

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.

U.S. Patent No. 10,633,344

**DECLARATION OF ROBIN D. ROGERS, Ph.D.
IN SUPPORT OF PETITIONER'S REPLY IN THE
INTER PARTES REVIEW OF U.S. PATENT NO. 10,633,344**

TABLE OF CONTENTS

I.	INTRODUCTION	6
II.	MATERIALS CONSIDERED	9
III.	RESPONSES TO DR. WARD’S BACKGROUND OPINIONS	9
A.	The ’344 Patent	10
1.	Claim Construction of “Permits Formation”	10
2.	The ’956 Application’s/’344 Patent’s Examples	11
3.	Figure 24 of the ’956 Application/’344 Patent Is Just a Trial- and-Error Research Plan, Not Enablement or Written Description Support	13
4.	Co-Crystallization Is Separate from Formulation of Pharmaceutical Compositions in the Context of the ’956 Application/’344 Patent	20
B.	Knowledge of the HHS Solvent Guidance Would Not Have Allowed a POSA to Make and Use or “Visualize or Recognize” the Full Scope of Claimed Co-Crystals	24
C.	High-Throughput Screening Would Not Have Allowed a POSA to “Visualize or Recognize” the Full Scope of Claimed Co-Crystals, or to Make and Use them Without Undue Experimentation	31
1.	High-Throughput Screening Is Not Disclosed in the ’956 Application or ’344 Patent and There Is No Evidence that It Was Used in March 2003 to Screen for Co-Crystals.....	34
2.	High-Throughput Screening Would Not Have Allowed a POSA to “Visualize or Recognize” the Full Scope of Claimed Co- Crystals.....	36
3.	Even with High-Throughput Screening, Undue Experimentation Would Have Been Required to Make and Use the Full Scope of Claimed Co-Crystals	36

4.	Determining Whether the Products from the Screening Experiments Resulted in Co-Crystals Within the Scope of the Challenged Claims Could Not Have Been Done Automatically With High-Throughput Screening Equipment.....	43
D.	Hydrogen Bonding Principles and Etter’s “Rules” Would Not Have Allowed a POSA to “Visualize or Recognize” or “Make and Use” the Full Scope of Claimed Co-Crystals.....	46
1.	Hydrogen Bonding Principles and Etter’s “Rules” Are Not Disclosed in the ’956 Application or ’344 Patent.....	47
2.	Dr. Ward and Patent Owners Never Explain How to Apply Hydrogen Bonding Principles or Etter’s “Rules” or Show Any Examples of Their Prospective Application to Co-Crystals.....	49
3.	Etter’s “Rules” Have Limitations	50
IV.	CLAIMS 10, 11, AND 18 ARE NOT ENTITLED TO A MARCH 2003 PRIORITY DATE BECAUSE THE ’956 APPLICATION DOES NOT PROVIDE ADEQUATE WRITTEN DESCRIPTION SUPPORT FOR THE FULL SCOPE OF CLAIMED CO-CRYSTALS	57
A.	It is Undisputed that the ’956 Application Fails to Disclose a Representative Number of Co-Crystals of the Claimed Genus	57
B.	The ’956 Application Fails to Disclose Common Structural Features of the Claimed Co-Crystal Genus	58
1.	The <i>Functional</i> Co-Crystal Limitations Are Not Supported By <i>Structural</i> Features Common to the Claimed Genus of Co-Crystals Allowing a POSA to “Visualize or Recognize” the Full Scope of Claimed Co-Crystals.....	58
2.	The ’956 Application’s Examples Do Not Disclose Structural Features Common to All Members of the Claimed Co-Crystal Genus.....	63
3.	The Additional Knowledge of Hydrogen Bonding Principles, Such as Etter’s “Rules,” Would Not Have Allowed a POSA to “Visualize or Recognize” the Full Scope of Claimed Co-Crystals.....	65

4.	The Additional Ability to Perform High-Throughput Screening Would Not Have Allowed a POSA to “Visualize or Recognize” the Full Scope of Claimed Co-Crystals	68
V.	CLAIMS 10, 11, AND 18 ARE NOT ENTITLED TO A MARCH 2003 PRIORITY DATE BECAUSE THE ’956 APPLICATION DOES NOT ENABLE THE FULL SCOPE OF CLAIMED CO-CRYSTALS	69
A.	The Nature of the Invention Weighs in Favor of Non-Enablement....	70
B.	The Relative Skill of Those in the Art Is Neutral with Respect to Enablement.....	72
1.	Knowledge of and the Ability to Perform High-Throughput Co-Crystal Screening Would Not Have Allowed a POSA to Make and Use the Full Scope of Claimed Co-Crystals Without Undue Experimentation	73
2.	Knowledge of the “Formulation of Pharmaceutical Compositions” and “Co-Crystal Formation” Would Not Have Allowed a POSA to Make and Use the Full Scope of Claimed Co-Crystals Without Undue Experimentation.....	75
3.	Knowledge of Hydrogen Bonding Principles, Such as Etter’s “Rules,” Would Not Have Allowed a POSA to Make and Use the Full Scope of Claimed Co-Crystals Without Undue Experimentation	76
C.	The State of the Art & Unpredictability of the Art Weigh in Favor of Non-Enablement.....	77
1.	Dr. Ward and Patent Owners Are Incorrect that I “Selectively Quote[]” Desiraju 2001 in my Opening Declaration	81
2.	Dr. Ward’s and Patent Owners’ Arguments Regarding Fleischman 2003 and Other Co-Crystal Failures Further Support the Unpredictability of Forming Co-Crystals Within the Scope of the Challenged Claims	84
D.	The Quantity of Experimentation Weighs in Favor of Non-Enablement.....	87

E.	The Presence or Absence of Working Examples Weighs in Favor of Non-Enablement.....	90
F.	The Lack of Direction or Guidance Weighs in Favor of Non-Enablement.....	92
VI.	CONCLUSION.....	97

I, Robin D. Rogers, Ph.D., hereby declare as follows:

I. INTRODUCTION

1. I am the same Robin D. Rogers who submitted a declaration (Ex. 1002, “Opening Declaration”) in support of Novartis’s Petition for *Inter Partes* Review (“petition”) of U.S. Patent No. 10,633,344 (“the ’344 patent”).

2. I have been asked to consider and respond to the Corrected Declaration of Michael Ward, Ph.D. (Ex. 2014, the “Ward Declaration” or “Dr. Ward’s declaration”) submitted in support of Patent Owners’ Response to Novartis’s petition (the “Patent Owners’ Response” or “POR”).

3. Specifically, I was asked to consider and respond to the opinions of Dr. Ward that U.S. Application No. 10/378,956 (“the ’956 application,” Ex. 1015), the ’344 patent’s parent application, (i) sufficiently describes the claimed genus of co-crystals so as to satisfy the written description requirement and (ii) enables the claimed genus of co-crystals such that the challenged claims (*i.e.*, claims 10, 11, and 18) are entitled to the March 3, 2003 priority date of the ’956 application.

4. Based on my review of Dr. Ward’s declaration and the Patent Owners’ Response, there are no disputed claim construction issues that impact the outcome of this proceeding. In section VIII.A of my Opening Declaration (Ex. 1002), I provided the definitions of “API,” “API homosynthons,” “carbonyl,” “carboxamide,” “co-former,” “heterosynthon dimer,” and “supramolecular

synthon” that I applied in connection with my opinions (and that I apply in this declaration), which Dr. Ward does not dispute. And in section VIII.B of my Opening Declaration, I provided the definition of “co-crystal” that Petitioner’s counsel asked me to adopt, and that Dr. Ward adopted in forming his opinions. Ex. 1002, Opening Declaration section VIII.B; Ex. 2014, Ward Declaration ¶ 30. Although there is one term—“permits formation” (discussed in section III.A.1 below)—that Dr. Ward and I disagree on, for the purposes of this proceeding, my conclusions do not change regardless of which definition is used. *See below* section III.A.1.

5. Neither Dr. Ward nor Patent Owners dispute that U.S. Provisional Application No. 60/360,768 (“the ’768 application,” Ex. 1014), the application to which the ’344 patent claims earliest priority, does not adequately describe or enable the challenged claims and therefore, the challenged claims are not entitled to a priority date of March 1, 2002 (the filing date of the ’768 application). Accordingly, I do not discuss the ’768 application in this declaration. Moreover, although Dr. Ward discusses the alleged priority date as “2002/2003,” which he refers to as the “Critical Date,” (Ex. 2014, Ward Declaration ¶ 17), the earliest priority date the challenged claims could now be entitled to is March 3, 2003 (which I will refer to as “March 2003”).

6. I note that Dr. Ward admits that the specification of the '956 application is the same as that of the '344 patent and therefore he refers to those specifications interchangeably. Ex. 2014, Ward Declaration ¶ 32 n.1. For the purposes of providing my opinions in this declaration, I focus on the '956 application, but I agree with Dr. Ward that the specifications of the '344 patent and '956 application are the same, including the nineteen examples, and, for clarity, I may at times refer to both specifications.

7. Additionally, neither Dr. Ward nor Patent Owners dispute (or even discuss) the opinions in my Opening Declaration that the challenged claims are anticipated or obvious. Ex. 1002, Opening Declaration sections XI, XII. Therefore, I do not discuss these issues in this declaration.

8. Patent Owners' Response and the Ward Declaration do not change my opinions that the challenged claims lack an adequate written description in, and are not enabled by, the '956 application for the full scope of claimed co-crystals. Importantly, Dr. Ward and Patent Owners do not dispute or address my opinion that the claimed genus of co-crystals is extremely broad and includes an *almost infinite* number of co-crystals. Ex. 1002, Opening Declaration ¶¶ 74, 115-118; *see below* ¶¶ 70, 95.

9. Patent Owners' Response and the Ward Declaration do not change my opinion that the earliest priority date the challenged claims could be entitled to is

February 13, 2014, the filing date of U.S. Application No. 14/179,862 (“the ’862 application”), which issued as the ’344 patent. For this reason, it is still my opinion that the challenged claims are invalid as anticipated and/or obvious as of February 13, 2014 in view of the art cited in my Opening Declaration. Ex. 1002, Opening Declaration sections XI, XII; *see also* ¶ 7, above.

II. MATERIALS CONSIDERED

10. In forming my opinions in this declaration, I considered the materials set forth in this declaration, including Patent Owners’ Response and the Ward Declaration (Ex. 2014) and the exhibits referenced therein.

III. RESPONSES TO DR. WARD’S BACKGROUND OPINIONS

11. Section VI of Dr. Ward’s declaration provides his opinions on the background of the ’344 patent, as well as topics that he purports relate to the ’344 patent and its claimed subject matter—pharmaceutical formulation, hydrogen bonding and Etter’s “rules,” and high-throughput and manual screening. I disagree with certain opinions expressed by Dr. Ward (and Patent Owners) related to these topics and discuss those disagreements below. None of Dr. Ward’s (or Patent Owners’) opinions on this background information would have allowed a POSA in March 2003 to “visualize or recognize” or “make and use” the full scope of claimed co-crystals.

A. The '344 Patent

1. Claim Construction of “Permits Formation”

12. Dr. Ward and I disagree on the construction of the claim term “permits formation” in the limitation of claim 10 that recites “wherein the API has a first chemical functionality that *permits formation* of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form.” Ex. 1001, '344 patent, col. 25, ll. 24-27 (emphasis added). In my opinion, this limitation requires actual formation of API homosynthons and not simply the possibility of interaction. In other words, the identical first chemical functionalities on adjacent API molecules must interact (by non-covalent hydrogen bonding) with one another. Ex. 1002, Opening Declaration ¶ 31. On the other hand, in Dr. Ward's opinion, “permits formation” means “allows for formation.” Ex. 2014, Ward Declaration ¶ 51. The specification supports my opinion. The specification instructs a POSA to select a chemical functionality on the API that is “capable of forming supramolecular synthons.” Ex. 1001, '344 patent, col. 3, ll. 65-67, col. 7, ll. 47-49, *see also* col. 3, ll. 41-44, col. 3, ll. 51-56, col. 9, ll. 57-62. The specification further instructs that “capable of forming” means that API homosynthons can, and, in fact, are, formed. Ex. 1001, '344 patent, col. 4, ll. 13-33 *see also* col. 3, l. 60 – col. 4, l. 12, col. 4, ll. 50-55, col. 7, l. 42 – col. 8, l. 15. Regardless, the construction of this term does not affect my conclusions in this

IPR. First, my enablement and written description opinions do not rely on the meaning of “permits formation.” Second, in my Opening Report, my anticipation and obviousness arguments include only APIs that do in fact form API homosynthons, which would satisfy either Dr. Ward’s or my construction.

2. The ’956 Application’s/’344 Patent’s Examples

13. Dr. Ward alleges that the ’344 patent specification’s nineteen examples “describe the limitations of [] claims 10, 11, and 18.” Ex. 2014, Ward Declaration ¶ 32; POR at 1 (“The [’956 application’s] specification contains nineteen unique examples, exemplifying various limitations in the Challenged Claims.”).

14. To the extent Dr. Ward is suggesting that each of the examples describes the limitations of the challenged claims, I disagree. Dr. Ward admits in Appendix C of his declaration—a chart identifying which examples he believes describe each claim element of the challenged claims—that not all nineteen examples satisfy *all* the elements of the claimed co-crystals. Ex. 2014, Ward Declaration, Appendix C; *see also* Ex. 1002, Opening Declaration ¶¶ 77-79, 82, 127-128 (explaining that not all nineteen examples meet the co-crystal limitations of the challenged claims). Specifically, in Appendix C, Dr. Ward identifies only nine examples—less than half—falling within claims 10 and 18 (*i.e.*, Examples 2,

7-11, 13-14, and 19) and only three of those nine examples falling within claim 11 (*i.e.*, Examples 11, 13, and 19). Ex. 2014, Ward Declaration, Appendix C.

15. I also disagree with Dr. Ward's allegation that the '344 patent's examples "provid[e] at least one example of each limitation" of claims 10, 11, and 18. Ex. 2014, Ward Declaration ¶ 53. Dr. Ward's own Appendix C does not identify any examples in the '344 patent or '956 application wherein the first chemical functionality of the API is a carbonyl or amine—two of the three first chemical functionality options for claims 10 and 11; in fact, his chart does not even include a row for "carbonyl." Ex. 2014, Ward Declaration, Appendix C. Therefore, by his own admissions, Dr. Ward acknowledges there is no support in the examples for the "carbonyl" or "amine" limitations of claims 10 and 11. Further, the co-crystals of the challenged claims require "at least one [API]" and "at least one co-former," and there are no examples of co-crystals of any of claims 10, 11, or 18 comprising more than one API and/or co-former as the claims allow. *See* Ex. 2014, Ward Declaration, Appendix C; Ex. 1001, '344 patent, col. 25, ll. 18-23; POR at 5 (Patent Owners admitting that the claimed co-crystals include "one or more co-formers").

3. Figure 24 of the '956 Application/'344 Patent Is Just a Trial-and-Error Research Plan, Not Enablement or Written Description Support

16. Dr. Ward and Patent Owners rely on Figure 24 of the '344 patent/'956 application for their enablement argument (discussed in section V.F below) and Patent Owners further rely on Figure 24—without support from Dr. Ward—for their written description opinion. However, I disagree with their characterization of this figure and their suggestion that it provides any meaningful enablement or written description support.

