

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 PETITION FOR *INTER PARTES* REVIEW**

TABLE OF CONTENTS

I.	INTRODUCTION	7
II.	QUALIFICATIONS	7
III.	MATERIALS CONSIDERED	14
IV.	LEVEL OF ORDINARY SKILL IN THE ART	14
V.	RELEVANT LEGAL STANDARDS	17
VI.	OVERVIEW OF THE '344 PATENT	17
A.	Summary of Challenged Claim 16	18
B.	Brief History of the '344 Patent and Applicants' Purported Invention	24
VII.	BACKGROUND ON THE TECHNOLOGY OF THE '344 PATENT	25
A.	Background on Chemistry and Chemical Structures	25
B.	Multiple-Component Crystalline Solids	26
VIII.	CLAIM CONSTRUCTION	36
A.	Terms With Agreed-Upon Constructions	37
B.	Term Where I Was Asked to Adopt Patent Owners' Proposed Construction for the Purpose of this Declaration	40
IX.	CLAIM 16 IS NOT ENTITLED TO A 2002/2003 PRIORITY DATE	40
A.	Claim 16 Lacks an Adequate Written Description in the Priority Applications for the Full Scope of Claimed Solvates of Co-Crystals	41
1.	The Priority Applications Fail to Disclose Common Structural Features of Solvates of Co-Crystals Falling Within the Scope of Claim 16	46
2.	The Priority Applications Fail to Disclose a Representative Number of Solvates of Co-Crystals of the Claimed Genus	46

3.	The Prosecution History of the Related '223 Application and Almarsson Patent Further Reinforce That There Is a Lack of Adequate Written Description in the Priority Applications for the Claimed Genus of Solvates of Co-Crystals	59
B.	The Full Scope of Claimed Solvates of Co-Crystals in Claim 16 Is Not Enabled by the Priority Applications	84
1.	Supramolecular Synthons Non-Covalently Bonded to One Another by Non-Covalent Bonding to a Solvent Molecule Is Not Enabled.....	84
2.	The Prosecution History of the Related Almarsson Patent Further Reinforces That the Priority Applications Do Not Enable the Claimed Genus of Solvates of Co-Crystals	102
C.	API Homosynthons Wherein the First Chemical Functionality Is a Carbonyl Is Not Enabled by the Priority Applications	112
X.	OVERVIEW OF THE STATE OF THE ART.....	119
XI.	INVALIDITY GROUND 1: CHALLENGED CLAIM 16 IS OBVIOUS OVER UETO 2012 IN VIEW OF LI 2011, MARTINDALE 2011, THE '006 PUBLICATION, AND REMINGTON 2012	121
A.	Overview of Ueto 2012	121
B.	Overview of Li 2011	122
C.	Overview of Martindale 2011	122
D.	Overview of the '006 Publication	123
E.	Overview of Remington 2012	124
F.	Obviousness of Claim 16 – Element by Element Claim Analysis....	125
1.	[10b]: a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former.....	126

2.	[10c]: 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.....	130
3.	[10d]: wherein the co-former has a second chemical functionality compl[e]mentary to the first chemical functionality via non-covalent hydrogen bonding.....	132
4.	[10e]: wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form	134
5.	[10f]: wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former	135
6.	[10g]: wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine	137
7.	[16b]: wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule	137
8.	[10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [a co-crystal].....	143
9.	Motivation to Combine Ueto 2012, Li 2011, Martindale 2011, the '006 Publication, and Remington 2012	146

XII. INVALIDITY GROUND 2: CHALLENGED CLAIM 16 IS OBVIOUS OVER THE '408 APPLICATION AND/OR SOWA 2013 IN VIEW OF MARINI 2007, LI 2011, THE '006 PUBLICATION AND REMINGTON 2012 152

A.	Overview of the '408 Application.....	152
B.	Overview of Sowa 2013	155
C.	Overview of Marini 2007	158

D.	Overview of Li 2011	159
E.	Overview of the '006 Publication	159
F.	Overview of Remington 2012	159
G.	Obviousness of Claim 16 – Element by Element Claim Analysis....	159
1.	[10b]: a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former.....	160
2.	[10c]: 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.....	166
3.	[10d]: wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding.....	166
4.	[10e]: wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form	168
5.	[10f]: wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former	169
6.	[10g]: wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine	172
7.	[16b]: wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule	173
8.	[10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [a co-crystal].....	178

9.	Motivation to Combine the '408 Application and/or Sowa 2013 with Marini 2007, Li 2011, the '006 Publication, and Remington 2012	182
XIII.	OBVIOUSNESS - SECONDARY CONSIDERATIONS	190
A.	There is No Evidence of Any Unexpected or Surprising Results Commensurate in Scope With the Challenged Claim 16.....	191
B.	There is No Evidence that There Was a Long Felt But Unmet Need for the Purported Invention of Challenged Claim 16 Commensurate in Scope With Claim 16	194
XIV.	THE PETITION SHOULD NOT BE DISCRETIONARILY DENIED.....	198
A.	Part 1: The Same or Substantially the Same Art and Arguments Were Not Previously Presented to the Patent Office.....	199
1.	Factor (a): The Similarities and Material Differences Between the Asserted Art and the Prior Art Involved During Examination	200
2.	Factor (b): The Cumulative Nature of the Asserted Art and the Prior Art Evaluated During Examination	222
3.	Factor (d): The Extent of the Overlap Between the Arguments Made During Examination and the Manner in Which Petitioner Relies on the Prior Art or Patent Owners Distinguish the Prior Art	222
4.	Part 1 Conclusion	225
XV.	AVAILABILITY FOR CROSS EXAMINATION.....	226
	APPENDIX A.....	227
	APPENDIX B	234
	APPENDIX C	241

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

I. INTRODUCTION

1. I have been retained as an expert by counsel for Novartis Pharmaceuticals Corporation (“Petitioner” or “Novartis”). I have been asked by counsel to provide my expert opinions regarding the validity of claim 16 of U.S. Patent No. 10,633,344 (“the ’344 patent”) in support of Novartis’s Petition for *Inter Partes* Review (“petition”) of the ’344 patent. For the reasons set forth below, it is my opinion that claim 16 of the ’344 patent is unpatentable.

II. QUALIFICATIONS

2. I am currently a Professor Emeritus at The University of Alabama, Tuscaloosa, Alabama, USA and President, Owner, and Founder of 525 Solutions, Inc., also in Tuscaloosa, Alabama, USA, a research and development (R&D) company that focuses on developing proprietary, broad-based ionic liquid technologies applicable in medicinal, pharmaceutical, and materials fields. I am also co-Founder and co-Owner of Wyonics LLC, Laramie, WY; CalAgua Innovations Corp., Calgary, AB, Canada; and Adjacency Labs Corp., Calgary, AB, Canada. I also am an Adjunct Professor at the University of Wyoming and an Honorary Professor in the School of Engineering, University of Kwazulu-Natal, Pietermaritzburg, South Africa. My most recent previous academic appointments included Tage Erlander Guest Professor at Stockholm University (2019-2020),

Canada Excellence Research Chair in Green Chemistry and Green Chemicals at McGill University (2015-2017), and Distinguished Research Professor, Robert Ramsay Chair of Chemistry, and Director of the Center for Green Manufacturing at The University of Alabama (1996-2014).

3. I received a B.S. in chemistry (*summa cum laude*) in 1978 and a Ph.D. in chemistry in 1982 from The University of Alabama. During the period of 1982-1996, I was successively an assistant, associate, full, and Presidential Research Professor at Northern Illinois University. During the period of 1991-1998, I also held a faculty appointment at the Argonne National Research Laboratory, Argonne, Illinois. In 1996, I became a Professor of Chemistry at The University of Alabama and, in 1998, I was named Director of The University of Alabama's Center for Green Manufacturing. I was awarded the titles Distinguished Research Professor in 2004 and Robert Ramsay Chair of Chemistry in 2005. From 2007-2009, I held a joint appointment as Chair in Green Chemistry in the School of Chemistry & Chemical Engineering and Director of the Queen's University Ionic Liquid Laboratories ("QUILL") at Queen's University of Belfast, Belfast, Northern Ireland, UK.

4. I am, or have been, a member of various professional societies, including the American Association for the Advancement of Science (Fellow), American Chemical Society (Fellow), American Crystallographic Association,

American Institute of Chemical Engineers, Materials Research Society, American Association for Crystal Growth, and Royal Society of Chemistry (Fellow).

5. In 1989, I joined the Editorial Board of the *Journal of Chemical Crystallography* (then named *Journal of Crystallographic and Spectroscopic Research*). I became Associate Editor of the journal in 1993 and was the Editor from 1996 to 2000. In 1998, I founded the journal *Crystal Engineering* and served as Editor until 1999. In 2000, I was asked by the American Chemical Society (“ACS”) to found a new journal called *Crystal Growth & Design*, for which I served as Founding Editor-in-Chief until December 31, 2019. I also have served or currently serve as editor or on the editorial board of the following journals:

- *Separation Science and Technology*, Associate Editor, 1996-1999; Editorial Board, 1999-present;
- *Industrial & Engineering Chemistry Research*, Editorial Board, 1999-2001;
- *Journal of Chromatography B*, Guest Editor, Volume 743 (1 + 2), 2000;
- *Solvent Extraction and Ion Exchange*, Editorial Board, 2002-present;
- *Green Chemistry*, International Advisory Board, 2002-present;
- *Chemical Communications*, Editorial Advisory Board, 2005-present;

- *Accounts of Chemical Research*, Guest Editor (with G. A. Voth), *Special Issue on Ionic Liquids*, Volume 40(11), 2007;
- *ChemSusChem*, International Advisory Board, 2008-2019;
- *Chemistry Letters*, Advisory Board, 2010-present;
- *Australian Journal of Chemistry*, Guest Editor (with K.R. Seddon), *Research Front on Crystal Engineering*, Volume 63(4), 2010;
- *Separation Science & Technology*, Guest Editor (with H. Rodriguez and J. Chen), *Special Issue on Ionic Liquids*, 2012;
- *Chemical Communications*, Guest Editor (with D. MacFarlane and S. Zhang), *Special Issue on Ionic Liquids*, 2012;
- *Science China – Chemistry*, Guest Editor (with S. Zhang), *Special Issue on Ionic Liquids*, 2012;
- *Catalysis Today*, Guest Editor (with S. Zhang), *Special Issue on Ionic Liquids*, 2012;
- *Green Chemistry and Sustainable Technology*, Springer, Heidelberg, Germany, Book Series Editor (with L.-N. He, D. Su, P. Tundo, and Z. C. Zhang), 2013-2019;
- *Chimica Oggi/Chemistry Today*, Scientific Advisory Board, 2014-present;
- *Green Energy & Environment*, Advisory Board, 2016-present; and

- *Journal of Ionic Liquids, Editorial Board, 2021-present.*

6. In my position as Founding Editor-in-Chief of the American Chemical Society journal *Crystal Growth & Design*, I regularly evaluated and judged suitability for publication of numerous manuscripts which utilize and study crystal growth and the characterization of solid-state materials, including co-crystals. Accordingly, I am quite familiar with the academic and scientific standards for experimental work in this field, and I have evaluated countless numbers of single crystal structures.

7. In 2004, 2005, and 2008, I organized three special issues of *Crystal Growth & Design* dedicated to the phenomenon of polymorphism and in 2009, I organized a special issue dedicated to pharmaceutical co-crystals. Many of these papers addressed pharmaceutical compounds, solid forms, co-crystals, salts, hydration, solvation, and the use of single crystal X-ray diffraction techniques.

8. In 2010, I was co-founder, co-organizer, and Vice Chair of the first Gordon Research Conference devoted to the topic of Crystal Engineering (Waterville Valley Resort, NH, June 6-11, 2010). I was the organizer and Chair of the second Gordon Research Conference on Crystal Engineering (Waterville Valley Resort, NH, June 10-15, 2012). The Gordon Research Conference is a non-profit organization that brings together scientists throughout the world to discuss the latest research in their field. I was also the co-founder, co-organizer, and Chair

of the first Gordon Research Conference devoted to the topic of Ionic Liquids (Newry, ME, August 17-22, 2014).

9. I have published more than 900 articles in refereed journals, edited 14 books, and have been named as an inventor on more than 60 domestic and foreign patents. I have also given over 1,100 presentations before regional, national, and international meetings, and over 250 seminars worldwide. In both 2014 and 2015, I was named to the Thomson Reuters Highly Cited Researchers List, ranking among the top 1% most cited in chemistry and listed in the top 2% ranking of world scientists.

10. I use and have used over the past 45 years, including as of 2002, 2003, and 2014, X-ray diffraction techniques including single crystal X-ray diffraction in my research efforts. I am familiar with and use crystallization techniques to create and isolate solid-state forms of compounds in my research efforts. Through my own research, as well as through my service as an editor or on the editorial board of numerous scientific journals, I have extensive experience solving and analyzing single crystal structures of compounds. I have submitted the results of over 1,300 single crystal X-ray diffraction studies to the Cambridge Structural Database, the world-leading repository for single crystal structures. Additionally, since 1996, I have had a leadership role in the development of the field of ionic liquids (pure salts liquid at low temperature), probing their fundamental nature while advancing

their technological relevance in areas which include crystallization and novel pharmaceutical forms.

11. I have collaborated with organic chemists in industry and in academia as part of a team in the discovery and characterization of novel drug compounds. I have also acted as a consultant in industry in the development of pharmaceutical drug compounds. Within my research group, I regularly hire and supervise Ph.D. organic chemists and direct their research in the synthesis and characterization of novel forms of active pharmaceutical ingredients.

12. My work has been recognized with several awards including the 2005 Presidential Green Chemistry Challenge Award, the 2011 American Chemical Society Award in Separations Science and Technology, the 2013 Paul Walden Award in Ionic Liquids, the 2018 Max Bredig Award in Molten Salt and Ionic Liquid Chemistry, the 2018 American Chemical Society/Environmental Protection Agency Green Chemistry Challenge Award Focus Area 2: Greener Reaction Conditions, and in being elected in 2012 as a Fellow of the American Association for the Advancement of Science.

13. As of 2002, 2003, and 2014 I was, and still am, an expert in the field of chemistry including solid-state chemistry, including crystal engineering of multi-component crystals such as co-crystals and the application of crystalline

forms of drugs in pharmaceutical products. Accordingly, I believe that I am competent to express the opinions set forth below.

14. A complete listing of my qualifications, experience, publications, and professional activities is set out in my curriculum vitae (Ex. 1553).

15. I am being compensated for my work in this proceeding at my standard hourly consulting rate of \$700 per hour. My compensation is in no way contingent on the substance of my opinions or the outcome of this proceeding.

16. The bases for my opinions are set forth in this declaration.

III. MATERIALS CONSIDERED

17. In preparing this declaration, I reviewed the materials in **Appendix A**, including the '344 patent (Ex. 1501), its prosecution history (Ex. 1516), and the prosecution history of the '344 patent's parent application, U.S. Application No. 10/378,956 ("the '956 application") (Ex. 1515).

IV. LEVEL OF ORDINARY SKILL IN THE ART

18. I was asked to opine on the experience and level of skill of a person of ordinary skill in the art ("POSA") of the '344 patent as of March 1, 2002,¹ March

¹ I understand from Petitioner's counsel that March 1, 2002 is the filing date of U.S. Provisional Application No. 60/360,768 ("the '768 application"), the application to which the '344 patent claims earliest priority.

3, 2003² (which I will abbreviate as “2002/2003”), and February 13, 2014³ (which I will abbreviate as “2014”).

19. In my opinion, a POSA as of 2002/2003 or 2014 would have had a Ph.D. in chemistry or a related field with at least two years of experience in solid state chemistry, including experience preparing multiple-component crystalline solids and evaluating their single crystal structures, and the POSA would consult with others having ordinary experience in other disciplines, such as formulation of pharmaceutical compositions comprising such multiple-component crystalline solids. Alternatively, a POSA as of 2002/2003 or 2014 would have had a Ph.D. in chemistry, pharmacy, or a related field with at least two years of experience in formulation of pharmaceutical compositions, and the POSA would consult with others having ordinary experience in other disciplines, such as solid-state chemistry, including experience preparing multiple-component crystalline solids and evaluating their single crystal structures. Alternatively, a POSA could have

² I understand from Petitioner’s counsel that March 3, 2003 is the filing date of the ’956 parent application to which the ’344 patent claims priority.

³ I understand from Petitioner’s counsel that February 13, 2014 is the filing date of U.S. Application No. 14/179,862 (“the ’862 application), which issued as the ’344 patent.

had a Master's degree in one of the above disciplines plus relatively more experience.

20. Petitioner and the Patent Owners (collectively, "the Parties") are involved in a district court case, *The Regents of the University of Michigan et al., v. Novartis Pharmaceuticals Corporation*, Case No. 3:22-cv-04913 (N.D. Cal.), in which I am serving as an expert on behalf of Petitioner, and I understand that the Patent Owners' expert in that case, Dr. Scott Childs, provided a different definition of a POSA as of 2002/2003. According to Dr. Childs, a POSA as of 2002/2003 would have had the following:

at least a Ph.D. in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with experience working in pharmaceutical development and/or solid-state chemistry, or a person with less education with at least two years of relevant experience. The POSITA could consult with others having ordinary experience in other disciplines.

21. In my opinion, Dr. Childs' definition requires less experience working in pharmaceutical development and/or solid-state chemistry. However, the differences between my definition of a POSA and Dr. Childs' definition do not affect my opinions in this declaration.

22. A POSA with respect to claim 16 of the '344 patent would have had at least the level of education, knowledge, and experience provided in Dr. Childs'

POSA definition. As of 2002/2003 and 2014, I had at least the education, knowledge, and experience under either Petitioner's or Patent Owners' POSA definition.

V. RELEVANT LEGAL STANDARDS

23. In rendering my analysis in this declaration, Petitioner's counsel has informed me about certain aspects of U.S. patent law that are relevant to my opinions. The legal principles provided to me by Petitioner's counsel are in **Appendix B**. I have applied those principles in arriving at my conclusions expressed in this declaration.

VI. OVERVIEW OF THE '344 PATENT⁴

24. The '344 patent is titled "Multiple-Component Solid Phases Containing At Least One Active Pharmaceutical Ingredient" and lists on its face three inventors: Michael J. Zaworotko, Nair Rodriguez-Hornedo, and Brian Moulton.

25. The '344 patent issued on April 28, 2020 from the '862 application, filed on February 13, 2014. Ex. 1501, cover. I understand from Petitioner's counsel that the '344 patent has expired. I also understand that the '862 application is a

⁴ The description of the '344 patent in this declaration is not an admission that the '344 patent adequately discloses or enables any claim.

continuation of the '956 application, filed on March 3, 2003 and now abandoned. I further understand that the '956 application purports to claim priority to the '768 provisional application, filed March 1, 2002. I collectively refer to the '956 and '768 applications throughout this declaration as the "Priority Applications."

A. Summary of Challenged Claim 16

26. I have been asked by Petitioner's counsel to consider the patentability of claim 16 of the '344 patent. Claim 16 depends from independent claim 10⁵ and therefore includes all the limitations of claim 10. Claims 10 and 16 are reproduced below. I have broken them down into several elements to simplify my analyses in this declaration.

27. Independent claim 10 recites:

[10a] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of

[10b] a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

⁵ Claim 10 is challenged in a separate petition.

[10c] 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,

[10d] wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding,

[10e] wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

[10f] wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

[10g] wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.

Ex. 1501, col. 25, ll. 18-39.

28. Dependent challenged claim 16 recites:

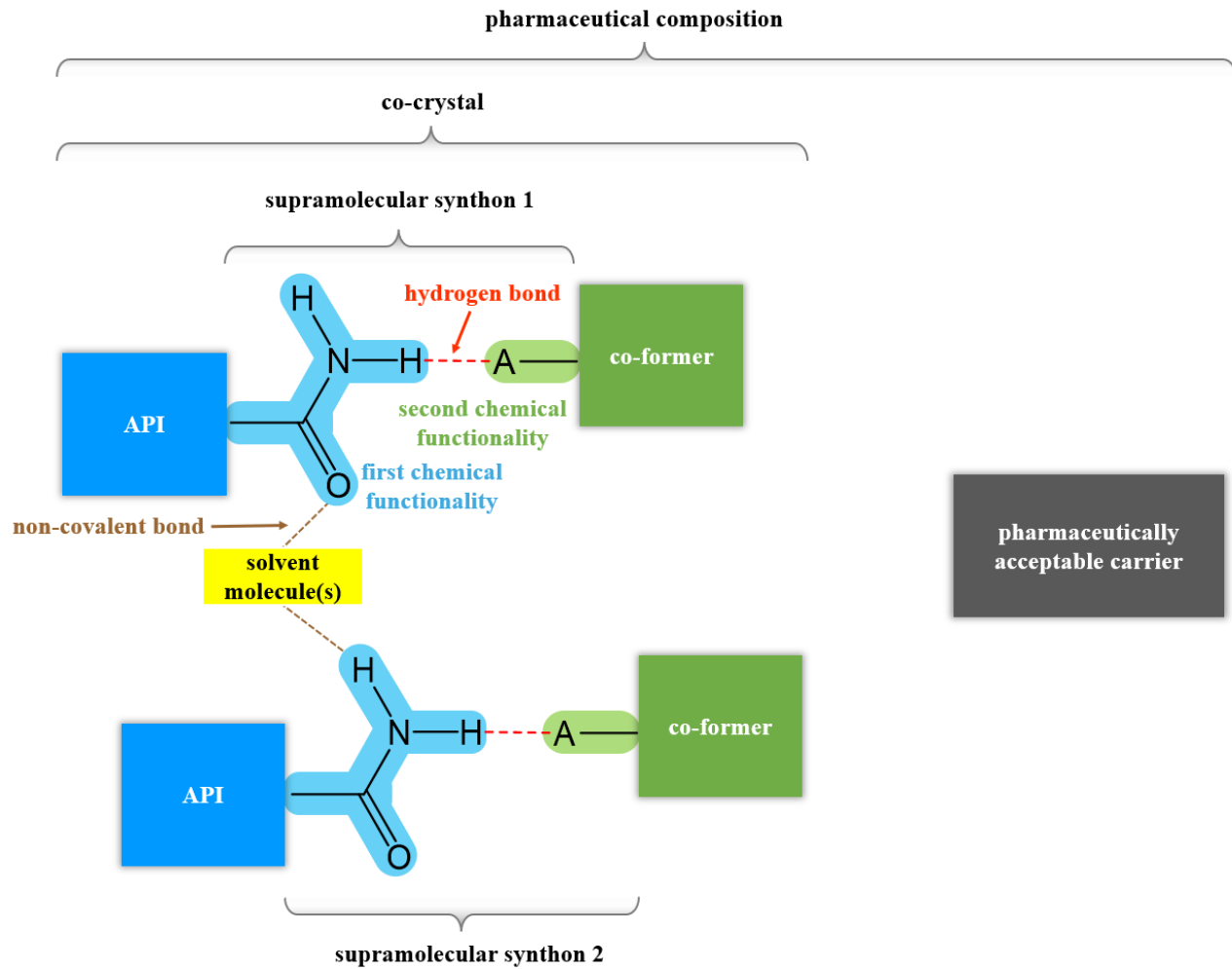
[16a] The pharmaceutical composition of claim 10,

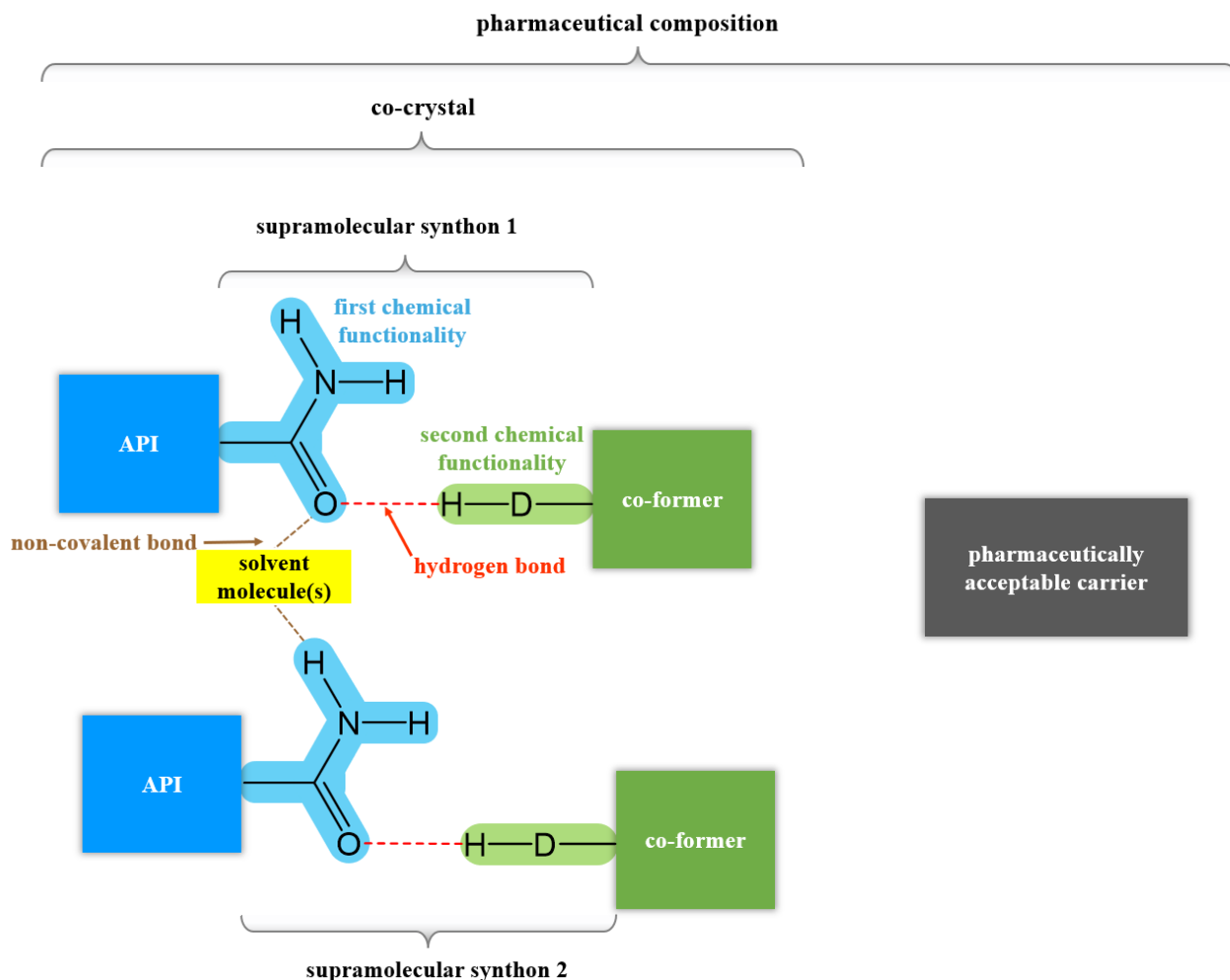
[16b] wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.

