent Owners never explain how a POSA would apply those rules across the scope of the claims, and Patent Owners have not identified any prior art indicating a POSA could do so. Ex. 1072, ¶¶59-60. Dr. Rogers' deposition testimony that a POSA would have understood that Etter's work could be applied to co-crystals because Etter was "simply the concept of hydrogen bonding" (Ex. 2016 at 39:22-40:5) is certainly not an admission that Etter's "rules" could have been used to predict formation of any co-crystals, let alone the full scope of claimed co-crystals, as Patent Owners imply. *See* POR at 7-8; Ex. 1072, ¶60.

It is unsurprising that Patent Owners failed to provide any evidence that Etter's rules could be used to predict co-crystals across the full scope of the challenged claims. Etter's "rules" were subject to various limitations and exceptions relevant here, which Patent Owners acknowledge, but never address. Ex. 1072, ¶¶ 61-68; Ex. 2014, ¶¶40, 55. For example, Dr. Etter herself indicates that the "rules" are most useful in systems with a "limited number of functional

² Several Etter papers were disclosed in an IDS (*see* POR at 7) alongside hundreds of other references and were never cited by the examiner or applicants. Ex. 1072, ¶59 n.7; *see* Ex. 1016 *generally* and at p. 215; *see* Ex. 1017 *generally* and at p. 196.

groups,” yet the challenged claims do not limit the number of functional groups on the API(s) or co-former(s) and therefore encompass co-crystal components with multiple functional groups. *Id.*; Ex. 2005 at 121. Dr. Ward also acknowledges that “other factors could steer synthon formation toward combinations that do not follow the ranking suggested by ... Dr. Etter’s ‘rules.’” Ex. 2014, ¶55. These “other factors,” which include other intermolecular interactions, steric interference, and geometry, are also relevant here in view of the breadth of possible APIs and co-formers encompassed by the challenged claims. Ex. 1072, ¶¶61-66; Ex. 1080 at 505; Ex. 2008 at 8456-57. Consistent with these known exceptions, the art before and after March 2003 includes numerous examples that do not follow Etter’s “rules.” *See, e.g.*, Ex. 1072, ¶67; Ex. 2008 at 8456-57 (co-authored by ’344 patent inventor Moulton); Ex. 1081 at 2209, Ex. 1082 at 789. In addition, Etter’s “rules” do not address co-crystals that include solvent along with the API(s) and co-former(s), or co-crystals with multiple API(s) and/or co-former(s), yet the challenged claims encompass such co-crystals. Ex. 1072, ¶66.

**B. Pharmaceutical Composition
Formulation and Pre-Formulation Testing**

Patent Owners assert that co-crystallization is a “purification step in the formulation of a pharmaceutical composition.” POR at 8, 19. But the ’956 application never characterizes co-crystallization as a formulation step, and the discussion of pharmaceutical composition formulation focuses on combining an

already-made co-crystal with excipients—not preparing a new co-crystal. Ex. 1015 at 16-33 (examples 1-19); Ex. 1072, ¶¶23-25. The sole reference Patent Owners cite (Ex. 2011, Morrisette 2004) is not prior art and simply states that “[m]ost APIs . . . are purified and isolated by crystallization from an appropriate solvent during the final step in the synthetic process.” Ex. 2011 at 276. This sentence discusses synthesis of an API, not pharmaceutical composition formulation, and no evidence directs it to co-crystals rather than single-component APIs. Ex. 1072, ¶26.

Because Patent Owners’ formulation argument fails, so too does their follow-on argument that by the time a POSA arrived at formulation, “he or she would have already tested and understood the solubility parameters of that API and any suitable co-formers, the types of available solvents and co-formers appropriate for pharmaceutical use, and the solvent(s) and co-former(s) in which the API and co-former prospects would or would not be soluble.” POR at 8-9. This incredibly significant amount of “pre-formulation” work (for no less than 50 APIs, thousands of co-formers, and numerous solvents) is precisely the work a POSA would have had to do to make and use the full scope of the invention because the ’956 application lacks the necessary guidance. Indeed, determining which co-formers are “suitable” for each API is a critical component of the alleged invention. Ex. 1072, ¶¶24-29. If anything, this argument reinforces that the ’956 application discloses nothing more than a research plan.

