

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner,

v.

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

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

PATENT OWNERS' RESPONSE

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	THE INVENTION OF THE '344 PATENT	3
	A. Priority of the '344 Patent	3
	B. The '344 Patent Specification	4
	C. Background of the '344 Patent	6
	1. Hydrogen Bonding	6
	2. Formulation of Pharmaceutical Compositions	8
	3. Co-Crystals	10
	4. High-Throughput Screening	10
III.	PERSON OF ORDINARY SKILL IN THE ART	11
IV.	CLAIM CONSTRUCTION	12
V.	LEGAL STANDARDS	12
	A. Written Description	12
	B. Enablement	14
VI.	PETITIONER FAILS TO SHOW THAT THE CHALLENGED CLAIMS ARE OBVIOUS	16
	A. The '956 Application Provides Written Description Support for the Claimed Co-Crystals	16
	B. The '956 Application Enables the Claimed Co-Crystals	21
	1. The relative skill of those in the art	22
	2. The quantity of experimentation necessary, the state of the prior art, and the predictability or unpredictability of the art	22

3.	The amount of direction or guidance presented and presence of working examples	25
4.	The nature of the invention	25
VII.	CONCLUSION	25

LIST OF EXHIBITS

Exhibit Number	Description
2001	Declaration of Taylor Burgener in support of Motion for <i>Pro Hac Vice</i> Admission
2002	Declaration of Jacqueline T. Moran, Ph.D. in support of Motion for <i>Pro Hac Vice</i> Admission
2003	RESERVED
2004	RESERVED
2005	Margaret C. Etter, “ <i>Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds</i> ,” Acc. Chem. Res. 1990, 23, 120-126 (“Etter Rules”)
2006	Peterson et al., “ <i>Iterative High-Throughput Polymorphism Studies on Acetaminophen and an Experimentally Derived Structure for Form III</i> ,”” J. Am. Chem. Soc., 2002, 124, 10958-10959 (“Peterson”)
2007	Walsh et al., “ <i>Crystal Engineering of the Composition of Pharmaceutical Phases</i> ”, The Royal Society of Chemistry Chem. Commun., 2003, 186–187 (“Walsh”)
2008	Remenar et al., “ <i>Crystal Engineering of Novel Cocrystals of a Triazole Drug with 1,4-Dicarboxylic Acids</i> ”, J. Am. Chem. Soc., 2003, 125, 8456-8457 (“Remenar”)
2009	Yusov et al., “ <i>Hydrogen Bonded Frameworks: Smart Materials Used Smartly</i> ,” Mol. Syst. Des. Eng., 2021, 6, 756-778 (“Yusov”)
2010	Etter and MacDonald, et al., “ <i>Graph-Set Analysis of Hydrogen-Bond Patterns in Organic Crystals</i> ,”” Acta Cryst., . (1990,). B46, 256-262-266 (“Etter 1990”)
2011	Morissette et al., “ <i>High-Throughput Crystallization: Polymorphs, Salts, Co-Crystals and Solvates of Pharmaceutical Solids</i> , Advanced Drug Delivery Reviews, 2004, 56, 275-300 (“Morissette”)
2012	<i>Guidance for Industry Q3C—Tables and Lists</i> , Food and Drug Administration, November 2003 (“HHS Guidance 2003”)

2013	<i>Guidance for Industry Q3C Impurities: Residual Solvents</i> , Food and Drug Administration, December 1997 (“HHS Guidance 1997”)
2014	Declaration of Michael D. Ward, Ph.D.
2015	Deposition Transcript of Leah Appel, Ph.D. May 8, 2024
2016	Deposition Transcript of Robin D. Rogers, Ph.D. May 23, 2024

The Regents of the University of Michigan and University of South Florida (“Patent Owners”) submit this Patent Owners’ Response to the petition filed by Novartis Pharmaceuticals Corporation (“Petitioner”) requesting *inter partes* review of claims 10, 11, and 18 of U.S. Patent No. 10,633,344 (“the ’344 Patent”).