17. Dr. Ward and Patent Owners describe Figure 24 as “providing [a] scheme for preparing claimed co-crystals.” Ex. 2014, Ward Declaration ¶ 78; POR at 5 (alleging that Figure 24 “explains how to prepare the claimed co-crystals”). But Figure 24 does not disclose *any* co-crystals, it is not specifically focused on preparation of the co-crystals of the challenged *claims*, and it does not provide any specific details on how to prepare a co-crystal of any two (or more) API and/or co-former components. Moreover, neither Dr. Ward nor Patent Owners explain how a POSA in March 2003 would have applied Figure 24 to make and use (or to “visualize or recognize”) the full scope of claimed co-crystals, either on its own or in connection with other techniques like manual or high-throughput screening (discussed in section III.C below).

18. Figure 24, which the '344 patent and '956 application describe as “an exemplified scheme for preparing multiple-component phase compositions of the subject invention,” (Ex. 1001, '344 patent, col. 7, ll. 13-15; Ex. 1015, '956 application ¶ [0037]), merely presents a trial-and-error research or experimental design plan for preparing multiple component crystals (which includes co-crystals) in a flow chart. Ex. 1002, Opening Declaration ¶¶ 32, 132. Nothing in this figure or elsewhere in the '344 patent or '956 application explains how a POSA could have used this figure to “visualize or recognize” the full scope of claimed co-crystals.

19. Nor does Figure 24 provide any direction or guidance for how a POSA could have made and used the full scope of claimed co-crystals, as this figure lacks numerous pieces of information that a POSA would have needed in March 2003 to attempt to do so. For instance, Figure 24 does not provide any exemplary APIs or co-formers that fall within the full scope of the claims. Nor does it provide any structural information about such APIs or co-formers or how to identify them. Though the '956 application and '344 patent provide a few examples of APIs and co-formers that qualify as such within the context of the challenged claims, these examples are not representative of the entire genus of APIs, the entire genus of co-formers, or the entire genus of API and co-former combinations, covered by the challenged claims. Ex. 1002, Opening Declaration ¶¶ 76, 78, 82. In my Opening Declaration, I explained that the API(s) can be any

“biologically active moiety having a therapeutic effect on a human or animal” (Ex. 1002, Opening Declaration ¶¶ 55, 70, citing Ex. 1001, ’344 patent, col. 9, ll. 27-34), having a carboxamide, carbonyl, or amine. This is without regard to shape, size, complexity, or the number of additional functional groups. I further identified over fifty examples of molecules having a “-C(=O)NH₂” (*i.e.*, a carboxamide) group that would have qualified as APIs by March 2003 and explained that many more would have qualified. Ex. 1002, Opening Declaration ¶¶ 71, 116. I also identified over one hundred GRAS compounds that would have qualified as co-formers by this same time and also explained that thousands of other molecules would have qualified as co-formers (Ex. 1002, Opening Declaration ¶¶ 72-74, 117-118), which neither Dr. Ward nor Patent Owners dispute.

20. In addition, Figure 24 lacks at least the following information that a POSA would have needed in March 2003 to make and use the full scope of claimed co-crystals and neither Dr. Ward nor Patent Owners explain how the POSA would have determined this information at all, let alone without expending an unreasonable amount of time and effort:

- (i) how to evaluate each API, including what “[e]valuat[ion]” is needed, the tests and analyses to perform for the evaluation, how to perform them, and what information to obtain (Step 1);

- (ii) how to determine, based on the evaluation in Step 1, which APIs to select for Step 2;
- (iii) how to identify the chemical functionalities on each API molecule that are “suitable ... for form[ing] ... supramolecular synthons via [] self-assembly” (*i.e.*, API homosynthons), including how to determine whether a chemical functionality is “complementary from the perspectives of geometry/shape and molecular recognition” (Step 2);
- (iv) for *each* API that is suitable for forming API homosynthons in Step 2, how to determine which chemical functionalities on the API “from within a plurality of [unidentified] chemical functionalities”
 - (a) will form a new supramolecular synthon (presumably with the second chemical functionality of an unidentified co-former but Figure 24 also lacks this information) without disrupting the API homosynthons in Step 2 (part 1 of Step 3a), and
 - (b) will form a new supramolecular synthon (presumably with the second chemical functionality of an unidentified co-former but Figure 24 also lacks this information) by

disrupting the API homosynthons in Step 2 (part 2 of Step 3a);

- (v) for *each* API that proceeds to Step 3a, how to identify co-formers (which I explained above can include thousands of possible molecules, ¶ 19) “suitable for use” with that API “based upon the results from Step 3,” including what tests and analyses to perform, how to perform them, what information to obtain, and how to use the information obtained to determine whether a given co-former is “suitable for use” with that API (Step 4);
- (vi) for *each* API and co-former combination (including combinations of more than one API and/or co-former) identified after Step 4, how to prepare co-crystals that satisfy *all* limitations of the claimed co-crystals, including what co-crystallization method(s) to try (Figure 24 provides four examples—crystallization from solution, cooling the melt, sublimation, and grinding—which contain no details or guidance in the figure itself or elsewhere in the specification about how to perform them), what co-crystallization conditions and variables to modify for each co-crystallization method tried and how to do so (Step 5); and

- (vii) for *each* solid form resulting from following Steps 1-5, how to analyze the crystal structure to determine (a) whether a co-crystal actually formed *and*, if it did, (b) whether it had all the non-covalent hydrogen bonding interactions required by the challenged claims, including what characterization technique(s) to use, how to perform the analyses, what data to obtain, how to obtain the data, how to process the data, and how to use the data to make these determinations.

21. For Step 5 of Figure 24, depending on the co-crystallization method selected from amongst those identified in Figure 24 (and a POSA may have had to try more than one method for each combination of API(s) and co-former(s)), for *each* API and co-former combination (including combinations of more than one API and/or co-former), a POSA would have had to consider an array of co-crystallization conditions and variables, such as (i) the amount(s) (and stoichiometric ratio) of each of the API(s) and co-former(s), (ii) the solvent(s), solvent combination(s), solvent ratio(s), and solvent concentration(s), (iii) the time for each step in the co-crystallization (*e.g.*, the time(s) to dissolve each of the API(s) and co-former(s) (and any other components), the evaporation time, and the incubation time to allow the co-crystal to form), (iv) the temperature(s) and/or temperature range(s) for each step in the co-crystallization (*e.g.*, the temperature(s)

at which to dissolve each of the API(s) and co-former(s) (and any other components), and the incubation temperature), (v) the heating rate(s), (vi) the cooling rate(s), (vii) the mixing/stirring rate(s) and time(s) (including whether to mix/stir at all), (viii) the evaporation rate(s), (ix) the carrier gas(es), carrier gas combination(s), and carrier gas combination ratio(s) to use for evaporation, (x) the degree of supersaturation to induce the co-crystallization, (xi) the additive type(s) and concentration(s) of the additive(s), (xii) the pH of the solution(s), (xiii) the co-crystallization vessel (including the vessel material and type), etc. And, further, for *each* combination of API(s) and co-former(s), a POSA also would have had to consider whether and how to vary each of these different conditions and variables—both in isolation and in conjunction with the other conditions and variables—effectively resulting in an incalculable number of experiments.

22. Co-crystal formation is unpredictable (*e.g.*, Ex. 1002, Opening Declaration section IX.B.1.c; section V.C below) and, thus, preparing the full scope of claimed co-crystals in March 2003 by following the scheme in Figure 24 would have been mere trial-and-error experimentation, requiring the POSA to undergo an unreasonable number of experiments—no less than hundreds of thousands of experiments with no guarantee that any given API and co-former within the scope of the challenged claims would ever form a co-crystal. Ex. 1002, Opening Declaration ¶¶ 32, 132, 133; POR at 5, 22, 25. In view of this trial-and-

error experimentation, a POSA could not have used Figure 24 to “visualize or recognize” the full scope of claimed co-crystals or to make and use the full scope without undue experimentation.

4. Co-Crystallization Is Separate from Formulation of Pharmaceutical Compositions in the Context of the '956 Application/'344 Patent

23. Dr. Ward and Patent Owners allege that a POSA in 2002/2003 would have viewed co-crystallization of an API as a purification step in the formulation of a pharmaceutical composition. Ex. 2014, Ward Declaration ¶ 44; POR at 8, 19. I disagree that a POSA would have understood co-crystallization in the context of the '956 application or '344 patent to be part of the formulation of a pharmaceutical composition. See ¶¶ 24-27 below. But regardless of whether a POSA would have considered co-crystallization to occur during “formulation of a pharmaceutical composition” (as Dr. Ward and Patent Owners allege) or prior to formulation of the pharmaceutical composition (as reflected in the '956 application and '344 patent), my conclusion that a POSA could not have made and used the full scope of the claims without undue experimentation does not change. See section V below.

24. Neither Dr. Ward nor Patent Owners identify any disclosures in the '956 application or '344 patent to support their allegation that preparation of co-crystals, *i.e.*, co-crystallization, was part of the formulation of a pharmaceutical

composition. In fact, both the '956 application and '344 patent describe preparing a co-crystal as a *separate step* from formulation of the pharmaceutical composition containing that co-crystal. Specifically, both specifications state:

The multiple-component phase compositions [for example, co-crystals] can be formulated according to known methods for preparing pharmaceutically useful compositions. Such pharmaceutical compositions can be adapted for various forms of administration, such as oral, parenteral, nasal, topical, transdermal, etc. The multiple-component phase solids of the subject invention can be made into solutions or amorphous compounds, as injections, pills, or inhalants, for example. Optionally, the pharmaceutical compositions can include a pharmaceutically acceptable carrier or diluent. Formulations are described in a number of sources which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* (Martin E W [1995] Eastone Pennsylvania, Mack Publishing Company, 19th ed.) describes formulations that can be used in connection with the subject invention

Ex. 1015, '956 application ¶ [0049] (emphasis added); Ex. 1001, '344 patent, col. 10, ll. 6-21 (similar). In other words, formulation of the co-crystal into a pharmaceutical composition occurs *after* the co-crystal has already been prepared, *i.e.*, after co-crystallization.

25. Further, the '956 application and '344 patent were filed based on the alleged discovery of novel co-crystals, not their formulation by “known methods for preparing pharmaceutically useful compositions.” Neither the '956 application nor the '344 patent mention formulation of pharmaceutical compositions in the “Abstract,” “Background of the Invention” or “Brief Summary of the Invention” sections or disclose that any co-crystal in the examples was ever formulated into a

pharmaceutical composition. *See generally* Ex. 1015, '956 application Abstract, ¶¶ [0001]-[0013], [0056]-[0177]; Ex. 1001, '344 patent, Abstract, col. 1, l. 17 – col. 5, l. 14, col. 11, l. 60 – col. 23, l. 59. Further, the '956 application and '344 patent focus on *making new co-crystals, not purifying already made co-crystals* for pharmaceutical formulation. Thus, co-crystallization in the context of the '956 application and '344 patent refers to preparing co-crystals *prior to* formulation into a pharmaceutical composition.

26. Dr. Ward's sole support for co-crystallization being a purification step in the context of the '956 application and '344 patent is a statement from Morissette 2004 (which was not prior art as of March 2003)—“Most APIs ... are purified and isolated by crystallization from an appropriate solvent during the final step in the synthetic process.” Ex. 2014, Ward Declaration ¶ 44 (citing Ex. 2011, Morissette 2004 at 276). I disagree that this statement supports his conclusion. This sentence in Morissette 2004 is discussing the “synthetic process” (*i.e.*, preparing the API), not formulating it into a pharmaceutical composition. Further, Morissette 2004 discusses, in addition to co-crystals, polymorphs, salts, solvates, and amorphous pharmaceutical solids (Ex. 2011, Morissette 2004 at 275-78), and Dr. Ward provides no explanation for how this statement, which omits any mention of co-crystals, co-crystallization, *or* formulation, relates to these concepts, much less supports his opinion.

27. Because co-crystallization according to the '956 application and '344 patent (*i.e.*, preparing the co-crystal) is *not* a step in the formulation of a pharmaceutical composition, I disagree with Dr. Ward and Patent Owners' subsequent argument that by the time a POSA arrived at the co-crystallization step, he or she would have "already tested and understood the solubility parameters of [the] 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." Ex. 2014, Ward Declaration ¶ 44; POR at 8-9. To the contrary, this "pre-formulation" work is a critical part of the work that a POSA would have needed to do to make and use the full scope of claimed co-crystals, and the POSA would have had to determine these properties largely through unpredictable trial-and-error experimentation as I discussed in section III.A.3 above. In addition, although Dr. Ward and Patent Owners do not explain what they mean by identifying "suitable" co-formers for any API, to the extent they mean co-formers that will interact with that API, this work is a key aspect of the invention – not merely "pre-formulation" work.

28. I note that if Dr. Ward is taking the position that co-crystals are first made and then subsequently purified, and he is only focusing on the subsequent purification step in his analysis, he is intentionally ignoring the most relevant step—formation of the co-crystal for the first time. My opinions in this declaration

about the amount of work required to prepare co-crystals apply to preparation of the co-crystals for the first time.

29. I further note that if by “pharmaceutical composition,” Dr. Ward is referring to a co-crystal by itself (not a co-crystal with excipients for pharmaceutical use), and if by “formulation,” Dr. Ward is referring to synthesizing (not combining the co-crystal with excipients for pharmaceutical use), his use of these terms is confusing and inconsistent with how these terms are used in the ’956 application and ’344 patent, as well as the challenged claims. Regardless, my opinions would not change. Attempting to prepare a co-crystal involving any particular combination of API(s) and co-former(s) was not predictable and would have required extensive trial-and-error experimentation, including evaluating (as Dr. Ward acknowledges, Ex. 2014, Ward Declaration ¶ 44) “the solubility parameters of [the] API[s], 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.” *See above* section III.A.3.

B. Knowledge of the HHS Solvent Guidance Would Not Have Allowed a POSA to Make and Use or “Visualize or Recognize” the Full Scope of Claimed Co-Crystals

30. Dr. Ward refers to guidance from the U.S. Department of Health and Human Services (“HHS”) “list[ing] solvents ... based on their assigned classes”

that a POSA allegedly would have been aware of as of March 2003 (Ex. 2014, Ward Declaration ¶ 45 (citing Ex. 2012, November 2003 HHS Guidance)), but he fails to explain how it is relevant to his opinions and, specifically, how it would have allowed a POSA in March 2003 to make and use or “visualize or recognize” the full scope of claimed co-crystals.

31. As I explained in section III.A.3 above, preparing the full scope of the claimed co-crystals would have required trial-and-error experimentation of no less than hundreds of thousands of co-crystallization experiments with no guarantee that a given API and co-former within the scope of the challenged claims would ever co-crystallize. Selecting the different solvents, solvent combinations, solvent ratios, and solvent concentrations to test would have been a complex undertaking in and of itself and would have been only a small part of this multifaceted process.

32. If Dr. Ward is relying on this November 2003 HHS Guidance (which was not prior art as of March 2003) to allege that it would have provided a POSA with a finite list of solvents to try, even the twenty-seven class 3 solvents the guidance discloses—solvents not known “as a human health hazard at levels normally accepted in pharmaceuticals” (Ex. 2012, November 2003 HHS Guidance at 7)—would have made this experimentation unreasonable. For each co-crystallization method that requires solvent, just considering these twenty-seven solvents alone, including different single solvents, different solvent combinations

(comprising any two or more solvents), different ratios of the solvent combinations, and different concentrations of the single solvents and solvent combinations, would have resulted in thousands upon thousands of combinations to try. And this does not even take into account the numerous other variables a POSA would have needed to consider when trying to co-crystallize *each* API and co-former combination (see also paragraphs 20-21 above). The November 2003 HHS Guidance and 1997 HHS Guidance (Ex. 2013) that Dr. Ward discusses lack any guidance for how a POSA would have selected the appropriate solvent(s) and/or solvent combination(s) for co-crystallizing any given combination of API(s) and/or co-former(s), and they lack any solubility information about any APIs or co-formers in any of the disclosed solvents. Further, no understanding of, and/or the ability to perform, manual or high-throughput screening for co-crystals (discussed in section III.C below), would have provided a POSA in March 2003 with this solvent or solubility information or made the amount of experimentation required to identify such information reasonable.