Patent Owners’ attempt to attack Dr. Rogers’ credibility fares no better. Patent Owners allege Dr. Rogers’ testimony that he would not rule out using toxic or carcinogenic co-formers and solvents in the claimed pharmaceutical compositions under certain circumstances “strains ... a plausible reading” of the patent. POR at 9. But toxic and carcinogenic co-formers and solvents are used in the ’956 application examples, which Patent Owners relied on during prosecution as support for the claimed pharmaceutical compositions. Ex. 1016 at pp. 256-59; Ex. 1072, ¶¶34-37. For example, the co-crystal of example 17 uses formamide as a co-former and examples 3, 7, 8, 11, 13, 14, 17, and 19 use the solvents hexane, methanol, tetrahydrofuran, and/or dichloromethane. Ex. 1015 at 18, 22–23, 26, 28–29, 31–32. According to the 2003 HHS Guidance cited by Dr. Ward (Ex. 2012 at 8), these are all “class 2” solvents with “inherent toxicity” whose use in pharmaceutical products “should be limited.” But even excluding toxic or carcinogenic compounds, the scope of the claims remains incalculable and the challenged claims lack written description and enablement support. Ex. 1072, ¶¶30-33, 38.

C. High-Throughput Screening (HTS)

Patent Owners are not clear on how a POSA would use HTS, sometimes suggesting it would be used to identify crystallization conditions for a single API-co-former combination, *e.g.*, POR at 2, 11, 19, and elsewhere implying it could be

used across the scope of the claims, *e.g.*, Ex. 2014, ¶¶62, 64. Regardless, HTS does not remedy the '956 application's shortcomings. *Contra* POR at 10-11, 23; Ex. 1072, ¶¶ 39-57. First, neither HTS nor its application to co-crystals is mentioned in the specification. *Id.*, ¶42. Nor have Patent Owners cited any prior art using HTS for co-crystal screening. Ex. 1072, ¶¶43-45. Patent Owners' own expert states that the use of HTS to evaluate "crystallization methods" was only "emerging" in 2002-2003 (Ex. 2014, ¶49) and, according to Luu 2012, Remenar (Ex. 2008), which was published in June 2003 (after the March 2003 date of the '956 application), was the first example of HTS being used to prepare co-crystals. Ex. 1072, ¶¶43-45; Ex. 1077 at 356. Thus, Patent Owners have no evidence that as of March 2003, HTS had been used to screen for co-crystals or that a POSA could have used it for this purpose.

Second, the use of HTS was far from straightforward. *Contra* POR at 11. In describing the complexities of HTS, Morisette 2004 underscores the amount of work required to design the HTS experiments, execute them, and analyze the resulting data. Ex. 1072, ¶¶47-53; Ex. 2011 at 278-79. At the design stage (as with manual screening), the POSA would have been required to select the API(s), co-former(s) and solvent(s) or solvent combinations for each experiment, their concentrations, the temperature and duration of each step, heating rates, cooling rates, carrier gasses, anti-solvents, degree of super-saturation, additives, solution

pH, and analytical methods. Ex. 1072, ¶¶48-53. In view of the breadth of the claims, this would have required an inordinate amount of work. *Id.*

Third, even if a POSA could have designed HTS experiments, executed them, and analyzed the results using HTS equipment, HTS alone would not have allowed a POSA to identify co-crystals with the claimed non-covalent bonds—nor have Patent Owners alleged it could. Ex. 1072, ¶¶54-57. This requires analysis by single crystal X-ray diffraction (“SCXRD”), as in the ’956 application’s examples. *Id.*; Ex. 1015 at 16-33 (examples 1-19). SCXRD is a time-intensive task (requiring anywhere from 1-2 hours to several months per sample) and can only be performed on crystals of sufficient size and quality (samples produced by HTS are unlikely to qualify). Ex. 1072, ¶56.