I. INTRODUCTION

Claims 10, 11, and 18 (“Challenged Claims”) of the ’344 Patent should be found patentable because none of Petitioner’s presented grounds render these claims obvious. As explained below, and in more detail throughout this Patent Owners’ Response (“Response”) and in the accompanying declaration of Dr. Michael Ward (*see* EX2014 (Ward Declaration)), the ’344 Patent is entitled to a priority date of no later than the filing date of U.S. Application No. 19/378,956 (“the ’956 Application”), March 3, 2003. The ’956 Application provides ample written description support for and enables the Challenged Claims.

Careful review of Petitioner’s written description arguments simply confirms that Petitioner’s challenge is without basis. As shown below, the ’956 Application specification fully supports the claims. The specification contains nineteen unique examples, exemplifying various limitations in the Challenged Claims. Petitioner argues the claims are invalid because they fail to disclose a representative number of species that fall within the claims. But given the high level of training and education that a POSITA would have held – a definition that

both Petitioner and Patent Owners agree on – 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. All the features that Petitioner contends are inadequately disclosed correspond to a structure that both it and its expert acknowledge were well within the knowledge of a POSITA. Petitioner's written description arguments, thus, fail.

Petitioner's enablement arguments fare no better. No undue experimentation would have been required to assess whether the claimed co-crystals would form. Based on the disclosure of the '956 Application, a POSITA would have been able to predict whether a co-crystal would form and could have utilized high-throughput crystallization and screening to assess the conditions under which formation would occur. Petitioner fails to address the availability of high-throughput screening for crystallization at all in their Petition. Petitioner's enablement arguments fail.

Petitioner falls short of proving that the '344 Patent is not entitled to the priority filing date of the '956 Application. Given that Petitioner focuses on an alleged 2014 priority date and only asserts prior art that was available after 2003, all grounds must fail. The patentability of the Challenged Claims should, therefore, be confirmed.

II. THE INVENTION OF THE '344 PATENT

In the pharmaceutical industry, it is important for drugs to be both effective and accessible. A drug's therapeutic benefit can be limited due to its chemical properties. EX1001 (U.S. Patent No. 10,633,344) at 2:25-29. For example, a drug's chemical properties can make it less soluble, poorly absorbed, or more easily broken down in the body. *Id.* The properties of a crystalline solid of a drug depend upon the internal arrangement of its components. *Id.* at 2:13-15. The '344 Patent relates to the design of new crystalline versions of drugs having chemical and physical properties that improve functional characteristics, like solubility, dissolution rate, and stability. *Id.* at 2:20-24, 2:67-3:28.

A. Priority of the '344 Patent

The application for the '344 Patent – Application No. 14/179,862 (“the '862 Application”) – was filed on February 13, 2014. EX1016 (U.S. Patent No. 10,633,344 Prosecution History Part 1 of 2) at 4-53. The '862 Application was a continuation of U.S. Application No. 19/378,956 (“the '956 Application”), which was filed on March 3, 2003. The specification of the '956 Application and the

'862 Application are identical.¹ EX1016 at 54-85. The '956 Application claimed priority to U.S. Provisional Application No. 60/360,768, filed on March 1, 2002. The '344 Patent issued on April 28, 2020.

B. The '344 Patent Specification

The '344 Patent claims pharmaceutical compositions comprising co-crystals formed between an API and a co-former. *See, e.g.*, EX1001 at claim 10. As the parties agree for purposes of this proceeding, a “co-crystal” is a “[a] multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.” EX1002 (Rogers Declaration) at ¶65.

The '344 Patent describes the different components of the claimed co-crystals. The patent describes “active pharmaceutical ingredients” or “APIs” as “any biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.” EX1001 at 9:27-34. The APIs may serve a prophylactic, palliative, or curative effect. *Id.* at 9:34-40.

¹ Because the specifications of the '956 Application and the '862 Application are identical, Patent Owners refer to the specification of the '344 Patent and the '956 Application interchangeably.

The '344 Patent further describes the claimed co-crystal formers or co-formers. *Id.* at 3:19-26. These co-formers may be solvent molecules, other drug molecules, GRAS compounds, or approved food additives. EX1001 at 3:35-37; *see also id.* at Fig. 24.