Ex. 1501, col. 26, ll. 12-14.

29. The exemplary figures in paragraph 30 below illustrate the general aspects of what is covered by challenged claim 16. The claimed pharmaceutical composition comprises a co-crystal (in a therapeutically effective amount) and a pharmaceutically acceptable carrier. The co-crystal comprises regularly repeating units of an active pharmaceutical ingredient (“API,” shown in blue) having a “first chemical functionality” (shaded light blue; a carboxamide is used in the figures below as an example), a co-former (shown in green) having a complementary “second chemical functionality” (shaded light green, shown generically using “A” to depict a hydrogen bond acceptor in the first figure and “H—D” to depict a hydrogen bond donor in the second figure) and solvent molecule(s) (shown in yellow). The first chemical functionality of the API, which can be a carboxamide, carbonyl, or amine according to challenged claim 16, forms a non-covalent hydrogen bond (shown by the red dashed line) with the second chemical functionality of the co-former, forming supramolecular synthons. It is important to note that the term supramolecular synthon in the ’344 patent refers only to the two or more chemical functionalities and the non-covalent bond(s) between them, not the *entire* structures of the API and co-former molecules. *See e.g., infra* § VIII.A (claim construction of “supramolecular synthon”); Ex. 1519, Plaintiffs’ Opening Claim Construction Brief at 2-3 (“[A] supramolecular synthon consists of two or more chemical functionalities and the noncovalent bond(s) between them.”).

30. The solvent links two adjacent supramolecular synthons together by non-covalent bonding (shown by the brown dashed line in the figures below in this paragraph). There are at least three types of possible solvent connections linking the supramolecular synthons that are covered by claim 16: (1) solvent linking the first chemical functionalities of APIs on adjacent supramolecular synthons, (2) solvent linking the second chemical functionalities of co-formers on adjacent supramolecular synthons and, (3) solvent linking the first chemical functionality of the API of one supramolecular synthon and the second chemical functionality of the co-former of an adjacent supramolecular synthon. Combinations of these connections are also possible. In the exemplary figures below in this paragraph, solvent non-covalently links supramolecular synthon 1 to supramolecular synthon 2 by linking the first chemical functionalities of APIs on adjacent supramolecular synthons. Examples where solvent non-covalently links supramolecular synthon 1 to supramolecular synthon 2 as required by claim 16 (and those where solvent does not) are more fully discussed in ¶¶ 48-51 below (background on the technology of the '344 patent).





31. Additionally, claim 16 requires, based on its dependency from claim 10, that (i) the first chemical functionality of the API permits formation of API homosynthon when the API is in its pure form (*i.e.*, the identical first chemical functionalities on adjacent API molecules interact (by non-covalent hydrogen bonding) with one another), and (ii) the co-former be a solid at room temperature and atmospheric pressure when in its pure form.

B. Brief History of the '344 Patent and Applicants' Purported Invention

32. Claim 16 of the '344 patent is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal. Ex. 1501, col. 24, l. 4 – col. 26, l. 59; *supra* § VI.A (summary of challenged claim 16). However, the specification generally describes the purported invention as a research plan (*i.e.*, a method) for “identifying complementary chemical functionalities to form a desired supramolecular synthon.” *E.g.*, Ex. 1501, col. 3, l. 60 – col. 4, l. 49 (disclosing, as different “aspects” of the invention, different “methods for identifying complementary chemical functionalities to form a desired supramolecular synthon”); col. 7, l. 42 – col. 8, l. 31 (same). Figure 24 of the '344 patent exemplifies the inventors' alleged research plan in a flow chart. Ex. 1501, Figure 24, col. 7, ll. 13-15.

33. The '344 patent provides nineteen numbered Examples, each describing a co-crystal, Ex. 1501, col. 11, l. 60 – col. 23, l. 59. Although none of the Examples describes a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal as claimed, the '344 patent provides that multiple-component phase compositions “can be formulated according to known methods for preparing

pharmaceutically useful compositions.” Ex. 1501, col. 10, ll. 6-15. The ’344 patent further provides that “[f]ormulations [of pharmaceutical compositions] 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* (Martine E W [1995] Eastone Pa., Mack Publishing Compound, 19th ed.) [] describes formulations that can be used in connection with the [’344 patent] invention.” Ex. 1501, col. 10, ll. 15-39.

VII. BACKGROUND ON THE TECHNOLOGY OF THE ’344 PATENT

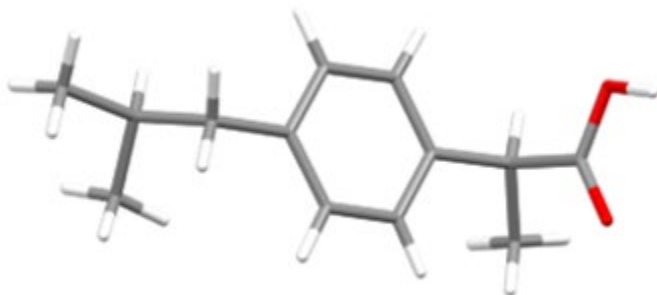
34. Below is a summary of the concepts of chemistry that are relevant to my opinions set forth in this declaration.

A. Background on Chemistry and Chemical Structures

35. Chemists may convey the structure of organic molecules in several different ways, including by using formal chemical nomenclature (*i.e.*, formal names of molecules), common names, or drawings called chemical structures, which are usually two-dimensional illustrations.

36. Chemists may also show chemical structures using illustrations that represent the molecule in three-dimensions, such as the stick model shown below. In these illustrations, different atoms may be represented by different colors. Typically, carbon (C) is grey, hydrogen (H) is white, nitrogen (N) is blue, and

oxygen (O) is red. For example, a stick model of ibuprofen, which contains carbon, hydrogen, and oxygen, is shown below.



B. Multiple-Component Crystalline Solids

37. The '344 patent is directed to multiple-component crystals, *i.e.*, crystals with more than one type of molecule (molecular component). “Multiple-component crystals,” as the term is understood in the '344 patent, includes co-crystals, which Patent Owners proposed means “[a] multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.” Ex. 1518, Joint Claim Construction & Prehearing Statement, Ex. A at 1-5; *see* § VIII.B (claim construction of “co-crystal”).

38. At least one of the components of the multiple-component crystal is an active pharmaceutical ingredient (“API”). Ex. 1501, title, col. 3, ll. 6-13 (The '344 patent is directed to “the design of new pharmaceutical phases that contain more than one molecular component,” that is, “multiple-component solids”

containing at least one API), col. 7, ll. 19-23 (“The subject invention relates to . . . the design of new multiple-component solid phases, such as multiple-component crystals, having at least one active pharmaceutical component.”), col. 10, ll. 51-55 (“The subject invention concerns multiple-component compositions. . . .”); *see also* col. 3, ll. 12-13 (“The subject invention concerns multiple-component solids having at least one active pharmaceutical ingredient.”). The ’344 patent uses various different terms, including “multiple-component solids,” “multiple-component phases,” “multiple-component solid phases,” “multiple-component solid phase composition[s],” “multiple-component crystals,” “multiple-component crystalline phases,” “multiple-component compounds,” “multiple-component compositions,” “binary phase compositions,” and “pharmaceutical phases,” to describe multiple component solids. *See, e.g.*, Ex. 1501, title, abstract, col. 3, ll. 8-34, col. 5, ll. 4-13, col. 7, ll. 19-23, col. 8, ll. 32-46, col. 9, ll. 10-15, col. 10, ll. 40-55, col. 11, ll. 39-42.

39. The ’344 patent uses the term “co-crystal former” (or “co-former”) to describe the second, different component of the multiple-component crystals. Ex. 1501, col. 3, ll. 19-26; *see id.* col. 9, ll. 10-26.

40. A crystalline solid is a solid in which molecules are arranged in a regular pattern that is repeated in three dimensions, and the molecules are held together by *intermolecular* interactions, meaning interactions *between* different

individual molecules. *See* Ex. 1501, col. 1, ll. 44-51. The interactions between components in a crystal are called *non*-covalent interactions (or non-covalent bonds).⁶

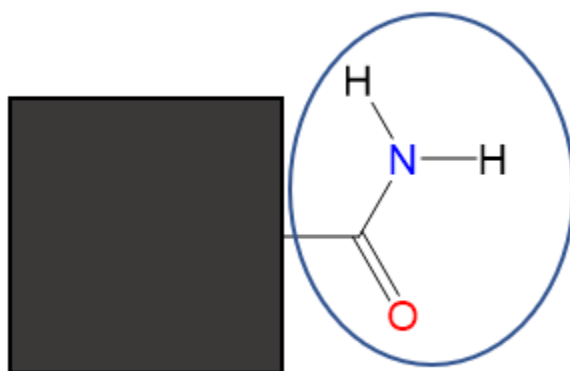
41. A technique called single crystal X-ray diffraction can be used to obtain the three-dimensional structure of a crystalline solid. The resulting three-dimensional structure is referred to as a single crystal structure. Single crystal X-ray diffraction can be used to analyze the crystal structure of a single crystal made up of a single molecule. It can also be used to analyze the crystal structure of a single crystal of a multiple-component crystalline solid, such as a co-crystal.

42. A POSA as of 2002/2003 or 2014 would have understood that “each [three dimensional] crystal structure is the result of a delicate balance between a range of intermolecular forces [between the molecules in the crystal]” Ex. 1548, Aakeröy 1997 at 570-71.

43. The interactions between molecules in a crystal occur between certain groups of atoms on each molecule. Ex. 1501, col. 3, ll. 37-59, col. 9, l. 43 – col. 10, l. 5. The ’344 patent specification refers to such groups of atoms as “chemical

⁶ The intrinsic evidence uses “non-covalent” and “noncovalent” (with or without a hyphen) interchangeably. In this declaration, I will use “non-covalent” as this term appears in challenged claim 16.

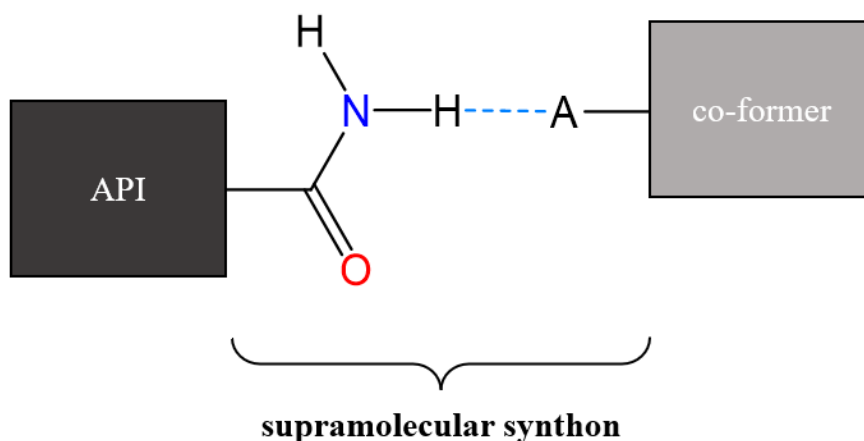
functionalities.” In this declaration, I will use the terms “chemical functionality” and “chemical group” interchangeably. An example of a chemical functionality discussed in the ’344 patent specification is a carboxamide, which the Parties agree covers “-C(=O)NH₂.” *See infra* § VIII.A (claim construction of “carboxamide”). An exemplary molecule (represented by a black box) having a carboxamide chemical functionality is shown in this paragraph below.



44. “Supramolecular synthon” is defined in the ’344 patent as “the sum of the components of a multiple-component non-covalent interaction, wherein the non-covalent interaction contributes to the formation of a discrete supramolecular entity or polymeric structure, wherein each component is a chemical functionality.” Ex. 1501, col. 3, ll. 37-59, col. 9, l. 43 – col. 10, l. 5. In other words, the term “supramolecular synthon” in the ’344 patent collectively refers to two or more chemical functionalities (*e.g.*, the first chemical functionality of the API and

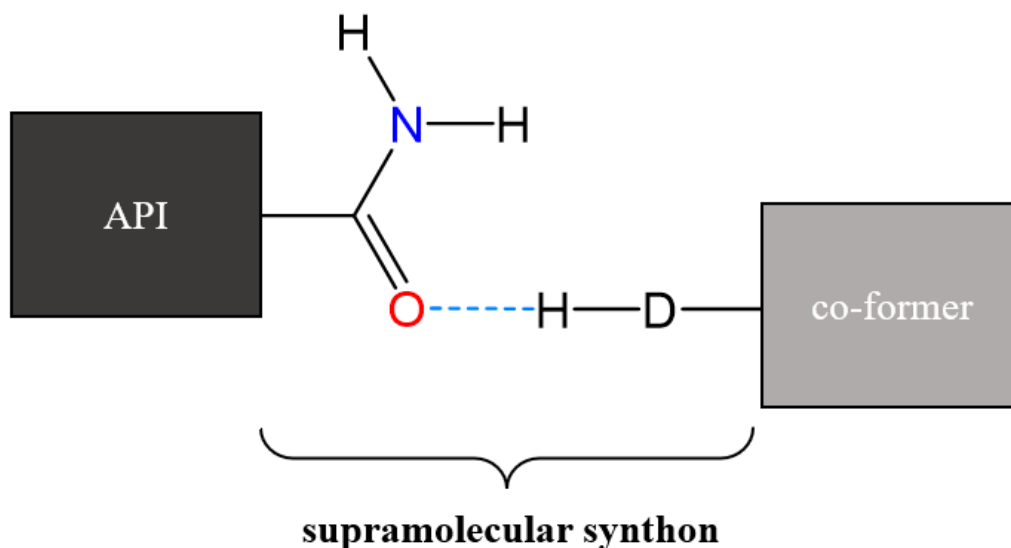
the second chemical functionality of the co-former) and the non-covalent bond(s) (e.g., hydrogen bond(s)) between them. *See id.; infra* § VIII.A (claim construction of “supramolecular synthon”).

45. An example of a supramolecular synthon formed via non-covalent hydrogen bonding of a first chemical functionality of an API and a second chemical functionality of a co-former is shown below. In this example, a first chemical functionality of the API, called a carboxamide (having a chemical formula that the Parties agree includes -C(=O)NH_2 , *see infra* § VIII.A (claim construction of “carboxamide”), is hydrogen bonded to a second chemical functionality of the co-former (generically denoted with “A” to indicate that the second chemical functionality of the co-former is a hydrogen bond acceptor).



46. A second example is shown below. In this example, a first chemical functionality of the API (a carboxamide) is hydrogen bonded to a second chemical

functionality of the co-former (generically denoted with “H—D” to indicate that the second chemical functionality is a hydrogen bond donor).



47. The '344 patent specification explains that supramolecular synthons may be homosynthons or heterosynthons. I understand that the Parties in the district court litigation agree that “API homosynthons” means “synthons formed between identical and complementary chemical functionalities of the API.” Ex. 1518, Joint Claim Construction & Prehearing Statement, Ex. A at 6-7; *see infra* § VIII.A (claim construction of “API synthons”). Consistent with this, the '344 patent specification discloses that a homosynthon is a synthon formed from the interaction of two identical chemical groups or chemical functionalities:

Examples of the groups commonly found in active pharmaceutical ingredients, and which are capable of forming supramolecular synthons include, but are not limited to, acids, amides, aliphatic nitrogen bases,

unsaturated aromatic nitrogen bases (e.g. pyridines, imidazoles), amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles (saturated or unsaturated), and O-heterocycles. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetates, nitrils, oximes, and organohalides. ***Some of these groups can form supramolecular synthons with identical groups in similar or different molecules and are termed homosynthons***, e.g. acids and amides.”

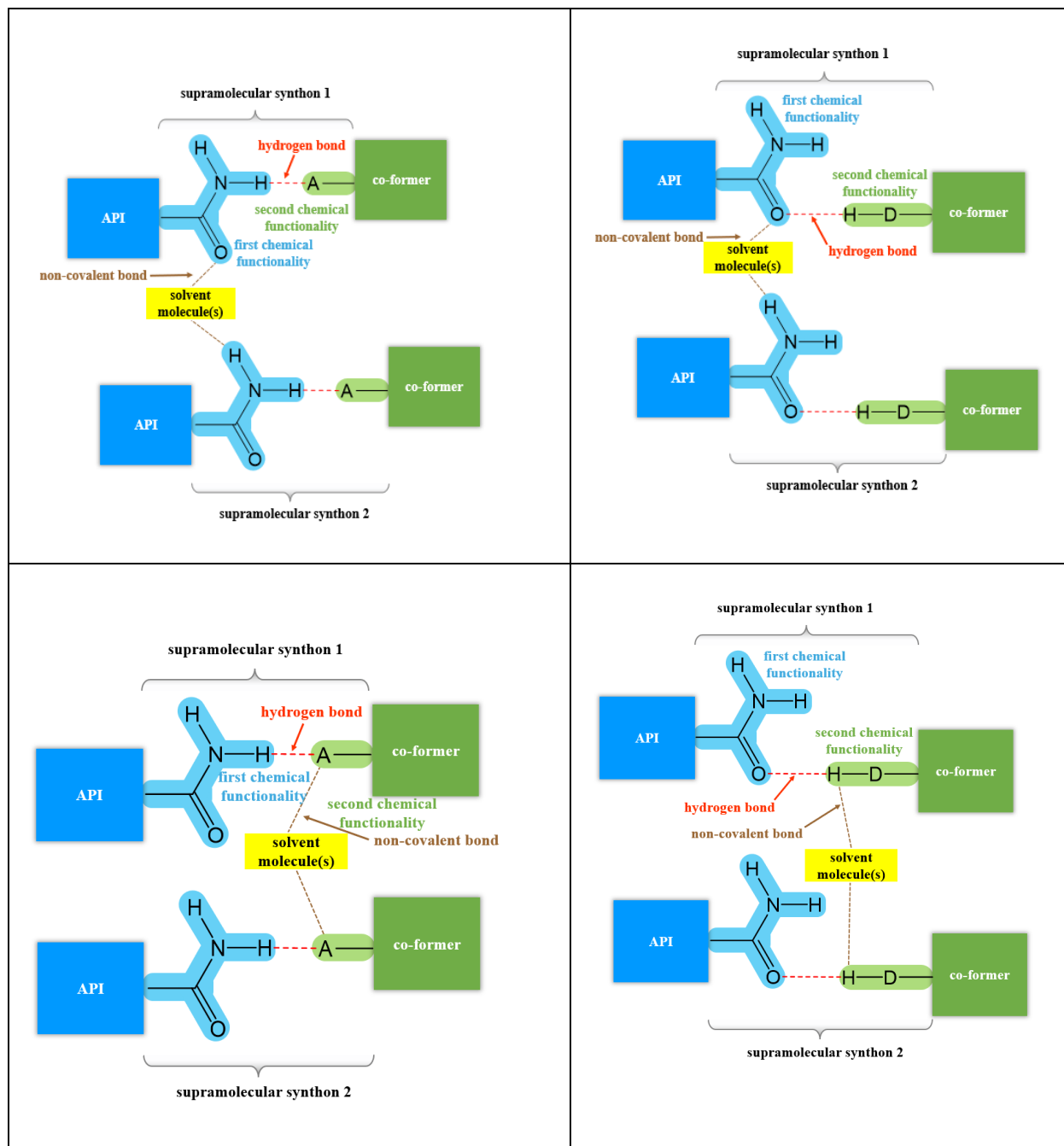
Ex. 1501, col. 3, ll. 41-53 (emphasis added), col. 9, ll. 47-59 (same); *see also, e.g.*, col. 4, ll. 52-53 (“non-covalent bonding between identical functionalities (homosynthon)”), col. 11, ll. 48-54 (“In each example, the nature of the pure phase is discussed and it is sustained by a supramolecular homosynthon (self-complementary functionalities).”), col. 5, l. 38 – col. 7, l. 12 (describing figures), Figures 4A, 5A, 6C, 7B, 8B, 10A, 14A, 15A, 16A, 17A, 18A, 19A, 20A, 21A, 22A, and 23A; Ex. 1517, p. 3464,⁷ ’956 application file history, October 22, 2010

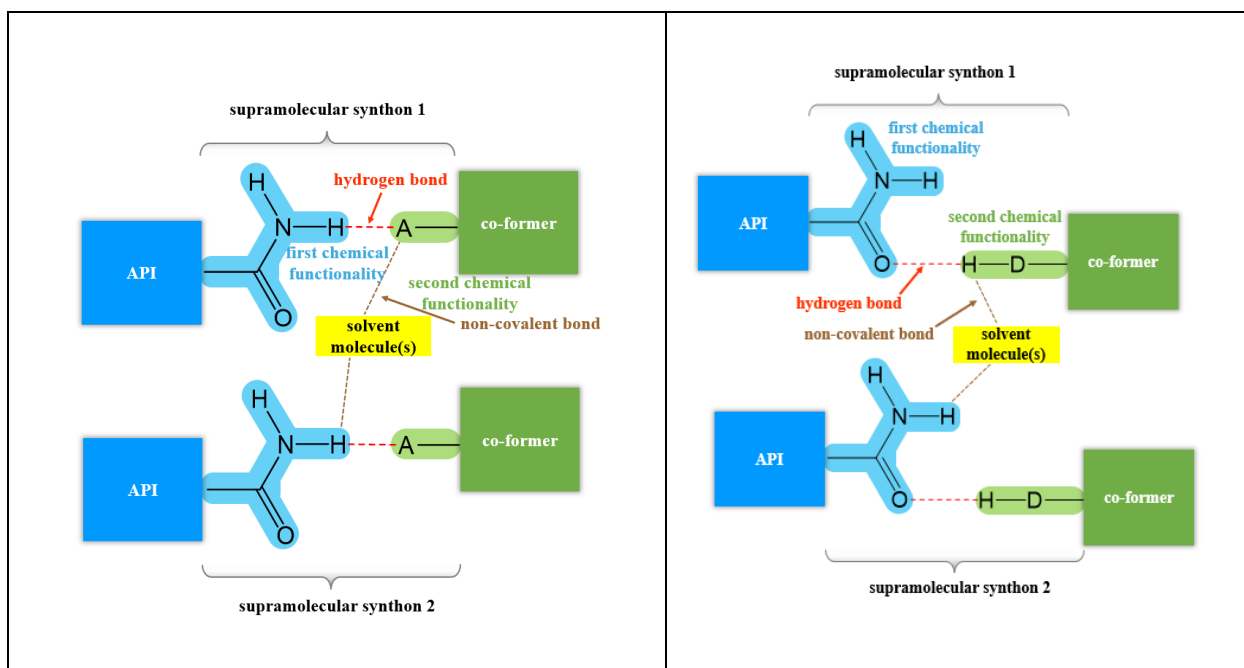
⁷ To facilitate locating the cited information within the file histories cited throughout this declaration, for citations to file history exhibits only, I have included the page number(s) of the IPR petition exhibit stamp where the cited information can be found. All other page citation(s) refer to the pages of the underlying document rather than the stamped page number(s).

Amendment in Response to Office Action at 8 (“Homosynthons are disclosed, for example in paragraph [0009], page 4 of the specification [which corresponds to col. 3, ll. 29-59 of the ’344 patent] with examples thereof given in Examples 1-19 and Figures 4A, 5A, 6C, 7B, 8B, 10A, 14A, 15A, 16A, 17A, 18A, 19A, 20A, 21A, 22A, and 23A.”).

48. Challenged claim 16 requires “wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.” Ex. 1501, col. 26, ll. 12-14. A POSA as of 2002/2003 or 2014 would have understood that a solvent is a substance that is able to dissolve another substance. For example, water is a solvent that can, for instance, dissolve sugar. *See, e.g.*, Ex. 1573, Huheey 1993 at UM00005308 (listing water as a solvent); Ex. 1572, Housecroft 2012 at UM00005304 (same). I understand that the Parties in the district court litigation agree that “wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule” means “wherein one or more solvent molecules are non-covalently bonded to two or more supramolecular synthons, linking the supramolecular synthons to one another.” Ex. 1518, Joint Claim Construction & Prehearing Statement at 1; *See* § VIII.A (claim construction of claim element [16b], *i.e.*, “wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule”).