IV. CLAIM CONSTRUCTION

The parties agree on the construction of claim terms (or the relevant portions thereof) to be used for purposes of this IPR (*see* POR at 12), with the exception of “permits formation,” a term that is not discussed in the POR and whose construction does not impact any issue; the claims are unpatentable under either party’s construction. Ex. 1072, ¶¶4, 9, 12.

V. THE '956 APPLICATION LACKS WRITTEN DESCRIPTION FOR THE FULL SCOPE OF CLAIMED CO-CRYSTALS

A. The '956 Application Does Not Disclose Representative Species or Common Structural Features

For genus claims, written description requires the disclosure of either a representative number of species or common structural features to support the full scope of the claim. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010); Paper 8 (Institution Decision) at 6.

Patent Owners did not contest that the '956 application lacks disclosure of a representative number of species (or to the extent they did, these arguments are not supported by Dr. Ward and are only attorney argument³), therefore waiving any argument under this test.⁴ See POR at 16-21 (never mentioning representative

³ *Parkervision, Inc. v. Vidal*, 88 F.4th 969, 982 (Fed. Cir. 2023) (attorney argument is not evidence).

⁴ To the extent Patent Owners contend the examples are representative of the full breadth of the broad claims, Petitioner disagrees. See Petition at 13-26; see also p. 2 and §§ II, V.B, VI.A.5 herein. Petitioner does not demand any specific “perfect example” (*contra* POR at 20); Petitioner (and the public) request only examples commensurate with the full scope of the numerous and diverse co-crystals within the claims, which are absent here.

species); Ex. 2014, ¶¶53-57 (same); Paper 9 at 9. Therefore, that only leaves the common structural features test. But the common structural features test does not support description of the claimed co-crystals because, for example, there are no structural features common to all APIs (beyond specifying the first chemical functionality) or co-formers included in the claimed co-crystals, let alone their structures when combined into a co-crystal. Ex. 1002, ¶¶75, 89-100; Ex. 1072, ¶¶75-77. The challenged claims do not otherwise limit the API or co-former structures, let alone their structures when combined into a co-crystal. Pet. 13; Ex. 1002, ¶¶69, 75. Instead, the claimed co-crystals are defined in-part by functional language, for example, the API(s) and co-former(s) must *form* supramolecular synthons between the first chemical functionality of the API(s) (carboxamide, carbonyl, or amine) and the unspecified complementary second chemical functionality of the co-former(s). Ex. 1002, ¶69; Ex. 1072, ¶¶ 74.

Patent Owners allege that “a POSITA would recognize that the claimed co-crystals have similar structures based on the hydrogen bonding between the active pharmaceutical ingredients and their co-formers.” POR at 2. But by focusing on the co-crystals themselves (rather than the API(s) and co-former(s)), Patent Owners skirt a key issue—how does a POSA know which of the large genus of co-formers will form co-crystals with any given API(s) in the large genus of APIs? Patent Owners have identified no structural features common to APIs and co-

formers that enable a POSA to reasonably predict which ones would form a claimed synthon or co-crystal (and thus meet the functional limitation of forming a co-crystal). Ex. 1002, ¶¶75; Ex. 1072, ¶¶78. In view of the large number of possible APIs and co-formers, and the fact that co-crystal formation was (and still is) unpredictable (*see* § III.A, VI.A.4), Patent Owners have disclosed nothing more than a research plan. This does not establish possession. *Ariad*, 598, F.3d at 1353-54.