The '344 Patent describes how the claimed co-crystals are formed. As illustrated in Figure 24 of the patent, the patent explains how to prepare the claimed co-crystals. The first step is to evaluate the API. EX1001 at Fig. 24. The second step is to identify if there are chemical functionalities in the API that are suitable for forming supramolecular synthons with itself. If the API will form a supramolecular synthon by itself, step 3a is to determine which chemical functionalities on the API will form a *new* supramolecular synthon without disrupting the supramolecular synthon from step 2. *Id.* Step 4 requires the identification of co-crystal formers, or co-formers, that are suitable for use based on the chemical functionalities identified in Step 3. *Id.* As noted above, Figure 24 specifies that the co-formers may be other APIs, GRAS compounds, or food additives. *Id.* Lastly, the co-crystals are made with the API and one or more co-formers. *Id.* Exemplary methods of preparation include “crystallization from solution, cooling the melt, sublimation or grinding[.]” *Id.*

The '344 Patent also provides 19 examples of co-crystals. As Dr. Ward has shown, the examples illustrate the claim limitations of claim 10, 11, and 18.

EX2014 at ¶53.

C. Background of the '344 Patent

As discussed below in Section III, the level of skill for a person of ordinary skill in the art is very high. Both experts – Petitioner's and Patent Owners' – agree with this high level of skill. EX2014 at ¶¶22-24; EX1002 at ¶126; EX2016 (Rogers Deposition) at 31:2-8. Given this high level of skill, a POSITA would bring an understanding of the basic principles that underlie the claimed technology.

1. Hydrogen Bonding

As one example, a POSITA would have a deep understanding of hydrogen bonding. In the '344 patent, the claimed supramolecular synthons are formed through non-covalent hydrogen bonding between first chemical functionality of the API and the second chemical functionality of the co-former. *See, e.g.*, EX1001 at claim 10. Non-covalent bonds do not share electron pairs but are intermolecular forces (i.e., forces that occur between molecules) resulting from the attraction between molecules. EX2014 at ¶35. Hydrogen bonding is a type of non-covalent chemical bond where a hydrogen atom is bonded to an atom with an electronegative charge. *Id.* In a hydrogen bond, a "hydrogen bond donor," which

has a partial positive charge, “donates” a hydrogen to the “hydrogen bond acceptor” which has the negative charge. *Id.*

By 2002-2003, a POSITA would have well-understood the principles of hydrogen bonding. EX2014 at ¶38; EX2016 at 34:10-35:24, 39:4-40:5. The seminal work on hydrogen bonding was published years prior by Dr. Margaret Etter in the 1990s. EX2014 at ¶¶38-39. Both experts – Petitioner’s and Patent Owners’ – appreciate that the POSITA would have been familiar with the work of Dr. Etter. EX2014 at ¶¶38-39; EX2016 at 39:4-9. In fact, multiple papers of Dr. Etter on hydrogen bonding were cited during prosecution. *See* EX1001 at page 6 (References Cited).

Dr. Etter published the basic principles for hydrogen bonding. EX2014 at ¶¶38-43; EX2005 (Etter Rules) at 124-25. Dr. Etter published “General Rules for Hydrogen Bonding,” including that “[a]ll good proton donors and acceptors are used in hydrogen bonding.” EX2005 at 124-25. Dr. Etter even recognized that these general principles of hydrogen bonding can be applied to co-crystals. *Id.*; EX2014 at ¶39. Petitioner’s expert, Dr. Rogers, agreed – when asked whether a POSITA as of 2002-2003 would have been aware that Dr. Etter’s work could apply to co-crystals, Dr. Rogers said, “[b]y 2002-2003 I would say yes, because it was simply the concept of hydrogen bonding.” EX2016 at 39:22-40:5. A POSITA

would, thus, have understood that the generally recognized principles of hydrogen bonding can be applied to co-crystals. EX2014 at ¶39.