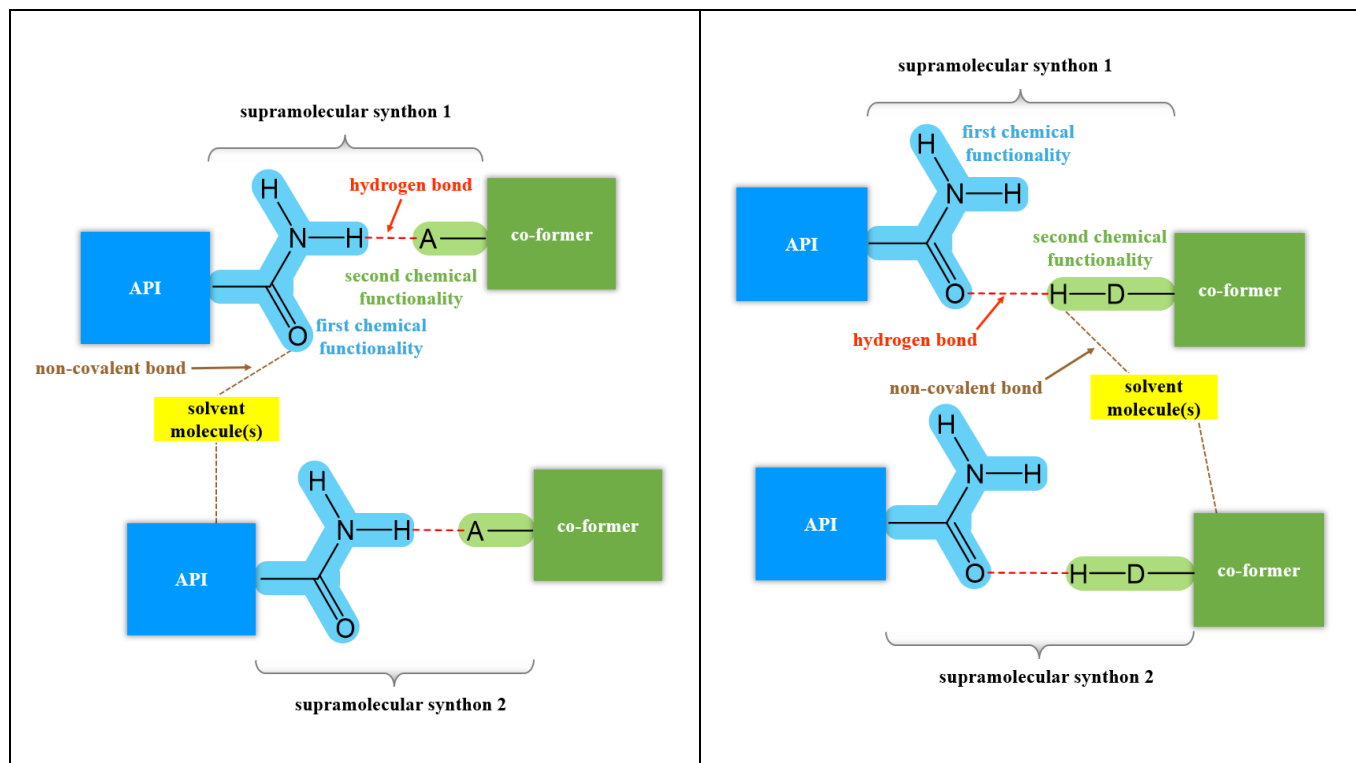
49. Some examples that meet the solvent limitation of challenged claim 16 are shown below.





50. For a co-crystal to be within the scope of claim 16 (as shown in the figures in the above paragraph), the solvent has to connect a chemical functionality (either the first chemical functionality of the API or the second chemical functionality of the co-former) of one supramolecular synthon to the chemical functionality (either the first chemical functionality of the API or the second chemical functionality of the co-former) of another supramolecular synthon. When a solvent does not link the first and/or second chemical functionalities of the supramolecular synthons and instead links another part of the API or co-former molecule (*i.e.*, a chemical functionality that is not the first chemical functionality of the API or the second chemical functionality of the co-former), the co-crystal is outside the scope of claim 16.

51. Two examples that do not meet the solvent limitation of claim 16 are shown below.



VIII. CLAIM CONSTRUCTION

52. The legal principles provided to me by Petitioner's counsel that are relevant to claim construction are provided in **Appendix B**, which provides the legal standards that I considered when forming my opinions in this declaration.

53. I have been asked by Petitioner's counsel to consider claim construction as of the 2002/2003 and 2014 priority dates. My opinions are the same regardless of which date is used.

54. Below, I discuss the claim construction of certain terms in challenged claim 16 that are necessary for me to provide opinions in this declaration. I understand there are disputes between the Parties in the district court litigation as to the claim construction of certain terms.

55. I have grouped the terms into the following categories: (A) terms with agreed-upon constructions in the district court litigation (or agreed-upon portions of constructions where the disputed portions are not relevant to my opinions in this declaration) and (B) terms currently disputed in the district court litigation but where I have been asked to assume Patent Owners' proposed construction for the purposes of this declaration.

A. Terms With Agreed-Upon Constructions

56. **“active pharmaceutical ingredient (API)”**: In the district court litigation, the Parties agree that the term “active pharmaceutical ingredient (API)” means “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.” *See* Ex. 1519, Plaintiffs' Opening Claim Construction Brief at 21 (Patent Owners stating that the term “active pharmaceutical ingredient (API)” has a “[p]lain and ordinary meaning, which is ‘biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration’”). This definition is

consistent with the definition of “API” in the ’344 patent, which states that the term “API” “refer[s] to 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.” Ex. 1501, col. 9, ll. 27-34.

57. **“API homosynthons”**: The Parties in the district court litigation agree that “API homosynthons” means “synthons formed between identical and complementary chemical functionalities of the API.” Ex. 1518, Joint Claim Construction & Prehearing Statement, Ex. A at 6-7.

58. **“carbonyl”**: In the district court litigation, the Parties agree that “carbonyl” refers to the group having the chemical formula “-C(=O)-” (*e.g.*, a -C(=O)- group where the carbon has a double bond to oxygen) and that it does not refer to the -C(=O)- portion of another functional group such as carboxylic acid or carboxamide. Ex. 1518, Joint Claim Construction & Prehearing Statement at 1; *see also infra* § IX.C (lack of priority: enablement) (further discussing carbonyl).

59. **“carboxamide”**: Though the Parties in the district court litigation dispute the scope of the term “carboxamide” as used in the ’344 patent and whether it is indefinite, they agree that “carboxamide” would have been understood by a POSA as encompassing -C(=O)NH₂ and that carbamazepine (“CBZ”) has a carboxamide group. *See* Ex. 1519, Plaintiffs’ Opening Claim Construction Brief at 22; Ex. 1501, ’344 patent, col. 6, ll. 35-38, 43-46 (discussing

Figures 10A and 10B and referring to “the dimer formed between the carboxamide moieties of each CBZ molecule”), col. 16, ll. 4-53 (Example 7, discussing “hydrogen bonded carboxamide homodimers” of carbamazepine), col. 16, l. 55 – col. 18, l. 67, col. 19, l. 51 – col. 20, l. 14, col. 20, l. 51 – col. 22, l. 54 (Examples 8-10, 12, 14-17, discussing carboxamide moieties of CBZ in Figures 11, 12, 14B, 16B, 18B, 19B, 20B, and 21B).

60. “**co-former**”: In the district court litigation, the Parties agree that the term “co-former” is used synonymously with the term “co-crystal former” and that a co-former is a component of a co-crystal. Ex. 1518, Joint Claim Construction & Prehearing Statement, Ex. A at 5-6. I understand that Petitioner describes the co-former as a “molecular *component*” whereas Patent Owners describe it as a “*component* compound.” *Id.* (emphasis added). However, that dispute is not relevant to my opinions in this declaration.

61. “**supramolecular synthon**”: In the district court litigation, the Parties agree that the ’344 patent defines the term “supramolecular synthon” as “[t]he sum of the components of a multiple-component non-covalent interaction, wherein the non-covalent interaction contributes to the formation of a discrete supramolecular entity or polymeric structure, wherein each component is a chemical functionality.” Ex. 1518, Joint Claim Construction & Prehearing Statement at 1; Ex. 1501, col. 3, ll. 37-59, col. 9, l. 43 – col. 10, l. 5.

62. **“wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule”**: The Parties in the district court litigation agree that this term means “wherein one or more solvent molecules are non-covalently bonded to two or more supramolecular synthons, linking the supramolecular synthons to one another.” Ex. 1518, Joint Claim Construction & Prehearing Statement at 1. Water is one example of a solvent. *See, e.g.*, Ex. 1572, Housecroft 2012 at UM00005304 (listing water as a solvent); Ex. 1573, Huheey 1993 at UM00005308 (same). Examples that meet this limitation of claim 16 are shown in paragraph 49 above.

B. Term Where I Was Asked to Adopt Patent Owners’ Proposed Construction for the Purpose of this Declaration

63. **“co-crystal”**: In the district court litigation, the Parties dispute the meaning of the term “co-crystal” and whether it is indefinite, but for the purpose of this declaration, Petitioner’s counsel has asked me to adopt Patent Owners’ construction that “co-crystal” means “[a] multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.” Ex. 1518, Joint Claim Construction & Prehearing Statement, Ex. A at 1-5.

IX. CLAIM 16 IS NOT ENTITLED TO A 2002/2003 PRIORITY DATE

64. The ’344 patent, filed February 13, 2014, claims priority to the ’956 application (Ex. 1515), filed March 3, 2003, and the ’768 provisional application

(Ex. 1514), filed March 1, 2002. Ex. 1516, p. 10, '344 patent file history, February 13, 2014 Application Data Sheet at 4.

A. Claim 16 Lacks an Adequate Written Description in the Priority Applications for the Full Scope of Claimed Solvates of Co-Crystals⁸

65. For the reasons discussed below, challenged claim 16 of the '344 patent is not adequately described in the Priority Applications and therefore, claim 16 is not entitled to a 2002/2003 priority date.

66. As I understand from Petitioner's counsel, sufficient written description of a genus requires the disclosure of either structural features common to all members of the genus so that a POSA can visualize or recognize all members of the genus or a representative number of species falling within the scope of the genus. In my opinion, the Priority Applications neither disclose structural features common to all members of the claimed genus of solvates of co-crystals nor a representative number of co-crystals falling within the scope of the claimed genus of solvates of co-crystals.

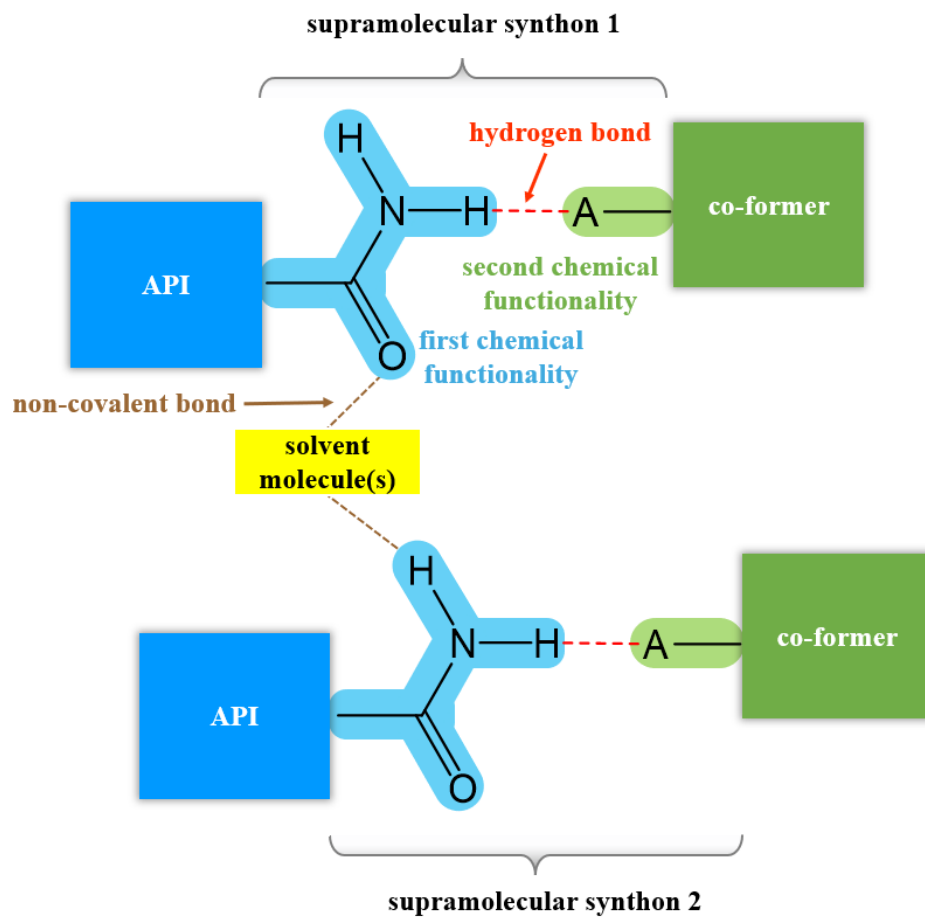
⁸ The term "solvate" refers to a crystalline solid where solvent, such as water, is part of the crystal structure. For the purpose of this declaration, "solvates of co-crystals" refers to co-crystals that include an API, co-former, and solvent.

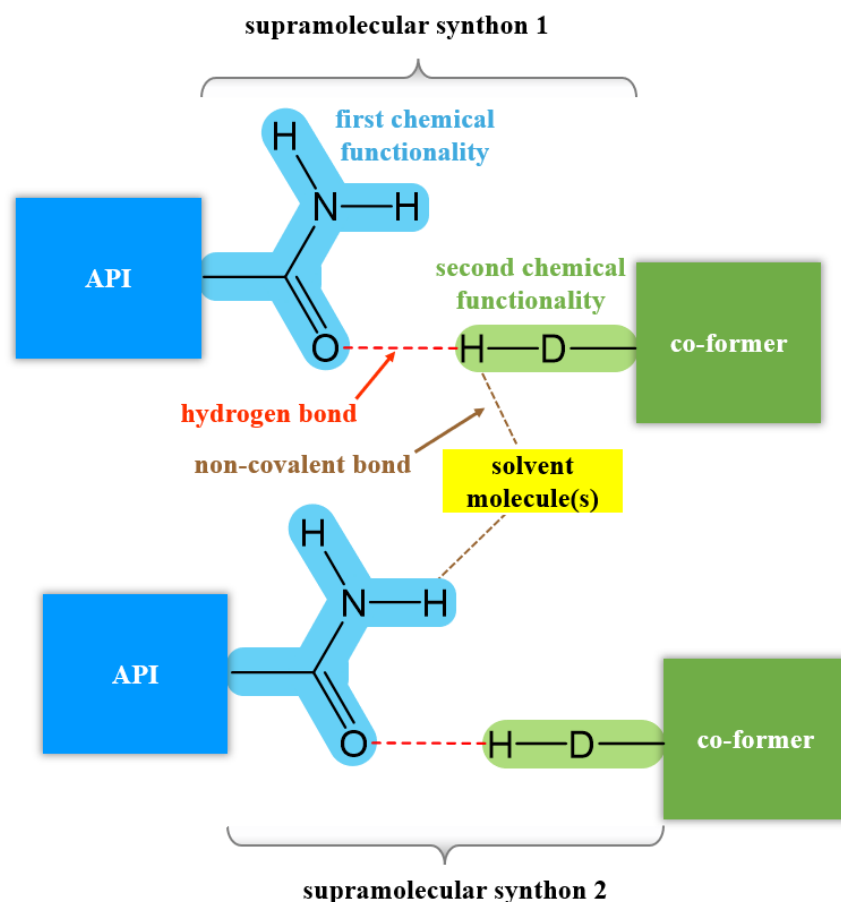
67. Claim 16 requires, based on its dependency from claim 10, a co-crystal comprising supramolecular synthons formed from a certain first chemical functionality of an API and a second chemical functionality of a co-former “wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.” Ex. 1501, col. 25, ll. 18-39. Claim 16 further requires that “the supramolecular synthons [of claim 10] are non-covalently bonded to one another by non-covalent bonding to a solvent molecule,” Ex. 1501, col. 26, ll. 12-14, meaning that “one or more solvent molecules are non-covalently bonded to two or more supramolecular synthons, linking the supramolecular synthons to one another.” *Supra* § VIII.A (claim construction of claim element [16b]). For simplification, throughout this declaration, I refer to co-crystals that are non-covalently bonded to a solvent as “solvates of co-crystals.” *Supra* p. 41, fn. 8.

68. Other than the structural feature of the first chemical functionality of the API that is a carboxamide, carbonyl, or amine, the limitations of claim 16 are described in terms of function, not structure, *i.e.*, the co-crystal is *formed from* the API, co-former, and solvent; the API and co-former must *form* supramolecular synthons between the first chemical functionality of the API (carboxamide, carbonyl, or amine) and the second chemical functionality of the co-former; and the supramolecular synthons must *non-covalently bond* to a solvent molecule.

69. As I explain in more detail in section VII above, which provides background on the technology of the '344 patent, the term “supramolecular synthon” in the '344 patent collectively refers to two or more chemical functionalities and the non-covalent bond(s) between them, not the *entire* structures of the API and co-former molecules. *See supra* § VIII.A (claim construction of “supramolecular synthon”). Ex. 1519, Plaintiffs’ Opening Claim Construction Brief at 2-3 (“[A] supramolecular synthon consists of two or more chemical functionalities and the noncovalent bond(s) between them.”).

70. Below in this paragraph, I provide two examples that meet the solvent limitation of claim 16. Paragraph 49 above (background of the technology of the '344 patent) includes additional examples.





In the first figure, one or more solvent molecules link the first chemical functionality of the API of one supramolecular synthon (supramolecular synthon 1) to the first chemical functionality of the API of an adjacent supramolecular synthon (supramolecular synthon 2) via non-covalent bonding. In the second figure, one or more solvent molecules link the second chemical functionality of the co-former in one supramolecular synthon to the first chemical functionality of the API in an adjacent supramolecular synthon.

71. There is no disclosure in the Priority Applications of solvent molecules non-covalently linking supramolecular synthons as required by claim 16.

1. The Priority Applications Fail to Disclose Common Structural Features of Solvates of Co-Crystals Falling Within the Scope of Claim 16

72. Since challenged claim 16, particularly the co-crystal and supramolecular synthon limitations, are described in terms of their function, not structure (other than the first chemical functionality of the API) (*supra* ¶ 68), there are no structural features common to all embodiments of challenged claim 16. As a result, the common structural features test for assessing whether there is sufficient written description does not apply.

2. The Priority Applications Fail to Disclose a Representative Number of Solvates of Co-Crystals of the Claimed Genus

73. There are no Examples in the Priority Applications that describe the feature that supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule. Of the nineteen Examples disclosed in the Priority Applications, the first nine (Examples 1-9) of which are disclosed in both Priority Applications and the remaining ten (Examples 10-19) of which are disclosed in only the '956 application, only Examples 1 and 3 of the '956 and '768 applications and Example 11 of the '956 application purport to disclose a product

that includes an API, co-former, and solvent. However, a POSA would not have understood that any of these have the feature “wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.”

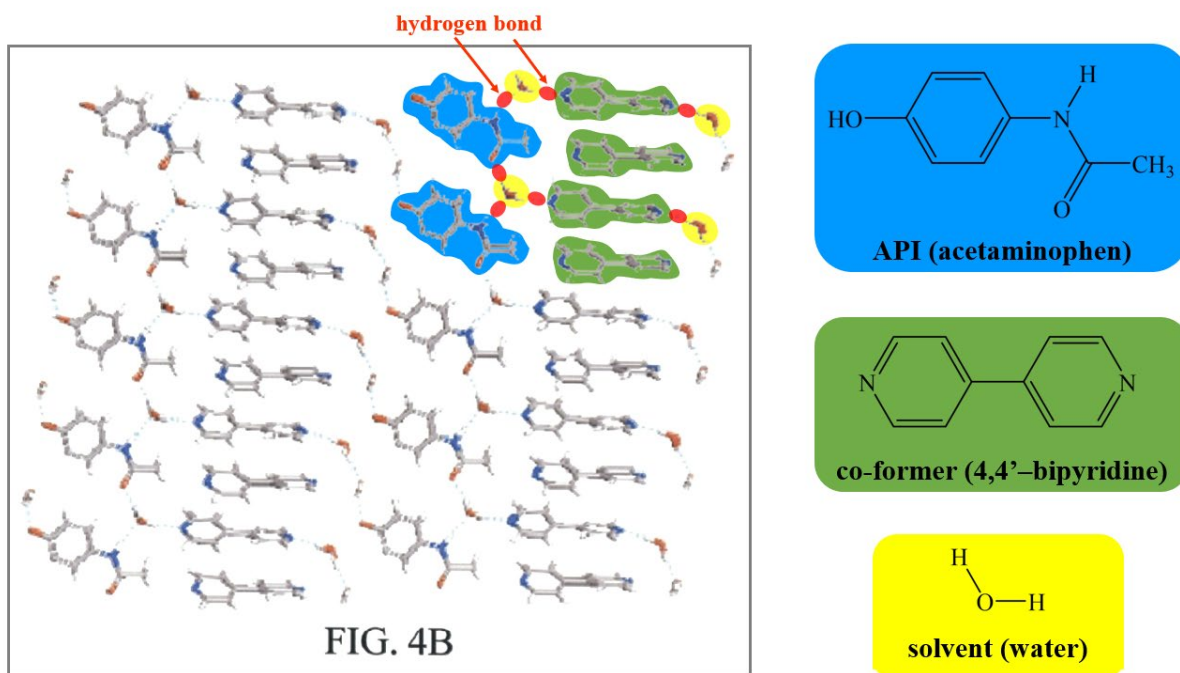
74. In addition, the co-crystal in Example 1 does not teach supramolecular synthons formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former (element [10f], *supra* § VI.A (summary of challenged claim 16), and the co-crystal in Example 3 does not have a first chemical functionality that is a carboxamide, carbonyl, or amine (element [10g], *supra* § VI.A).

75. Even if all three Examples fell within the scope of challenged claim 16 (I disagree), three Examples are not representative of the entire broad genus of solvates of co-crystals falling within the scope of claim 16. *Infra* § IX.B.1.a (lack of priority: enablement (breadth of the claims)).

a. Example 1 of the Priority Applications Does Not Describe the Limitations of Claim 16

76. Example 1 purports to disclose a “1:1:1 acetaminophen/4,4’-bipyridine/water co-crystal, as shown in FIG. 4B.” Ex. 1514, ’768 application, ¶ [0043], Figure 4B; Ex. 1515, ’956 application, ¶ [0056], Figure 4B (same). Figure 4B from the Priority Applications is shown below (replicated in color to display

annotations)⁹. I have annotated it to point out the API (acetaminophen, shaded blue), co-former (4,4'-bipyridine, shaded green), and solvent (water, shaded yellow). The non-covalent hydrogen bonds are the dashed lines shaded red.



⁹ Since Figures 1-13C of the Priority Applications are the same as those of the '344 patent (and Figures 14A-23B of the '956 application are the same as those of the '344 patent), which are in color, I have relied on the color figures from the '344 patent (which I have annotated) to aid in my analysis in this section. *Compare* Ex. 1515, '956 application, Figures 1-13C and Ex. 1514, '768 application, Figures 1-13C *with* Ex. 1501, Figures 1-13C (and *compare* Ex. 1515, '956 application, Figures 14A-23B *with* Ex. 1501, Figures 14A-23B).

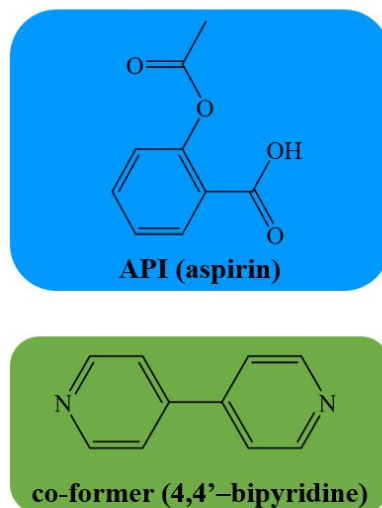
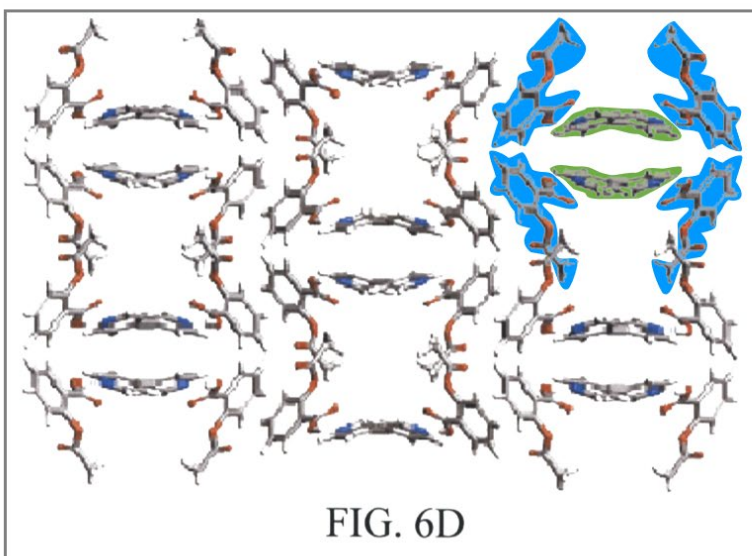
77. Claim 16, through its dependency of claim 10, requires that the “supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.” Ex. 1501, col. 25, ll. 34-37. As shown in Figure 4B, there are no non-covalent hydrogen bonds between *any* chemical functionality of the API and *any* chemical functionality of the co-former in the co-crystal of Example 1. Nor are there any hydrogen bonds between such chemical functionalities described in the Example. *See* Ex. 1515, ’956 application, ¶ [0058]; Ex. 1514, ’768 application, ¶ [0045]. The only non-covalent hydrogen bonds in this co-crystal are between (i) a chemical functionality on the API (acetaminophen, shaded blue) and the solvent (water, shaded yellow) or (ii) a chemical functionality on the co-former (4,4’-bipyridine, shaded green) and the solvent.