Figure 24 and the '956 application examples do not help. *Contra* POR at 16, 17, 20. Figure 24's flow chart does nothing more than outline a high-level research plan that must be tested by trial-and-error. Ex. 1072, ¶¶16-22. And, apart from disclosing a handful of co-crystals actually made, the examples do not enable the POSA to visualize or recognize which other combinations of APIs and co-formers will in fact form the claimed co-crystals. Ex. 1072, ¶¶79-84. The examples fail to account for the diversity and breadth of claims, encompassing myriad combinations of no less than 50 APIs, thousands of co-formers, and 27 solvents (*see* p. 3, *supra*). They also fail to exemplify any co-crystals with more than one API or co-former, and two of the three recited "first chemical functionalit[ies]" of claims 10 and 11 ("carbonyl" and "amine", *see id.* at 3-4). Ex. 1072, ¶¶79, 83. Given the unpredictability of co-crystal formation, this would not have enabled a POSA to predict which combinations of components would form the claimed co-

crystals. *PureCircle USA, Inc. v. Sweegen, Inc.*, No. 2022-1946, 2024 U.S. App. LEXIS 2, *8 (Fed. Cir. Jan. 2, 2024) (“In general the need for extensive trial and error testing argues against a finding of adequate written description.”).

B. Knowledge of Hydrogen Bonding Principles and HTS Does Not Overcome Lack of Predictability

Patent Owners attempt to salvage their insufficient disclosure by relying on information outside the '956 application, namely, the highly skilled POSA's alleged knowledge of “well-known principles of hydrogen bonding” (Etter's “rules”) and HTS. *See* POR at 16-20. This is improper. *Ariad*, 598 F.3d at 1351. Moreover, while the specification should be considered from a POSA's perspective, the POSA's knowledge is not a substitute for disclosure. *See e.g.*, *PureCircle*, 2024 U.S. App. LEXIS at *8-13 (declining to rely on POSA's knowledge to overcome lack of written description in case involving unknown structure-function correlation and extensive testing). And where the field is not mature like here (*see* POR at 10), and the art not predictable (*see* §§ III.A, VI.A.4, Petition at 27-29), the specification must disclose *more* detail—not less. *Ariad*, 598 F.3d at 1351.

Because Patent Owners and Dr. Ward have not cited any prior art applying hydrogen bonding principles to predict co-crystals or using HTS for co-crystals (Ex. 1072, ¶¶43-45, 86), they have no basis to argue that this knowledge was “conventional and generally widely known” and thus exempt from disclosure.

Contra POR at 13, citing MPEP § 608.01(a). *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (PTAB Aug. 24, 2022) (precedential) (unsupported expert testimony entitled to little weight). Likewise, this type of knowledge (predicting novel co-crystals and applying HTS to co-crystals) plainly is distinguishable from the information in Patent Owners’ cases that did not require disclosure, even if the POSA here is highly skilled: *Falkner v. Inglis*, 448 F.3d 1357, 1367-68 (Fed. Cir. 2006) (known DNA structures); *Capon v. Eshhar*, 418 F.3d 1349, 1360-61 (Fed. Cir. 2005) (same); *Zoltek Corp. v. U.S.*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (commercially available starting material). And in *Boston Scientific*, although the court stated that in some instances, “well-known” information need not be disclosed, the court declined to rely on such extrinsic information, concluding that it did not “represent[] existing knowledge in the art so well known as to excuse including a more detailed disclosure [of the claimed subject matter].” *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011). The same applies here.

But even if it were permissible to rely on information outside the specification for hydrogen bonding principles and HTS, this would not establish possession. Patent Owners have not explained how a POSA would use hydrogen bonding principles or Etter’s “rules” to predict any co-crystal, let alone the full scope of claimed co-crystals. *See* § III.A; Ex. 1072, ¶¶85-91. This is particularly

true as it is undisputed that Etter’s “rules” have limitations when applied to systems with multiple functional groups or “other competing forces” such as intermolecular interactions, sterics, and geometry (*see* POR at 17-18; Ex. 2014, ¶¶40, 55)—all of which apply here given the breadth of possible APIs and co-formers. *See* § III.A. There is also no evidence that Etter’s “rules” apply to co-crystals with more than one API and/or co-former. Ex. 1072, ¶90.