2. Formulation of Pharmaceutical Compositions

As of 2003, a POSITA would have viewed co-crystallization of an API as purification step in the formulation of a pharmaceutical composition. EX2014 at ¶44. A POSITA would also have understood the basic principles of formulating a pharmaceutical composition, including testing the various properties of a formulation such as solubility. *Id.* First, a POSITA would need to understand the goals of formulating the pharmaceutical composition, such as the desired stability. EX2015 (Appel Deposition) at 33:17-35:17. Then a POSITA would enter the pre-formulation stage, where they would run tests to understand the physicochemical properties of the drug, such as the pH and solubility. *Id.* at 35:19-36:14. Based on the physicochemical properties of the API, a POSITA would ascertain how that API may be appropriately formulated so that there is good bioavailability. *Id.* at 36:22-38:4. This process would be the same for formulating an API not in a co-crystal as well as formulating a multiple-component co-crystal comprising an API. *Id.* at 72:7-74:16. Therefore, by the time a POSITA arrived at the co-crystallization stage of the formulation process for a given API, 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. EX2014 at ¶44.

When choosing excipients for pharmaceutical compositions, like the claimed pharmaceutical compositions, a POSITA would have had several references in hand, such as *Remington's* or the Handbook of Pharmaceutical Excipients. *Id.* at 51:16-52:3, 67:17-69:16; *see also* EX1001 at 10:15-21 (referring to *Remington's* as “a source that can be used in connection with the subject invention”). Because the claimed pharmaceutical compositions were intended for an animal or human suffering from a condition, *see* Section II(B) *supra*, a POSITA would have generally looked at excipients that were already approved for use by the FDA. EX2015 at 85:19-86:21. A POSITA would have also looked at solvents that were *not* approved by FDA or whose use was restricted by FDA, before formulating a pharmaceutical composition to exclude such solvents. EX2014 at ¶45.

Petitioner's expert, Dr. Rogers, strains credibility, and a plausible reading of the '344 Patent, when he suggests that a POSITA would have used known carcinogens as co-formers or solvents in a pharmaceutical composition. Dr. Rogers applied the parties' definition of “active pharmaceutical ingredient” as “any biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.” EX1002 at ¶55. Despite applying that definition, Dr. Rogers

refused to concede that a POSITA would *not* have used a known carcinogen or toxic co-former or solvent in the claimed pharmaceutical composition. EX2016 at 60:1-68:25.

3. Co-Crystals

A POSITA would also have been familiar with co-crystals. EX2014 at ¶31. As of 2002-2003, co-crystals were well-known in the art. *Id.*; *see* EX2007 (R.D.B. Walsh, et al., Crystal Engineering of the composition of pharmaceutical phases, *Chem. Commun.* (2003) 186-87 (disclosing carboxylic acid-pyridine supramolecular heterosynthons generating binary crystalline phases involving *rac*-ibuprofen, *rac*-flurbiprofen, or aspirin)); *see also* EX2008 (J.F. Remenar, et al., Crystal Engineering of novel co-crystals of triazole drug with 1,4-dicarboxylic acids, *J. Am. Chem. Soc.* 215 (2003) 8456-57 (describing co-crystals of *cis*-itraconazole with 1,4-dicarboxylic acids)). Pharmaceutical co-crystals, however, were just emerging according to the method described in the '344 Patent. EX2014 at ¶31.

4. High-Throughput Screening

A POSITA would have been familiar with both manual or high-throughput screening (choice to be determined by the number of parameters tested) to identify and optimize the conditions for co-crystallization. EX2014 at ¶¶46-49. Both

methods were already known in the prior art. *Id.* A POSITA would also have been familiar with high-throughput screening and its application to crystallization. *Id.* at ¶¶47-49. High-throughput screening is the ability to simultaneously assess a vast library of compounds for certain properties, for example, solubility, by testing numerous solvents and conditions at the same time. *Id.* at ¶47. By 2002-2003, high-throughput screening for polymorphs was well-known. *Id.* at ¶48. The basic steps of high-throughput screening include: (1) preparing samples and compound libraries, (2) automating relevant benchtop testing procedure(s), (3) configuring a robotic workstation to execute the automated procedure(s), and (4) acquiring and processing the testing data. *Id.* at ¶47. As of 2002-2003, a POSITA would have recognized that these same basic steps could be applied to high-throughput crystallization. *Id.* at ¶49. This screening technique was available to a POSITA to identify the conditions under which co-crystals would form. *Id.* Using the same basic steps as high-throughout screening for polymorphism, a POSITA would have been able to identify, for example, different solvents to see which could be used to form a co-crystal. *Id.* at ¶¶48-49.