78. Without this required interaction between the first and second chemical functionalities of the API and co-former, respectively, no claimed supramolecular synthons are formed in the co-crystal in Example 1. Moreover, without the claimed supramolecular synthons, there can be no solvent bonding such supramolecular synthons together as required by claim 16.

79. For these reasons, a POSA would not have understood the co-crystal of Example 1 to describe the limitations of claim 16.

b. Example 3 of the Priority Applications Does Not Describe the Limitations of Claim 16

80. Example 3 of the Priority Applications purports to disclose a “2:1 aspirin/4,4’-bipyridine co-crystal, as shown in Fig. 6D.” Ex. 1514, ’768 application, ¶ [0054]; Figure 6D; Ex. 1515, ’956 application, ¶ [0067], Figure 6D (same). Figure 6D from the Priority Applications is shown below (replicated in color to display annotations). I have annotated it to point out four API molecules (aspirin, shaded blue) and two co-former molecules (4,4’-bipyridine, shaded green).



A POSA looking at Figure 6D would have noticed that it does not show *any* solvent molecules, much less non-covalent interactions between the

supramolecular synthons and solvent molecules satisfying the limitation of claim 16.

81. The Priority Applications describe the co-crystal in Example 3 as “an *inclusion compound* containing disordered solvent in the channels.” Ex. 1514, ’768 application, ¶ [0056] (emphasis added); Ex. 1515, ’956 application, ¶ [0069] (same). A POSA would have understood this to mean that the solvent is trapped (*i.e.*, included) by the compound’s structure and disordered in the channels, not non-covalently bonded to that structure. No interactions between the compound and the solvent are described in Example 3. *See* Ex. 1515, ’956 application, ¶ [0069]; Ex. 1514, ’768 application, ¶ [0056].

82. Consistent with Figure 6D, the name of the co-crystal of Example 3, 2:1 aspirin/4,4'-bipyridine co-crystal, does not refer to any solvent molecules and there is no evidence in the Priority Applications that the supramolecular synthons are linked by solvent molecules as required by claim 16. Thus, a POSA would not have understood Example 3 to describe the co-crystal as having supramolecular synthons that are non-covalently bonded to one another by non-covalent bonding to a solvent molecule. *See* Ex. 1515, ’956 application, ¶ [0069] (describing the crystal packing, wherein the solvent is described as “disordered [] in the channels”); Ex. 1514, ’768 application, ¶ [0056] (same).

83. Furthermore, the API aspirin does not have a first chemical functionality that is a carboxamide, carbonyl, or amine,¹⁰ as required by claim 16 (in view of its dependency on claim 10). *Supra* § VIII.A (claim constructions of “carboxamide” and “carbonyl”); *infra* § IX.C (lack of priority: enablement) (further discussing carbonyl); *see supra* ¶ 80, showing the chemical structure of aspirin); **Appendix C** (showing the chemical structures of the APIs disclosed in the Priority Applications). And a POSA would not have understood 4,4’-bipyridine to qualify as the API as there is no disclosure in the Priority Applications that 4,4’-bipyridine is a “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.” *Supra* § VIII.A (claim construction of “API”); Ex. 1501, col. 9, ll. 27-34.

¹⁰ The IUPAC (the International Union of Pure and Applied Chemistry) 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).” Ex. 1532, Moss 1995 at 1316. “Hydrocarbyl groups” is defined as “[u]nivalent groups formed by removing a hydrogen atom from a hydrocarbon . . . [e].g. ethyl, phenyl.” Ex. 1532, Moss 1995 at 1341 (emphasis omitted)).

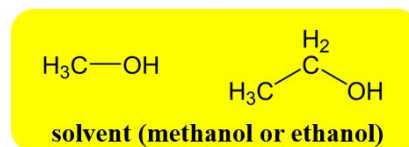
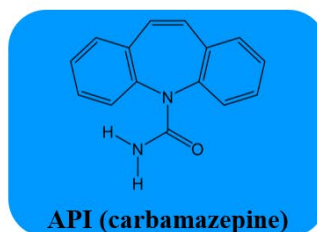
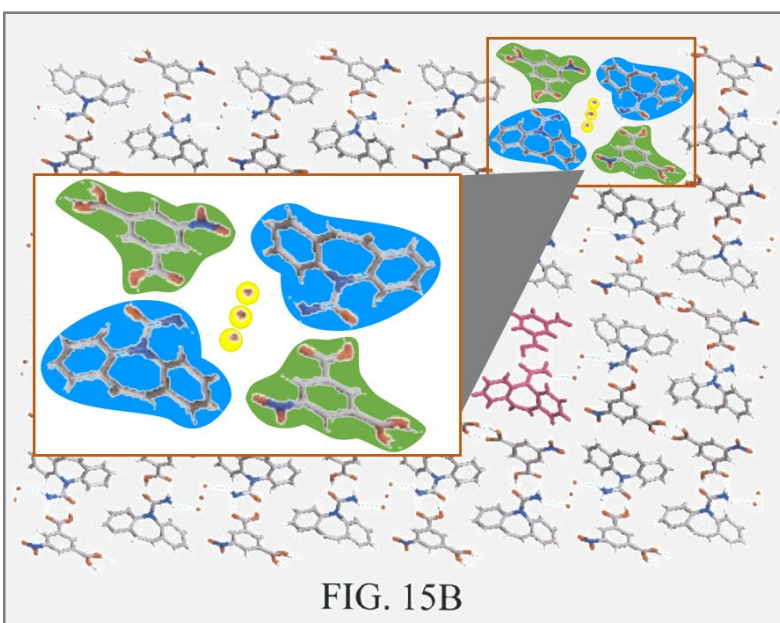
84. Therefore, a POSA would not have understood the co-crystal of Example 3 to describe the limitations of claim 16.

c. Example 11 of the '956 Application Does Not Describe the Limitations of Claim 16

85. Example 11 of the '956 application purports to disclose a “1:1 carbamazepine/5-nitroisophthalic acid co-crystal, as shown in FIG. 15B.” Ex. 1515, '956 application, ¶ [00122]. Notably, the name of the co-crystal in Example 11 does not refer to any solvent molecule being part of it.

86. The carbamazepine/5-nitroisophthalic acid co-crystal was prepared by dissolving 40 mg (0.1693 mmol) of carbamazepine and 30 mg (0.1421 mmol) of 5-nitroisophthalic acid in approximately 3 mL of methanol or ethanol. *Id.* Slow evaporation of the solvent (*i.e.*, methanol or ethanol) resulted in the 1:1 carbamazepine/5-nitroisophthalic acid co-crystal. *Id.* The '956 application explains that “[t]he co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between the two 5-nitroisophthalic acid moieties and hydrogen bonded carboxy-amide heterodimers between the carbamazepine and 5-nitroisophthalic acid moiety. *There is solvent hydrogen bonded to an additional N—H donor from the carbamazepine moiety.*” Ex. 1515, '956 application, ¶ [00124] (emphasis added).

87. Figure 15B from the '956 application is shown below (replicated in color to display annotations), which I have annotated to point out two API molecules (carbamazepine, shaded blue) and two co-former molecules (5-nitroisophthalic acid, shaded green). I have also shaded yellow three atoms that a POSA reading Example 11 of the '956 application in 2002/2003 would have understood to be atoms of either methanol or ethanol because methanol or ethanol are the only components other than carbamazepine and 5-nitroisophthalic that are disclosed in Example 11.



88. A POSA reading Example 11 and looking at Figure 15B would have recognized that the three atoms are not connected to one another, meaning that each of the three atoms shown is an atom of a *different* molecule. A POSA also

would have noticed that the three atoms appear to be too close to one another to reasonably be present in those positions; they are closer to one another in Figure 11 than the atoms that make up carbamazepine and 5-nitroisophthalic acid.

Accordingly, a POSA would have understood each of the three yellow-shaded atoms to represent an atom of one solvent molecule (*i.e.*, methanol or ethanol; Example 11 does not specify which one, *see* Ex. 1515, '956 application, ¶ [00124]) disordered over three positions, meaning that there is just one solvent molecule present that can be found at any of the three noted positions. Disorder occurs when a molecule (or portions of a molecule), here the solvent molecule (methanol or ethanol), is found at more than one location or position within a unit cell of a crystal structure, but can only occupy one of those positions in any given unit cell. In one location, the solvent forms a hydrogen bond with the chemical functionality of one carbamazepine molecule, and in a different location, the solvent forms a hydrogen bond with the chemical functionality of a different carbamazepine molecule, but the solvent cannot occupy both positions within that unit cell.

89. Example 11 explains that “[*t*]*here is solvent hydrogen bonded to an additional N—H donor from the carbamazepine moiety.*” Ex. 1515, '956 application, ¶ [00124] (emphasis added). A POSA would have understood from this description in Example 11 that *a* solvent molecule (*i.e.*, methanol or ethanol) is hydrogen bonded to only *one* chemical functionality, *i.e.*, the carboxamide (the

first chemical functionality) of the carbamazepine (the API). In other words, the solvent molecule is not non-covalently linking the first chemical functionality of the API or second chemical functionality of the co-former in two or more supramolecular synthons to one another as required by claim 16. *See supra* § VIII.A (claim construction of claim element [16b]).

90. Thus, a POSA would not have understood the co-crystal of Example 11 to meet the limitations of claim 16.

d. At Most Three Examples Are Not a Representative Number of Species Falling Within the Scope of Claim 16

91. Even if a POSA as of 2002/2003 had understood the co-crystals of Examples 1, 3, and/or 11 to meet the limitations of claim 16 (I disagree), given the incredibly broad scope of the genus of solvates of co-crystals falling within the scope of claim 16 and the unpredictability in the field which I discuss below with respect to enablement (*infra* § IX.B.1.a (breadth of the claims)), these three Examples are not representative of all the types of non-covalent hydrogen bond interactions that can exist between the full scope of the supramolecular synthons and solvent combinations of the solvates of co-crystals covered by challenged claim 16. The Priority Applications do not set forth any information that would allow a POSA to extrapolate these three Examples to different API, co-former, and solvent combinations. Said another way, there is no evidence that APIs, co-

formers, and solvents having different structures from those in the three Examples (even if they include the same first and second chemical functionalities), will provide the same function (forming the claimed solvates of co-crystals).

92. The genus of solvates of co-crystals falling within the scope of claim 16 is diverse. *See e.g.*, Ex. 1507, Ueto 2012 (furosemide/nicotinamide/water co-crystal); Ex. 1512, Sowa 2013 (genistein/nicotinamide/water co-crystal); Ex. 1511, '408 Application (genistein/nicotinamide/water co-crystal); Ex. 1574, Das 2011 (nicotinamide/dipicolinic acid/water co-crystal and isonicotinamide/dipicolinic acid/water co-crystal). For example, the following co-crystals fall within the scope of claim 16:

- **Ueto 2012** teaches a co-crystal comprising nicotinamide (an “API”) having a first chemical functionality that is a carboxamide, furosemide (a “co-former”) having a second chemical functionality, and water (a solvent). Ex. 1507, Ueto 2012 at 485-94. The second chemical functionality of furosemide interacts with the first chemical functionality of nicotinamide to form supramolecular synthons, and two solvent molecules non-covalently bond to two or more supramolecular synthons, linking the supramolecular synthons to one another. Ex. 1507, Ueto 2012 at 490-92 (including Figure 11), Ground 1 (*infra* § XI (Invalidity Ground 1));
- **The '408 Application** and **Sowa 2013** each teaches a co-crystal comprising nicotinamide (an “API”) having a first chemical

functionality that is a carboxamide, genistein (a “co-former”) having a second chemical functionality, and water (a solvent). Ex. 1512, Sowa 2013 at 7696-98, 7700, 7702-07; Ex. 1511, ’408 Application at 1-7. The second chemical functionality of genistein interacts with the first chemical functionality of nicotinamide to form supramolecular synthons, and a solvent molecule non-covalently bonds to two or more supramolecular synthons, linking the supramolecular synthons to one another. Ex. 1512, Sowa 2013 at 7697, 7700, 7702-03 (including Figure 9), Ex. 1511, ’408 Application at 8-9 (including Figures 2 and 3); Ground 2 (*infra* § XII (Invalidity Ground 2));

- **Das 2011** teaches a co-crystal comprising nicotinamide (an API) having a first chemical functionality that is a carboxamide, dipicolinic acid (a co-former) having a second chemical functionality, and water (a solvent). Ex. 1574, Das 2011 at 5526-28, 5531. The first chemical functionality of nicotinamide interacts with the second chemical functionality of dipicolinic acid to form supramolecular synthons, and two solvent molecules non-covalently bond to two or more supramolecular synthons, linking the supramolecular synthons to one another. Ex. 1574, Das 2011 at 5526-28, 5531 (including Figure 3). Das 2011 also teaches a co-crystal comprising isonicotinamide (an API) having a first chemical functionality that is a carboxamide, dipicolinic acid (a co-former) having a second chemical functionality, and water (a solvent). Ex. 1574, Das 2011 at 5522-24, 5527-28, 5531. The first chemical functionality of isonicotinamide interacts with the second chemical

functionality of dipicolinic acid to form supramolecular synthons, and a solvent molecule non-covalently bonds to two or more supramolecular synthons, linking the supramolecular synthons to one another. Ex. 1574, Das 2011 at 5527-28, 5531 (including Figure 4).

The co-crystals taught in Examples 1, 3, and 11 of the Priority Applications are not representative of the diverse genus of solvates of co-crystals covered by claim 16.

93. For these reasons, it is my opinion that claim 16 is not adequately described in the Priority Applications and, therefore, claim 16 is not entitled to a priority date of 2002/2003.

3. The Prosecution History of the Related '223 Application and Almarsson Patent Further Reinforce That There Is a Lack of Adequate Written Description in the Priority Applications for the Claimed Genus of Solvates of Co-Crystals

94. The prosecution histories of substantially similar claims in related applications, *i.e.*, U.S. Application No. 15/639,223 (the "'223 application"), which was abandoned in December 2022, and U.S. Application No. 10/660,202 (the "Almarsson application"), which issued as U.S. Patent No. 7,927,613 ("Almarsson"), further reinforce that the Priority Applications lack an adequate written description of the claimed genus of solvates of co-crystals covered by claim 16.

a. U.S. Application No. 15/639,223

95. The '223 application has the same named inventors as the '344 patent and they prosecuted substantially similar patent application claims as challenged claim 16 of the '344 patent. The '223 application was examined by a different primary examiner (Noble E. Jarrell) than the '344 patent and the '956 application (Sahar Javanmard). *Compare, e.g.*, Ex. 1522, pp. 242-43, 248-49, '223 application file history, November 5, 2019 Non-Final Office Action at cover page, Office Action summary, 6-7 *with* Ex. 1516, pp. 485-86, 500, '344 patent file history, July 12, 2016 Non-Final Office Action at cover page, Office Action Summary, 15 and Ex. 1517, pp. 3261-62, 3266, '956 application file history, October 5, 2009 Non-Final Office Action at cover page, Office Action Summary, 5.

96. The '223 application claims priority to the same two applications as the '344 patent, *i.e.*, the Priority Applications. Ex. 1522, p. 5, '223 application file history, June 30, 2017 Application Data Sheet at 4 ("Domestic Priority Information," listing '956 application and '768 application); Ex. 1501, cover, col. 1, ll. 8-16 (claiming priority to the '956 and '768 applications). The specification of the '223 application is also substantively the same as that of the '956 application and, therefore, the '223 application, like the '956 application, does not describe any co-crystal within the scope of claim 16 of the '344 patent (*supra* ¶¶ 65, 71).

Compare Ex. 1521, '223 application at 1-34 *with* Ex. 1515, '956 application at 1-34.¹¹

97. Application claim 37 of the '223 application originally recited as follows:

37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active

¹¹ I also note that some of the patent attorneys who prosecuted the '223 application also prosecuted the '344 patent (*i.e.*, Edward R. Gates & David F. Cauble).

Compare, e.g., Ex. 1522, p. 14, '223 application file history, June 30, 2017

Preliminary Amendment at 3, and *id.* p. 232, July 23, 2019 Response to Non-Final

Office Action at 9 *with* Ex. 1516, p. 264, '344 patent file history, July 10, 2014

Amendment in Response to Non-Final Office Action at 14, and *id.* p. 448, August

10, 2017 Appeal Brief at 24. And the assignments filed in connection with both the

'223 application and '344 patent to the Patent Owners (*i.e.*, Regents of the

University of Michigan and University of South Florida) are the same. *Compare*

Ex. 1551, USPTO Assignment Database Entry for U.S. Patent No. 10,633,344 *with*

Ex. 1552, USPTO Assignment Database Entry for U.S. Patent Application No.

15/639,223.

pharmaceutical ingredient (API) and at least one co-crystal former, 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, wherein the co-crystal former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding, wherein supramolecular synthons comprise non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former.

Ex. 1522, p. 225, '223 application file history, July 23, 2019 Response to Non-Final Office Action at 2; Ex. 1522, p. 267, '223 application file history, April 3, 2020 Response to Non-Final Office Action at 2.

98. In a February 5, 2021 Office Action, the examiner of the '223 application rejected pending application claims 37-50 for lack of an adequate written description in the specification (which is substantively the same specification as the '956 application), the examiner stating that:

It is unquestionable that [application] claim(s) 37-50 is/are *broad and generic*, with respect to all possible compounds encompassed by the claims. The *possible structural variations are limitless* to any a pharmaceutical composition comprising an API and a co-crystal former that are associated through non-covalent hydrogen binding. *Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation*

between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of examples 1-18 [sic, 19] and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

Ex. 1522, pp. 316-18, '223 application file history, February 5, 2021 Non-Final Office Action at 2-4 (emphases added). In these comments, the examiner recognized that the disclosures in the '223 application could not be extrapolated to non-exemplified species. *See id.*

99. In response to the February 5, 2021 Office Action, the '223 Applicants argued that the written description rejection should be withdrawn because “[t]here is a well-established correlation between structure and function in the context of hydrogen bonding” and the disclosure of structure and function together with the nineteen working examples that show this relationship and discussion in the specification about “functional groups which may participate in hydrogen bonding,” satisfies the written description requirement. Ex. 1522, p. 329, '223 application file history, May 27, 2021 Amendment in Response to Office

Action at 6. Further, “the [’223] application describes adequate exemplary structures and working examples, i.e., each of Examples 1-19.” *Id.*

100. The examiner rejected these arguments, and maintained the written description rejection in an August 11, 2021 Final Office Action. The ’223 examiner reiterated that “[t]he description requirement of the patent statu[t]e requires a description of an invention, not an indication of a result that one might achieve if one made that invention” and “the instant claims do not show possession of the complete scope of non-covalent interactions through hydrogen bonding.” Ex. 1522, pp. 355-59, ’223 application file history, August 11, 2021 Final Office Action at 3-7. The examiner also reiterated that pending application claims 37-50 “are broad and generic” and “[t]he possible structural variations are limitless.” *Id.* p. 355, at 3. “Although [the 19] examples [in the specification] show the relationship of different groups for H-bonding . . . they do not limit the scope of the claims” and application claim 37 “encompasses more than groups participating in H-bonding in examples 1-19.” Ex. 1522, p. 359, ’223 application file history, August 11, 2021 Final Office Action at 7.

101. The ’223 examiner also maintained a prior rejection of the claims as incomplete for omitting essential elements, namely, the required structural components of the entire API and co-crystal former molecules in addition to the

chemical functional groups (*i.e.*, chemical functionalities) that are used for non-covalent bonding, stating:

This rejection is maintained because the applicants have not fully defined the complexes formed. [Application] [c]laims 37-50 do not fully characterize or describe the active pharmaceutical ingredient (API) and the co-crystal former. *[Application] [c]laim 37 only recites that the API is pharmaceutically active. What or how is the ingredient active? What are the required structural features of the API? The co-crystal former is unclear because it only defined as having a complimentary chemical functionality to the API.* Application [c]laim 38 recites four different generic co-crystal formers defined by property not by the required structural elements. One looking at the claim cannot determine the complex that the pharmaceutical composition contains. Applicants point to a laundry list of different functional groups that can participate in H-bonding. It is improper to limit the claims with the specification. Paragraph [0009] is open-ended (“non-limiting”) with regard to a functional group that can be used.

Ex. 1522, pp. 359-60, '223 application file history, August 11, 2021 Final Office Action at 7-8.

102. In response to this August 11, 2021 Final Office Action, the '223 Applicants amended application claim 37 as follows (underlining shows newly added language):

37. (Currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-crystal former and each supramolecular synthon comprising a heterosynthon formed via non-covalent hydrogen bonding,

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, and wherein the first chemical functionality is selected from carboxylic acid, amide, N-heterocycle, and alcohol;

wherein the co-crystal former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding, wherein supramolecular synthons comprise non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former, and

wherein the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol.

Ex. 1522, p. 368, '223 application file history, November 12, 2021 Response After Final at 2. The '223 Applicants argued that the amended application claims

overcome the written description rejection and should be allowed. *Id.* pp. 371-72, at 5-6.

103. The examiner of the '223 application maintained the rejection of claim 37 (along with all remaining pending claims) in a subsequent office action, finding that “the [application] claims do not show possession of the complete scope of non-covalent interactions through hydrogen bonding.” Ex. 1522, pp. 393-98, '223 application file history, March 22, 2022 Non-Final Office Action at 2-7. Again, the examiner stated:

It is unquestionable that [application] claim(s) 37-41, 43-47, 49, and 50 is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any a pharmaceutical composition comprising an API and a co-crystal former that are associated through non-covalent hydrogen binding. Although the [application] claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of examples 1-18 [*sic*, 19] and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statu[t]e requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does “little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.”)[.] Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the [application] claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Ex. 1522, pp. 394-95, '223 application file history, March 22, 2022 Non-Final Office Action at 3-4.

104. The examiner further stated that although the Examples “show the relationship of different groups for H-bonding . . . they do not limit the scope of the claims” because application claim 37 “encompasses more than the functional groups participating in H-bonding . . . [t]he whole structure of each component of the co-crystal has to be taken into consideration.” Ex. 1522, pp. 395-98, '223 application file history, March 22, 2022 Non-Final Office Action at 4-7.

105. The '223 examiner also maintained the rejection of the pending application claims as incomplete for omitting essential elements, namely, “the required structural components of an API and a co-crystal former,” stating: “[n]one

of claims 37-41, 43-47, 49, and 50 fully define the required structural elements of the API or the cocrystal former.” Ex. 1522, p. 398, ’223 application file history, March 22, 2022 Non-Final Office Action at 7.

106. The ’223 Applicants did not respond to this office action and instead, abandoned the ’223 application. Ex. 1522, pp. 414-15, ’223 application file history, December 6, 2022 Notice of Abandonment.

107. A comparison of independent application claim 37 of the ’223 application when it was abandoned (the only independent application claim when the application was abandoned) and dependent claim 16 of the ’344 patent (which depends from claim 10) is provided below. The differences are underlined¹² and explanation of the differences is provided in italics.

’223 Application, Application Claim 37	’344 Patent, Claim 16
	[16a] <u>The pharmaceutical composition of claim 10,</u> <i>[See [10a]-[10g] below.]</i>

¹² The parties agree that co-former and co-crystal former are used synonymously in the ’344 patent (*supra* § VIII.A (claim construction of “co-former”)), so these differences are not underlined.

'223 Application, Application Claim 37	'344 Patent, Claim 16
	[16b] <u>wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.</u>
37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of	[10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of
a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-crystal former	[10b]: a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,
<u>and each supramolecular synthon comprising a heterosynthon formed via non-covalent hydrogen bonding,</u>	<i>[The supramolecular synthons of claim 16 of the '344 patent can be heterosynthons or homosynthons formed via non-covalent hydrogen bonding.]</i>
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	[10c]: 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

'223 Application, Application Claim 37	'344 Patent, Claim 16
form, <u>and</u>	form,
wherein the first chemical functionality is <u>selected from carboxylic acid, amide, N-heterocycle, and alcohol</u> ;	[10g] ¹³ : wherein the first chemical functionality is (i) <u>a carboxamide</u> , (ii) <u>a carbonyl</u> , or (iii) <u>an amine</u> . [A “carboxamide” is a type of “amide.” See Ex. 1533, IUPAC 1998 at 14, 85.]
wherein the co-crystal former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,	[10d]: wherein the co-former has a second chemical functionality compl[e]mentary to the first chemical functionality via non-covalent hydrogen bonding,
<u>[The '223 application provides that the co-former can be an API, GRAS compound, a food additive, a low toxicity organic, or a metal-organic complex, Ex. 1521, '223 application ¶ [0042], nearly all of which will be solids at room temperature and atmospheric pressure.]</u>	[10e]: <u>wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form</u> ,

¹³ Element [10g] of claim 10 of the '344 patent is listed out of order to facilitate comparing the claims.

'223 Application, Application Claim 37	'344 Patent, Claim 16
wherein supramolecular synthons <u>comprise</u> non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former, and	[10f]: wherein supramolecular synthons <u>are formed via</u> non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former,
<u>wherein the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol.</u>	<i>[As a result of limitation [10g], above, the supramolecular synthons of claim 16 of the '344 patent must comprise a carboxamide (a type of amide), carbonyl, or amine.]</i>

Ex. 1522, p. 368, '223 application file history, November 12, 2021 Amendment in Response to Office Action at 2; Ex. 1501, claims 10, 16.