Finally, to the extent Patent Owners are relying on HTS for written description support (*see* POR at 19, not citing any evidence), this is only a testing technique, and Patent Owners do not explain its relevance to written description. Ex. 1072, ¶92; *see also* §§ III.C, VI.A.2 (explaining why Patent Owners’ HTS arguments are flawed).

For these reasons, the ’956 application, alone or combined with the POSA’s alleged knowledge, fails to provide written description support for the full scope of the challenged claims. Ex. 1072, ¶¶69-93.

VI. THE ’956 APPLICATION LACKS ENABLEMENT SUPPORT FOR THE FULL SCOPE OF CLAIMED CO-CRYSTALS

It is well settled that “the specification must enable the full scope of the invention as defined by its claims” and “[t]he more one claims, the more one must enable.” *Amgen Inc. v. Sanofi*, 143 S. Ct. 1243, 1254 (2023). Because the challenged claims here indisputably are very broad, and co-crystal formation was (and still is) not predictable (*see* § III.A, VI.A.4; Petition at 27-29), the POSA

would have needed to pursue trial-and-error experimentation to practice the full scope of the claims. The exorbitant amount of such experimentation is undue, even with HTS. Ex. 1072, ¶¶94-154; *Amgen*, 143 S. Ct. at 1254-58 (recognizing that in some cases, a few examples may suffice for enablement, but holding overbroad claims that required trial-and-error experimentation invalid for lack of enablement).

A. The *Wands* Factors Confirm Non-Enablement

Patent Owners' *Wands* analysis is premised on two key arguments: (1) a POSA would have been able to use hydrogen bonding principles (Etter's "rules") to "predict whether a co-crystal of an API satisfying claims 10, 11, and/or 18 would form" and (2) the use of HTS to identify co-crystallization conditions and/or prepare co-crystals would have eliminated any undue experimentation. POR at 17, 22-25; Ex. 2014, ¶62. Because these two assumptions are unsupported (*see* §§ III.A, III.C, V.B), Patent Owners' enablement arguments collapse. The *Wands* factors support non-enablement.

1. Breadth of the Claims

Patent Owners do not dispute that the challenged claims are broad, nor that their breadth weighs in favor of non-enablement. *See* POR at 21 (acknowledging that one *Wands* factor does not support enablement and omitting any discussion of claim breadth); Ex. 1072, ¶95.

2. POSA's Relative Skill

Patent Owners argue that the POSA's high skill level and knowledge of "hydrogen bonding, formulation of pharmaceutical compositions, co-crystals, and high-throughput screening" supports enablement. POR 22. But no amount of skill or knowledge would permit the POSA to reasonably predict whether co-crystals would form; to make and use the full scope of claimed co-crystals, the POSA would need to engage in undue trial-and-error experimentation. Ex. 1072, ¶¶103-113. *See e.g., Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1346 n.3, 1346-47, 1349 (Fed. Cir. 2019) (finding claims non-enabled in "highly unpredictable" art where level of ordinary skill required a doctorate); *Syngenta Crop Protection AG v. FMC Corp.*, PGR2020-00028, Paper 33 at 17 (PTAB Aug. 31, 2021) (balancing high skill in a mature field against unpredictability, ultimately finding claims non-enabled). As such, the POSA's skill level is neutral.

Patent Owners' arguments fail for other reasons too.

For example, Patent Owners incorrectly allege that the '956 application teaches how to apply "hydrogen bonding, formulation of pharmaceutical compositions, co-crystals, and high-throughput screening" to "pharmaceutical compositions." POR at 22. The cited passages include no such teachings. They merely reference characterization of co-crystal properties (Ex. 1001, 3:19-26), list potential categories of co-formers (*id.* at 3:35-37), define "API" (*id.* at 9:27-30),

and set forth a high level trial-and-error research plan (*id.* at Fig. 24). Ex. 1072, ¶¶146-152. Notably, the specification never mentions general hydrogen bonding principles, Etter’s “rules,” or HTS, and neither the specification nor Patent Owners describe how to apply them to the claimed subject matter. *See* §§ III.A, III.C. Attempting to rely on the knowledge of a POSA as a substitute for an enabling disclosure, as Patent Owners do, is contrary to the law. *See, e.g., Enzo*, 928 F.3d at 1348.