III. PERSON OF ORDINARY SKILL IN THE ART

For the limited purpose of this Patent Owners' Response, Patent Owners do not contest the level of ordinary skill in the art set forth in the Petition. *See* Petition at 7-8. And, as stated earlier, the level skill here is very high.

IV. CLAIM CONSTRUCTION

Patent Owners agree with the application of the parties' constructions from the district court litigation identified in the Petition. *See* Petition at 8-10.

V. LEGAL STANDARDS

A. Written Description

To satisfy the written description requirement, the specification must describe the invention sufficiently to convey to a POSITA that the patentee had “possession” of the claimed invention at the time of the application. *Ariad Pharms. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The “possession” inquiry is not limited to the “four corners of the specification,” rather, it is viewed objectively “from the perspective of a person of ordinary skill in the art.” *Id.* The required level of detail to satisfy the written description requirement varies depending on the nature and scope of the claims, the existing knowledge in the particular field, the extent and content of the prior art, and the maturity and predictability of the technology. *Id.* “It is not necessary that the application describe the claim limitations exactly, . . . but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that [the inventors] invented processes including those limitations.” *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976). A “patent need not teach, and preferably omits, what is well known in the art.” *Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir.

2006) (citation omitted); *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) (“The ‘written description’ requirement must be applied in the context of the particular invention and the state of the knowledge.”); *see also Zoltek Corp. v. United States*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (“The written description ‘need not include information that is already known and available to the experienced public.’”) (citation omitted). “Because the specification is viewed from the perspective of one of skill, in some circumstances, a patentee may rely on information that is ‘well-known in the art’ for purposes of meeting the written description requirement.” *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011). Likewise, the Patent Office affirmatively advises applicants that when processes are “conventional and generally widely known in the field of the invention described, and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail.” M.P.E.P. § 608.01(a).

One test of whether there is adequate written description in the specification is “either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350 (citing *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)). “Adequate written description does not require a

perfect correspondence between the members of the genus and the asserted common structural feature; for a functionally defined genus like the one at issue here, we have spoken more modestly of a ‘correlation between structure and function.’” *Ajinomoto Co., Inc. v. Int’l Trade Comm’n*, 932 F.3d 1342, 1360 (Fed. Cir. 2019) (citing *Ariad*, 598 F.3d at 1350); *see also Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 996-1001 (Fed. Cir. 2020) (finding adequate written description support because a person of ordinary skill in the art of petroleum refining with the claimed chemical and physical properties in mind, would have been able to envision and readily produce a composition having those characteristics).

B. Enablement

35 U.S.C. § 112(a) states that: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms are to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. “To prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without ‘undue experimentation’.” *Alcon Research v. Barr Labs., Inc.*,

745 F.3d 1180, 1188 (quoting *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988)). “[T]he artisan’s knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.” *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). “Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *Wands*, 858 F.2d at 737. The *Wands* factors are: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *Id.* “[I]t may suffice to give an example (or a few examples) if the specification also discloses ‘some general quality . . . running through’ the class that gives it ‘a peculiar fitness for the particular purpose.’ In some cases, disclosing that general quality may reliably enable a person skilled in the art to make and use all of what is claimed, not merely a subset.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 611 (2023) (quoting *Incandescent Lamp Patent*, 159 U.S. 465, 475 (1895)).

VI. PETITIONER FAILS TO SHOW THAT THE CHALLENGED CLAIMS ARE OBVIOUS

Petitioner's contention that the prior art renders the Challenged Claims obvious has no merit. The asserted references are not prior art to the '344 Patent because at least the '956 Application provides written description support for and enables the Challenged Claims, which are therefore entitled to a priority date no later than 2003 and predates all of the asserted prior art.