108. Application claim 37 of the '223 application does not disclose the solvent limitation of claim 16 of the '344 patent (which is not disclosed in the Priority Applications as discussed above); however, there is considerable overlap in the remaining claim elements. Given the similarities between these claims, the examiner's discussion of application claim 37 of the '223 application is relevant to claim 16 of the '344 patent. Like '223 application claim 37 at the time it was abandoned, claim 16 of the '344 patent is also "broad and generic" and encompasses "limitless" structural variations. *See* Ex. 1522, pp. 316-18, '223

application file history, February 5, 2021 Non-Final Office Action at 2-4; pp. 394-95, '223 application file history, March 22, 2022 Non-Final Office Action at 3-4. In addition, because the 2003 '956 application is substantively the same as the '223 application that the examiner discussed (*see* paragraph 96 above), the '223 examiner's statements about the '223 application also apply to the '956 application. In particular, the '223 examiner stated that the application provides "no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification." *See* Ex. 1522, pp. 316-18, '223 application file history, February 5, 2021 Non-Final Office Action at 2-4; pp. 394-95, '223 application file history, March 22, 2022 Non-Final Office Action at 3-4. Further, the 2003 '956 application (and thus also the 2002 '768 application which has even less disclosure) "lacks sufficient variety of species to reflect th[e] variance in the [claimed] genus" and "does not provide sufficient descriptive support for the myriad of compounds embraced by the claims." *See* Ex. 1522, pp. 394-95, '223 application file history, March 22, 2022 Non-Final Office Action at 3-4.

109. Additionally, like application claim 37 of the '223 application, challenged claim 16 of the '344 patent "encompasses more than groups participating in [hydrogen]-bonding," *i.e.*, the first and second chemical functionalities. Ex. 1522, p. 359, '223 application file history, August 11, 2021

Final Office Action at 7; p. 398, '223 application file history, March 22, 2022 Non-Final Office Action at 7. Claim 16 of the '344 patent encompasses the structures of the API and co-former *in their entirety* and, thus, any structure-function relationship between the structures of the first and second chemical functionalities in the Examples cannot be applied to other API-co-former combinations involving the same first and second chemical functionalities. The structure-function relationship must address the entirety of the API and co-former that hydrogen bond to one another to form the claimed co-crystals. No such relationships are taught in the Priority Applications. Therefore, the Priority Applications are insufficient to support the broad genus of solvates of co-crystals encompassed by challenged claim 16.

b. Almarsson

110. The Almarsson application, which issued as the '613 patent ("Almarsson"), was filed as a continuation-in-part of the '956 application on September 11, 2003, and has overlapping teachings with the '956 application, including overlapping Examples. Ex. 1505, Almarsson, cover page at (22), (60); *e.g., compare* Ex. 1523, pp. 57-70, Almarsson file history, Almarsson application at 55-68 (Examples 24-37) *with* Ex. 1515, '956 application at ¶¶ [0056]-[00128], [00135]-[00146], [00171]-[00177] (Examples 1-11, 13, 14, 19). Also, Almarsson

incorporates by reference the '956 application. Ex. 1505, Almarsson, col. 1, ll. 13-15 and 22-25.

111. The Almarsson application has the same inventors as the '344 patent, plus others, and also claims priority to several applications including the same Priority Applications as the '344 patent. Ex. 1505, Almarsson, cover page at (60). The primary patent examiners for Almarsson (Abigail Manda Cotton and Deirdre Renee Claytor) were different than the examiner who examined the '344 patent and the '956 application (Sahar Javanmard). *Compare, e.g.*, Ex. 1523, pp. 643-44, 667, Almarsson file history, March 30, 2007 Non-Final Office Action at cover page, Office Action Summary, 23, and *id.* pp. 742-43, 758-59, December 10, 2007 Final Office Action at cover page, Office Action Summary, 16-17 *with* Ex. 1516, pp. 485-86, 500, '344 patent file history, July 12, 2016 Non-Final Office Action at cover page, Office Action Summary, 15 and Ex. 1517, pp. 3261-62, 3266, '956 application file history, October 5, 2009 Non-Final Office Action at cover page, Office Action Summary, 5.

112. Independent application claim 1 of the Almarsson application initially recited:

1. A pharmaceutical co-crystal composition, comprising: an API and a co-crystal former, wherein the API is a liquid or solid at room temperature and the co-crystal former is a solid at room temperature,

and wherein the API and co-crystal former are hydrogen bonded to each other.

Ex. 1523, pp. 419-38, Almarsson file history, Almarsson application at 417-36 (application claims).

113. The Almarsson examiner found that the initial Almarsson application claims were not entitled to claim benefit to priority “applications nos. 10/378,956 . . . , as well as the provisional . . . applications to which they claim priority,” which included the ’768 application, because those applications “fail[ed] to provide adequate support” for these claims. Ex. 1523, pp. 647-48, Almarsson file history, March 30, 2007 Non-Final Office Action at 3-4. According to the examiner:

The disclosure of the prior-filed applications, including application nos. 10/378,956, 10/367,829, 10/449,307 and 10/601,092, as well as the provisional and non-provisional applications to which they claim priority, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. In particular, these prior applications do not provide adequate support for all pharmaceutical co-crystal compositions in general having an API that is a liquid or a solid at room temperature, and a co-crystal former that is solid at room temperature, where the API and co-crystal former are hydrogen bonded to each other, as recited in [application] claim 1. . . . Accordingly, the [application] claims do not receive benefit of the filing dates of these prior applications or the

provisional and non-provisional application to which they claim priority.

Ex. 1523, pp. 647-48, Almarsson file history, March 30, 2007 Non-Final Office Action at 3-4 (underlining in original; emphases added); *see also id.* pp. 649-56, at 5-12 (providing additional detail on the written description rejection).

114. In response to the examiner's rejection, the Almarsson Applicants amended independent application claim 1 to exclude certain co-crystals, as shown below, and argued that the written description and enablement rejections should be withdrawn. Ex. 1523, pp. 718-29, Almarsson file history, October 1, 2007 Response to Office Action at 2-13.¹⁴

1 (currently amended). A pharmaceutical co-crystal composition, comprising: an API and a co-crystal former, wherein:

- a) the API is a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature;~~and wherein~~
- b) the API and co-crystal former are hydrogen bonded to each other; and
- c) specifically excluding a co-crystal selected from the group consisting of: [specific co-crystals].

¹⁴ I understand throughout this section that for claim amendments, strikethrough text means subject matter has been removed from the claims and underlined text means that subject matter has been added.

Ex. 1523, pp. 718-21, Almarsson file history, October 1, 2007 Response to Office Action at 2-5.

115. Despite the amendment, the Almarsson examiner maintained the lack of written description rejection for Almarsson application claim 1, explaining that:

[C]laim 1 broadly reads on any solid API and any co-crystal former that is liquid or solid, and where the components are hydrogen bonded to one another, or the co-crystals with any of the numerous diverse and different co-crystal formers in [application] claim 2 or Apls as in [application] claim 9. There is no description to convey to one of skill in the art that the inventors were in possession of the numerous and diverse co-crystals as claimed, including any API and any co-crystal former that are hydrogen bonded and are solid or liquid. Therefore, the rejection is maintained.

Ex. 1523, pp. 744-45, Almarsson file history, December 10, 2007 Final Office Action at 2-3 (underlining in original); *id.* pp. 746-47, at 4-5 (same). *See also* Ex. 1523, pp. 767-68, Almarsson file history, March 10, 2008 Response to Final Office Action at 2-3 (Applicants arguing that the application claims have an adequate written description); Ex. 1523, p. 777, Almarsson file history, March 25, 2008 Advisory Action at 2 (the examiner maintaining the lack of written description rejection after further argument from the applicants, because “[t]here is no description [in the specification] to convey to one of skill in the art that the inventors were in possession of the numerous and diverse co-crystals as claimed,

including any API and any co-crystal former that are hydrogen bonded and are a solid or liquid”).

116. After these rejections, the Almarsson Applicants amended the Almarsson application claims to recite in claim 1 only specific APIs that were used in the co-crystals disclosed in the Almarsson application’s Examples, and in claim 11, only the specific co-crystals disclosed in the Examples (naming both the API and co-former). Below I reproduce the amendments to claims 1 and 11.

1 (currently amended). A pharmaceutical co-crystal composition, comprising: an API and a co-crystal former, wherein:

- a) the API is selected from celecoxib, carbamazepine, 5-fluorouracil, acetaminophen, aspirin, flurbiprofen, phenytoin or ibuprofen ~~a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature;~~
- b) the API and co-crystal former are hydrogen bonded to each other; and
- c) specifically excluding a co-crystal selected from the group consisting of: 5-fluorouracil:9-ethylhypoxanthine, 5-fluorouracil:cytosine dihydrate, 5-fluorouracil:theophylline monohvdrate, acetaminophen:piperazine and acetaminophen:theophylline[.]¹⁵

¹⁵ Note that element (c) of application claim 1 originally recited about three pages of excluded co-crystals. All the recited co-crystals in (c) other than those listed

11 (currently amended). A co-crystal comprising an API and a co-crystal former selected from:

- (a) carbamazepine and saccharin;
- (b) carbamazepine and nicotinamide;
- (c) carbamazepine and trimesic acid;
- (d) celecoxib and nicotinamide;
- ~~(e) olanzapine and nicotinamide;~~
- ~~(f)~~(e) celecoxib and 18-crown-6;
- ~~(g)~~
- ~~(f)~~modafinil and malonic acid;
- ~~(g)~~modafinil and benzamide;
- ~~(h)~~modafinil and mandelic acid;
- ~~(i)~~modafinil and glycolic acid
- ~~(j)~~modafinil and fumaric acid;
- ~~(k)~~modafinil and maleic acid;
- ~~(n)~~(f) 5-fluorouracil and urea;
- ~~(o)~~(g) acetaminophen and 4,4'-bipyridine;
- ~~(p)~~(h) phenytoin and pyridone;
- ~~(q)~~(i) aspirin and 4,4'-bipyridine;
- ~~(r)~~(j) ibuprofen and 4,4'-bipyridine;
- ~~(s)~~(k) flurbiprofen and 4,4'-bipyridine;

above were deleted in the May 29, 2008 Amendment. *See* Ex. 1523, pp. 779-82,

Almarsson file history, May 29, 2008 Amendment in Response to Office Action at 2-5.

~~(t)~~(l) flurbiprofen and trans-1,2-bis(4-pyridyl) ethylene;
~~(u)~~(m) carbamazepine and p-phthalaldehyde;
~~(v)~~(n) carbamazepine and 2,6-pyridinecarboxylic acid;
~~(w)~~(o) carbamazepine and 5-nitroisophthalic acid;
~~(x)~~(p) carbamazepine and 1,3,5,7-adamantane tetracarboxylic acid; or
~~(y)~~(q) carbamazepine and benzoquinone.

Ex. 1523, pp. 779-83, Almarsson file history, May 29, 2008 Supplemental Amendment at 2-6. Notably, as a result of these amendments, Almarsson application claim 1 was limited to specific APIs, unlike challenged claim 16 of the '344 patent.

117. Despite the Almarsson Applicants' amendments, the Almarsson examiner maintained the written description rejection. Ex. 1523, p. 803, Almarsson file history, July 17, 2008 Advisory Action at 2 (the examiner maintaining the lack of written description rejection because "Applicants have only shown the formation of the particular co-crystals listed in [application] claim 11," *i.e.*, those in the application's Examples, "but do not exemplify the formation of all co-crystals with the APIs listed in amended [application] claim 1," and further stating that "[i]t is not described or shown how the numerous and diverse different co-crystals could be obtained").

118. Ultimately, the Almarsson Applicants cancelled all pending application claims and added new application claims 43-78 directed to specific co-crystals described in the patent Examples where both the API and co-former were specified in the claims, and pharmaceutical compositions comprising those co-crystals. Ex. 1523, pp. 807-13, Almarsson file history, October 10, 2008 Amendment in Response to Advisory Action at 2-8.

119. In response, the Almarsson examiner withdrew the written description rejection and the application claims ultimately issued as the Almarsson patent. Ex. 1523, p. 823, Almarsson file history, March 24, 2009 Non-Final Office Action at 2 (the examiner stating that “[t]he 35 USC 112, first paragraph rejections have been withdrawn as the claims and the subject matter reading on this rejection have been cancelled”).

120. Although the Almarsson claims do not include the solvent limitation of claim 16 of the '344 patent, many of the Almarsson examiner's comments summarized above also apply to challenged claim 16 of the '344 patent, which are not limited to any specific structures of the APIs, any specific structures of the co-formers, or any specific API-co-former combinations. Similar to Almarsson's specification (which incorporates by reference the Priority Applications and includes additional Examples, tables, and figures), the Priority Applications do not “describe[] or show[] how the numerous and diverse different co-crystals

[encompassed within the scope of challenged claim 16] could be obtained.” *See* Ex. 1523, p. 803, Almarsson file history, July 17, 2008 Advisory Action at 2; p. 777, March 25, 2008 Advisory Action at 2; p. 747, December 10, 2007 Final Office Action at 5. Thus, neither of the Priority Applications provides written description support for challenged claim 16 of the ’344 patent.

* * *

121. In addition to my analyses of the ’223 application and Almarsson above, I point out that neither the ’223 application claims nor the Almarsson claims include the limitation of challenged claim 16 that the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule, a claim limitation that is not described anywhere in the Priority Applications.

122. For these reasons, it is my opinion that challenged claim 16 is not entitled to a priority date of March 1, 2002 or March 3, 2003, the filing dates of the Priority Applications, respectively. Therefore, I understand that the earliest priority date challenged claim 16 is entitled to is February 13, 2014, the filing of the ’862 application (which issued as the ’344 patent).

B. The Full Scope of Claimed Solvates of Co-Crystals in Claim 16 Is Not Enabled by the Priority Applications

123. For the reasons discussed below, the Priority Applications do not teach a POSA how to make and use a single species falling within the scope of claim 16, much less the full scope of the solvates of co-crystals of claim 16, without undue experimentation. Therefore, claim 16 is not enabled and thus is not entitled to a priority date of 2002/2003.

1. Supramolecular Synthons Non-Covalently Bonded to One Another by Non-Covalent Bonding to a Solvent Molecule Is Not Enabled

124. Claim 16 requires that the “supramolecular synthons [of claim 10] are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.” Ex. 1501, col. 26, ll. 12-14. Below is my analysis of the factors relevant to assessing whether undue experimentation is required to practice claim 16. These factors are listed in **Appendix B**, ¶ 21, which provides the relevant legal principles I applied in rendering my analysis in this declaration.

a. The Breadth of the Claim

125. Claim 16 depends from independent claim 10 and therefore includes all the limitations of claim 10. Claim 10 covers a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective

amount of a co-crystal. The co-crystal can comprise (1) *any* API¹⁶ having a first chemical functionality that is a carboxamide, carbonyl,¹⁷ or amine that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form, (2) *any* co-former that is a solid at room temperature and atmospheric pressure when the co-former is in its pure form and that has a second chemical functionality that is complementary to the first chemical functionality of the API, (3) the API and co-former in *any* stoichiometric ratio, and (4) *any* pharmaceutically acceptable solvent that links supramolecular synthons by non-covalent bonding.

¹⁶ I understand it is Petitioner's position that Applicants disclaimed salts during prosecution and therefore the API cannot itself be a salt. However, whether the API can be a salt does not affect my opinions in this declaration regarding the breadth of claim 16. If the API could be a salt, claim 16 would be even broader, and there are no examples of such APIs in the Priority Applications.

¹⁷ As discussed in section IX.C below, an API having a first chemical functionality that is a carbonyl and that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form is an inoperable embodiment and, therefore, is not enabled by the Priority Applications.

126. An API in the context of '344 patent is a “biologically active moiety having a therapeutic effect on a human or animal suffering from a pathological condition, when administered in a given concentration.” *Supra* § VIII.A (claim construction of “API”); Ex. 1501, col. 9, ll. 27-34. As of 2002/2003, even just focusing on molecules with a first chemical functionality that is -C(=O)NH₂ (*i.e.*, a carboxamide), there was a very large number of known and possible molecules comprising a first chemical functionality that is a carboxamide. In this declaration, I have identified, in the 2001 Merck Index alone, over fifty examples of molecules with a “-C(=O)NH₂” group (*i.e.*, a carboxamide) that were known as of 2002/2003 to have a therapeutic effect on a human or animal suffering from a pathological condition when administered in a given concentration,¹⁸ but there would have been

¹⁸ Ex. 1549, 2001 Merck Index at 6-7 (entry 26, aceglutamide), 43 (entry 222, aldioxa), 49 (entry 254, allantoin), 70 (entry 396, amicoumacin A), 80-81 (entry 458, aminopentamide), 116 (entry 690, anthramycin), 147 (entry 863, atenolol), 205 (entry 1208, bidisomide), 234 (entry 1381, bromisovalum), 268-69 (entry 1599, buzepide), 298 (entry 1788, carbamazepine), 317-18 (entry 1886, carumonam), 326 (entry 1931, cefcapene pivoxil), 330 (entry 1947, cefotetan), 330-31 (entry 1949, cefoxitin), 333 (entry 1958, cefsulodin), 335 (entry 1966, cefuroxime), 337 (entry 1974, cellocidin), 340 (entry 1990, cephalonium), 341

many more known as of this date and even more that could have been identified by testing for therapeutic activity. Thus, the group of possible choices for the API in claim 16 as of 2002/2003 was very broad.

(entry 1995, cephamycins), 379 (entry 2211, chlortetracycline), 413-14 (entry 2390, clocapramine), 495 (entry 2848, darifenacin), 507 (entry 2905, demeclocycline), 591-92 (entry 3395, disopyramide), 606-07 (entry 3474, doxycycline), 638 (entry 3631, enviomycin), 665 (entry 3766, ethenzamide), 887 (entry 4962, indecainide), 978 (entry 5482, levetiracetam), 1032 (entry 5801, meclocycline), 1095 (entry 6170, metopimazine), 1101 (entry 6199, micafungin), 1112 (entry 6249, modafinil), 1128 (entry 6329, muramyl dipeptide), 1205 (entry 6753, nosiheptide) & (entry 6755, novobiocin), 1242-43 (entry 7011, oxiracetam), 1249 (entry 7046, oxytetracycline), 1292 (entry 7280, phenacemide), 1297 (entry 7309, pheneturide), 1335 (entry 7535, pipamazine) & (entry 7536, pipamperone), 1342 (entry 7569, piracetam), 1344 (entry 7581, piritramide), 1391 (entry 7863, progabide), 1479 (entry 8319, ritipenem), 1501-02 (entry 8446, saquinavir), 1614 (entry 9135, taltirelin), 1630 (entry 9218, temozolomide), 1631 (entry 9221, tenidap), 1764 (entry 9967, valdetamide), 1766 (entry 9978, valnoctamide) & (entry 9980, valpromide), 1782 (entry 10062, viomycin).

127. A co-former in the context of the '344 patent can be, for example, “other drug molecules [(for example, a molecule with therapeutic activity, regardless of whether it has a chemical functionality that is a carboxamide, carbonyl, or amine)], GRAS compounds,¹⁹ or approved food additives.” Ex. 1501, col. 3, ll. 35-37; col. 8, ll. 35-37 (same). Claim 16 (in view of its dependency on claim 10) limits the co-former to being a solid at room temperature and atmospheric pressure when the co-former is in its pure form. As of 2002/2003, there were well over one hundred GRAS compounds alone that were a solid at room temperature and atmospheric pressure when in pure form. Ex. 1531, 21 C.F.R. § 184 (2000). And there were thousands of known drug molecules. Ex. 1549, 2001 Merck Index, Foreword at v (reporting over 4,000 monographs on “a wide variety of drugs and pharmaceuticals”); Ex. 1540, Martindale 1999, Preface at vii (reporting 4,336 monographs on “drugs and groups of drugs that have similar uses or actions” and 827 monographs on “new drugs,” “drugs not easily classified,” “herbals,” and “drugs no longer used clinically but still of interest”). Even excluding drugs that are not solid at room temperature and atmospheric pressure in pure form, the group of possible co-formers covered by claim 16 is

¹⁹ A GRAS compound is one that is “Generally Regarded as Safe by the Food and Drug Administration (FDA).” Ex. 1501, col. 9, ll. 21-26.

extremely broad. Very conservatively, as of 2002/2003, thousands of molecules would have qualified as a co-former as the term is used in challenged claim 16 of the '344 patent.

128. Moreover, considering the over fifty possible APIs I identified with a -C(=O)NH₂ group in the 2001 Merck Index alone, and thousands of possible co-formers, the number of potential co-crystals falling within the scope of claim 16 would be no less than hundreds of thousands, which is enormously broad. Further, the API and co-former can be present in any stoichiometric ratio, making the number of possible co-crystals covered by claim 16 almost infinite.

129. In addition, the solvent can link supramolecular synthons with any type of non-covalent bond, not limited to hydrogen bonds, via (i) the first chemical functionalities of adjacent synthons, (ii) the second chemical functionalities of adjacent synthons, or (iii) from the first chemical functionality of one synthon to the second chemical functionality of an adjacent synthon. Thus, claim 16 is incredibly broad, which weighs in favor of non-enablement.

b. The Nature of the Invention

130. The nature of the purported invention of claim 16 of the '344 patent is a pharmaceutical composition comprising a genus of solvates of co-crystals containing an API and a co-former having certain properties and non-covalent interactions. *Supra* § VI (overview of the '344 patent). Because the formation of

solvates, co-crystals, and solvates of co-crystals are all unpredictable (*infra* § IX.B.1.c (unpredictability in the art)), this factor weighs in favor of non-enablement.

c. The State of the Art & Unpredictability of the Art

131. As of 2002/2003, it was not possible to predict with any reasonable certainty whether a solvate would form between two or more components or whether a co-crystal would form between two or more components, much less whether a solvate of a co-crystal would form that includes an API, co-former, and solvent and, specifically, one having the interactions required by challenged claim 16. As explained in Vippagunta 2001, “Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds *uniquely* to the possible formation of solvates or hydrates and hence *generalizations cannot be made* for a series of related compounds. . . . [N]o computer programs are currently available for predicting the crystal structures of hydrates and solvates.”). Ex. 1575, Vippagunta 2001 at 18; *see also id.* at 15 (“It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. . . ; “The mere presence of water in a system is not a sufficient reason to expect hydrate formation, because some compounds, though they are soluble in water, do not form hydrates.”); Ex.

1507, Ueto 2012 at 487 (Table 2 showing that a co-crystal screen of furosemide and nicotinamide with N,N-dimethylformamide as the crystallization solvent did not result in any co-crystal, hydrate, or solvate). A POSA would have understood that the unpredictability of solvates or hydrates of a compound discussed in Vippagunta 2001 is equally (or even more so) applicable to solvates of co-crystals, which includes the additional component of a co-former that (with the API) makes up the crystal lattice of the co-crystal.

132. It was also not possible as of 2002/2003 to predict with any reasonable certainty whether, to the extent a co-crystal did form, what non-covalent interactions, such as hydrogen bonding, would exist between the co-crystal components. *See, e.g.*, Ex. 1524, Desiraju 2001 at 398 (“In any supramolecular assembly, a large number of intermolecular interactions is possible – but only a few are actually observed. The weakness of these interactions makes it difficult to predict supramolecular structures.”), 399 (“Predicting supramolecular structures is hard, not only because of the sheer numbers of possible interactions involved, but also because in energetic terms there is not much to choose between these various interactions. . . .”; “In crystal engineering, the supramolecular chemist aims to design and control packing arrangements to design crystals with specific properties. But this is not routinely possible from knowledge of the molecular structure.”; “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.”; “And the synthon concept tries to simplify what is essentially a very difficult problem. But even with apparently straightforward synthons, things can go wrong.”), 400 (“Molecules seem to know how to crystallize into the correct structure, even if chemists cannot predict it.”); Ex. 1525, Aakeröy 2003 at 164 (“Cocrystals are not necessarily easy to prepare . . .”); Ex. 1526, Dunitz 2003, at 546 (“One can *describe* almost any observed crystal structure in terms of [hydrogen bond] interactions. The trouble with this approach is that its physical basis is shaky and its predictive capacity is poor. Of course, inspired guessing may occasionally lead to a correct prediction with any approach.” (emphasis in original)); Ex. 1534, Gavezzotti 1994 at 309-14 (explaining that the formation and structure of crystals are unpredictable); *infra* § IX.B.2 (prosecution of the Almarsson patent) (“The skilled artisan would view the formation of different crystalline forms as being unpredictable due to the numerous different crystallization factors needing to be controlled to provide different crystal states, as well as the unpredictability in predicting the different types of crystals that may exist.”).

133. Further, there were numerous examples of failed attempts to predict whether a co-crystal would form at all and, if it did, what interactions would exist within the co-crystal. *See, e.g.*, Ex. 1527, Reddy 2004 at 90 (“Cocrystallization of

benzoic acid and pentafluorobenzamide using [certain] conditions did not afford the expected molecular complex $[C_6H_5COOH \cdot C_6F_5CONH_2]$.”); Ex. 1525, Aakeröy 2003 at 160 (“Despite numerous attempts (about 25 different compounds) at forming cocrystals with [maleic hydrazide] and a variety of aromatic (including heterocyclic) or aliphatic compounds with different functional groups, e.g., carboxylic acids, amides, oximes, etc., we were only ever able to isolate unreacted starting materials.”); Ex. 1507, Ueto 2012 at 487 (Table 2 showing that a co-crystal screen of furosemide and nicotinamide with N,N-dimethylformamide as the crystallization solvent did not result in any co-crystal, hydrate, or solvate); Ex. 1524, Desiraju 2001 at 399 (“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.”).