Etter/hydrogen bonding/co-crystal formation: As explained above (§ III.A), Patent Owners have no support that Etter’s “rules” (or hydrogen bonding principles generally) had been used to predict co-crystal formation, let alone that they could be used to predict the full scope of claimed co-crystals. Ex. 1072, ¶111. These deficiencies are particularly problematic as it is undisputed that the Etter “rules” have limited applicability to systems with multiple functional groups and may not apply if there are “other competing forces” (non-hydrogen-bond intermolecular interactions); these limitations are all relevant here as the claims do not limit the complexity or number of functional groups for the APIs and co-formers. *Id.* Nor is there any evidence that Etter’s “rules” apply to systems with multiple APIs and/or co-formers, or those involving solvent, the latter being particularly notable in view of ’344 patent inventor Zaworotko’s admission that the composition and structure of co-crystal hydrates is unpredictable. Ex. 1072, ¶66; Ex. 1078 at 2152, 2166-67.

Formulation: Patent Owners’ confusing arguments about “formulation” (POR at 8-10) appear to mix up preparing (synthesizing) a co-crystal with formulating that co-crystal into a pharmaceutical composition. In any event, preparing the full scope of claimed co-crystals would have required undue trial-and-error experimentation (*see, e.g.*, §§ I, II, III.B, V). Ex. 1072, ¶¶109-110.

HTS: Patent Owners do not cite any prior art using HTS to screen for co-crystals, let alone to screen and identify co-crystals with particular hydrogen bonding. Ex. 1072, ¶¶105-106. Nor do they provide any guidance on how to set up such experiments. The amount of work required to design, execute, and analyze any HTS results would still be undue given the breadth of the claims, and the fact that the HTS products would need to be separately analyzed by SCXRD to determine whether they had the requisite hydrogen bonding—a non-trivial task requiring anywhere from 1-2 hours to several months of analysis per sample. Ex. 1072, ¶¶107-108.

3. Nature of the Invention

The parties agree the nature of the invention is a pharmaceutical composition comprising a genus of co-crystals having certain properties. Petition at 27; POR at 25. Patent Owners acknowledge that as of 2002/2003, “knowledge of pharmaceutical co-crystals” was only “emerging.” Ex. 2014, ¶31. That the field

was not an established one, combined with the unpredictability of co-crystals, supports non-enablement. Ex. 1072, ¶100.

Although Patent Owners contend that the nature of the invention weighs in favor of enablement because the POSA has a high level of skill (POR at 25), the relevance of the POSA's skill level is diminished because the claimed co-crystals are not predictable. *See* § III.A, VI.A.4. In view of that unpredictability, this factor weighs in favor of non-enablement. Ex. 1072, ¶¶98-101.

4. State of the Art, Predictability of the Art, and Quantity of Experimentation

Patent Owners allege that because a POSA would understand “how hydrogen bonding works” and could therefore predict co-crystals, the state of the art, predictability of the art, and quantity of experimentation together support enablement. POR at 22-25. Not so. This argument again is premised on the flawed assumption that co-crystal formation was predictable. “[I]dentify[ing] appropriate APIs and other materials to create the claimed co-crystals” (POR at 22) is only one step. Even with a list of suitable APIs and co-formers in hand, a POSA would not know which APIs and co-formers will form co-crystals or, if formed, what stoichiometries they will have, whether solvent will be a component, and/or what bonds they will have. Ex. 1072, ¶¶133-136, 145-152.