A. The '956 Application Provides Written Description Support for the Claimed Co-Crystals

The '956 Application provides written description support for the full scope of the Challenged Claims. As a result, the Challenged Claims are entitled to the 2003 filing date of the '956 Application.

A POSITA would have understood that the inventors possessed the full scope of the claimed co-crystals. For example, Dr. Ward demonstrated that all of the claim limitations of the Challenged Claims are present in the examples of the '956 Application. EX2014 at ¶¶32, 53. Not only do the examples provide adequate written description support, but as discussed above in Section II(B), the '956 Application further provides information on the types of compounds that can be used as APIs and co-formers. EX1001 at 3:35-37; *see also id.* at Fig. 24. The '344 Patent even provides a flow chart to assist in the selection of an API and co-former based on their chemical functionalities. *Id.* at Fig. 24.

The well-known principles of hydrogen bonding, including those set forth by Dr. Etter as discussed above in Section II(C)(1), would allow a POSITA to predict whether a co-crystal of an API satisfying claims 10, 11, and/or 18 would form, regardless of whether a particular polymorph of a co-crystal forms or not. EX2014 at ¶54. A POSITA in 2003 would have understood the likelihood of certain functional groups to form supramolecular synthons and crystal packing motifs defined by those synthons, based on numerous examples in single-component crystals and literature descriptions of hydrogen-bonding patterns. *Id.* This is evident from Dr. Etter's seminal work describing the "rules" for predicting hydrogen bonding motifs based on the "strength" of hydrogen bond donors and acceptors. *See supra* Section II(C)(1); *see also* EX2014 at ¶54.

A POSITA in 2003 would also have a good understanding of the likelihood of certain functional groups forming supramolecular synthons. EX2014 at ¶55. In fact, a POSITA would have an understanding of the ranking of certain functional groups to form supramolecular synthons in the event multiple hydrogen bonding groups were present. EX2014 at ¶¶54-55. And a POSITA would have had sufficient working knowledge of whether hydrogen bonds between the API and some collection of co-formers were likely and, in the event of multiple potential synthons, the POSITA would have had a sufficient working knowledge of which ones would be preferred, even though other factors could steer synthon formation

toward combinations that do not follow the ranking suggested by prior studies of single component compounds and Dr. Etter's "rules." EX2014 at ¶55.

The claimed co-crystals have structural features that are common to the members of the genus. One test of whether there is adequate written description in the specification is "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (citing *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)). Novartis focuses all of its attention on the first test – representative species – and summarily discounts the second test without an in-depth look at what a person of ordinary skill in the art would already know from the teachings in the art. Petition at 13; EX1002 at ¶¶ 69, 75.

Petitioner's arguments ignore the high level of education and training a POSITA would bring to their understanding of the disclosure of the '956 Application. A "patent need not teach, and preferably omits, what is well known in the art." *Falkner*, 448 F.3d at 1365; *Capon*, 418 F.3d at 1358 ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge."); *see also Zoltek*, 815 F.3d at 1308 ("The written description need not include information that is already known and available to the experienced public."). Because "the specification is viewed from the perspective

of one of skill, in some circumstances, a patentee may rely on information that is ‘well-known in the art’ for purposes of meeting the written description requirement.” *Bos. Sci.*, 647 F.3d at 1366. Petitioner’s arguments ignore that “conventional and generally widely known” principles in the field, such as the principles of hydrogen bonding, Dr. Etter’s rules, formulation of pharmaceutical compositions, and co-crystals themselves would have been known to a POSITA. *See* Section II(C)(2) *supra*.

Given this high level of education and training, particularly with respect to hydrogen bonding and the formulation of pharmaceutical compositions, a POSITA would have understood that the crystallization of the API is a purification process and, by that time, the API has been highly characterized. EX2014 at ¶44. A POSITA would have already known the functional groups on the API that were available for bonding and, thus, would have been able to predict the formation of a co-crystal based on the structure of the compound. *Id.* at ¶¶54-56. A POSITA would use their knowledge of the formulation of pharmaceutical compositions to understand what FDA-approved solvents, co-formers, and/or GRAS compounds could be used in the crystallization step. *Id.* at ¶¶44-45. Then, a POSITA would then have been able to use high-throughput crystallization to quickly and easily identify for the appropriate conditions under which a co-crystal would form by, for example, testing numerous solvents at once. *Id.* at ¶¶47-49.