134. Even the ’344 patent Applicants themselves acknowledged that co-crystal formation is complex and unpredictable when they argued during prosecution of the ’956 application that “prior to this invention, . . . random trial-and-error was used to isolate [co-crystals]” and “making numerous such co-crystals without trial and error . . . heretofore *was not remotely possible*.” Ex. 1517, pp. 4071-72, ’956 application file history, January 14, 2014 Response at 8-9

(emphasis added). Applicants argued that they “discovered the critical aspects which control the formation of drug co-crystals, and demonstrated the power of this discovery by making numerous such co-crystals without trial and error.” *Id.* However, the disclosures in the Priority Applications are not commensurate in scope with the broad class of solvates of co-crystals covered by claim 16, as they fail to teach any solvates of co-crystals falling within the scope of claim 16. *Supra* § IX.A.2 (lack of priority: written description). Thus, there is no evidence in the Priority Applications that solvates of co-crystals covered by claim 16 could be made at all, much less made predictably. But even three Examples would not be a representative number of species to support the broad scope of claim 16. *Id.*

135. Furthermore, the inventors’ own work confirms that co-crystal formation is challenging and unpredictable. For example, Fleischman 2003, submitted for publication on March 3, 2003 (*i.e.*, the same day that the ’956 application was filed) by Michael J. Zaworotko, Nair Rodriguez-Hornedo, and Brian Moulton (among others), reported thirteen purportedly new co-crystals of carbamazepine (the API used in Examples 7-19 of the ’956 application) with a co-former after experimenting with about fifty co-formers, which the authors said was a “success ratio” of only 20%. Ex. 1528, Fleischman 2003 at 911. With respect to one of the co-crystals (*i.e.*, 1:1 carbamazepine and nicotinamide), Fleischman 2003 explained that this co-crystal had an “*unexpected* exterior hydrogen-bonded

pattern.” *Id.* at 913. Fleischman 2003 also stated that “the crystal packing of APIs tends to *be even less predictable* than that of other organics because they often have multiple avenues for self-assembly and are therefore predisposed to exhibit polymorphism.” *Id.* at 911 (emphasis added).

136. This unpredictability is further supported by references such as Aitipalmula 2010 and Ueto 2012 where co-crystals did not always result from solvent-based crystallization methods, much less solvates of co-crystals. Ex. 1529, Aitipamula 2010 at 2232 (describing solvate experiments using at least fifteen different solvents where solvates “readily form[ed]” from only eight of the solvents); Ex. 1507, Ueto 2012 at 487 (discussing a co-crystal screening experiment of furosemide and nicotinamide using sixteen different solvents, seven of which resulted in co-crystals, eight of which resulted in solvates of co-crystals, and one of which failed to produce a co-crystal).

137. Similarly, all nineteen Examples disclosed in the ’956 application (and all nine Examples disclosed in the ’768 application) were prepared by solvent-based crystallization methods. Yet, only three Examples in the ’956 application (two in the ’768 application) resulted in a final product that includes a solvent, *see* Ex. 1515, ’956 application, ¶¶ [0056]-[0059], [0067]-[0072], [00122]-[00128] (Examples 1, 3, and 11); Ex. 1514, ’768 application, ¶¶ [0043]-[0046],

[0054]-[0059] (Examples 1 and 3), none of which meets the limitations of claim

16. *Supra* § IX.A.2 (lack of priority: written description).

138. For these reasons, a POSA as of 2002/2003 would have understood that formation of solvates, co-crystals, and solvates of co-crystals were all unpredictable, which weighs in favor of non-enablement.

d. The Relative Skill of Those in the Art

139. I defined the person of ordinary skill in the art of the '344 patent as of 2002/2003 (or 2014) in paragraph 19 above. The relative skill of a POSA is high. In particular, it requires someone with an advanced degree in chemistry or a related field and experience in solid state chemistry, including experience preparing multiple-component crystalline solids and evaluating their single crystal structures. *Supra* ¶ 19; *infra* § IX.B.2 (prosecution of the Almarsson patent) (“[T]he relative skill of those in the art is typically very high, i.e. experienced scientists having advanced degrees in the chemical and biochemical fields.”). Although the level of skill is high, formation of solvates, co-crystals, and solvates of co-crystals are all unpredictable. *Supra* § IX.B.1.c (unpredictability in the art). Therefore, this factor is neutral with respect to enablement.

e. The Presence or Absence of Working Examples

140. There are no Examples in the Priority Applications that teach a POSA how to make and use the subject matter of claim 16 of the '344 patent. *Supra* §

IX.A.2 (lack of priority: written description); *see infra* § IX.B.2 (prosecution of the Almarsson patent) (“The specification does not provide working examples that are sufficient to show one of ordinary skill in the art how to arrive at all of the co-crystal forms.”).

141. Even if Examples 1, 3 and/or 11 fell within the scope of claim 16 (I disagree, *see supra* § IX.A.2 (lack of priority: written description)), three Examples are not a sufficient number of working examples to teach a POSA how to make and use the full scope of the claim 16, which covers co-crystals having (1) any API that has a carboxamide, carbonyl, or amine first chemical functionality,²⁰ and (2) any solid complementary co-former, (3) in any stoichiometric ratio, and (4) with any compound that can dissolve another substance (*i.e.*, a solvent) and that links the supramolecular synthons by non-covalent bonding, particularly given the unpredictability of the formation of solvates, co-crystals, and solvates of co-crystals. *Supra* §§ IX.B.1.a (breadth of the claims), IX.B.1.c (unpredictability in the art). *Infra* § IX.B.2 (prosecution of the Almarsson patent) (“The specification does not provide working examples that are sufficient to show one of ordinary skill in the art how to arrive at all of the co-crystal forms.”). These three Examples

²⁰ *Supra* p. 85, fn. 16 (Applicants’ disclaimer of salts during prosecution).

would not support the full breadth of claim 16. Therefore, this factor weighs in favor of non-enablement.

f. The Amount of Direction or Guidance

142. As explained above, there are no Examples in the Priority Applications that are covered by claim 16. Even if Examples 1, 3, and/or 11 fell within the scope of claim 16 (I disagree), these few Examples are insufficient to teach a POSA how to make and use the full scope of claim 16. *Supra* §§ IX.A.2 (lack of priority: written description), IX.B.1.e (working examples).

143. Moreover, the Priority Applications do not provide any guidance on how to prepare co-crystals where solvent non-covalently bonds supramolecular synthons to one another, such as what API, co-former, and solvent combination to select and in what stoichiometric ratio. Further as I explained above, disclosure of solvent-based crystallization methods does not provide sufficient guidance, as such methods do not always result in solvates. *Supra* § IX.B.1.c (unpredictability in the art).

144. Additionally, a POSA as of 2002/2003 would have understood that solvent can actually disrupt the hydrogen bonding in the formation of a co-crystal. For example, as explained in Guillory 1999, “[t]he morphology of acetanilide crystals can be controlled by choosing solvents that promote or inhibit the formation of [a certain] hydrogen-bond chain. . . . Solvents that are proton donors

or proton acceptors inhibit chain formation by competing with amide molecules for hydrogen-bonding sites. Thus, acetone inhibits chain growth at the —NH end, and methanol inhibits chain growth at the carbonyl end of the chain.” Ex. 1530, Guillory 1999 at 192; *see also id.* at 193 (“Some solvents favor the crystallization of a particular form or forms because they selectively adsorb to certain faces of some polymorphs, thereby either inhibiting their nucleation or retarding their growth to the advantage of others.”).

145. The absence of guidance in the Priority Applications as to whether and what solvents may disrupt the formation of hydrogen bonds when trying to form a co-crystal is an additional reason why a POSA would not have been able to make and use the full scope of the purported invention of claim 16 based on disclosures in either priority application. Therefore, this factor weighs in favor of non-enablement.

g. The Quantity of Experimentation Necessary

146. Without any examples or guidance in the Priority Applications as to how to prepare co-crystals falling within the scope of claim 16, much less examples or guidance commensurate in scope with the solvates of co-crystals covered by claim 16, *supra* §§ IX.B.1.a (breadth of the claims), IX.B.1.e (working examples), IX.B.1.f (amount of direction or guidance), and because solvent incorporation into a co-crystal is not predictable, *supra* § IX.B.1.c (unpredictability

in the art), preparing co-crystals meeting the limitations of claim 16 would require significant experimentation. *See infra* § IX.B.2 (prosecution of the Almarsson patent) (“As the specification does not provide adequate guidance to allow one of ordinary skill in the art to readily determine the manufacturing conditions required to achieve crystallization of all of API/co-crystal formers, nor to determine which combinations of API and co-crystal former would even be capable of being recovered in crystal form, it is considered that one of ordinary skill in the art would have to engage in **undue experimentation** in order to be able to fully make and use the invention to the full extent of the claims.” (emphasis in original)).

147. At most, the Priority Applications provide a general research plan for trial-and-error experimentation that involves screening candidate co-formers to identify those having a complementary chemical functionality that forms supramolecular synthons with an API’s first chemical functionality. *See* Ex. 1515, ’956 application, ¶¶ [0010]-[0012], [0039]-[0041] (disclosing “methods for identifying complementary chemical functionalities to form a desired supramolecular synthon”), ¶ [0037] (describing Figure 24 as showing “an exemplified scheme for preparing multiple-component phase compositions of the subject invention”), Figure 24; Ex. 1514, ’768 application at ¶¶ [0010]-[0012], [0028]-[0030] (disclosing “method[s] for identifying complementary chemical functionalities to form a desired supramolecular synthon”). *Supra* § VI (overview

of the '344 patent). This research plan provides no guidance for how to prepare a co-crystal comprising a solvent, let alone solvates of co-crystals that meet the limitation of claim 16.

148. To practice the broad scope of claim 16, a POSA would first need to select a particular API and co-former combination having a certain stoichiometry and then undergo extensive trial-and-error experimentation, dissolving the API and co-former in different solvents (and possibly different mixtures of solvents at different ratios) under different conditions (*e.g.*, different temperatures) having no guidance as to what solvent(s) or conditions are most likely to result in co-crystals of the API and co-former at all, much less result in a solvate of a co-crystal that satisfies the specific non-covalent bonding limitations of claim 16. *Supra* § IX.B.1.f (amount of direction or guidance). Such experimentation would be undue to make and use the full scope of the subject matter of claim 16 and, therefore, this factor weighs in favor of non-enablement.

* * *

149. Based on my analysis of the enablement factors above, in my opinion, a POSA in 2002/2003 would not have been able to make and use the full scope of the subject matter of claim 16 based on the disclosures in the Priority Applications without undue experimentation. Thus, in my opinion, claim 16 is not enabled by either application.

150. Furthermore, if Patent Owners were to argue there was no reasonable expectation of success of formulating a pharmaceutical composition comprising a pharmaceutically acceptable carrier and therapeutically effective amount of the co-crystals disclosed in the art of Ground 1 or 2 (*infra* §§ XI-XII (Invalidity Grounds 1 and 2)), the Priority Applications would lack enablement as they do not provide any specific guidance on how to formulate any of the co-crystals disclosed or claimed into a pharmaceutical composition in a therapeutically effective amount, along with a pharmaceutically acceptable carrier.

2. The Prosecution History of the Related Almarsson Patent Further Reinforces That the Priority Applications Do Not Enable the Claimed Genus of Solvates of Co-Crystals

151. The prosecution history of the Almarsson patent demonstrates that the Priority Applications also do not enable challenged claim 16. As I already explained above, the Almarsson application, which issued as the Almarsson patent, has the same inventors as the '344 patent, plus others, and also claims priority to the Priority Applications like the '344 patent does. Ex. 1505, Almarsson, cover page at (22) (60); Ex. 1501, cover, col. 1, ll. 8-15 (claiming priority to the '956 and '768 applications). Additionally, the primary patent examiners for Almarsson were different than the primary examiner who reviewed the '344 patent and the '956 application. *Supra* § IX.A.3.b (lack of priority: written description (Almarsson patent prosecution history)).

152. Independent application claim 1 of the Almarsson application originally recited “[a] pharmaceutical co-crystal composition, comprising: an API and a co-crystal former, wherein the API is a liquid or solid at room temperature and the co-crystal former is a solid at room temperature, and wherein the API and co-crystal former are hydrogen bonded to each other.” Ex. 1523, pp. 419-38, Almarsson file history, Almarsson application at 417-36 (application claims; *see also* application claim 11 originally reciting “A co-crystal comprising an API and a co-crystal former selected from: (a) carbamazepine and saccharin; (b) carbamazepine and nicotinamide; (c) carbamazepine and trimesic acid; (d) celecoxib and nicotinamide; (e) olanzapine and nicotinamide; (f) celecoxib and 18-crown-6; (g) itraconazole and succinic acid; (h) itraconazole and fumaric acid; (i) itraconazole and tartaric acid; (j) itraconazole and malic acid; (k) itraconazole[] HCl and tartaric acid; (l) modafinil and malonic acid; (m) modafinil and benzamide; (n) modafinil and mandelic acid; (o) modafinil and glycolic acid; (p) modafinil and fumaric acid; (q) modafinil and maleic acid; (r) topiramate and 18-crown-6; (s) 5-fluorouracil and urea; (t) hydrochlorothiazide and nicotinic acid; (u) hydrochlorothiazide and 18-crown-6; (v) hydrochlorothiazide and piperazine; (w) acetaminophen and 4,4’-bipyridine; (x) phenytoin and pyridone; (y) aspirin and 4,4’-bipyridine; (z) ibuprofen and 4,4’-bipyridine; (aa) flurbiprofen and 4,4’-bipyridine; (bb) flurbiprofen and trans-1,2-bis(4-pyridyl) ethylene; (cc)

carbamazepine and p-phthalaldehyde; (dd) carbamazepine and 2,6-pyridinecarboxylic acid; (ee) carbamazepine and 5-nitroisophthalic acid; (ff) carbamazepine and 1,3,5,7-adamantane tetracarboxylic acid; or (gg) carbamazepine and benzoquinone.”). The examiner found that the Almarsson application claims were not entitled to claim benefit to earlier priority applications because those applications, which included the Priority Applications, “fail[ed] to provide adequate [] enablement” for these claims. Ex. 1523, pp. 647-48, Almarsson file history, March 30, 2007 Non-Final Office Action at 3-4. According to the examiner:

The disclosure of the prior-filed applications, including application nos. 10/378,956, 10/367,829, 10/449,307 and 10/601,092, as well as the provisional and non-provisional applications to which they claim priority, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. . . . U.S. Patent Application Serial No. 10/378,956, for example, discloses that co-crystals can comprise specific co-crystal combinations such as carbamazepine and nicotinamide, but does not disclose the general co-crystal formulations as recited in [application] claims 1-2, 9-10, and 37, and also does not disclose certain specific co-crystal combinations as recited in [application] claim 11, such as modafinil and mandelic acid. Accordingly, the [application] claims do not receive benefit of the filing dates of these prior applications or the

provisional and non-provisional application to which they claim priority.

Ex. 1523, pp. 647-48, Almarsson file history, March 30, 2007 Non-Final Office Action at 3-4 (emphases added).

153. In response to the examiner's rejection in Almarsson, the Almarsson Applicants amended independent application claim 1 to exclude certain co-crystals as follows (I understand that strikethrough text means subject matter has been removed from the claims and underlined text means that subject matter has been added):

1 (currently amended). A pharmaceutical co-crystal composition, comprising: an API and a co-crystal former, wherein:

- a) the API is a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature; ~~and wherein~~
- b) the API and co-crystal former are hydrogen bonded to each other; and
- c) specifically excluding a co-crystal selected from the group consisting of: [specific co-crystals].

Ex. 1523, pp. 718-21, Almarsson file history, October 1, 2007 Response to Office Action at 2-10. Claim 11 was amended to recite one of 24 specific co-crystals: "A co-crystal comprising an API and a co-crystal former selected from: (a) carbamazepine and saccharin; . . ." *Id.* pp. 723-24, at 7-8.

154. The Almarsson examiner maintained the lack of enablement rejection for Almarsson application claim 1, explaining that:

[T]he specification is enabled for the preparation and use of the particular pharmaceutical co-crystals as recited in [application] claim 11; however, the specification is not enabled for the preparation of all co-crystals having any API that is solid, as broadly recited in [application] claim 1. As discussed in the rejection, the state of the art regarding the formation of different crystalline forms is unpredictable due to the numerous different crystallization factors needed to be controlled to provide different crystal states. Further, the formation of crystals is usually arrived at via experimentation. The scope of [application] claim 1 is very broad and reads on any API that is solid with any crystal co-former that is solid or liquid and where the components are hydrogen bonded. As explained previously, the specification does not provide any direction or guidance as to how to go about manufacturing all of the different crystal forms that contain an API and a co-crystal former that are hydrogen bonded to one another. Accordingly, the rejection is being maintained.

Ex. 1523, pp. 744-45, Almarsson file history, December 10, 2007 Final Office Action at 2-3.

155. Based on an analysis of the enablement factors, the Almarsson examiner further explained that:

The state of the prior art: The skilled artisan would view the formation of different crystalline forms as being unpredictable due to the

numerous different crystallization factors needing to be controlled to provide different crystal states, as well as the unpredictability in predicting the different types of crystals that may exist. For example, as disclosed by Angelo Gavezzotti (“Are Crystal Structures Predictable?” by Gavezzotti, Acc. Chem. Res, 1994, Vol. 27, pages 309-314), the formation and structure of crystals are unpredictable at best (see first full paragraph, in particular.) Gavezzotti teaches that it can be unpredictable whether compounds will crystallize at all, crystal growth from solution is known to be problematic, and in general “a crystal is more readily destroyed than built” (see first full paragraph of right hand column on page 309.) Thus, Gavezzotti teaches that the production of crystals is unpredictable at best, with the particular process parameters suitable for crystallizing a compound typically not being known in advance, and thus desired crystals can generally only be arrived at via experimentation and dealing with “tough problems in the control of solidification, crystal growth, and crystal morphology, mainly due to perverse kinetic control of nucleation[”] (see first full paragraph of right hand column on page 309.)

The relative skill of those in the art: [T]he relative skill of those in the art is typically very high, i.e. experienced scientists having advanced degrees in the chemical and biochemical fields.

The predictability of the art: As discussed [], the production of crystal forms is highly unpredictable, with crystal growth from solution being problematic. (see page 309 of Gavezzotti, in particular.)

The breadth of the claims: [T]he unpredictable nature of the invention is exacerbated by the breadth of the [application] claims. The claims require co-crystal composition that has any API that is solid, in general, with any crystal co-former that is solid or liquid, in general, where the components are hydrogen bonded, as in [application] claim 1. Thus, the claims as [] presented encompass all co-crystals having any solid API and any solid or liquid co-crystal former, where the components are hydrogen bonded to one another.

The amount of direction or guidance presented: [T]he specification does not provide any direction or guidance as to how to go about manufacturing and/or finding all of the different crystal forms that contain an API and a co-crystal former and that are hydrogen bonded to one another, and that thus fall within the scope of the [application] claim. The specification generally teaches that hydrogen bonding is a dominant interaction in the formation of a co-crystal (see page 10 of specification, in particular), but does not teach how one of ordinary skill in the art would go about finding the proper crystallization process parameters, such as the proper crystallization solvent, temperature, etc, to allow for the formation of all of the co-crystals encompassed by the [application] claims, without requiring undue experimentation.

The presence or absence of working examples: The specification does not provide working examples that are sufficient to show one of ordinary skill in the art how to arrive at all of the co-crystal forms. Instead, the specification merely provides examples showing the fabrication of the particular co-crystals recited in [application] claim

11, including carbamazepine and saccharin, and topiramate and 18-crown-6 co-crystals (see Examples 1-37, in particular.) Thus, while the specification provides guidance for forming the particular co-crystals specifically disclosed in the specification and recited in [application] claim 11, the specification does not provide adequate guidance as to how one of ordinary skill in the art could prepare all other crystals containing any API and co-crystal former.

The quantity of experimentation necessary: As the specification does not provide adequate guidance to allow one of ordinary skill in the art to readily determine the manufacturing conditions required to achieve crystallization of all of API/co-crystal formers, nor to determine which combinations of API and co-crystal former would even be capable of being recovered in crystal form, it is considered that one of ordinary skill in the art would have to engage in **undue experimentation** in order to be able to fully make and use the invention to the full extent of the [application] claims. . . .

Ex. 1523, pp. 747-51, Almarsson file history, December 10, 2007 Final Office Action at 5-9 (emphases in original). Based on this analysis, the Almarsson examiner concluded that to make and use the claimed invention of application claim 1, a POSA “would have to engage in undue experimentation to make and use all of the co-crystal compositions encompassed by the instant [application] claims, with no assurance of success.” *Id.* p. 753, at 11 (italics and underlining in original).

156. The Almarsson Applicants argued in response that “the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” Ex. 1523, pp. 770-71, Almarsson file history, March 10, 2008 Response to Office Action at 5-6. After receiving an Advisory Action on March 25, 2008, the examiner again rejected the application claims for lack of enablement. Applicants then amended the pending application claims, limiting application claim 1 to co-crystals including APIs disclosed in the Examples (with no specific co-formers specified), and limiting application claim 11 to co-crystals disclosed in the Examples (where the claim specifies both the API and co-former). Ex. 1523, pp. 776-77, Almarsson file history, March 25, 2008 Advisory Action at 2; Ex. 1523, pp. 779-83, Almarsson file history, May 29, 2008 Supplemental Amendment at 2-6. These claims are reproduced above in paragraph 116 (lack of priority: written description (Almarsson patent prosecution history)).

157. The Almarsson examiner maintained the enablement rejection for application claim 1 stating: “It is not described or shown how the numerous and diverse different co-crystals could be obtained. Regarding the Enablement rejection, the specification is enabled for the preparation and use of the particular co-crystals recited in [application] claim 11 but is not enabled for the preparation of all co-crystals with the particular API’s listed and any co-crystal former.” Ex. 1523, p. 803, Almarsson file history, July 17, 2008 Advisory Action at 2.

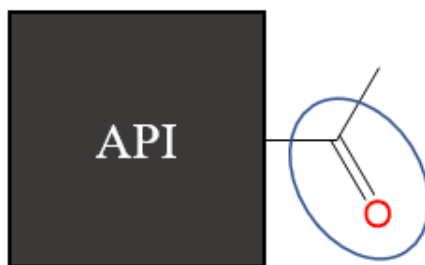
158. Subsequently, the Almarsson Applicants canceled all the application claims and filed new application claims limited to specific co-crystals disclosed in the Almarsson application Examples where both the API and co-former were specified in the claims, and new application claim 43 was identical to cancelled application claim 11. *See supra* § IX.A.3.b at ¶¶ 116-118 (lack of priority: written description (Almarsson patent prosecution history)); Ex. 1523, pp. 807-13, Almarsson file history, October 10, 2008 Amendment in Response to Advisory Action at 2-8. In response, the Almarsson examiner withdrew the enablement rejection and the claims ultimately issued as the Almarsson patent. Ex. 1523, p. 823, Almarsson file history, March 24, 2009 Non-Final Office Action at 2 (the examiner stating that “[t]he 35 USC 112, first paragraph rejections have been withdrawn as the claims and the subject matter reading on this rejection have been cancelled”).

159. Similar to the Almarsson specification, due to the unpredictability of co-crystal formation, the Priority Applications only enable a POSA to prepare and use the particular co-crystals recited in those applications (none of which falls within the scope of claim 16), not all co-crystals falling within the scope of challenged claim 16 of the '344 patent. Thus, the prosecution history of Almarsson further supports that claim 16 is not enabled by the Priority Applications.

C. API Homosynthons Wherein the First Chemical Functionality Is a Carbonyl Is Not Enabled by the Priority Applications

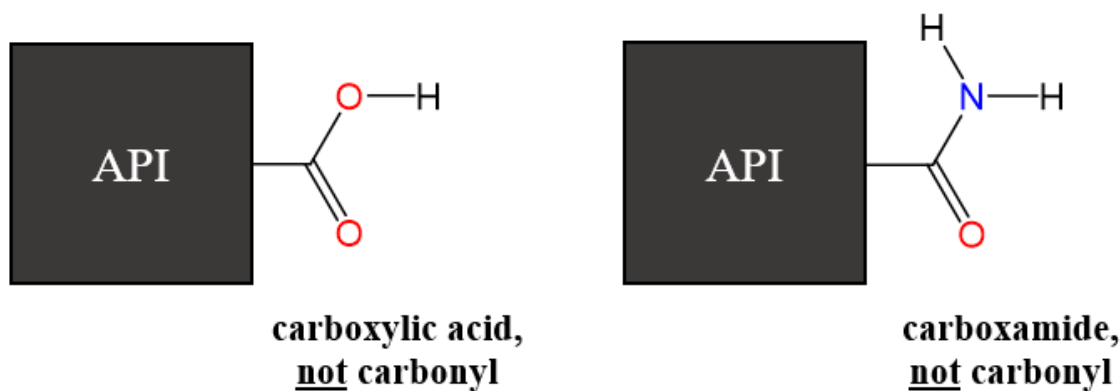
160. Claim 16 (in view of its dependency on claim 10) requires that the API (1) have “a first chemical functionality” that is “(i) a carboxamide, (ii) a carbonyl, or (iii) an amine” and (2) “permit[] formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form.” Ex. 1501, col. 25, ll. 24-27, 34-39, col. 26, ll. 12-14.