33. Thus, the HHS guidance documents, and/or the ability to perform manual or high-throughput screening for co-crystals, would not have allowed a POSA in March 2003 to make and use the full scope of claimed co-crystals without undue experimentation or to “visualize or recognize” the full claim scope.

34. Lastly, Patent Owners’ contention that I “refused to concede that a POSITA would *not* have used a known carcinogenic or toxic co-former or solvent in the claimed pharmaceutical composition” (POR at 9-10 (citing Ex. 2016, Rogers Dep. Tr. at 60:1-68:25)), takes my testimony out of context and disregards that I repeatedly explained that it was necessary to understand the purpose of making the pharmaceutical composition before opining on its components. Ex. 2016, Rogers Dep. Tr. at 49:19-54:8, 63:20-67:10. For example, as I explained, a POSA could use a known carcinogen if the purpose was to make a new co-crystal or conduct toxicity testing. Ex. 2016, Rogers Dep. Tr. at 50:7-51:7. I also explained that it was necessary to know more about which specific chemical was being considered, how toxic it was, and how it was being used; all compounds are toxic at some concentration. *See, e.g.*, Ex. 2016, Rogers Dep. Tr. at 53:13-24; *see also* 50:7-24, 51:8-16; 52:13-21. *See also e.g.*, Ex. 1073, 67 Fed. Reg. 61,910 (Oct. 2, 2002) (stating that “[e]xcipients are potential toxicants” so “[i]t is important to perform risk-benefit assessments on excipients for use in drug products and *to establish permissible limits for these compounds” in pharmaceuticals* (emphasis added)). Ex. 1074, Osterberg (June) 2003 at 377-79 (explaining that (i) “[e]xcipients are essential ... components of drug products” and, “[l]ike all chemicals, excipients are potential toxicants”; (ii) “[e]ach proposed use of an excipient must be considered on a case-by-case basis and must be consistent with a positive risk-benefit

assessment”; and (iii) “it may be justifiable in the development of an excipient intended for inclusion in life-saving therapies that toxicity requests be reduced ... or completed post approval”). “[A] lot of work with pharmaceuticals is done with very toxic compounds,” and I would not rule out using toxic solvents because sometimes using a toxic solvent is the only way to prepare a particular compound or composition. *E.g.*, Ex. 2016, Rogers Dep. Tr. at 50:7-24, 52:13-53:2, 66:13-67:10.

35. Toxicity is concentration dependent. Even water can be toxic. Indeed, the '344 patent inventors themselves used co-formers and solvents in some of the '344 patent's/'956 application's examples that are toxic at certain concentrations according to Dr. Ward's interpretation of the November 2003 HHS Guidance. Ex. 2014, Ward Declaration ¶ 45 (citing Ex. 2012, November 2003 HHS Guidance at 5-10; contending that class 2 solvents “should be limited in pharmaceutical products because of their inherent toxicity”). Specifically, the '344 patent inventors used the class 2 solvents hexane, methanol, tetrahydrofuran, and/or dichloromethane to synthesize the co-crystals of Examples 3, 7, 8, 11, 13, 14, 17, and 19. Ex. 2012, November 2003 HHS Guidance at 5-10 (identifying hexane, methanol, tetrahydrofuran, and dichloromethane as class 2 solvents); Ex. 1015, '956 application, Examples 3, 7, 8, 11, 13, 14, 17, and 19 (using hexane, methanol, tetrahydrofuran, and/or dichloromethane to synthesize co-crystals); Ex. 1001, '344

patent, Examples 3, 7, 8, 11, 13, 14, 17, and 19 (same). The '344 patent inventors also used formamide—a class 2 solvent—as the co-former (and not merely as a solvent used during manufacture) in the co-crystal of Example 17 (1:1 carbamazepine:formamide) in an amount (19 mg/day, as calculated below) that would far exceed HHS's 2.2 mg/day permitted daily exposure ("PDE") limit for formamide when this co-crystal is used therapeutically. Ex. 1001, '344 patent, Example 17; Ex. 2012, November 2003 HHS Guidance at 6. Specifically, based on the lowest dosage of 100 mg of carbamazepine per day for its indicated uses,¹ a carbamazepine:formamide co-crystal containing a 100 mg daily dose of carbamazepine contains 19 mg of formamide:

$$\begin{aligned} \text{Molecular weight of carbamazepine} &= 236.3 \text{ g/mol}^2 * 1000 \text{ mg/1 g} = \\ &236,300 \text{ mg/mol} \end{aligned}$$

¹ See Ex. 1075, Martindale 1999 at 339, 342 (for treatment of **epilepsy** recommending an initial dose of 100 to 200 mg once or twice daily; for treatment of **trigeminal neuralgia**, recommending an initial dose of 100 mg once or twice daily; for the prophylaxis of **manic depression**, recommending an initial dose of 400 mg daily).

² Ex. 1075, Martindale 1999 at 339.

Molecular weight of formamide = $45.04 \text{ g/mol}^3 * 1000 \text{ mg/1 g} =$
45,040 mg/mol

For each mg of carbamazepine, there is 0.19 mg of formamide:

$(45,040 \text{ mg formamide}) / (236,300 \text{ mg carbamazepine}) =$
0.19 mg formamide per mg carbamazepine

0.19 mg formamide * 100 mg daily dose of carbamazepine =
19 mg formamide per day

36. The '344 patent inventors also used 4,4'-bipyridine as the co-former to prepare the co-crystals of Examples 1 and 3-5 of the '344 patent, yet 4,4'-bipyridine was known in the art by March 2003 to be toxic to animals. Ex. 1076, Groce 1982 at 363-71 (disclosing that 4,4'-dipyridyl, which a POSA would have understood is also known as 4,4'-bipyridine, exhibits toxicological effect in rats at oral doses above 175 mg/kg in male rats and 172 mg/kg in female rats, including, among other things, labored breathing, convulsions, pulmonary hemorrhages, pulmonary edema, and kidney and spleen congestion).

37. Despite the known toxicity by March 2003 of these solvents and co-formers used in the '956 application's/'344 patent's examples (¶¶ 35-36 above), Applicants relied on Examples 1, 3-5, 7, 8, 11, 13, 14, 17, and 19 during prosecution as support for application claims to pharmaceutical compositions that

³ Ex. 1075, Martindale 1999 at 1378.

later issued as the challenged claims. Ex. 1016, ‘344 patent prosecution history at UM00000274-76, 277 (arguing that amended application claim 52 (which is identical to issued claim 10) and amended application claim 56 (which is identical to issued claim 18) are supported by, *e.g.*, Examples 1-19); *see also* UM00000074-77, 78 (arguing that application claims directed to pharmaceutical compositions are supported by, *e.g.*, Examples 1-19).

38. Even setting aside toxic or carcinogenic compounds, the scope of the claims remains incalculable. As I explained above, even considering only the twenty-seven class 3 solvents not known “as a human health hazard at levels normally accepted in pharmaceuticals” (Ex. 2012, November 2003 HHS Guidance at 7), the experimentation required to “visualize or recognize” the full scope of claimed co-crystals, or to make and use them, would be unreasonable. *See* ¶ 32.

C. High-Throughput Screening Would Not Have Allowed a POSA to “Visualize or Recognize” the Full Scope of Claimed Co-Crystals, or to Make and Use them Without Undue Experimentation

39. Dr. Ward and Patent Owners rely on a POSA’s alleged knowledge of (and a POSA’s ability to perform) high-throughput screening for their enablement opinions. Patent Owners also rely on such alleged knowledge—without support from Dr. Ward or any other support—for their written description opinion.

40. As an initial matter, Patent Owners and Dr. Ward are not particularly clear on how they say a POSA would have used high-throughput screening,

sometimes suggesting that it would be used on a particular API-co-former combination “to quickly and easily identify for the appropriate conditions under which a co-crystal would form by, for example, testing numerous solvents at once” (e.g., POR at 19; *see also* POR at 11) or “to assess the conditions under which formation [of a co-crystal] would occur” (e.g., POR at 2),⁴ but elsewhere suggesting it could be used more broadly to test a given API with different co-formers or solvents (e.g., “a POSA would have known high-throughput screening techniques were available to test which co-former or solvent would form co-crystals with a given API,” Ex. 2014, Ward Declaration, ¶ 62), and in other places applying high-throughput screening even more broadly (e.g., “[t]he availability of this technique would have significantly reduced the length of time and effort required for a POSA to test for co-crystals under various conditions,” Ex. 2014, Ward Declaration, ¶ 64). If Dr. Ward and Patent Owners are suggesting that high-

⁴ I note that these arguments assume that the particular API-co-former combination would form a co-crystal, but without prior evidence of such formation, a POSA would not reasonably expect any given API-co-former combination would co-crystallize at all. Ex. 1001, Opening Declaration section IX.B.1.c; *see below* section V.C.

throughput screening would be used to randomly test all combinations of possible APIs, co-formers and solvents across the scope of the claim (e.g., Ex. 2014, Ward Declaration, ¶¶ 62, 64), this contradicts their argument that the POSA need not conduct such random testing because the POSA could predict which co-crystals would form from the information in the specification and hydrogen bonding principles (Ex. 2014, Ward Declaration, ¶¶ 54-55). My comments about high throughput screening will apply to all these options unless I indicate that I am specifically addressing only one of them.

41. The alleged knowledge of and ability to perform trial-and-error experimentation using high-throughput screening to attempt to identify and optimize conditions for co-crystallization or prepare co-crystals (something I disagree a POSA would have had the knowledge and capability to do by March 2003, section III.C.1 below), would not have allowed a POSA in March 2003 to “make and use” or “visualize or recognize” the full scope of claimed co-crystals without undue experimentation because (i) high-throughput screening nonetheless requires significant work and user input (particularly if used to test more than one API-co-former combination as Patent Owners and Dr. Ward sometimes allege) and would not have reduced the co-crystal screening experimentation to a reasonable amount of experimentation and (ii) even with the ability to perform high-throughput screening, a POSA would have needed to individually analyze the

crystal structures of any crystalline products produced by the screening experiments.

1. High-Throughput Screening Is Not Disclosed in the '956 Application or '344 Patent and There Is No Evidence that It Was Used in March 2003 to Screen for Co-Crystals

42. There is no disclosure in the '956 application or '344 patent regarding screening at all, much less high-throughput screening. Nor is there any disclosure regarding how to use *any* screening technique (manual or high-throughput) to evaluate and optimize conditions for co-crystallization of *any* API and co-former combination, much less disclosure on how to make and use *any* co-crystal, let alone the full scope of claimed co-crystals. And Dr. Ward and Patent Owners fail to explain how a POSA in March 2003 would have employed high-throughput screening for these purposes.

43. Further, neither Dr. Ward nor Patent Owners provide any evidence that high-throughput screening had been used by *anyone* as of March 2003 to evaluate or optimize co-crystallization conditions to prepare novel co-crystals, let alone those within the scope of the challenged claims. Nor does either provide any evidence of how a POSA would do so, or that high-throughput screening for this purpose was within the POSA's capabilities or routinely used. In fact, Luu 2012 (Ex. 1077) explains that Remenar (Ex. 2008), which was published in June 2003 (i.e., after the March 2003 date of the '956 application), was the first example of

the use of high-throughput screening to prepare co-crystals. Ex. 1077, Luu 2012 at 356 (referring to Remenar (June) 2003 (i.e., Exhibit 2008 cited by Patent Owners), which was not prior art as of March 2003).

44. Relying on Morrisette 2004 (Ex. 2011) and Peterson 2002 (Ex. 2006), Dr. Ward alleges that high-throughput screening techniques “have been used in the pharmaceutical context since at least 2002/2003.” (Ex. 2014, Ward Declaration ¶ 48 (citing Ex. 2011, Morisette 2004 at 276, 279 and Ex. 2006, Peterson 2002 at 10958)). But Morisette 2004 was not prior art and Peterson 2002 does not discuss co-crystals at all. In addition, Dr. Ward does not offer any evidence that the “pharmaceutical context” that he references concerns co-crystallization.

45. Further, Dr. Ward’s argument is inconsistent with his own statement that in 2002/2003, the use of high-throughput screening principles to evaluate crystallization methods for polymorphs and co-crystals was just “emerging[.]”. Ex. 2014, Ward Declaration ¶ 49 (quoting Ex. 2011, Morisette 2004 at 275, 279). In fact, Morisette explained that even for high-throughput crystallization screening generally, *i.e.*, not specific to co-crystals, “only limited information on the use and performance of HT [high-throughput] form screening systems is available in the literature, indicating that the benefits of these new methodologies *have just begun to be realized.*” Ex. 2011, Morisette 2004 at 285 (emphasis added).

2. High-Throughput Screening Would Not Have Allowed a POSA to “Visualize or Recognize” the Full Scope of Claimed Co-Crystals

46. Even if Dr. Ward or Patent Owners had shown that high-throughput screening was used in March 2003 to evaluate or optimize co-crystallization conditions (which I disagree with), screening—whether by high-throughput or manual means—is merely a *technique* or methodology for performing experiments. *See, e.g.*, Ex. 2011, Morissette 2004 at 278 (explaining that high-throughput screening is a “methodology” that uses computer automation to perform a large number of experiments). It does not enable the POSA to predict the results before running the tests and evaluating the results. Therefore, it would not allow a POSA to predict which API(s) and co-former(s) would form co-crystals within the scope of the claims.

3. Even with High-Throughput Screening, Undue Experimentation Would Have Been Required to Make and Use the Full Scope of Claimed Co-Crystals

47. In addition, even if Dr. Ward or Patent Owners had shown that high-throughput screening was used in March 2003 for co-crystals (which I disagree with), Dr. Ward and Patent Owners grossly oversimplify high-throughput screening. *See* Ex. 2014, Ward Declaration ¶¶ 46, 47, 64, 65; POR at 10-11. The availability of high-throughput screening does not eliminate the undue experimentation required to make and use the full scope of the claims.

48. Employing high-throughput screening to evaluate or optimize co-crystallization conditions for even a single API and co-former combination (that could have various stoichiometries) and/or to determine whether a co-crystal would form at all, much less a co-crystal within the scope of the challenged claims, would have required trying different co-crystallization methods amenable to high-throughput screening (not all co-crystallization methods could have been used with high-throughput screening, which would have meant performing manual experimentation for those methods) and modifying the numerous conditions and variables, both in isolation and in combination with the other conditions and variables. See ¶¶ 20-21. Neither Dr. Ward nor Patent Owners provided any evidence that any of these methods could have been used with any high-throughput screening technique.

49. I previously identified over fifty molecules that would have qualified as carboxamide-containing APIs and explained that thousands of compounds would have qualified as co-formers as of March 2003, and there would have been many other qualifying APIs and co-formers at that time. See ¶ 19, above; Ex. 1002, Opening Declaration ¶¶ 71-74, 116-118. Performing co-crystallization experiments using high-throughput screening for even these API and co-former combinations, including the various stoichiometric ratios of each API and co-former combination, to determine the co-crystallization conditions that would result in co-crystals at all,

much less those within the scope of the challenged claims, would have required an unreasonable number of experiments. Also, to be clear, it would not be possible to use the same high-throughput set-up and methodology to randomly test every possible API covered by the claims. As just one example, the solvents used will vary for each API and co-former combination, which Dr. Ward seems to acknowledge. *See, e.g.*, Ex. 2014, Ward Declaration, ¶ 44 (discussing solvents and solubility parameters for a given API and given potential co-former(s)).