Petitioner makes hay in its Petition that there is no *perfect* example of the claimed co-crystals, lining up with each and every claim limitation. Petition at 13-15. That is not required. “It is not necessary that the application describe the claim limitations exactly, . . . but only so clearly that person of ordinary skill in the art will recognize from the disclosure that the inventors invented processes including those limitations.” *In re Wertheim*, 541 F.2d at 262. A POSITA would have recognized from the disclosure of the ’956 Application that the inventors invented the claimed co-crystals and the different embodiments of the examples.

Petitioner, through its expert Dr. Rogers, conducts the wrong analysis, focusing on whether a POSITA would be able to predict the *particular structure* of a co-crystal before it forms. *See* EX1002 at ¶78 (“A POSA would have understood that the *entire* structure of the API and co-former must be taken into account in determining whether any particular co-crystal will form; it is not sufficient to just look at the functional groups.”) (underlining emphasis added); *id.* at ¶120 (“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.”) (underlining emphasis added) (citing EX1024 (Desiraju 2001)); *id.* at ¶124 “Fleischman 2003 also stated that ‘the crystal packing of APIs tends to *be even less predictable* than that of other organics because they often have multiple avenues for self-assembly and are therefore predisposed to exhibit

polymorphism.” (underlining emphasis added). In each of these quotations, Dr. Rogers focused on predicting whether a *particular* co-crystal will form, not whether a co-crystal will form at all as the Challenged Claims require. The Challenged Claims do not require a particular polymorph of the claimed co-crystal, they simply require a co-crystal with the claimed limitations.

Given the disclosure in the specification, and the relatively high knowledge of the art, a POSITA would understand that the inventors were in possession of the claimed cocrystals. EX2014 at ¶57.

B. The '956 Application Enables the Claimed Co-Crystals

The '956 Application enables the full scope of the Challenged Claims. “Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *Wands*, 858 F.2d at 737. The *Wands* factors are: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *Id.*

Under the *Wands* factors, 7 out of 8 factors support the enablement of the Challenged Claims.

1. The relative skill of those in the art

As both Petitioner's and Patent Owners' experts agree, the relative skill of those in the art is high. EX2014 at ¶¶23-24; EX1002 at ¶126; EX2016 at 31:2-8. As discussed above in Section II(C) *supra*, given this high level of education and training, a POSITA would have in-depth knowledge of hydrogen bonding, formulation of pharmaceutical compositions, co-crystals, and high-throughput screening. And the '956 application teaches a POSITA how to apply those principles to pharmaceutical compositions. EX1001 at 3:19-26, 3:365-27, 9:27-30, Fig. 24.

This factor weighs in favor of enablement. EX2014 at ¶¶59-63.

2. The quantity of experimentation necessary, the state of the prior art, and the predictability or unpredictability of the art

The quantity of experimentation necessary, the state of the prior art, and the predictability or unpredictability of the art can be considered together. The quantity of experimentation to achieve the claimed co-crystals is relatively low. As discussed above in Section II(C) *supra*, a POSITA would understand how hydrogen bonding works and the formulation of pharmaceutical compositions. EX2014 at ¶¶34-46. Given this high level of understanding, a POSITA would be able to identify appropriate APIs and other materials to create the claimed co-crystals.

No undue experimentation would be required to assess whether the claimed co-crystals would form. As Dr. Ward acknowledged, high-throughput crystallization was available and could reduce the amount of experimentation required to test for co-crystals. EX2014 at ¶¶47-49, 64-65.