161. With respect to the “first chemical functionality” limitation, the Parties in the district court litigation agree that the term “carbonyl” in the intrinsic evidence refers only to a “-C(=O)-” group and does not refer to the -C(=O)- portion of another functional group such as carboxylic acid or carboxamide. *Supra* § VIII.A (claim construction of “carbonyl”). An example of a carbonyl group is shown circled below:



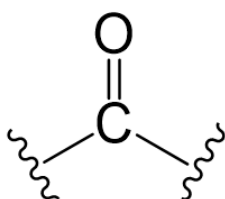
162. The Parties’ agreed-upon construction of “carbonyl” is consistent with the intrinsic evidence, which shows that the claimed first chemical functionality “carbonyl” does not cover the -C(=O)- portion of chemical functionalities that

includes -C(=O)- as part of a different, larger chemical functionality, such as a carboxylic acid or carboxamide group as shown below:

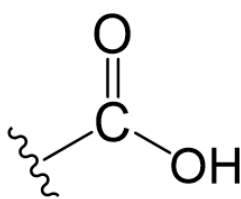


163. Specifically, to overcome a prior art rejection during prosecution, Applicants told the examiner that the patent application claims had been amended “to *exclude* supramolecular heterosynthons formed by hydrogen bonding involving a *first chemical functionality comprising a carboxylic acid*” (shown in the middle figure below in this paragraph). Ex. 1516, pp. 256-58, 261-63, ’344 patent file history, July 10, 2014 Response to Office Action at 6-8, 11-13 (emphases added). At the time, pending application claim 57 of the ’862 application (which issued as the ’344 patent) recited: “The pharmaceutical composition of claim 52, wherein *the first chemical functionality is a carbonyl*.” Ex. 1516, pp. 256-58, ’344 patent file history, July 10, 2014 Response to Office Action at 6-8 (emphasis added). When Applicants made this statement (and thereafter), the patent application claims continued to include the option of a “carbonyl” for the first chemical functionality.

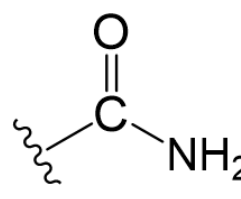
Accordingly, “carbonyl” could not have covered a carboxylic acid or carboxamide group (which includes but is not limited to a -C(=O)- group). These functional groups (carbonyl, carboxylic acid, and carboxamide) are shown side-by-side below. Applicants’ conduct during prosecution confirms that “carbonyl” as used in the patent does not cover -C(=O)- as part of a larger functional group.



carbonyl



carboxylic acid



carboxamide

164. Consistent with Applicants’ statements and submissions during prosecution, the claims of the ’344 patent separately recite and claim the carbonyl group (-C(=O)-) and the carboxamide group (-C(=O)NH₂), which comprises a -C(=O)- group, as chemical functionalities. Specifically, claims 10 (excerpt only), 18, 19, and 21 (excerpt only) recite as follows:

10. . . . wherein the first chemical functionality is (i) a *carboxamide*,
(ii) a *carbonyl*, or (iii) an amine.

18. The pharmaceutical composition of claim 10, wherein the first chemical functionality is a *carboxamide*.

19. The pharmaceutical composition of claim 10, wherein the first chemical functionality is a *carbonyl*.

21. . . . wherein the first chemical functionality and the second chemical functionality form (i) a *carbonyl:amide* hydrogen bond, (ii) a *carbonyl:amine* hydrogen bond, (iii) a *carboxylic acid:pyridine* hydrogen bond, (iv) a *carboxylic acid:aromatic amine* hydrogen bond, (v) a *carboxylic acid:carboxylic acid* hydrogen bond, (vi) a *carboxylic acid:carboxamide* hydrogen bond, (vii) a *carboxylic acid:amine* hydrogen bond, (viii) a *carboxylic acid:carbonyl* hydrogen bond, (ix) an *amine:sulfonamide* hydrogen bond, or (x) a *carbonyl:sulfonamide* hydrogen bond.

Ex. 1501, claims 10, 18, 19, 21 (emphases added). Claim 10 separately recites “carbonyl” and “carboxamide”; claim 21 separately recites “carbonyl,” “carboxamide,” and “carboxylic acid”; claim 18 separately claims the pharmaceutical composition of claim 10, where the first chemical functionality is a “carboxamide”; and claim 19 separately claims the pharmaceutical composition of claim 10, where the first chemical functionality is a “carbonyl.” If “carbonyl” covered a carboxamide group or carboxylic acid group (which include but are not limited to -C(=O)-), in claim 10 or claim 21, respectively, then there would have been no need to separately recite “carboxamide” or “carboxylic acid” in those claims. For a similar reason, a functional group such as an ester (having the

chemical formula -C(=O)-O-) would also not be considered a carbonyl under the Parties' agreed-upon construction because the -C(=O)- portion of the ester is part of the larger functional group.

165. With respect to the API homosynthon limitation, the Parties in the district court litigation agree that the term "API homosynthons" means "synthons formed between identical and complementary chemical functionalities of the API." *See* § VIII.A (claim construction of "API homosynthons"). As I explain below, a carbonyl cannot form API homosynthons.

166. During prosecution of the '956 application, to overcome a prior art reference authored by one of the inventors of the '344 patent, Applicants explained that a chemical functionality must have *both* a hydrogen bond donor and a hydrogen bond acceptor to be capable of forming a homosynthon:

The office action states that Zaworotko [the '365 patent], entitled "Substituted Diazaanthracene Compounds having Pharmaceutical Utility" teaches co-crystal formation between a diazaanthracene, the active pharmaceutical ingredient (API) 1,8-DAA-3[,]6-(Me)₂, and a co-crystal former, fumaric acid. This composition found in example 9 of Zaworotko *does not teach an API that has a first supramolecular synthon comprising a hydrogen bond, as recited in amended [application] claim 25, as the API has no hydrogen bond donor.* Homosynthons are disclosed, for example in paragraph [0009], page 4 of the specification with examples thereof given in Examples 1-19 and

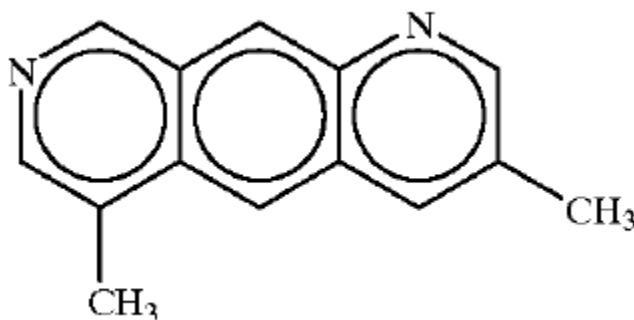
Figures 4A, 5A, 6C, 7B, 8B, 10A, 14A, 15A, 16A, 17A, 18A, 19A, 20A, 21A, 22A, and 23A. These *homosynt[h]on functionalities are those that contain hydrogen bond donors and hydrogen bond acceptors, as would be appreciated upon inspection by those skilled in the art. The ability to form a homosynthon is lacking in 1,8-DAA-3[,]6-(Me)₂, which although possessing a pair of hydrogen [bond] acceptors, lacks any hydrogen bond donors.*

Ex. 1517, p. 3464, '956 application file history, October 22, 2010 Response to Office Action, at 8 (emphases added); *see also* Ex. 1515, '956 application, ¶ [0009].

167. Similar to the diazaanthracene discussed during prosecution (structure shown below in this paragraph, *see* Ex. 1558, '365 patent, col. 5, ll. 53-65), which includes only carbon-carbon, carbon-hydrogen, and carbon-nitrogen bonds, a carbonyl lacks a hydrogen bond donor and can only accept a hydrogen bond.²¹

²¹ *See, e.g.,* Ex. 1576, Palleros 2000 at 22-23 (“[N]ot all H-bond acceptors are donors. For example, there are molecules with oxygen or nitrogen but without O-H and N-H bonds such as aldehydes, ketones, ethers, esters, nitrocompounds, and so on, which can accept H-bonds but cannot donate them. Hydrogens attached to carbon do not participate in H-bonds.”); Ex. 1577, Olmsted 1997 at 489 (“A hydrogen-bond

Thus, applying Applicants' own reasoning, like 1,8-DAA-3,6-(Me)₂, a carbonyl does not have the capability of forming homosynthons.



168. For these reasons, a POSA as of 2002/2003 would have understood that an API having a first chemical functionality that is a carbonyl that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form is an inoperable claim limitation. Thus, all embodiments in the Priority Applications where the first chemical functionality is a carbonyl are inoperable. Because one of the three chemical functionalities of the API is inoperable, a POSA would not have been able to make and use the full scope of the purported invention of claim 16 based on the teachings in the Priority Applications and therefore, claim 16 is not enabled by the Priority Applications.

* * *

donor must have a hydrogen atom bonded to F, O, or N, and a hydrogen-bond acceptor is an electronegative atom with a lone pair of electrons.”).

169. For the reasons above, it is my opinion that claim 16 is not enabled by the Priority Applications and therefore, claim 16 is not entitled to a priority date of 2002/2003. Therefore, I understand that the earliest priority date that challenged claim 16 is entitled to is February 13, 2014, the filing date of the '862 application (which issued as the '344 patent).

X. OVERVIEW OF THE STATE OF THE ART

170. Claim 16 is directed to a pharmaceutical composition comprising a co-crystal comprising supramolecular synthons formed via non-covalent hydrogen bonding between at least one API and co-former where the first chemical functionality of the API is a carboxamide, a carbonyl, or an amine and where the supramolecular synthons are linked by non-covalent bonding to one another by one or more solvent molecules. Ex. 1501, claim 16. But co-crystals falling within the scope of claim 16 were already known in the art by 2014 and preparing the claimed pharmaceutical compositions comprising such co-crystals would have been obvious as of this date. *See infra* §§ XI-XII (Invalidity Grounds 1 and 2). Further, to the extent Patent Owners argue that the '344 patent discloses the subject matter of claim 16, those same disclosures were published in the '006 Publication, which was publicly available as of its publication date of December 4, 2003. Ex. 1509, '006 Publication, at cover.

171. Moreover, as of 2014, a POSA would have known how to formulate a co-crystal into a pharmaceutical composition, and pharmaceutical compositions including a co-crystal had been prepared. *See, e.g.*, Ex. 1504, Hickey 2007, Ex. 1505, Almarsson; Ex. 1510, Remington 2012 at 581-610; Ex. 1509, the '006 Publication at 5-6; Ex. 1503, Appel Declaration ¶¶ 34-44. Pharmaceutical compositions comprising a therapeutically effective amount of a co-crystal were commercially available by 2014. For example, the commercial products Coumadin[®], Vibramycin[®], and Amoxil[®], each contained a therapeutically effective amount of a co-crystal as Patent Owners have defined the term “co-crystal.” *Supra* § VIII.B (claim construction of “co-crystal”). Specifically:

- Coumadin[®] is a co-crystal of warfarin sodium and was FDA approved as an anticoagulant. Ex. 1535, Physicians’ Desk Reference 2004 at 1048-52; *see id.* at 1048 (“Crystalline warfarin sodium is an isopropanol clathrate.”); Ex. 1537, October 2011 Coumadin[®] Label at 1;
- Vibramycin[®] Hyclate is a co-crystal of doxycycline hyclate and was FDA approved as an antibacterial to treat a variety of infections. Ex. 1535, Physicians’ Desk Reference 2004 at 2665-68; Ex. 1538, January 2023 Vibramycin[®] Label 4-5;
- Amoxil[®] is a co-crystal of amoxicillin trihydrate and was FDA approved as an antibacterial to treat infections. Ex. 1535, Physicians’ Desk Reference 2004 at 1427-31; Ex. 1539, September

2015 Amoxil® Label at 1; Ex. 1536, Hilton 1993 at Abstract (“A controlled-release tablet of amoxicillin trihydrate was developed...”).

172. The Appel Declaration provides further background on the state of the art of formulating pharmaceutical compositions containing co-crystals as of 2014. Ex. 1503, Appel Declaration ¶¶ 45-56.

XI. INVALIDITY GROUND 1: CHALLENGED CLAIM 16 IS OBVIOUS OVER UETO 2012 IN VIEW OF LI 2011, MARTINDALE 2011, THE '006 PUBLICATION, AND REMINGTON 2012

173. As challenged claim 16 is not entitled to a priority date before 2014, it is my opinion that claim 16 is obvious over Ueto 2012 in view of Li 2011, Martindale 2011, the '006 Publication, and Remington 2012.

A. Overview of Ueto 2012

174. Ueto 2012, titled “Polymorphs and a Hydrate of Furosemide–Nicotinamide 1:1 Cocrystal” and published in *Crystal Growth & Design*, investigates pharmaceutical co-crystals and discloses a co-crystal of furosemide (“FS”), nicotinamide (“NCT”), and water having a stoichiometric molar ratio of 1:1:2. Ex. 1507, Ueto 2012 at 485-93; 490 (“The asymmetric unit of the hydrate consists of one FS molecule, one NCT molecule, and two water molecules.”).

175. Ueto 2012 discloses that furosemide is a “loop diuretic drug.” Ex. 1507, Ueto 2012 at 486. A POSA would have recognized that nicotinamide is a water-soluble form of vitamin B (*see infra* § XI.C, overview of Martindale 2011) and that water is a solvent. Ex. 1572, Housecroft 2012 at UM00005304 (listing water as a solvent); Ex. 1573, Huheey 1993 at UM00005308 (same).

B. Overview of Li 2011

176. Li 2011, titled “New polymorphs of isonicotinamide and nicotinamide,” published in *Chemical Communications*, discloses the single crystal structure of nicotinamide, including images from its single crystal structure. Ex. 1508, Li 2001 at 1531 (Figure 6, Nic2 (right)).

177. Li 2011 discloses homosynthons of nicotinamide. Specifically, when in its pure form, the carboxamide of nicotinamide interacts with an identical carboxamide on an adjacent molecule of nicotinamide through non-covalent hydrogen bonding, forming an API homosynthon. Ex. 1508, Li 2011 at 1531; *supra* § VIII.A (claim construction of “API homosynthons”).

C. Overview of Martindale 2011

178. Martindale 2011, titled “The Complete Drug Reference,” is a drug reference that provides up-to-date information on drugs and other compounds used throughout the world, such as their nomenclature, pharmaceutical information,

pharmacological and therapeutic indications, and dose information. Ex. 1506, Martindale 2011 at Preface v-vi.

179. Martindale 2011 discloses that nicotinamide is vitamin B and is used in the treatment and prevention of nicotinic acid deficiency and that it is commonly found in foods such as yeast, meat, fish, potatoes, legumes, and cereals. Ex. 1506, Martindale 2011 at 2117-19. Nicotinamide is given orally at “[d]oses of up to 500 mg daily.” *Id.* at 2119.

180. Martindale 2011 also discloses that furosemide, which exists in pure form as a “crystalline powder” and is “[p]ractically insoluble in water,” is used to treat hypertension. Ex. 1506, Martindale 2011 at 1421-25. In the treatment of hypertension, furosemide is given orally at doses of 40 to 80 mg daily. Ex. 1506, Martindale 2011 at 1423.

D. Overview of the '006 Publication

181. The '956 application published as U.S. Patent Publication No. 2003/0224006 (“the '006 Publication”) on December 4, 2003. Ex. 1509, the '006 Publication, at cover. The '006 Publication discloses the same nineteen co-crystal Examples provided in the '956 application and further provides that formulating multiple-component phase compositions of the invention (*e.g.*, co-crystals) with a pharmaceutically acceptable carrier can be done using known methods, stating that “[f]ormulations are described in a number of sources which are well known and

readily available to those skilled in the art,” such as Remington 1995. Ex. 1509, the ’006 Publication, ¶¶ [0051], [0058]-[0179].

E. Overview of Remington 2012

182. Remington 2012 is a reference on “all aspects of pharmaceuticals, from the scientific fundamentals to the dosage forms and drug delivery systems to drug product analyses.” Ex. 1510, Remington 2012 at Preface vii; *see also* Ex. 1503, Appel Declaration ¶¶ 21, 55.

183. Remington 2012 teaches methods for formulating pharmaceutical compositions comprising a pharmaceutically acceptable carrier and one or more active pharmaceutical ingredients. Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10; *see also* Ex. 1501, col. 10, ll. 6-21, which cites an earlier version of Remington 2012 (*i.e.*, Remington 1995):

The multiple-component phase compositions can be formulated according to known methods for preparing pharmaceutically useful compositions. . . . 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 Pa., Mack Publishing Company, 19th ed.) [] describes formulations that can be used in connection with the subject invention.

F. Obviousness of Claim 16 – Element by Element Claim Analysis

184. Claim 16 depends from claim 10 and, therefore, incorporates all the features and limitations of claim 10. I have broken down claim 10 of the '344 patent into the following claim elements:

[10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of

[10b]: a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former

[10c]: 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

[10d]: wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding

[10e]: wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form

[10f]: wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former

[10g]: wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.

185. Dependent claim 16 recites:

[16a]: The pharmaceutical composition of claim 10,

[16b]: wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.

186. For the reasons below, claim 16 of the '344 patent is obvious over Ueto 2012 in view of Li 2011, Martindale 2011, the '006 Publication, and Remington 2012. For the purpose of simplifying my analysis, I discuss element [10a] last.

1. **[10b]: a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former**

187. Ueto 2012 in combination with Martindale 2011 teaches “a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former.”

188. As I explained in the claim construction section of this declaration, Petitioner’s counsel has asked me to adopt the Patent Owners’ proposed construction of “co-crystal,” which is “a multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.” *Supra* § VIII.B (claim construction of “co-crystal”).

189. Ueto 2012 discloses a co-crystal comprising furosemide (“FS”), nicotinamide (“NCT”), and water having a fixed stoichiometric molar ratio of 1:1:2, meaning that there is one molecule of furosemide for every molecule of nicotinamide and two molecules of water. Ex. 1507, Ueto 2012 at 485-93, 490

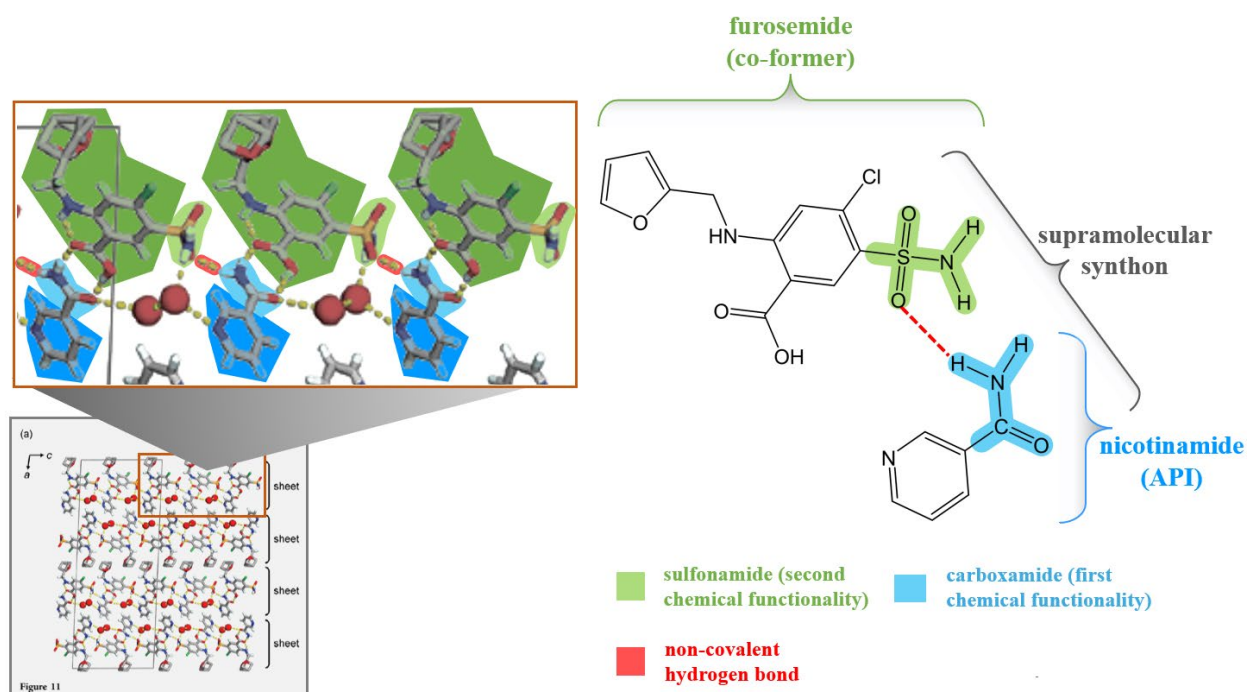
(“The asymmetric unit of the hydrate consists of one FS molecule, one NCT molecule, and two water molecules.”). Moreover, the co-crystal was analyzed using single crystal X-ray diffraction. *Id.* at 485-93. Single crystal data indicates that the co-crystal is in a single crystalline phase because a single crystal analysis cannot be done unless the co-crystal is in a single crystalline phase. Thus, the furosemide, nicotinamide, and water co-crystal qualifies as a co-crystal under Patent Owners’ proposed construction because it is “a multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.”

190. Martindale 2011 discloses that nicotinamide is vitamin B and is used in the treatment and prevention of nicotinic acid deficiency, Ex. 1506, Martindale 2011 at 2117-19, which a POSA would have understood to mean that nicotinamide is an “API” as that term is defined in the ’344 patent, *i.e.*, it is a “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.” *Supra* § VIII.A (claim construction of “API”); Ex. 1501, col. 9, ll. 27-34.

191. Ueto 2012 discloses that furosemide is a “loop diuretic drug.” Ex. 1507, Ueto 2012 at 486. The ’344 patent explains that the co-former can be a “drug molecule.” Ex. 1501, col. 3, ll. 35-37; col. 8, ll. 35-37 (same). This pharmaceutical use is confirmed by Martindale 2011 which discloses that furosemide is used to treat hypertension. Ex. 1506, Martindale 2011 at 1423. Further, Ueto 2012

discloses that the second chemical functionality of furosemide is complementary to, and forms a co-crystal with, the first chemical functionality of nicotinamide (*infra* § XI.F.3, claim element [10d]). Thus, a POSA would have understood that furosemide qualifies as a “co-former” according to the ’344 patent.

192. An image from the single crystal structure of the 1:1:2 furosemide, nicotinamide, and water co-crystal is shown in Figure 11(a) of Ueto 2012. Ex. 1507, Ueto 2012 at 492. I have annotated the figure to point out certain aspects of the co-crystal that are relevant to my analysis of claim 16.



193. Nicotinamide, the “API” according to the ’344 patent, has a first chemical functionality that is a carboxamide (shaded light blue), which the Parties agree covers “-C(=O)NH₂.” *Supra* § VIII.A (claim construction of

“carboxamide”). Furosemide, which meets the requirements of a “co-former” according to the ’344 patent, has a second chemical functionality that is a sulfonamide (shaded light green).

194. The carboxamide of nicotinamide and the sulfonamide of furosemide interact via non-covalent hydrogen bonding (shown by the dashed line shaded red), forming a supramolecular synthon (shown by the gray bracket on the far right side of the figure). The term “supramolecular synthon” is defined in the ’344 patent as “the sum of the components of a multiple-component non-covalent interaction, wherein the non-covalent interaction contributes to the formation of a discrete supramolecular entity or polymeric structure, wherein each component is a chemical functionality.” Ex. 1501, col. 9, l. 66 – col. 10, l. 4. In other words, as applied to the co-crystal in Ueto, this claim term refers only to the first chemical functionality of the “API” (here, the carboxamide of nicotinamide), the second chemical functionality of the “co-former” (here, the sulfonamide of furosemide), and the non-covalent bonds between them (here, a non-covalent hydrogen bond). *See supra* § VIII.A (claim construction of “supramolecular synthon”); *see also* Ex. 1501, col. 3, ll. 37-59, col. 9, l. 43 – col. 10, l. 5. Thus, the furosemide, nicotinamide, and water co-crystal taught in Ueto 2012 comprises supramolecular synthons.

195. Consistent with Figure 11(a), Ueto 2012 explains that the supramolecular synthon formed between the carboxamide (referred to as “amide” in Ueto 2012) first chemical functionality of the “API” and the sulfonamide second chemical functionality of the “co-former” forms as follows: “The FS and the NCT molecules form a pair sustained by carboxylic acid···amide hydrogen bonds (synthon E). *The pairs align parallel to the c-axis and form corrugated sheets stabilized by sulfonamide···amide hydrogen bonds (synthon D).*” (emphasis added). Ex. 1507, Ueto 2012 at 490.