50. Moreover, high-throughput screening is a methodology—without performing the experiments, it would not have provided a POSA with any guidance as to which co-crystallization methods, conditions, and variables to use for a given API and co-former combination, much less a specific stoichiometric ratio of API to co-former, nor how to optimize them or reduce the number of experiments required to prepare co-crystals within the full scope of the challenged claims. In designing a high-throughput screen, a POSA would need to identify the methods, conditions and variables to use. Additionally, as I explained in paragraph 48 above, not all co-crystallization methods could have been used with high-throughput screening, which would have required the POSA to undertake trial-and-error experimentation using manual screening means. The amount of experimentation required by a POSA in March 2003 to attempt to prepare the full scope of the claimed co-crystals would have been exorbitant.

51. Dr. Ward and Patent Owners’ description of high-throughput screening as involving the following four steps⁵ misleadingly oversimplifies this process: “(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.” Ex. 2014, Ward Declaration ¶ 47; POR at 11. Setting up a high-throughput screening system is not straightforward. Morissette 2004 explains that “[a] fully integrated HT [i.e., high throughput] crystallization system consists of a number of components, including experimental design and execution software, robotic dispensing and handling hardware, automated highspeed micro-analytical tools, end-to-end sample tracking and integrated cheminformatics analysis software for data visualization, modeling and mining.” Ex. 2011, Morissette 2004 at 279. Neither Dr. Ward nor Patent Owners ever explain how a POSA in March 2003 would have approached and performed these steps for evaluating or optimizing co-crystallization conditions, or for making and using *any* co-crystals, much less the

⁵ These steps are different than the steps I discussed in paragraphs 20-21 with respect to Figure 24 of the ’956 application/’344 patent as the ’956 application/’344 patent do not mention high-throughput screening.

full scope of claimed co-crystals. Namely, Dr. Ward and Patent Owners fail to explain how a POSA would have:

- (i) Identified the samples (*i.e.*, APIs) to prepare in Step 1 (I previously identified over fifty API molecules, but many more molecules would have qualified. *See* ¶ 19, above; Ex. 1002, Opening Declaration ¶¶ 71, 116), considering *e.g.*, each potential API's solubility in various solvents and mixtures of solvents at different concentrations and ratios;
- (ii) Prepared the (API) samples in Step 1;
- (iii) Identified the compounds for the (co-former) library in Step 1 (there were conservatively thousands of co-formers available as of March 2003. *See* ¶ 19, above; Ex. 1002, Opening Declaration ¶¶ 72-74, 117-118) considering, for example, each potential co-former's solubility in various solvents and mixtures of solvents at different concentrations and ratios;
- (iv) Prepared the (co-former) library samples in Step 1;
- (v) Identified the testing procedures to use in Step 2, including identifying which co-crystallization methods would have been applicable to high-throughput screening and, for those methods, identifying all the possible conditions and variables to consider in

an attempt to prepare co-crystals within the scope of the challenged claims (discussed in ¶¶ 20-21 above (Figure 24's trial-and-error research plan));

- (vi) Designed the testing procedures to use in Step 2 for the identified potential API and co-former combinations, including those with API:co-former stoichiometries other than 1:1, based on the possible co-crystallization methods, conditions, and variables, in an effort to evaluate and optimize co-crystallization conditions, particularly without knowing whether a given API would co-crystallize at all, much less with any particular co-former) (discussed in ¶¶ 20-22, 31, 50 above);
- (vii) Automated the testing procedures in Step 2 once all testing procedures were identified and designed;
- (viii) Developed, prepared, and configured the robotic workstation in Step 3 for the endless number of testing procedures in Step 2.

Morissette 2004 depicts in Scheme 1 nine different aspects of high-throughput screening that would have been a part of this step—experimental design, solids generation, solids detection, rearray and quench, primary analysis, initial informatics classification, secondary analysis, functional analyses, and comprehensive

information analysis—and explains the complexities of automating the workstation. Ex. 2011, Morissette 2004 at 279; *see generally* Ex. 2011, Morissette 2004 at 278-285;

- (ix) Acquired the testing data in Step 4, including strategically determining what data to acquire in the first place and the instrumentation necessary to do so and how to use that instrumentation to acquire the data; and
- (x) Processed the testing data in Step 4.

52. With regards to Step 4, Dr. Ward and Patent Owners also fail to explain how a POSA would have processed the testing data or used the processed testing data to determine whether a co-crystal actually formed *and*, if it did, whether it had all the non-covalent hydrogen bonding interactions required by the challenged claims. Importantly, they gloss over the fact that determining whether a co-crystal had all the non-covalent hydrogen bonding interactions required by the challenged claims would have required single crystal X-ray diffraction analysis that could not have been done as part of the high-throughput screening process, which I further discuss in section III.C.4 below.

53. As I explained in paragraphs 20-22, and 31 above when discussing Figure 24's trial-and-error research plan for preparing co-crystals, the testing in Step 2 alone to evaluate and optimize the co-crystallization conditions for the full

scope of claimed API and co-former combinations, including of varying stoichiometries, would have required an endless number of experiments, not to mention all the manual experimentation that would have been required for crystallization techniques not amenable to high-throughput techniques (¶¶ 48, 50 above). No screening technique, whether by manual or high-throughput means (or both), could have performed these co-crystallization experiments (outlined at an extremely high level in Figure 24 of the '956 application/'344 patent) in a reasonable amount of time and/or with a reasonable amount of effort.

4. Determining Whether the Products from the Screening Experiments Resulted in Co-Crystals Within the Scope of the Challenged Claims Could Not Have Been Done Automatically With High-Throughput Screening Equipment

54. Even if a POSA in March 2003 could have used high-throughput screening to attempt to evaluate and optimize co-crystallization conditions and/or prepare co-crystals within the scope of the challenged claims (neither Dr. Ward nor Patent Owners have provided any evidence that a POSA could), to determine whether a co-crystal actually formed that had all the non-covalent hydrogen bonding interactions required by the challenged claims, a POSA in March 2003 would have had to use single crystal X-ray diffraction. This is a characterization technique for analyzing a sample's crystal structure and is a step that Dr. Ward's and the Patent Owners' oversimplified high-throughput screening scheme fails to

consider. Single crystal X-ray diffraction analysis is what the '344 patent inventors used to analyze the products of their co-crystallization experiments. *E.g.*, Ex. 1015, '956 application ¶ [0055] (stating that the multiple component crystalline phases prepared in the examples were characterized using single crystal X-ray crystallography); ¶¶ [0056]- [00177] (describing the crystal packing of the products of Examples 1-19 based on analysis of the structures by single crystal X-ray crystallography, and reporting single crystal data in the Figures referenced in the examples); Ex. 1001, '344 patent, col. 11, l. 39 – col. 23, l. 16 (same disclosures as '956 application). *See also* Ex. 1028, Fleischman at 911-18 (the '344 patent inventors using single crystal X-ray diffraction to analyze the obtained co-crystal structures).

55. As Morissette 2004 explained, single crystal X-ray diffraction analysis as of 2004 could not have been used as part of the automated high-throughput screening process and, instead, would have required manual analysis for each sample (and this is still true today). Ex. 2011, Morissette 2004 at 285 (“While these new methodologies [*i.e.*, high-throughput screening] provide unprecedented capabilities for solid[] form discovery, it is clear that there remains a need for some level of *manual processing*, particularly *in the case of detailed form characterization such as single crystal structure determination.*” (emphases added)).

56. Dr. Ward does not consider or account for all the steps involved in performing single crystal X-ray diffraction analysis for even a single product resulting from a screening experiment. First and foremost, before even performing the single crystal X-ray diffraction analysis of a sample, a POSA would have needed a suitable single crystal to analyze, and it is unlikely that high-throughput screening would provide a suitable sample. Even if it did, single crystal X-ray diffraction analysis would have been time-consuming and challenging despite the POSA's high level of skill in the art, requiring the steps of mounting the single crystal on a diffractometer, collecting the data, solving the crystal structure, and analyzing the structure to confirm whether a co-crystal formed at all and, if so, whether it had all the non-covalent hydrogen bond interactions required by the challenged claims. For even a single sample, this would have taken about one or two days to several months. And, in situations where a single crystal resulted but it was not suitable for single crystal X-ray diffraction analysis—the more likely scenario for most co-crystallization experiments forming a solid product—a POSA would have needed to undergo the additional step of growing a suitable single crystal before performing the single crystal X-ray diffraction analysis (and confirming it was the same co-crystal as produced in the high-throughput experiment), which could have taken days, weeks, months, and, in some cases,

even years to prepare for one API and co-former combination having a specific stoichiometric ratio.

57. Thus, in addition to the high-throughput screening experimentation, which already would have required an unreasonable number of experiments to attempt to identify and optimize co-crystallization conditions and/or prepare co-crystals that *may* fall within the scope of the challenged claims, the POSA in March 2003 separately would have had to perform single crystal X-ray diffraction analysis to determine whether the resulting co-crystal had the non-covalent hydrogen bonding interactions required by the challenged claims at all, assuming a suitable single crystal could even be obtained. This would have made the amount of experimentation needed to make and use the full scope of claimed co-crystals even more undue.

D. Hydrogen Bonding Principles and Etter's "Rules" Would Not Have Allowed a POSA to "Visualize or Recognize" or "Make and Use" the Full Scope of Claimed Co-Crystals

58. Knowledge of hydrogen bonding principles, in particular, Etter's "rules," would not have allowed a POSA in March 2003 to "visualize or recognize" or "make and use" the full scope of claimed co-crystals.

1. Hydrogen Bonding Principles and Etter's "Rules" Are Not Disclosed in the '956 Application or '344 Patent

59. To support their written description and enablement arguments, Dr. Ward and Patent Owners provide a discussion on hydrogen bonding, focusing on “[f]undamental hydrogen bonding principles⁶” and, specifically on a 1990 paper by Dr. Etter describing “empirical hydrogen-bond rules [] for determining preferred modes of hydrogen bonding.” Ex. 2014, Ward Declaration ¶ 40 (citing Ex. 2005, Etter 1990 at 121-22)); *see also* Ex. 2014, Ward Declaration section VI.b; POR section II.C.1. These “rules,” which Dr. Etter states are intended to be used as “*indicators of hydrogen-bond preferences of a particular functional group,*” were developed based on a *retrospective analysis* of crystal structures from the Cambridge Crystallographic Database. Ex. 2005, Etter 1990 at 121 (emphasis added). But there is no disclosure in the '956 application or '344 patent of any hydrogen bonding principles to be applied in connection with the claims, including

⁶ I note that neither Dr. Ward nor Patent Owners identify any hydrogen bonding *principles* besides Dr. Etter's “rules” on hydrogen bonding that a POSA would have had knowledge of as of March 2003.

Etter's "rules".⁷ Nor is there any disclosure in either about how to apply these "rules" to predict or make *any* co-crystal, much less co-crystals across the scope of the challenged claims.

⁷ Patent Owners allege that "multiple papers of Dr. Etter on hydrogen bonding were cited during prosecution [of the '344 patent]." POR at 7 (citing Ex. 1001, '344 patent, at Page 6 (References Cited)). However, based on my review of the '344 patent file history (Ex. 1016), the four Etter references cited on page 6 of the '344 patent in the "References Cited" section were disclosed during prosecution in an approximately 600-reference IDS filed by Applicants that spanned twenty-seven pages. Ex. 1016, p. 215, '344 patent file history, February 13, 2014 IDS at 15 of 27. The patent examiner neither mentioned any of these Etter references (or any other Etter references), nor cited any of them as a basis for a rejection during prosecution. *See generally* Ex. 1016, '344 patent file history. The same is true of the '956 application: the four Etter references cited on page 6 of the '344 patent "References Cited" section were disclosed by Applicants during prosecution of the '956 application in an approximately 400-reference IDS that spanned thirty-three pages and were never mentioned by the patent examiner. *See* Ex. 1017, *generally* and at p. 196, '956 application file history, July 27, 2006 IDS at 22 of 33.

2. Dr. Ward and Patent Owners Never Explain How to Apply Hydrogen Bonding Principles or Etter's "Rules" or Show Any Examples of Their Prospective Application to Co-Crystals

60. Dr. Ward and Patent Owners never explain how a POSA would have applied hydrogen bonding principles or Etter's "rules" to "visualize or recognize" or "make and use" the full scope of claimed co-crystals. Nor have they identified a single example in the art as of March 2003 that shows such principles or "rules" could be used to predict the full scope of co-crystals encompassed by the challenged claims (let alone any co-crystal). In my opinion, that is because it simply could not be done. On this subject, Patent Owners attempt to argue that I testified during cross-examination that Dr. Etter's "rules" could be applied to predict that an API-co-former combination would form a co-crystal because I agreed that Etter's work could be applied to co-crystals and stated that Etter was "simply the concept of hydrogen bonding." POR at 7-8, citing Ex. 2016, Rogers Dep. Tr. at 39:22-40:5. This testimony certainly is not an admission that Etter's "rules" could have been used to prospectively predict formation of any co-crystals, let alone the full scope of claimed co-crystals. As I have repeatedly explained, I disagree that Etter's "rules" could be used to predict co-crystal formation or that Patent Owners or Dr. Ward have provided any evidence that they could be used in this way, let alone to predict the full scope of claimed co-crystals.

3. Etter's "Rules" Have Limitations

61. Dr. Ward and Patent Owners also fail to address the limitations on Etter's "rules" beyond recognizing that they exist. Dr. Etter herself explains, which Dr. Ward acknowledges, that her "rules" are most useful for predicting hydrogen-bonding patterns in "systems [e.g., co-crystals] with a limited number of functional groups" and "in the absence of other competing forces." Ex. 2005, Etter 1990 at 121; Ex. 2014, Ward Declaration ¶ 40 (quoting Ex. 2005, Etter 1990 at 121); *see also* ¶ 55 (admitting that "other factors could steer synthon formation toward combinations that do not follow the ranking suggested by ... Dr. Etter's 'rules'"); *see also* POR at 17-18. However, the challenged claims are not limited to APIs or co-formers with a limited number of functional groups or API-co-crystal combinations that lack "other competing forces."