Novartis focuses on Desiraju 2001 to support its statement that “[a]s of 2002/2003, it was not possible to predict with any reasonable certainty whether a co-crystal would form between two or more components, or to the extent one did form, what non-covalent interactions, such as hydrogen bonding, would exist between the co-crystal components.” EX1002 at ¶120 (citing Ex. 1024, Desiraju 2001). Novartis selectively quotes the article. EX2014 at ¶68; *see also id.* at ¶¶69-71. In fact, Desiraju clearly states that the hydrogen bond, one of the most important interactions for forming homosynthons or heterosynthons, is the “master key” in steering crystal structure. *See* Ex. 1024 at 399 (“Although at a simple level molecular recognition can be said to hinge on isotopic interactions, at a higher level it is an anisotropic interaction that is the master key: the hydrogen bond.”)

Novartis focuses on allegedly high failure rates for co-crystal experiments, alleging that the inventors published only a 20% “success ratio.” *See* Petition at 29 (citing Fleischman). Fleischman reported “[f]or the 10 new cocrystals reported, approximately 50 cocrystal formers were used with [carbamazepine], giving a success ratio of 20%.” EX2014 at ¶73. Dr. Rogers characterizes the remaining

80% as “failures.” EX1002 at ¶124. But, a POSITA in 2002/2003 would have recognized that the alleged “failures” in Fleischman were not reported; therefore, a POSITA could not have drawn any conclusions as to whether these alleged “failures” included chemical functional groups that would have been expected to form heterosynthons with carbamazepine. EX2014 at ¶73.

In addition, Novartis fails to appreciate that a 20% success rate would actually be considered good in this field. EX2014 at ¶74. Dr. Rogers fails to note the successes in the field when he points out alleged “failed attempts to predict” co-crystallization. *See, e.g.*, EX1002 at ¶121 (citing EX1027 (Reddy), EX1025 (Aakeroy), EX1007 (Ueto)); EX1027 (Reddy 2004) at 90, 92 (reporting formation of carboxylic acid and amide co-crystal)); EX1025 (Aakeroy 2003) at 164 (reporting that three compounds out of four formed co-crystals with at least one co-former); EX1007 (Ueto 2012) at 487 (reporting, in Table 2, FS-NCT cocrystals formed in 15 of the 16 crystallization solvents).

Furthermore, throughout Petitioner’s expert’s declaration, Dr. Rogers refers to the inability of a POSITA to *predict* the crystalline structures. But as Dr. Rogers admitted at his deposition, the Challenged Claims are directed to pharmaceutical compositions, *not* methods. EX2016 at 47:15-49:7. It does not matter whether a POSITA could *predict* the specific structure of the co-crystal as long as the POSITA could make the co-crystal and assess its structure.

This factor weighs in favor of enablement. EX2014 at ¶¶64-79.

3. The amount of direction or guidance presented and presence of working examples

There is ample description in the '956 Application to guide a POSITA on how to make a claimed co-crystal. Not only are there descriptions of appropriate APIs, co-formers, and solvents to use, *see* Section II(B), there are also 19 examples that provide guidance to a person of ordinary skill in the art. EX2014 at ¶¶77-79.

This factor weighs in favor of enablement.

4. The nature of the invention

Given the high level of a person of ordinary skill in the art, the nature of the inventions – pharmaceutical compositions comprising cocrystals – weighs in favor of enablement. EX2014 at ¶¶80-82.

VII. CONCLUSION

Seven out of eight *Wands* factors weigh in favor of enablement. The Board should find that the '956 Application enables the Challenged Claims, and that the Challenged Claims are entitled to a priority date of no later than 2003. For the foregoing reasons, Patent Owner respectfully requests a final written decision confirming patentability of the Challenged Claims.

Respectfully submitted,

Date: June 5, 2024

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CERTIFICATION UNDER 37 CFR § 42.24(d)

Under the provisions of 37 CFR § 42.24(d), the undersigned hereby certifies that the word count for the foregoing Patent Owner's Response to Petition totals 5,509, which is less than the 14,000 allowed under 37 CFR § 42.24(b)(1).

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), the undersigned certifies that on June 5, 2024, a complete and entire copy of this Patent Owners' Response and its supporting exhibits were provided via email, to the Petitioner by serving the email correspondence addresses of record as follows:

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