Patent Owners' reliance on HTS is similarly unhelpful. *See* POR at 23. No prior art shows the use of HTS for co-crystals and the '956 application never

mentions HTS, let alone describes how to apply it to the claimed co-crystals. *Supra* §§ III.C, V.B. And even if a POSA had used HTS, the amount of experimentation required to design, execute, and analyze the HTS results for all possible combinations of APIs and co-formers would still be undue, including because SCXRD would be required to analyze each HTS product that may be a co-crystal. *Id.*; Ex. 1072, ¶¶133-135.

Desiraju (and other art that Patent Owners did not address, *see* Petition at 27-28, citing Exs. 1025, 1026, 1034) fully supports the unpredictability of co-crystal formation, and it is Patent Owners, not Petitioner, who selectively quote Desiraju. Ex. 1072, ¶¶120-124. *Contra* POR at 23. That the hydrogen bond is the “master key” in “molecular recognition” (Ex. 1024 at 399) says nothing about the predictability (or unpredictability) of co-crystal formation. Ex. 1072, ¶122. On the issue of predictability, Desiraju is clear that knowledge of intermolecular interactions (e.g., hydrogen bonding) does not allow for prediction of co-crystal formation: “Even after identifying an important intermolecular interaction, failure to predict a crystal structure can arise because the same interaction can be used to make many different synthons. . . [T]he synthon concept tries to simplify what is essentially a very difficult problem. But even with apparently straightforward synthons, things can go wrong.” Ex. 1024 at 399.

Patent Owners’ arguments about Fleischman’s 80% failure rate (POR 23-24) are puzzling. If the Fleischman authors (which include the ’344 patent inventors), who were aware of Etter’s work and their own disclosures about carbamazepine’s hydrogen bonding, could not identify co-formers that had the *potential* to co-crystallize with carbamazepine, it strains credulity that a POSA could do so. Ex. 1072, ¶129. Additionally, given the breadth of the claims, a 20% success rate (reported for a single API having a single functional group) is not “good” or remotely sufficient for enablement purposes. Ex. 1072, ¶¶127-128.

Finally, Patent Owners criticize Petitioner for emphasizing the ability to predict whether co-crystals will form because the challenged claims cover compositions, not methods. POR at 24. But if it is not possible to predict whether co-crystals within the scope of the claims will form, and what conditions to use to obtain them, the POSA must undertake trial-and-error experimentation, and where that work is undue, the claims are not enabled. *Enzo*, 928 F.3d at 1344-49.

5. Working Examples and Amount of Direction or Guidance

Patent Owners allege that the ’956 application provides “ample description” “to guide a [POSA] on how to make *a* claimed co-crystal” because it describes the APIs, co-formers, and solvents to use and provides 19 examples. POR at 25. (emphasis added). Setting aside the examples’ deficiencies (*supra* §§ II, V.A; Ex. 1072, ¶¶137-142), simply listing APIs, co-formers, and solvents does not teach a

POSA which combinations are reasonably likely to form co-crystals within the scope of the challenged claims. Ex. 1072 ¶¶144-152; *supra* § VI.A.4. Furthermore, making “a claimed co-crystal” is not enough—a POSA must be able to practice the *full scope* of the challenged claims, which here are indisputably broad. Petition at 30-31; Ex. 1072, ¶¶137-153. Thus, these factors, like five of the factors above, also support non-enablement.

VII. CONCLUSION

Petitioner respectfully requests cancellation of claims 10, 11, and 18 of the '344 patent.

Date: August 28, 2024

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CERTIFICATION OF WORD COUNT

Under 37 C.F.R. § 42.24(d), Petitioner certifies that this Reply to Patent Owners' Response has a word count of 5,576 words, excluding the portions exempted by 37 C.F.R. § 42.24(a), as calculated by the built-in word-count function in the Microsoft Word software used to prepare this document.

CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing Petitioner's Reply to Patent Owner's Response, all supporting exhibits, and Petitioner's Updated Exhibit List were served on August 28, 2024 via electronic mail on the following counsel of record for Patent Owners:

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