62. Regarding the "other competing forces" or "other factors," they can include other intermolecular interactions—for example, ionic interactions, van der Waals interactions, charge-transfer interactions, and halogen-halogen interactions—sterics, and geometric fit. Ex. 2005, Etter 1990 at 126; Ex. 1080, Braga 2002 at 505 (explaining that sterics and electronic interactions can impact co-crystallization, which are not considered by Etter's "rules"); *see also* Ex. 2005, Etter 1990 at 126 (explaining that "[h]ydrogen bonds are not the only type of intermolecular interactions that are useful for directing molecular self-assembly");

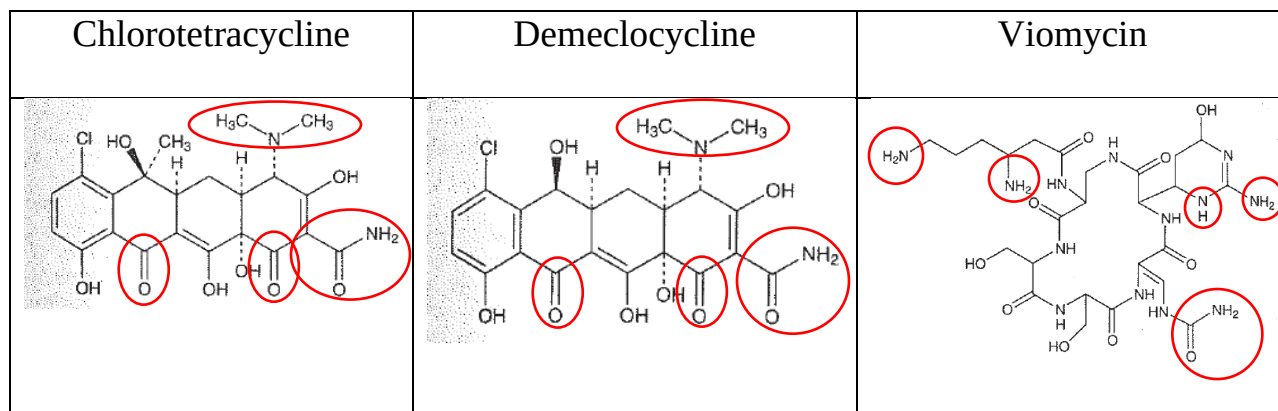
Ex. 2008, Remenar (June) 2003 at 8456-57 (discussing the impact of geometric fit on co-crystallization); Ex. 1015, '956 application ¶ [0046] (providing non-limiting examples of intermolecular interactions between co-crystal components, which include “hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions”); Figure 24 (discussing geometry, shape, and molecular recognition in connection with forming supramolecular synthons); Ex. 1001, '344 patent, col. 9, ll. 15-19; Figure 24 (same disclosures as the '956 application).

63. Etter explained that ionic interactions “are considerably stronger than hydrogen bonds and they usually *dominate a packing pattern*.” Ex. 2005, Etter 1990 at 126 (emphasis added). Remenar (June) 2003 (Ex. 2008), which was not prior art as of March 2003 but is cited by Patent Owners, explained that in certain co-crystallizations, the geometry of the co-crystal components may be more important than hydrogen-bonding principles in directing co-crystal formation. Ex. 2008, Remenar (June) 2003 at 8456-57 (reporting the failure to form co-crystals of itraconazole with malonic, glutaric, or adipic acid, which “indicate[s] that geometric fit may be more important than acid-base chemistry [*i.e.*, hydrogen-bonding principles] in directing crystallization of [itraconazole] with 1,4-dicarboxylic acids.”). And Dr. Braga explained in a 2002 paper that a POSA would not have understood from Etter’s “rules” how to assess hydrogen bonding donor

and acceptor capabilities, particularly in view of other factors such as sterics and electronic interactions (*e.g.*, ionic bonding). Ex. 1080, Braga 2002 at 505 (“[T]he so-called ‘Etter rules’ [] imply a hierarchy of donor with acceptor matching in terms of strength. How does one assess solid state donor and acceptor capabilities taking into account steric factors in addition to the electronic ones? Even if one could get a reliable scale of solid state donor and acceptor strengths, does crystallization proceed in this modular way? This is surely a question of major importance.”).

64. For example, to illustrate Etter’s limitations with respect to co-crystals having more than a “limited number of functional groups,” I provide below three example compounds from the 2001 Merck Index (Ex. 1049) that qualify as APIs in the context of the challenged claims (*see* Ex. 1002, Opening Declaration ¶ 71 n.

7)—chlorotetracycline (entry 2211), demeclocycline (entry 2905), viomycin (entry 10062).⁸ Ex. 1049, 2001 Merck Index at 379, 507, 1782.



65. In addition to having many other functional groups, each of these compounds has at least four functional groups that are a carboxamide, carbonyl, and/or amine (circled in red). Etter's "rules" 1-3 identified in paragraph 41 of the

⁸ The functional groups circled in red qualify as carboxamides (claims 10, 11, and 18), carbonyls (claims 10 and 11), and/or amines (claims 10 and 11) according to the definitions in my Opening Declaration. Ex. 1002, Opening Declaration ¶ 57 ("carbonyl" refers to "-C(=O)-" that is not part of a larger functional group); ¶ 61 ("carboxamide" encompasses "-C(=O)NH₂"); ¶ 76 n.9 (IUPAC defines "amines" as "[c]ompounds formally derived from ammonia by replacing one, two, or three hydrogen atoms by hydrocarbyl groups, and having the general structures RNH₂, (primary amines), R₂NH (secondary amines), R₃N (tertiary amines)").

Ward Declaration do not explain how a POSA in March 2003 would have determined which of the numerous functional group(s) would form hydrogen bond interaction(s) with any “suitable” co-former, if hydrogen bond(s) would form at all and, if they did, what those specific interaction(s) would be. Dr. Ward does not provide this explanation either. Similarly, neither Dr. Ward nor Etter’s “rules” explain how a POSA would have determined whether (and, if so, how) geometric or steric hinderance would impact hydrogen bond interactions between these APIs and co-formers.

66. In addition, because the claimed co-crystals include “at least one [API]” and “at least one co-former” (see Ex. 1001, ’344 Patent, claim 10), they could include multiple APIs and/or multiple co-formers, which Etter’s “rules” also do not address. Nor do Etter’s “rules” address co-crystals that also include solvent in the co-crystal structure, which Dr. Ward and Patent Owners have not disputed are also encompassed by the challenged claims. Applying Etter’s “rules” to co-crystals with more than one API, more than one co-former and/or solvent (including water) would have been even more complicated and challenging for a POSA, and ultimately, in my view – not possible for the diverse APIs, co-formers, and solvents falling within the scope of the challenged claims. In fact, even ’344 Patent inventor Dr. Zaworotko has acknowledged years after the March 2003 ’956 application filing date that co-crystal hydrates (a co-crystal that also includes

water) are unpredictable, calling water “the nemesis of crystal engineering.” Ex. 1078, Clarke 2010 at 2152, 21-67 (“[T]he promiscuity of water molecules in terms of their supramolecular synthons and their unpredictable thermal stability makes them a special challenge in the context of crystal engineering” and “the promiscuity of water molecules in terms of supramolecular synthons mean[s] that their composition, structure, and thermal stability remain largely unpredictable...”).

67. The limitations in applying Etter’s “rules” are confirmed by the numerous co-crystal examples in the art that did not follow these “rules.” For example, Remenar (June) 2003 (which was not prior art), cited by Dr. Ward (Ex. 2008) and co-authored by Brian Moulton (one of the ’344 patent inventors), disclosed an itraconazole-succinic acid co-crystal that had an “*unanticipated* and specific [hydrogen bond] interaction between the triazole of [itraconazole]” and the carboxylic acid of succinic acid (Ex. 2008, Remenar 2003 at 8456), an interaction the authors reported to be “inconsistent with [Etter’s] principle of strongest-to-strongest interactions dominating self-assembly^[9]” based on a retrospective

⁹ Rule 3 of Etter’s preferences states that “[t]he best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds to one another.” Ex. 2005, Etter 1990 at 124.

analysis of the co-crystal structure. Ex. 2008, Remenar 2003 at 8457 (referencing Ex. 2005, Etter 1990). Sharma 1993 (Ex. 1081) disclosed a 3,5-dinitrobenzoic acid-4-(*N,N*- dimethylamino) benzoic acid co-crystal containing “uncommon” O-H $\cdots$ O hydrogen-bonded carboxy homodimers rather than heterodimers, which the authors said, based on a retrospective analysis of the co-crystal structure, “contradicts [Etter’s] general principle that in hydrogen-bonded networks, the strongest proton donor hydrogen bonds to the strongest proton acceptor” due to important π - π stacking interactions. Ex. 1081, Sharma 1993 at 2209. And Vishweshwar (June) 2003 (Ex. 1082) disclosed two 1:1 co-crystals—glutaric acid-isonicotinamide and adipic acid-isonicotinamide—“in which hydrogen bonding does not follow from [Etter’s] best donor-best acceptor order,” due to “a combination of synthon energy and structural database derived arguments.” Ex. 1082, Vishweshwar (June) 2003 at 789 (retrospectively analyzing the co-crystal structures of glutaric acid-isonicotinamide and adipic acid-isonicotinamide to identify the hydrogen bonding interactions).

68. For these reasons, Dr. Ward and Patent Owners have not shown that Etter’s “rules” (or any other hydrogen bonding principles) could have been used by a POSA in March 2003 to “visualize or recognize” or “make and use” the full scope of claimed co-crystals.

IV. CLAIMS 10, 11, AND 18 ARE NOT ENTITLED TO A MARCH 2003 PRIORITY DATE BECAUSE THE '956 APPLICATION DOES NOT PROVIDE ADEQUATE WRITTEN DESCRIPTION SUPPORT FOR THE FULL SCOPE OF CLAIMED CO-CRYSTALS

69. I disagree with Dr. Ward and Patent Owners that the inventors had possession of the full scope of claimed co-crystals by March 2003. Ex. 2014, Ward Declaration ¶ 57; POR at 16.

70. Relevant to my opinions in this section, as I explained in paragraph 8 above, the claimed genus of co-crystals is incredibly broad, including an almost infinite number of co-crystals. *See also* Ex. 1002, Opening Declaration section IX.B.1.a, ¶ 74. Neither Dr. Ward nor Patent Owners disputes this.

A. It is Undisputed that the '956 Application Fails to Disclose a Representative Number of Co-Crystals of the Claimed Genus

71. Because neither Dr. Ward nor Patent Owners discussed the representative species test for written description or disputed that the '956 application does not disclose a representative number of co-crystals falling within the scope of the claimed genus, I understand this issue is undisputed.

72. My opinion regarding lack of representative species in the '956 application for the full scope of claimed co-crystals is fully explained in my Opening Declaration, including that even if all nineteen co-crystal examples disclosed in the '956 application fell within the full scope of the claimed co-crystals (they do not and Dr. Ward agrees, ¶ 14 above), they would not have been

representative of the almost infinite number of co-crystals covered by the challenged claims. Ex. 1002, Opening Declaration section IX.A.2, ¶ 128.

B. The '956 Application Fails to Disclose Common Structural Features of the Claimed Co-Crystal Genus

73. I disagree with Dr. Ward and Patent Owners that the '956 application's examples, alone or in combination with knowledge of any hydrogen bonding principles (and/or high-throughput screening—an allegation Patent Owners make without support from Dr. Ward, ¶ 39 above)—shows possession of the full scope of claimed co-crystals. I understand from counsel that to show possession (written description) of a claimed genus under the common structural features test, the application must disclose structural features common to all members of the claimed co-crystal genus such that a POSA as of the relevant date (here, March 2003) could have “visualize[d] or recognize[d]” all members of the claimed genus and distinguished the genus from embodiments not covered by the claims. Ex. 2014, Ward Declaration ¶¶ 53, 57; POR at 16-20.

1. The *Functional* Co-Crystal Limitations Are Not Supported By *Structural* Features Common to the Claimed Genus of Co-Crystals Allowing a POSA to “Visualize or Recognize” the Full Scope of Claimed Co-Crystals

74. The challenged claims include functional limitations. For example, the co-crystal is made up of supramolecular synthons “*formed* via non-covalent hydrogen bonding between the first chemical functionality of the API,” here a

carboxamide, carbonyl, or amine, “and the second chemical functionality of the co-former,” where neither the co-former nor the second chemical functionality are specified. Ex. 1002, Opening Declaration ¶¶ 69, 75.

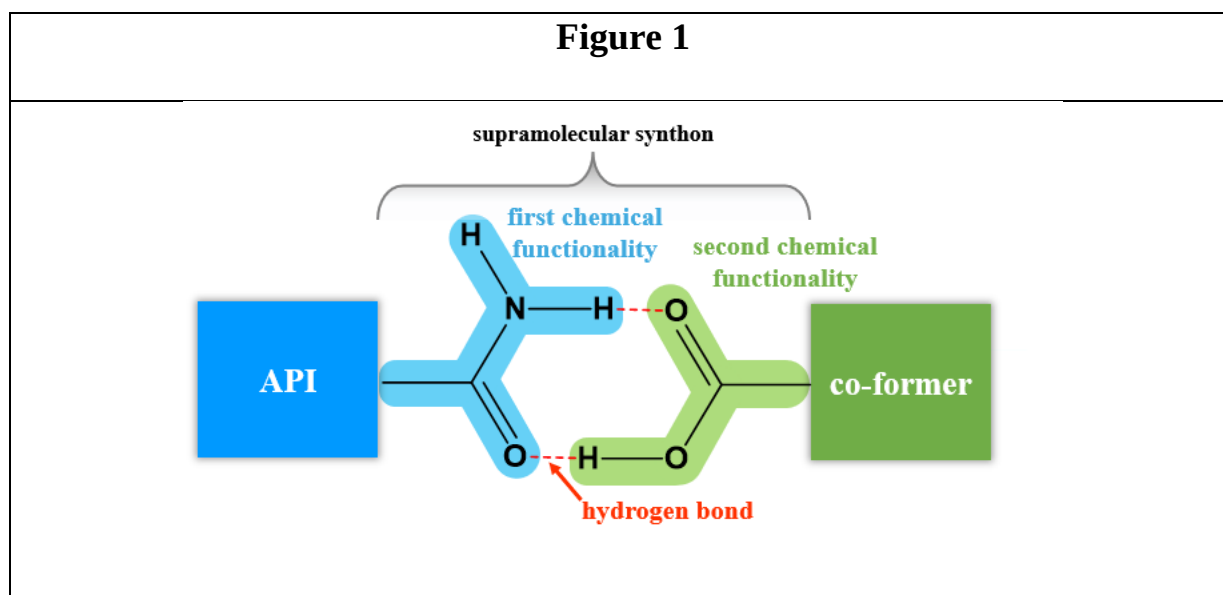
75. In my Opening Declaration, I identified over fifty molecules that would have qualified as APIs as of March 2003 (and there would have been many others), and undisputedly thousands of molecules would have qualified as co-formers at that time. Ex. 1002, Opening Declaration ¶¶ 71-74, 116-118; *see also* ¶ 19, section III.C.3, above. The claimed co-crystals broadly include *any* API(s) having a first chemical functionality that is a carboxamide (in claims 10, 11, and 18), carbonyl (in claims 10 and 11), or amine (in claims 10 and 11) and *any* solid co-former(s) in *any* stoichiometric ratio (and with *any* additional molecules, like solvent) having the hydrogen bonding interactions discussed in paragraph 74 above, resulting in an almost infinite number of possible co-crystals. Ex. 1002, Opening Declaration ¶¶ 74, 118. And there is no disclosure in the '956 application regarding structural features of either the API or co-former (other than the first chemical functionality of the API) that are common to all co-crystals falling within the scope of the claimed genus. Nor does the '956 application explain how a POSA in March 2003 would have identified the numerous and diverse co-crystals covered by the challenged claims, particularly since there is no evidence that the functional limitations of the claimed co-crystals (*e.g.*, forming the co-crystal or

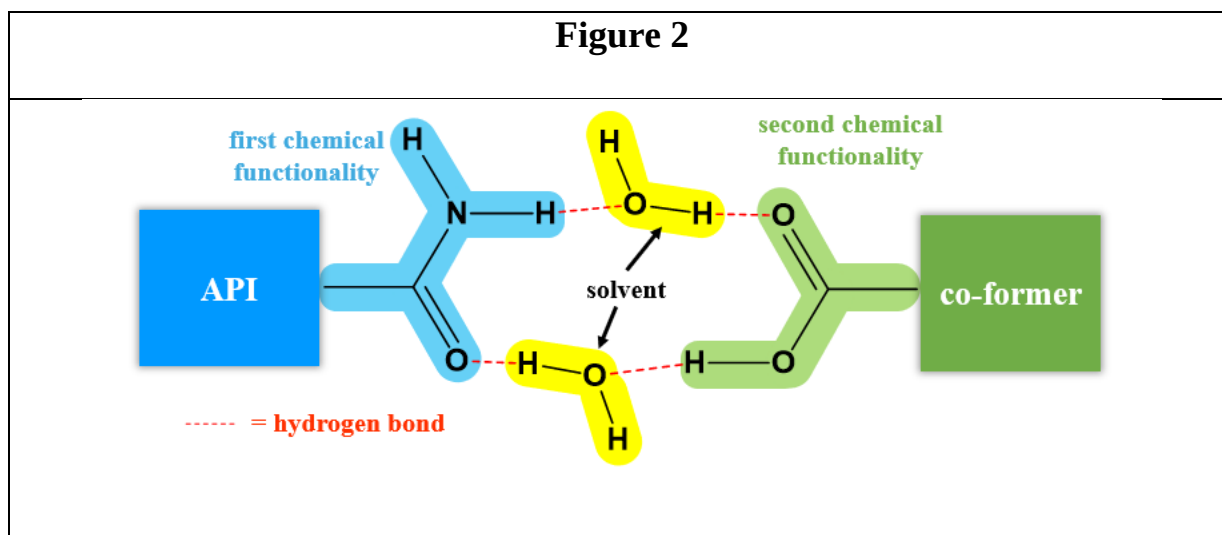
supramolecular synthon) correlate to any common structures on the APIs and co-formers across the full co-crystal genus. Ex. 1002, Opening Declaration ¶¶ 89, 94, 99, 106, 108, 111.

76. A POSA in March 2003 would not have been able to rely on the structure of the first chemical functionality of the API to distinguish potential API and co-former combinations falling within the scope of the claimed co-crystals (*e.g.*, those that form the claimed co-crystals) from those that do not. For example, just because an API has a carboxamide group and a co-former has a hydrogen bond donor or acceptor, that does not tell a POSA that the API and co-former will in fact form a supramolecular synthon via non-covalent hydrogen bonding between them. For example, the APIs may interact only with one another (rather than with the co-former), the APIs may form non-covalent bonds with any co-crystallization solvent (rather than the co-former), or the co-former may form non-covalent bonds with any co-crystallization solvent (rather than the API), or the API may form non-covalent bonds with any co-crystallization solvent, which then itself forms non-covalent bonds with the co-former. None of these would fall within the scope of the challenged claims.

77. To illustrate this point, I provide below (i) an example of an API having a carboxamide first chemical functionality that forms supramolecular synthons via non-covalent hydrogen bonding with the second chemical

functionality (a —COOH group (*i.e.*, carboxylic acid)) of a co-former as required by the challenged claims (Figure 1) and (ii) an example of an API having a carboxamide first chemical functionality that *does not* form supramolecular synthons via non-covalent hydrogen bonding with the same second chemical functionality of the co-former (Figure 2). Figure 1 would fall within the scope of the challenged claims if all other claim limitations are satisfied; Figure 2 does not because solvent (here, water) interrupts the formation of the supramolecular synthon by hydrogen bonding with the first chemical functionality of the API and second chemical functionality of the co-former (something that Etter's “rules” would not have predicted as they do not address solvent).





Thus, the structural feature of a first chemical functionality on the API that is a carboxamide would not have provided any indication as to whether a co-crystal would form (or even was likely to form) at all, much less form in the way required by the challenged claims.

78. 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. This is the only common structural feature identified by Dr. Ward or Patent Owners. I disagree that “hydrogen bonding between the active pharmaceutical ingredients and their co-formers” (i.e., looking at already-formed co-crystals that satisfy the functional claim limitations), would allow a POSA reading the ’956 application to “visualize or recognize” which other API and co-former combinations meet the functional limitations of forming synthons and co-crystals,

and this is the key issue here given the large number of possible API and co-former combinations and the inability to predict co-crystal formation.

2. The '956 Application's Examples Do Not Disclose Structural Features Common to All Members of the Claimed Co-Crystal Genus

79. Dr. Ward and Patent Owners allege that there is sufficient written description support in the '956 application for the challenged claims “at least because the specification provides examples that have common structural features as the members of the genus, including the claimed co-crystals.” Ex. 2014, Ward Declaration ¶ 53; see POR at 16. Specifically, Dr. Ward and Patent Owners allege that the '344 patent's and '956 application's examples (which are the same) “provid[e] at least one example of each limitation” of the challenged claims and, therefore, they “inform a POSA how to *implement* each of the claim limitations.” Ex. 2014, Ward Declaration ¶ 53 (emphasis added); see POR at 16, 20 (alleging that “all of the claim limitations of the Challenged Claims are present in the examples of the '956 Application”). But this is incorrect as I previously explained because, as Dr. Ward admits, none of the examples include an API with a first chemical functionality that is a carbonyl or an amine (in claims 10 and 11). See ¶ 15, above. Moreover, there are no examples of the co-crystals of any of claims 10, 11, or 18 comprising more than one API and/or co-former as those claims allow. See ¶ 15. Thus, contrary to Dr. Ward's and Patent Owners' allegation, a POSA

would not have understood from the limited examples how to “implement” the limitations of the claimed co-crystals, or to “visualize or recognize” the full scope of co-crystals falling within the claimed genus.

80. Dr. Ward alleges that even though the examples “do not account for every conceivable molecular entity and/or functional group, [] a POSA would be most interested in forming *any kind of co-crystal* based on these principles, regardless of the details of the crystal packing ... or which combination of functional groups formed synthons.” Ex. 2014, Ward Declaration ¶ 56 (emphasis added). I disagree.

81. First, my analysis focuses on preparing co-crystals falling within the scope of the challenged claims, *i.e.*, those having an API and co-former that have the specific non-covalent hydrogen bonding interactions required by claims 10, 11, and 18, regardless of their solid-state (*e.g.*, polymorphic) form.

82. Second, the “primary interest” of a POSA in the claimed subject matter would have been preparing co-crystals satisfying the limitations of claims 10, 11, and 18, not “forming any kind of co-crystal” as Dr. Ward alleges. *See* Ex. 2014, Ward Declaration ¶ 56. And even though the scope of the claimed co-crystal genus is indisputably almost infinite, not all co-crystals will fall within that scope.

83. Third, Dr. Ward has not explained how a POSA would have used the ’956 application’s examples, which he admits do not exemplify all the claimed co-

crystals (Ex. 2014, Ward Declaration ¶ 56), to identify the full (almost infinite) scope of claimed co-crystals.

84. For these reasons, the '956 application's examples would not have allowed a POSA in March 2003 to "visualize or recognize" the full scope of claimed co-crystals.

3. The Additional Knowledge of Hydrogen Bonding Principles, Such as Etter's "Rules," Would Not Have Allowed a POSA to "Visualize or Recognize" the Full Scope of Claimed Co-Crystals

85. I do not agree with Dr. Ward or Patent Owners that the POSA in March 2003 would have understood that the inventors were in possession of the claimed genus of co-crystals based on the '956 application's examples in conjunction with the "well-known principles of hydrogen bonding." Ex. 2014, Ward Declaration ¶ 57; POR at 16-20.

86. First, I understand from Petitioner's counsel that the POSA's knowledge is not a substitute for disclosure in the specification. And as I explained in paragraph 59 above, there is no disclosure in the '956 application of any hydrogen bonding principles, including Etter's "rules," or how to apply them to predict or prepare *any* co-crystal, let alone one within the claimed genus.

87. Second, I also understand from Petitioner's counsel that for more unpredictable fields or fields that are not mature (like the one relevant here, *see*

discussion in section V.C below), more disclosure in the specification is required to show that the inventors had possession of the full scope of the claimed subject matter. As I explained in my Opening Declaration (Ex. 1002, section IX.B.1.c) and as I further explain below (section V.C), whether a co-crystal would form at all, much less one satisfying the limitations of the challenged claims, was unpredictable as of March 2003 (and that is still true today). In view of this unpredictability, the lack of any disclosure in the '956 application about hydrogen bonding principles or Etter's "rules" and importantly, how to apply them to identify co-crystals falling within the full scope of the challenged claims, demonstrates that there is insufficient support for written description of the full breadth of claimed co-crystals.

88. Third, Both Dr. Ward and Patent Owners discuss hydrogen bonding principles, including Etter's "rules," in the context of "*postulat[ing]* whether a co-crystal of an API satisfying claims 10, 11, and/or 18 would likely form" and understanding "the *likelihood* of certain functional groups ... to form supramolecular synthons." Ex. 2014, Ward Declaration ¶ 54 (emphases added); POR at 17 (emphases added). However, given the unpredictability in the art and enormously broad scope of the claimed co-crystals, *hypothesizing* whether a co-crystal would form or understanding the *likelihood* that a supramolecular synthon would form would not have told a POSA anything about whether a co-crystal

would actually form, much less with any particular hydrogen bonding interactions. See ¶¶ 58-68.

89. As I explained in paragraph 60 above, Dr. Ward and Patent Owners do not explain how a POSA would have applied any hydrogen bonding principles, including Etter's "rules," to "visualize or recognize" any claimed co-crystal, much less the full scope of claimed co-crystals. Nor have they identified a single example in the art as of March 2003 that shows such principles or "rules" could be used to predict the full scope of co-crystals encompassed by the challenged claims (let alone any co-crystal). In my opinion, that is because it simply could not be done.

90. Lastly, that hydrogen bonding principles and/or Etter's "rules" could not have been used by a POSA in March 2003 with the '956 application's examples to "visualize or recognize" the full scope of claimed co-crystals is further supported by the limitations of using Etter's "rules" to predict hydrogen bonding interactions that I discussed in section III.D.3 above—for example, because (i) the co-crystal components have many functional groups or there are other competing forces (like ionic interactions) that dominate over hydrogen bonding to direct co-crystal formation—which Dr. Ward and Patent Owners concede (discussed in ¶ 61 above), (ii) the numerous examples in the literature of co-crystals that did not form hydrogen bonding interactions according to Etter's "rules" that I discussed in

paragraph 67 above (discussing Ex. 2008, Remenar (June) 2003 at 8456-57, Ex. 1081, Sharma 1993 at 2209, and Ex. 1082 Vishweshwar (June) 2003 at 789), and (iii) the fact that Etter’s rules do not address systems with multiple APIs and/or co-formers , which are encompassed by the scope of the challenged claims.

91. For these reasons, a POSA in March 2003 would not have understood that the inventors possessed the full scope of claimed co-crystals in view of the ’956 application’s examples and knowledge of hydrogen bonding principles, including Etter’s “rules.”

4. The Additional Ability to Perform High-Throughput Screening Would Not Have Allowed a POSA to “Visualize or Recognize” the Full Scope of Claimed Co-Crystals

92. In addition to the arguments I addressed above regarding written description, Patent Owners—without Dr. Ward’s support or any explanation—allege that a POSA’s ability in March 2003 to perform high-throughput screening further supports that the inventors were in possession of the full scope of claimed co-crystals. See POR at 19. I disagree with Patent Owners for the same reasons I discussed in section III.C above (discussing high-throughput screening) and that I discuss in section V below with respect to enablement.

* * *

93. For these reasons, it is still my opinion that the ’956 application lacks an adequate written description for the full co-crystal genus of claims 10, 11,

and/or 18, and, therefore, none of the challenged claims is entitled to a March 2003 priority date.

V. CLAIMS 10, 11, AND 18 ARE NOT ENTITLED TO A MARCH 2003 PRIORITY DATE BECAUSE THE '956 APPLICATION DOES NOT ENABLE THE FULL SCOPE OF CLAIMED CO-CRYSTALS

94. I disagree with Dr. Ward and Patent Owners that the '956 application enables the full scope of claimed co-crystals and, more specifically, that seven out of eight enablement factors weigh in favor of enablement. Ex. 2014, Ward Declaration ¶¶ 58, 82; POR at 21. As I explained in my Opening Declaration, seven out of eight factors weigh in favor of *non*-enablement and one—the relative skill of those in the art—is neutral. Ex. 1002, Opening Declaration section IX.B (enablement). For the reasons I discuss below, this is still my opinion.

95. Importantly, Dr. Ward and Patent Owners address only seven enablement factors and thus fail to address the eighth—the breadth of the claims. Thus, they have not disputed my opinion that the claimed genus of co-crystals is extremely broad and includes an *almost infinite* number of co-crystals, which weighs in favor of non-enablement. Ex. 1002, Opening Declaration section IX.B.1.a (enablement); *see also* ¶¶ 8, 70, above.

96. Regarding the other factors, Dr. Ward's and Patent Owners' enablement arguments primarily hinge on their opinion that co-crystal formation is a predictable art. But as I explained in my Opening Report and throughout this

declaration, there is no dispute that POSAs as of March 2003 understood that co-crystal formation was unpredictable. Ex. 1002, Opening Declaration section IX.B.1.c (enablement, unpredictability in the art); *see also* section V.C (enablement, unpredictability in the art), below and ¶ 87, above.

97. I respond to Dr. Ward’s and Patent Owners’ enablement arguments on the seven factors they did address below.

A. The Nature of the Invention Weighs in Favor of Non-Enablement

98. I disagree with Dr. Ward and Patent Owners that the nature of the invention weighs in favor of enablement. Ex. 2014, Ward Declaration ¶ 81; POR at 25.

99. Both Dr. Ward and Patent Owners agree with my description of the nature of the claimed invention—that is, “a pharmaceutical composition comprising a genus of co-crystals containing an API and a co-former having certain properties and non-covalent hydrogen bond interactions” (Ex. 1002, Opening Declaration ¶ 119; *see also* Ex. 2014, Ward Declaration ¶ 81; POR at 25). But then Dr. Ward alleges—without any support—that the field is “highly sophisticated.” Ex. 2014, Ward Declaration ¶ 81 (“Given the highly sophisticated nature of the field and the high level of skill in the art for a POSA ... this factor weighs in favor on enablement.”).

100. I disagree with Dr. Ward to the extent he is suggesting that “high[] sophisticat[ion]” is the nature (*i.e.*, the subject matter) of the claimed invention. Moreover, Dr. Ward fails to explain what he means by “*highly sophisticated* nature of the field” and how it, along with the POSA’s high level of skill, tips this factor in favor of enablement. It is also hard to square Dr. Ward’s opinions regarding the “highly sophisticated nature of the field” with his opinion that knowledge of pharmaceutical co-crystals was “emerging” as of 2002/2003. Ex. 2014, Ward Declaration ¶ 31. Even if the “nature of the field” was “highly sophisticated,” the field was certainly not established as of 2002/2003, as Dr. Ward admits. Ex. 2014, Ward Declaration ¶ 31.

101. Regardless of whether the field was “highly sophisticated” (which Patent Owners and Dr. Ward do not explain) and/or whether a POSA had a high level of skill in the art as of March 2003, the unpredictability of forming co-crystals at all, much less those within the scope of the claimed genus, tips this factor in favor of non-enablement. Ex. 1002, Opening Declaration section IX.B.1.c (enablement, unpredictability in the art); *see also* section V.C (enablement, unpredictability in the art), below; ¶¶ 87, 96.

B. The Relative Skill of Those in the Art Is Neutral with Respect to Enablement

102. Contrary to Dr. Ward's and Patent Owners' position, the relative skill of those in the art does not weigh in favor of enablement. Ex. 2014, Ward Declaration ¶¶ 59, 63; POR at 22. Rather, this factor is neutral. Opening Declaration ¶ 126.

103. The parties agree that the relative skill of a POSA as of March 2003—which I defined in paragraph 19 of my Opening Declaration and which Dr. Ward agrees with (Ex. 2014, Ward Declaration ¶¶ 23-24)—is high. Ex. 2014, Ward Declaration ¶ 59; POR at 6, 22; Ex. 1002, Opening Declaration ¶ 126. However, despite this high level of skill, as I have already discussed and will discuss further below, co-crystal formation, including formation of co-crystals falling within the scope of the challenged claims, is an unpredictable art. Even the most highly skilled experts could not predict co-crystal formation in March 2003 (or even today), diminishing the relevance of the POSA's skill level. Opening Declaration section IX.B.1.c (enablement, unpredictability in the art); section V.C (enablement, unpredictability in the art) below; see ¶¶ 87, 96, 101. Therefore, it remains my opinion that this factor is neutral with respect to enablement. Opening Declaration ¶ 126.

104. Dr. Ward and Patent Owners contend that a POSA's understanding of "principles of hydrogen bonding, Dr. Etter's 'rules,' formulation of pharmaceutical compositions, co-crystal formation, and high-throughput screening" supports that this factor weighs in favor of enablement. Ex. 2014, Ward Declaration ¶¶ 59-63; POR at 22. I disagree for the reasons I explain below.

1. Knowledge of and the Ability to Perform High-Throughput Co-Crystal Screening Would Not Have Allowed a POSA to Make and Use the Full Scope of Claimed Co-Crystals Without Undue Experimentation

105. As I discussed above, high-throughput screening and how to apply it to evaluate and/or optimize co-crystallization conditions to make and use co-crystals at all, much less those falling within the scope of the claims, is not disclosed anywhere in the '956 application. *See* ¶ 42. And neither Dr. Ward nor Patent Owners explain how a POSA would have implemented high-throughput screening for this purpose. *See* ¶ 42.

106. Further, neither Dr. Ward nor Patent Owners provide any evidence that high-throughput screening had been (or could have been) used as of March 2003 to evaluate or optimize co-crystallization conditions and/or to prepare any co-crystal, let alone the full scope of claimed co-crystals. *See* ¶ 43.

107. As I more fully explained in sections III.A.3 and III.C.3 above, identifying co-crystallization conditions and/or preparing the full scope of claimed

co-crystals would have required trial-and-error experimentation that was unpredictable and included an incredibly large number of co-crystallization experiments in view of the enormously broad scope of potential API and co-former combinations and all the co-crystallization variables a POSA would have needed to try. And even then, there would have been no guarantee that a given API and co-former within the scope of the challenged claims would ever form a co-crystal. This experimentation would have been further complicated by the time required to perform and the complexities of performing single crystal X-ray diffraction analysis to determine whether the screening products resulted in co-crystals having the non-covalent hydrogen bonding interactions required by the challenged claims. See section III.C.4.

108. In view of the immeasurable number of experiments that a POSA would have needed to perform to identify and optimize co-crystallization conditions to prepare the full scope of claimed co-crystals (some of which could not have been automated using high-throughput screening techniques and, instead, would have required manual experimentation, section III.C.3 above), along with the added complicated and time-consuming process of performing single crystal X-ray diffraction analysis, high-throughput screening would not have meaningfully “reduce[d] the amount of experimentation required to find suitable conditions ... for co-crystallization of a given API,” (Ex. 2014, Ward Declaration ¶ 62), much

less reduced it to an amount a POSA would have considered reasonable. Thus, even with the knowledge of and ability to perform high-throughput co-crystal screening in March 2003, a POSA would not have been able to prepare the full scope of claimed co-crystals without undue experimentation.

2. Knowledge of the “Formulation of Pharmaceutical Compositions” and “Co-Crystal Formation” Would Not Have Allowed a POSA to Make and Use the Full Scope of Claimed Co-Crystals Without Undue Experimentation

109. As I discussed above, a POSA in March 2003 would have understood co-crystallization in the context of the '956 application to refer to preparing the co-crystals and to be a separate step from formulation of that co-crystal into a pharmaceutical composition. See ¶¶ 23-26 (citing Ex. 1015, '956 application ¶ [0049]; Ex. 1001, '344 patent, col. 10, ll. 6-21); *see generally* section III.A.4 (discussing pharmaceutical formulation). But regardless of whether co-crystallization is considered a purification step or not, preparing the full scope of claimed co-crystals would have required an unreasonable amount of trial-and-error experimentation. In addition to the unpredictable work of attempting to prepare the co-crystals comprising API(s) and co-former(s), there would have been significant preparatory work to do, including at least identifying possible co-formers for each API, evaluating solubility parameters of each API and co-former, and identifying possible solvents for the attempted co-crystallization of the API(s) and co-

former(s) as I discussed in paragraphs 17-22, 31-33, and section III.C.3 above. Thus, I disagree with Dr. Ward's suggestion that a POSA would have had such information at his or her fingertips for every possible combination of API(s) and co-former(s) within the scope of the challenged claims or that the extensive effort that would have been required for the POSA to obtain this information should not be included when assessing undue experimentation. *See* Ex. 2014, Ward Declaration ¶¶ 44, 61.

110. For these reasons, a POSA in March 2003 could not have relied on knowledge of the “formulation of pharmaceutical compositions” or “co-crystal formation” to prepare the full scope of claimed co-crystals without undue experimentation.

3. Knowledge of Hydrogen Bonding Principles, Such as Etter's “Rules,” Would Not Have Allowed a POSA to Make and Use the Full Scope of Claimed Co-Crystals Without Undue Experimentation

111. As I previously explained, hydrogen bonding principles, including Etter's “rules,” and how to apply them to predict or make co-crystals at all, let alone those falling within the scope of the claims, are not disclosed anywhere in the '956 application. *See* ¶¶ 59, 86. And importantly, neither Dr. Ward nor Patent Owners explain how a POSA would have applied any hydrogen bonding principles, including Etter's “rules,” to prepare the full scope of claimed co-

crystals, particularly in view of (1) the limitations on applying those “rules” (such as when the API or co-former has multiple functional groups, or there are other non-covalent interactions, sterics, or geometric fit that impact whether and how co-crystals form) and the breadth of potential APIs and co-formers encompassed by the claims, and (2) the fact that Dr. Etter’s “rules” do not address systems with multiple API(s) and/or co-former(s) or systems that also include solvent, all of which are encompassed by the challenged claims. *See* ¶¶ 58-67.

112. In view of the incalculable number of unpredictable trial-and-error experiments required to prepare with the full scope of claimed co-crystals, even the (i) knowledge of and ability to perform high-throughput co-crystal screening, (ii) knowledge of the “formulation of pharmaceutical compositions” and “co-crystal formation,” *and* (iii) knowledge of the principles of hydrogen bonding and Etter’s “rules,” *together*, would not have allowed a POSA to prepare the full scope of claimed co-crystals without an unreasonable amount of experimentation.

113. Therefore, this factor weighs in favor of non-enablement.

C. The State of the Art & Unpredictability of the Art Weigh in Favor of Non-Enablement

114. I disagree with Dr. Ward and Patent Owners that the state of the art and predictability/unpredictability of the art weigh in favor of enablement. *Ex.* 2014, Ward Declaration ¶ 76; POR at 22-25.

115. Related to these factors, Dr. Ward improperly accuses me of arguing that the challenged claims are directed to methods, not pharmaceutical compositions. Ex. 2014, Ward Declaration ¶ 52 (“The claims are directed to ‘a *pharmaceutical composition* comprising cocrystals[,]’ not a research plan, as Dr. Rogers suggests.”), ¶ 67. But I make clear in my Opening Declaration that the challenged claims are directed to a pharmaceutical composition, and therefore, Dr. Ward and I agree on this point:

The claims of the '344 patent are directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal.

Ex. 1002, Opening Declaration ¶ 32 (emphasis added).

116. However, even though it is undisputed that the number of possible co-crystals covered by the challenged claims is almost infinite (Ex. 1002, Opening Declaration ¶¶ 74, 118), the challenged claims are not directed to a pharmaceutical composition comprising *any* co-crystal as Dr. Ward and Patent Owners suggest. Ex. 2014, Ward Declaration ¶ 56; POR at 4, 25. Rather, the claims are directed to only those co-crystals having the *specific* non-covalent hydrogen bonding interactions (among other limitations) recited in the claims. That is, the claimed co-crystals have, for example:

- (i) an API and co-former that *form supramolecular synthons via non-covalent hydrogen bonding between the first chemical functionality of an API (that is a carboxamide (claims 10, 11, and 18), carbonyl (claims 10 and 11), or amine (claims 10 and 11)) and an (unspecified) second chemical functionality of a co-former; and*
- (ii) a co-former that has an (unspecified) *second chemical functionality that is complementary to the first chemical functionality of the API and forms supramolecular synthons via non-covalent hydrogen bonding.*

Ex. 1001, '344 patent, col. 25, ll. 18-43, col. 26, ll. 22-23; see Ex. 1002, Opening Declaration ¶ 69.

117. Further, Dr. Ward and Patent Owners misunderstand my position with respect to predicting co-crystal formation. Specifically, it is their understanding that my analysis focuses on the predictability or unpredictability of whether a specific solid-state form (*e.g.*, a specific polymorph) of a co-crystal will form. Ward Declaration ¶ 75 (“[A] POSA would be concerned with whether a co-crystal would form and would not be concerned with predicting which particular polymorph would form”), ¶ 67, ¶ 70; see POR at 21 (“The Challenged Claims do not require a particular polymorph of the claimed co-crystal, they simply require a co-crystal with the claimed limitations.”); see ¶¶ 80-81 (discussing this misunderstanding). But this understanding is incorrect and Dr. Ward’s and Patent

Owners' arguments in response are subsequently irrelevant. My Opening Declaration focuses on preparing co-crystals falling within the scope of the challenged claims, *i.e.*, those having an API and co-former with the specific non-covalent hydrogen bonding interactions required by claims 10, 11, and 18, regardless of their solid-state (*e.g.*, polymorphic) form. See ¶¶ 80-81.

118. It is, in fact, Dr. Ward and Patent Owners who incorrectly focus their predictability/unpredictability analysis on whether *any* co-crystal would form, ignoring whether the co-crystal has the non-covalent hydrogen bonding interactions required by the challenged claims. Ex. 2014, Ward Declaration ¶ 70 (“The primary focus of the POSA, however, is to form a co-crystal that forms because of supramolecular synthons, *regardless of the details of the packing arrangements.*” (emphasis added)); ¶ 75 (“[A] POSA would be concerned with whether *a* co-crystal would form[.]” (emphasis added)); POR at 24 (“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.”); *see also* Ex. 2014, Ward Declaration ¶ 56 (“POSA would be most interested in forming *any kind of co-crystal* based on these principles, regardless of the details of the crystal packing ...or which combination of functional groups formed synthons.” (emphasis added)).

119. My opinion that co-crystal formation—whether a co-crystal will form at all, let alone one falling within the scope of the challenged claims—was an unpredictable art as of March 2003 is consistent with the opinions held by others in the field both prior to March 2003 and even after that date. Ex. 1002, Opening Declaration section IX.B.1.c; *see* ¶¶ 87, 96, 101, 103.

1. Dr. Ward and Patent Owners Are Incorrect that I “Selectively Quote[]” Desiraju 2001 in my Opening Declaration

120. In connection with the opinion in my Opening Declaration 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,” Ex. 1002, Opening Declaration ¶ 120, Dr. Ward and Patent Owners accuse me of “selectively quot[ing] Desiraju [2001 (Ex. 1024)].” Ex. 2014, Ward Declaration ¶ 68; *see also* Ex. 2014, Ward Declaration ¶¶ 69-71; POR at 23. I disagree that I selectively quoted from Desiraju 2001 to support my position.

121. In fact, it is Dr. Ward and Patent Owners who selectively quote from this reference, relying on one specific sentence that focuses on hydrogen bonding to support a co-crystal predictability allegation, *i.e.*, “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.” Ex. 2014, Ward Declaration ¶ 68 (quoting Ex. 1024, Desiraju 2001 at 399); POR at 23 (same). Yet this sentence does not discuss predictability (or unpredictability) of co-crystal formation at all.

122. Dr. Ward and Patent Owners allege, based on this one sentence in Desiraju 2001, that the hydrogen bond is “*one of the most* important interactions for forming homosynthons or heterosynthons.” Ex. 2014, Ward Declaration ¶ 68 (emphasis added); POR at 23 (same). But the sentence from Desiraju does not address the predictability (or unpredictability) of co-crystal formation. That hydrogen bonding, among other interactions, is *important* for forming homosynthons or heterosynthons does not suggest that co-crystal formation is a predictable art. And, as I discussed in paragraphs 61 and 67 above, both Dr. Ward and Patent Owners admit that there are various different factors and interactions that can “steer” co-crystal formation. See ¶¶ 61, 67 (both discussing Ex. 2014, Ward Declaration ¶ 55 and POR at 17-18).

123. In addition, as I explained several times above, as of March 2003, co-crystallization was unpredictable, and knowledge of hydrogen bonding principles, including Etter’s “rules,” does not change this. See sections III.D, IV.B.3. Further, neither Dr. Ward nor Patent Owners have explained how a POSA would have used any hydrogen bonding principles, including Etter’s “rules” to predict co-crystal

formation, or provided any examples of such use that support possession of the full scope of claimed co-crystals.

124. Dr. Ward's and Patent Owners' focus on the single sentence on page 399 of Desiraju 2001 disregards the remainder of the reference, which I discuss in my Opening Declaration and which states: "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, Desiraju 2001 at 399; Ex. 1002, Opening Declaration ¶¶ 81, 120, 121 (all quoting Desiraju at 399). This understanding would apply to predicting co-crystal formation generally as knowledge of a particular intermolecular interaction (such as a hydrogen bond) in one co-crystal would not have allowed a POSA to predict whether a different co-crystal could form.

125. That "additional hydrogen bonds would be viewed as helpful" as Dr. Ward alleges (Ex. 2014, Ward Declaration ¶ 71) misunderstands the issue here, which is whether forming a co-crystal between an API and co-former having the *specific* non-covalent interactions required by the challenged claims would have been predictable. Whether a co-crystal has (or would have) additional hydrogen bonds not covered by the challenged claims suggests nothing about predictability.

126. Furthermore, Dr. Ward’s contention that “[a] POSA concerned with making a co-crystal [] would not be concerned about which pairs of functional groups could form synthons,” makes no sense and is simply incorrect in view of the claim limitations which require specific interactions between the first and second chemical functionalities. Ex. 2014, Ward Declaration ¶ 69 (“The POSA would principally be concerned with making a co-crystal of a particular API regardless of which synthons promoted the function of the co-crystal.”), *see also* ¶¶ 56, 75. Whether a POSA in March 2003 would have been able to predict the formation of co-crystals having the *specific* interactions required by claims 10, 11, and 18 would have been the POSA’s concern when analyzing these enablement factors.

2. Dr. Ward’s and Patent Owners’ Arguments Regarding Fleischman 2003 and Other Co-Crystal Failures Further Support the Unpredictability of Forming Co-Crystals Within the Scope of the Challenged Claims

127. Dr. Ward and Patent Owners disagree that Fleischman (June) 2003 (Ex. 1028)—the ’344 patent inventor’s own work—and other co-crystal failures in the art that I discussed in my Opening Declaration support my opinion that “co-crystal formation is challenging and unpredictable.” Ex. 2014, Ward Declaration ¶¶ 72-74 (discussing Ex. 1002, Opening Declaration ¶¶ 121-124); *see also* POR at 23-24. First, Dr. Ward and Patent Owners allege that Dr. Ward and other POSAs as of

March 2003 “would have viewed a 20% success rate [in Fleischman 2003] in co-crystallizing an API as an acceptable benchmark for success.” Ex. 2014, Ward Declaration ¶ 74; POR at 24 (“Novartis fails to appreciate that a 20% success rate would actually be considered good in this field.”). But even if Dr. Ward (and/or other POSAs) in March 2003 would have allegedly viewed a 20% success rate “as an acceptable benchmark for success[,]” this does not mean that a POSA at that time trying to make and use the full scope of claimed co-crystals would have been able to do so without an unreasonable amount of experimentation (which I understand is the test for enablement, Ex. 1002, Opening Declaration, Appendix B section D.2). In fact, such a low success rate, coupled with the large breadth of the claims, would have suggested to a POSA just the opposite.

128. Second, Dr. Ward and Patent Owners contend that I “fail[ed] to note the [co-crystal] successes” in my discussion of failures in the art. Ex. 2014, Ward Declaration ¶ 74 (discussing Ex. 1002, Opening Declaration ¶ 121 and my references to Ex. 1027, Reddy 2004; Ex. 1025, Aakeroy (January) 2003; and Ex. 1007, Ueto 2012); POR at 24 (similar)). However, even if I “note[d] the successes” (which are reported in the art at an exponentially higher rate than failures), doing so would not detract from the fact that the art discloses numerous failed attempts at preparing co-crystals, demonstrating that co-crystal formation is in fact an

unpredictable art. Ex. 1002, Opening Declaration section X.B.1.c (enablement, unpredictability in the art).

129. Third, Dr. Ward and Patent Owners allege that because the details of the alleged co-crystal “failures” in Fleischman 2003 (Ex. 1028) were not reported, a POSA in March 2003 “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.” Ex. 2014, Ward Declaration ¶ 73; POR at 23-24 (same). This allegation is perplexing and inconsistent with Patent Owners’ enablement theory and arguments that co-crystals can be made predictably. Fleischman’s authors included the named inventors of the ’956 application and ’344 patent, the paper was published after the ’956 application was filed, and it cites Etter’s work. *See* Ex. 1028, Fleischman (June 2003 at 913 (citing Ex. 2005, Etter 1990 and discussing hydrogen bonding principles). If the forty failed co-formers (*i.e.*, 80% of the fifty tested co-formers) did not have *at least some* potential to co-crystallize with carbamazepine, why were they selected?

130. For the foregoing reasons, it is still my opinion that the state of the art of co-crystal formation was unpredictable as of March 2003 (and it still is today) and, therefore, that the state of the art and predictability/unpredictability of the art factors weigh in favor of non-enablement.

D. The Quantity of Experimentation Weighs in Favor of Non-Enablement

131. I do not agree with Dr. Ward's or Patent Owners' opinion that the quantity of experimentation necessary to prepare the full scope of claimed co-crystals is "relatively low" and, therefore, that this factor weighs in favor of enablement. *See* POR at 22-23, 25; Ex. 2014, Ward Declaration ¶ 66.

132. For this factor, Dr. Ward and Patent Owners rely on the alleged availability of using high-throughput screening to test for co-crystals, which purportedly "would have significantly reduced the length of time and effort required for a POSA to test for co-crystals under various conditions," as well as "available [solvent] guidance" (*i.e.*, the HHS Guidance (Exs. 2012 and 2013)), and "general knowledge of solubility properties of various moieties in the API or co-former." Ex. 2014, Ward Declaration ¶¶ 64-65; POR at 22-23. Patent Owners additionally rely on a POSA's knowledge of hydrogen bonding, as well as the "formulation of pharmaceutical compositions." POR at 22-23. But Dr. Ward's and Patent Owners' arguments on this factor are not supported by any explanation as to how a POSA in March 2003 would have actually utilized high-throughput screening, the HHS solvent guidance, solubility properties of the APIs and co-formers, knowledge of hydrogen bonding, and/or "formulation of pharmaceutical compositions" to make and use the full scope of claimed co-crystals.

133. I explained in sections V.B.1-V.B.3 above how each of (i) knowledge of and the ability to perform high-throughput screening; (ii) knowledge of “formulation of pharmaceutical compositions,” including the solubility properties of possible APIs and co-formers covered by the challenged claims; and (iii) knowledge of hydrogen bonding principles, including Etter’s “rules,” respectively, would not have allowed a POSA in March 2003 to make and use the full scope of claimed co-crystals without an unreasonable amount of experimentation. *See also* sections III.C (discussing high-throughput screening); III.A.4 (discussing formulation of pharmaceutical compositions and solubility properties; III.B (discussing HHS solvent guidance documents and solubility); III.D (discussing hydrogen bonding principles and Etter’s “rules”). I also explained in paragraph 112 how a POSA would not have been able to do so even with all this combined knowledge. I incorporate here my opinions from these cited sections and paragraphs.

134. In summary, preparing the full scope of claimed co-crystals would have required a POSA in March 2003 (and even today) to undergo extensive unpredictable trial-and-error experimentation—no less than hundreds of thousands of experiments, with no guarantee that co-crystals would form at all. And even if high-throughput co-crystal screening was available by March 2003 (which neither Dr. Ward nor Patent Owners have provided evidence of, ¶¶ 43-45 above), in view

of the essentially infinite amount of experimentation that would have been necessary to evaluate and optimize co-crystallization conditions and/or make and use the full scope of claimed co-crystals, this technique would not have meaningfully “minimize[d] the amount of time and effect a POSA would expend to complete such testing” as Dr. Ward and Patent Owners allege. *See* Ex. 2014, Ward Declaration ¶¶ 64-65; POR at 23.

135. Thus, none of the knowledge that Dr. Ward and Patent Owners rely on for this factor (¶¶ 132-133 above) would have made the requisite amount of experimentation reasonable for a POSA to perform in March 2003 (or even today). *See, e.g.*, Ex. 1083, Zhu 2024 at 4259 (“[T]he task of forecasting the crystallization tendencies of APIs remains a challenging and ongoing pursuit. The constraints of limited data sets, the intricate nature of the crystallization process, and the wide array of conditions and methodologies documented in existing literature all present substantial obstacles.”), 4260 (“[E]xperimental screening of ... cocrystals is often tedious and expensive.”) 4262 (“A large number of trial-and-error attempts are required to identify suitable cocrystal formers, highlighting the urgent need for prediction that can enhance the efficiency of cocrystal screening.”).

136. Therefore, this factor weighs in favor of non-enablement.

E. The Presence or Absence of Working Examples Weighs in Favor of Non-Enablement

137. I disagree with Dr. Ward and Patent Owners that the presence or absence of working examples weighs in favor of enablement. Ex. 2014, Ward Declaration ¶ 79; POR at 25.

138. Dr. Ward and Patent Owners allege that there are sufficient working examples disclosed in the '956 application to support enablement of the claimed co-crystal genus because “[e]ach limitation is described in at least one example which is sufficient for a POSA to understand how the limitation would be implemented in the claimed co-crystal” and “a POSA would have understood how each of the limitations of claims 10, 11, and 18 functioned having reviewed the nineteen examples.” Ex. 2014, Ward Declaration ¶ 77; *see also* POR at 25 (making the conclusory allegation, with no explanation, that there are “19 examples that provide guidance to a person of ordinary skill in the art”).

139. However, even if all nineteen co-crystal examples fell within the scope of the claimed genus (they indisputably do not), nineteen examples using a limited number of APIs and co-formers is not sufficient to teach a POSA how to make and use the breadth of the claimed co-crystals, which includes an almost infinite number of diverse co-crystals. Ex. 1002, Opening Declaration ¶¶ 79, 82, 128; *see* ¶ 72, above.

140. Additionally, Dr. Ward's allegation is incorrect in view of his own admission that the '956 application does not disclose *any* example of a co-crystal falling within the scope of claim 10 or 11 wherein the first chemical functionality is a carbonyl or amine. See ¶¶ 15, 79 (discussing Ex. 2014, Ward Declaration, Appendix C). Nor does the '956 application disclose any example of a co-crystal falling within the scope of any of claims 10, 11 or 18 that contains more than one API and/or co-former. See ¶¶ 15, 79.

141. But even if Dr. Ward's statements were correct (they are not), he fails to explain how an understanding of "how each of the limitations of claims 10, 11, and 18 functioned" based on the nineteen co-crystal examples disclosed in the '956 application would have allowed a POSA in March 2003 to make and use the full scope of the claimed co-crystals. Knowing how to "implement" each claim limitation *in isolation*, and the disclosure of a few non-representative examples (see Ex. 2014, Ward Declaration ¶ 77), would not have taught a POSA in March 2003 how to make and use the full breadth of claimed co-crystals. See ¶¶ 79-84.

142. And in view of the indisputably broad scope of diverse co-crystals covered by the challenged claims (¶¶ 75, 95 above; Ex. 1002, Opening Declaration ¶¶ 74, 118) and the unpredictability in the art of co-crystal formation (section V.C above), even if all nineteen co-crystal examples satisfied all the limitations of the claimed co-crystals (they do not), nineteen examples would not have been

sufficient to teach a POSA in March 2003 how to make and use the full scope of claimed co-crystals without undue experimentation. Ex. 1002, Opening Declaration section IX.B.1.e (enablement, presence or absence of working examples); *see also* section IX.A.2 (written description, representative species).

143. For these reasons, this factor weighs in favor of non-enablement.

F. The Lack of Direction or Guidance Weighs in Favor of Non-Enablement

144. I lastly disagree with Dr. Ward and Patent Owners that the amount of direction or guidance weighs in favor of enablement. Ex. 2014, Ward Declaration ¶ 79; POR at 25.

145. Dr. Ward and Patent Owners identify four disclosures in the '344 patent (which also appear in the '956 application) that they allege tip this factor in favor of enablement without providing an explanation for how a POSA would have used or applied these disclosures in March 2003 to prepare the full scope of claimed co-crystals: (1) column 9, lines 27-40 (corresponding to a portion of ¶ [0047] of the '956 application, Ex. 1015); (2) column 3, lines 35-37 (corresponding to a portion of ¶ [0009] of the '956 application), (3) column 3, lines 19-26 (corresponding to a portion of ¶ [0008] of the '956 application), and (4) Figure 24 (corresponding to Figure 24 of the '956 application). Ex. 2014, Ward Declaration ¶ 78 (citing (1), (2), and (4)); POR at 25 (referencing section II.B, citing (1) – (4)).

146. In my opinion, the four above-identified disclosures—with or without the '956 application's/'344 patent's nineteen examples (that do not all fall within the scope of the claimed co-crystals)—would hardly have provided a POSA in March 2003 (or even today) with sufficient direction or guidance to make and use the full co-crystal genus as of March 2003.

147. Column 9, lines 27-40, of the '344 patent provides the definition of “API” that I relied on in this proceeding, which is “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.” But this broad definition does not identify or provide any examples of molecules that would have qualified as APIs in March 2003 in the context of the challenged claims. And as I previously explained, I identified over fifty examples of molecules that would have qualified as carboxamide-containing APIs by March 2003, but many more would have qualified. Ex. 1002, Opening Declaration ¶¶ 71-74, 116-118; *see* ¶¶ 19, 75, section III.C.3, above. This disclosure lacks any guidance for how a POSA would have identified molecules satisfying the API limitations of the challenged claims, including the necessary non-covalent hydrogen bonding interactions with an unidentified co-former.

148. Column 3, lines 35-37, of the '344 patent provides non-limiting broad categories of compounds that qualify as co-formers according to the challenged

claims, for example, other drug molecules, GRAS compounds, and approved food additives. This broad disclosure, like the definition of API, does not identify or provide any examples of molecules that would have qualified as co-formers in March 2003 within the scope of the challenged claims. And I previously explained that thousands of molecules would have qualified as co-formers at that time. Ex. 1002, Opening Declaration ¶¶ 71-74, 116-118; ¶ 19, above. This disclosure, similarly, lacks any guidance for how a POSA would have identified molecules satisfying the co-former limitations of the challenged claims, including the necessary non-covalent hydrogen bonding interactions with an unidentified API having a carboxamide, carbonyl, or amine first chemical functionality.

149. Likewise, column 3, lines 19-26, of the '344 patent discusses characterization of co-crystals and notes that the physical and/or chemical properties of a co-crystal can be the same or different from the parent API due to “alternative molecular recognition patterns.” This disclosure does not inform a POSA how to identify molecules satisfying the API or co-former limitations, nor does it provide guidance to identify the necessary non-covalent hydrogen bonding interactions between the API and co-former.

150. Lastly, Figure 24 provides “an exemplified scheme for preparing multiple-component phase compositions” (Ex. 1001, '344 patent, col. 7, ll. 13-15), but it does not disclose *any* co-crystals and is not limited to preparing just the

claimed co-crystals. See ¶ 17. At best, Figure 24 provides a *trial-and-error research plan* for preparing co-crystals. See section III.A.3 (discussing Figure 24’s research plan); see also Ex. 1002, Opening Declaration ¶¶ 32, 132. I discussed in great detail in paragraphs 19-21 above all of the information lacking in Figure 24 that a POSA would have needed to prepare the full scope of claimed co-crystals and I incorporate that discussion here. Without that necessary information, following the exemplified scheme in Figure 24 to prepare the claimed genus of co-crystals (with or without using high-throughput (or manual) screening to evaluate or optimize co-crystallization conditions) would have been mere unpredictable trial-and-error experimentation that would have been unreasonable for a POSA to undergo—requiring no less than hundreds of thousands of experiments. See ¶ 22; section V.D (enablement, quantity of experimentation necessary). And considering these three disclosures together would not change my opinion even if a POSA considered them with the ’956 application as a whole.

151. That these disclosures allegedly “expressly provide[] descriptions of the types of appropriate APIs, co-formers, and solvents that could have been used in forming the co-crystals in the claimed pharmaceutical compositions” says nothing about how a POSA would have used these disclosures to make co-crystals at all, much less those within the scope of the challenged claims. Ex. 2014, Ward Declaration ¶ 78; POR at 25. None of these disclosures even relates to solvents,

other than that the co-formers can be “solvent molecules.” Ex. 1001, ’344 patent, col. 3, ll. 35-37.

152. Additionally, nowhere do Dr. Ward or Patent Owners even *attempt* to make the argument that these four disclosures would have provided a POSA with adequate direction or guidance to make the broad scope of claimed co-crystals. Patent Owners merely allege that these four disclosures (and the nineteen co-crystals, which I already discussed in section V.E above) provide “ample description ... to guide a POSITA on how to make **a** claimed co-crystal.” POR at 25 (emphasis and bold added). As I explained in paragraph 139 above, a few representative examples of co-crystals falling within the scope of the challenged claims—even nineteen—would not have been sufficient guidance for a POSA in March 2003 to make and use the full scope of claimed co-crystals without undue experimentation.

153. For these reasons, this factor weighs in favor of non-enablement.

* * *

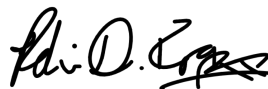
154. Therefore, it is still my opinion that the ’956 application fails to enable the full co-crystal genus of any of claims 10, 11, or 18 and, thus, none of the challenged claims is entitled to a March 2003 priority date.

VI. CONCLUSION

155. For the reasons discussed above and in my Opening Declaration (Ex. 1002), claims 10, 11, and 18 of the '344 patent lack sufficient written description and are not enabled by the '956 application (or '768 application) and, therefore, they are not entitled to a priority date of March 2003. Accordingly, it is my opinion that claims 10, 11, and 18 are invalid for anticipation and obviousness over the prior art identified in Grounds 1 and 2 of Novartis's petition.

156. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: August 27, 2024



Robin D. Rogers, Ph.D.