196. For these reasons, the co-crystal in Ueto 2012 meets element [10b].

2. [10c]: wherein the API has a first chemical functionality that permits formation of API homosynths through non-covalent hydrogen bonding when the API is in its pure form

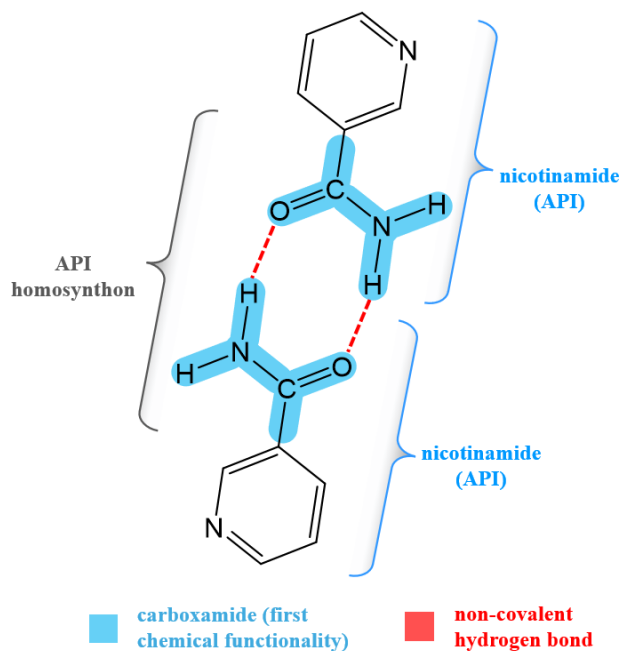
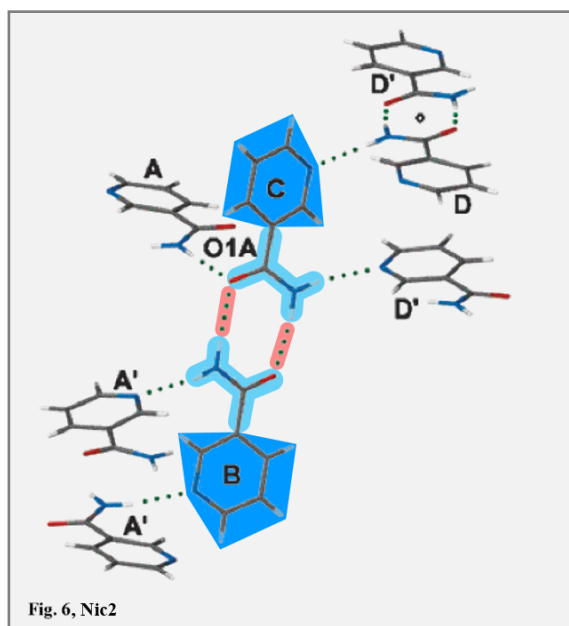
197. By disclosing nicotinamide, which has a carboxamide first chemical functionality (*see* Ex. 1507, Ueto 2012 at 485) and which forms API homosynths in its pure form, Ueto 2012 inherently discloses “wherein the API has a first chemical functionality that permits formation of API homosynths through non-covalent hydrogen bonding when the API is in its pure form” (and Li 2011 expressly discloses this claim element).

198. The Parties in the district court litigation agree that “API homosynths” means “synths formed between identical and complementary

chemical functionalities of the API.” *Supra* § VIII.A (claim construction of “API homosynthons”).

199. Nicotinamide has a first chemical functionality that is a carboxamide, Ex. 1507, Ueto 2012 at 485, which the Parties agree covers “-C(=O)NH₂.” *Supra* § VIII.A (claim construction of “carboxamide”). When nicotinamide is in its pure form (thus outside the context of the co-crystal), the carboxamide of nicotinamide interacts with an identical carboxamide on an adjacent molecule of nicotinamide through non-covalent hydrogen bonding, forming an API homosynthon.

200. Whether or not an API forms homosynthons in its pure form is a property of that API. In its pure form, nicotinamide forms API homosynthons, as demonstrated by Li 2011. Specifically, Figure 6 of Li 2011 depicts an image of the single crystal structure of nicotinamide alone, *i.e.*, in its pure form. Ex. 1508, Li 2011 at 1531 (Figure 6, Nic2 (right)). I have annotated Figure 6, Nic2 in this paragraph to point out the carboxamides (shaded in light blue) of nicotinamide in two adjacent molecules and the non-covalent hydrogen bond interactions between them (shown by the dashed lines shaded red), forming an API homosynthon (shown by the gray bracket). Ex. 1508, Li 2011 at 1531.



201. Thus, by disclosing nicotinamide, Ueto 2012 inherently discloses that nicotinamide has a first chemical functionality (carboxamide) that “permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,” meeting element [10c]. Further, Li 2011 expressly discloses this claim element.

3. [10d]: wherein the co-former has a second chemical functionality compl[e]mentary to the first chemical functionality via non-covalent hydrogen bonding

202. Ueto 2012 discloses “wherein the co-former has a second chemical functionality compl[e]mentary to the first chemical functionality via non-covalent hydrogen bonding.”

203. The second chemical functionality of furosemide interacts with the first chemical functionality of nicotinamide to form a co-crystal and, therefore, the second chemical functionality of furosemide is complementary to the first chemical functionality of nicotinamide via non-covalent hydrogen bonding. Specifically, as shown in annotated Figure 11(a) from Ueto 2012 (in paragraph 192 above, claim element [10b]), the 1:1:2 furosemide, nicotinamide, and water co-crystal has (i) an “API” (nicotinamide) that has a first chemical functionality (a carboxamide, shaded light blue), and (ii) a “co-former” (furosemide) that has a second chemical functionality (a sulfonamide, shaded light green). Ex. 1507, Ueto 2012 at 492. The sulfonamide of furosemide interacts with the carboxamide of nicotinamide via non-covalent hydrogen bonding, forming a supramolecular synthon. Ex. 1507, Ueto 2012 at 490 (“The FS and the NCT molecules form a pair sustained by carboxylic acid···amide hydrogen bonds (synthon E). *The pairs align parallel to the c-axis and form corrugated sheets stabilized by sulfonamide···amide hydrogen bonds (synthon D).*” (emphasis added)); see also Ex. 1507, Ueto 2012 at 486 (disclosing that furosemide “has suitable hydrogen bonding [groups] for crystallization such as carboxyl and *sulfonamide* groups”) (emphasis added). As a result of this non-covalent hydrogen bonding interaction, a POSA would have understood that the furosemide, nicotinamide, and water co-crystal taught in Ueto 2012 meets element [10d].

4. [10e]: wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form

204. By disclosing furosemide, Ueto 2012 inherently discloses “wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form” (and Martindale 2011 expressly discloses this claim element).

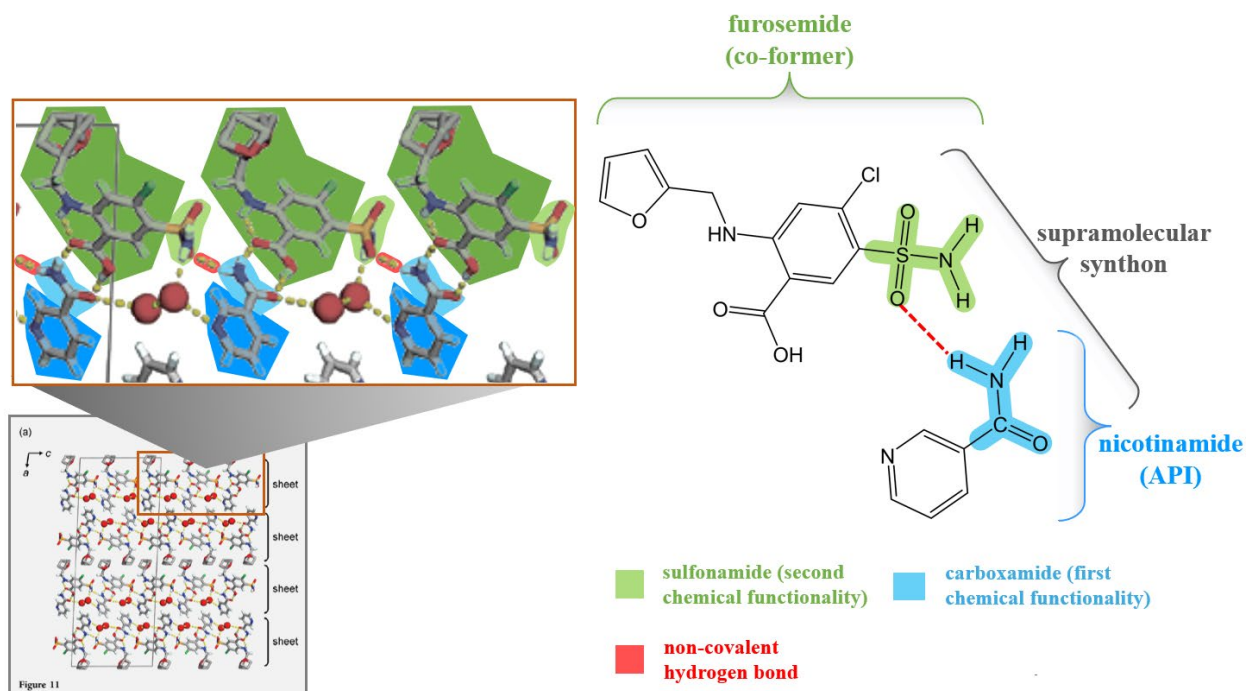
205. Martindale 2011 describes furosemide alone, *i.e.*, in pure form, as a “crystalline powder,” Ex. 1506, Martindale 2011 at 1421, which a POSA would have understood to mean that furosemide is a solid at room temperature and atmospheric pressure when in pure form. *See also* Ex. 1579, 2006 Merck Index at 740 (entry 4309) (disclosing that the melting point of furosemide alone (*i.e.*, when in pure form) is 206 °C, which is above room temperature, which a POSA would have understood to mean that furosemide is a solid at room temperature and atmospheric pressure).

206. Therefore, the furosemide, nicotinamide, and water co-crystal taught in Ueto 2012 inherently meets element [10e] (which is expressly confirmed by Martindale 2011 and the 2006 Merck Index).

5. [10f]: wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former

207. Ueto 2012 discloses “wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.”

208. Figure 11(a) from Ueto 2012 (in paragraph 192 above, claim element [10b]), which I reproduce again in this paragraph, shows that the 1:1:2 furosemide, nicotinamide, and water co-crystal has (i) an “API” (nicotinamide) that has a first chemical functionality (carboxamide, shaded light blue) and (ii) a “co-former” (furosemide) that has a second chemical functionality (sulfonamide, shaded light green). Ex. 1507, Ueto 2012 at 492. The carboxamide of nicotinamide and the sulfonamide of furosemide interact via non-covalent hydrogen bonding, which is shown by the dashed line shaded red, Ex. 1507, Ueto 2012 at 492, resulting in the formation of a supramolecular synthon, *i.e.*, the carboxamide and sulfonamide chemical functionalities and the non-covalent hydrogen bond interaction between them. *See supra* § VIII.A (claim construction of “supramolecular synthon”); *see also* Ex. 1501, col. 3, ll. 37-59, col. 9, l. 43 – col. 10, l. 5 (defining the term “supramolecular synthon”).



209. Consistent with Figure 11(a), Ueto 2012 explains that “[t]he FS [furosemide] and the NCT [nicotinamide] molecules form a pair sustained by carboxylic acid⋯amide hydrogen bonds (synthon E). *The pairs align parallel to the c-axis and form corrugated sheets stabilized by sulfonamide⋯amide hydrogen bonds (synthon D).*” (emphasis added). Ex. 1507, Ueto 2012 at 490; *see also* 486 (disclosing that furosemide “has suitable hydrogen bonding [groups] for crystallization such as carboxyl and *sulfonamide* groups”) (emphasis added).

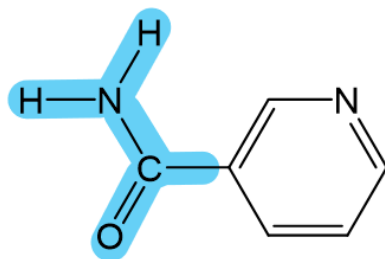
210. Therefore, the furosemide, nicotinamide, and water co-crystal taught in Ueto 2012 meets element [10f].

6. [10g]: wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine

211. Ueto 2012 discloses “wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.”

212. Nicotinamide (its chemical structure is shown below in this paragraph), the “API” in the 1:1:2 furosemide, nicotinamide, and water co-crystal taught in Ueto 2012, has a first chemical functionality that is a carboxamide (shaded light blue), which the Parties agree covers “-C(=O)NH₂,” meeting element [10g]. Ex. 1507, Ueto 2012 at 485; *see also id.* Figure 11(a); *supra* § VIII.A (claim construction of “carboxamide”).

nicotinamide (API)



7. [16b]: wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule

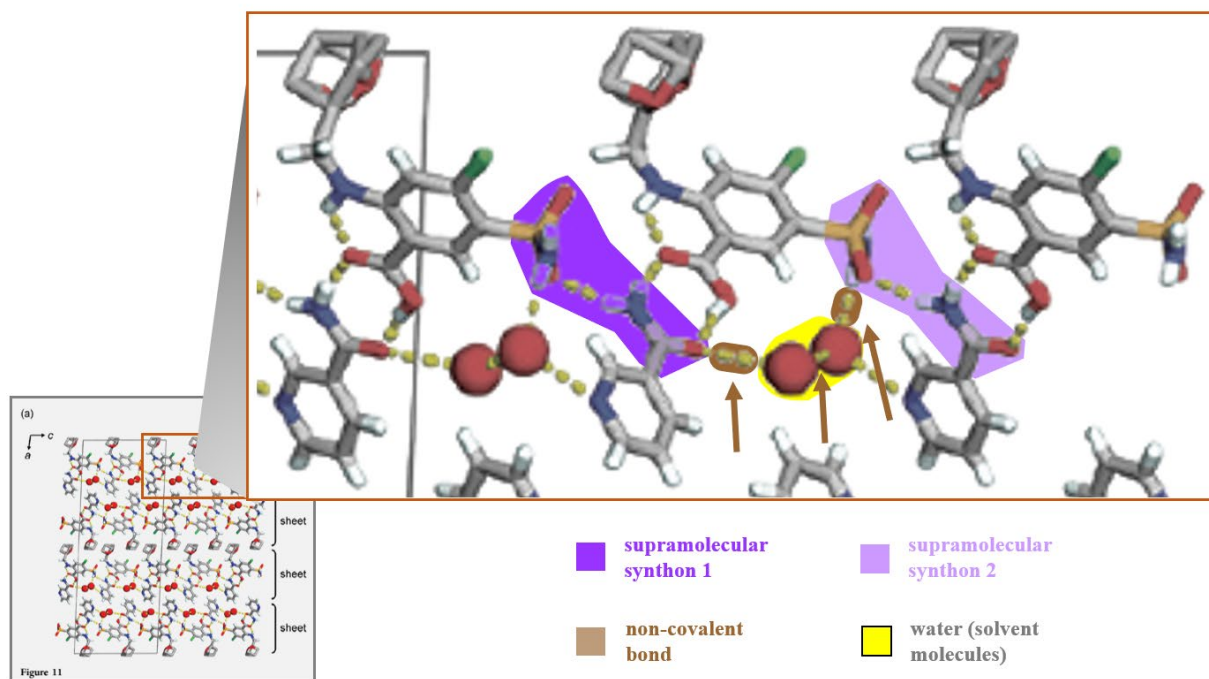
213. Ueto 2012 discloses “wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.”

214. The Parties in the district court litigation agree that limitation [16b] means “wherein one or more solvent molecules are non-covalently bonded to two

or more supramolecular synthons, linking the supramolecular synthons to one another.” *Supra* § VIII.A (claim construction of claim element [16b]). A POSA would have understood water to be a solvent. Ex. 1572, Housecroft 2012 at UM00005304 (listing water as a solvent); Ex. 1573, Huheey 1993 at UM00005308 (same). Simplified examples of solvates of co-crystals that meet this limitation are shown in paragraphs 30, 49, and 70 above.

215. Ueto 2012 discloses a 1:1:2 furosemide, nicotinamide, and water co-crystal where nicotinamide is the “API,” furosemide is the “co-former,” and water is the solvent. Ex. 1507, Ueto 2012 at 485-93. Nicotinamide has a first chemical functionality that is a carboxamide, and furosemide has a second chemical functionality that is a sulfonamide. The carboxamide of nicotinamide interacts with the sulfonamide of furosemide via non-covalent hydrogen bonding. This interaction forms supramolecular synthons. *Supra* § XI.F.5 (claim element [10f]).

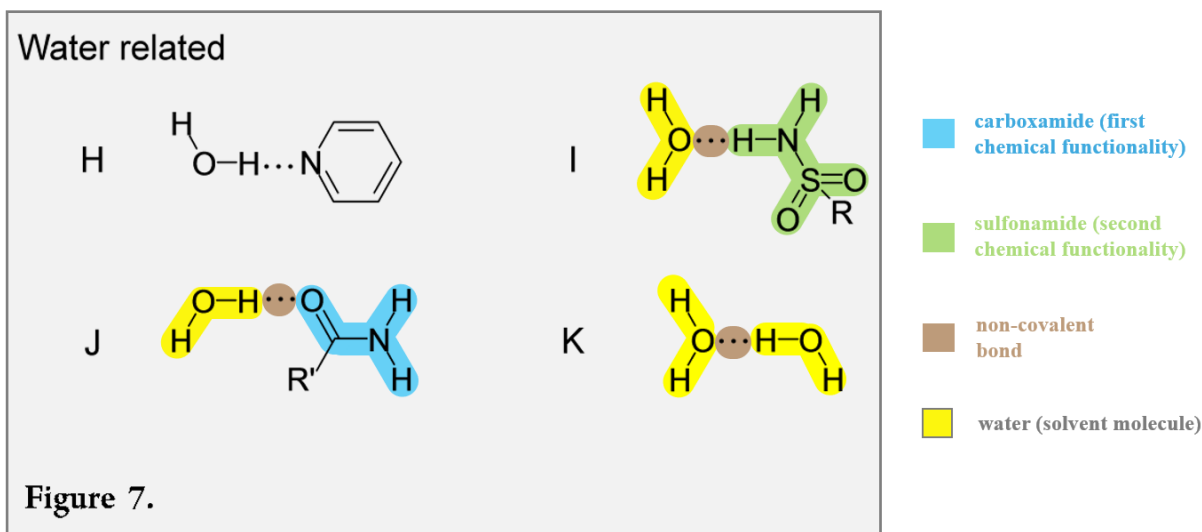
216. The supramolecular synthons formed by a non-covalent hydrogen bond between the carboxamide of nicotinamide and the sulfonamide of furosemide are non-covalently bonded to one another by non-covalent (hydrogen) bonding to water (solvent) molecules. This is shown in Figure 11(a) from Ueto 2012 which I annotate in this paragraph.



217. Specifically, two water molecules (red circles, shaded yellow) interact via non-covalent hydrogen bonding which is shown by the brown arrow in the middle. These water molecules link via non-covalent hydrogen bonding (shaded brown and identified with arrows), one supramolecular synthon (on the left, shaded dark purple) to an adjacent supramolecular synthon (on the right, shaded light purple). Ex. 1507, Ueto at 491-92.

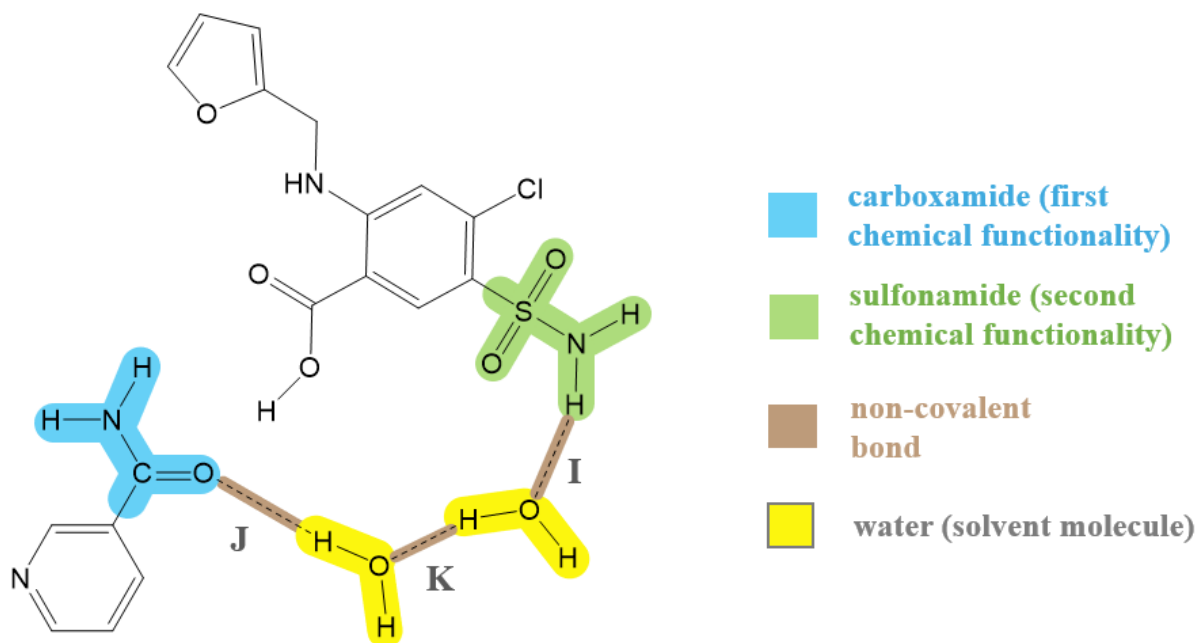
218. Consistent with Figure 11(a), Ueto 2012 states that “[t]he two water molecules bind to each other by hydrogen bonding (synthon K) and link to the sulfonamide of one FS [furosemide] and to the pyridine and the amide of one NCT [nicotinamide] molecule by hydrogen bonding (synthon H, I, J), shown in Figure 11c.” (emphases added). Ex. 1507, Ueto 2012 at 491. Synthons H, I, J, and K are

depicted in Figure 7 of Ueto 2012. I annotated synthons I and J of Figure 7 below in this paragraph to show how the first and second chemical functionalities interact with water molecules, and synthon K to show how the water molecules interact with one another. Ex. 1507, Ueto 2012 at 490-91.

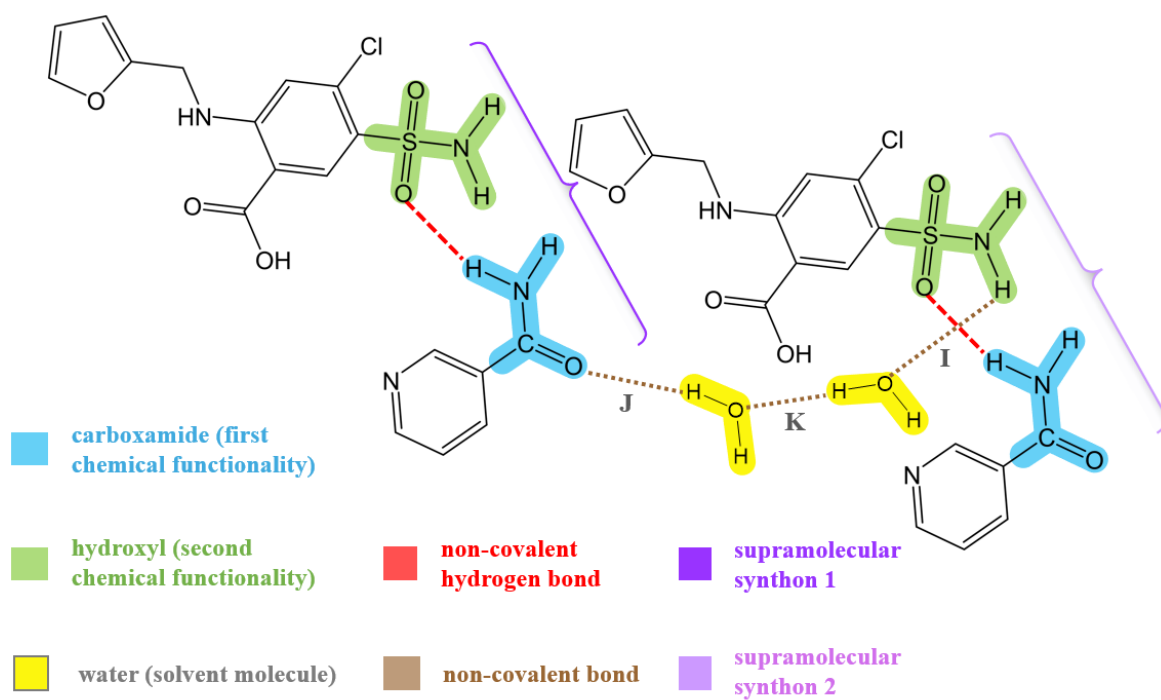


Synthon I shows the non-covalent hydrogen bond interaction (shaded brown) between the sulfonamide of furosemide (shaded light green) of one supramolecular synthon to a molecule of water (shaded yellow). Synthon J shows the non-covalent hydrogen bond interaction (shaded brown) between the carboxamide of nicotinamide (shaded light blue) of a second supramolecular synthon to a molecule of water (shaded yellow). Synthons I and J are linked by synthon K, which consists of two water molecules (shaded yellow) bonded to each other by non-covalent hydrogen bonding (shaded brown). Ex. 1507, Ueto 2012 at 490-91.

219. A simplified figure showing how synthons I, J, and K are connected in the co-crystal is shown below in this paragraph. Synthons I, J, and K are each labeled under the non-covalent bond forming the synthon.



220. I also provide a simplified figure below in this paragraph illustrating how the furosemide, nicotinamide, and water co-crystal in Ueto 2012 meets the limitations of element [16b].



221. As shown in the figure in paragraph 220, each supramolecular synthon (supramolecular synthon 1, shown by a dark purple bracket, and supramolecular synthon 2, shown by a light purple bracket) is formed by the first chemical functionality of the “API” (the carboxamide of nicotinamide, shaded light blue), the second chemical functionality of the “co-former” (the sulfonamide of furosemide, shaded light green), and the non-covalent hydrogen bond between them (shown by the red dashed line). *Supra* § VIII.A (claim construction of “supramolecular synthon”).

222. As also shown in paragraph 220, the solvent molecules (water, shaded yellow) are non-covalently (hydrogen) bonded to one another (shown with

the brown dashed line between the two water molecules) to form synthon K. The water molecules link the two supramolecular synthons to one another by forming non-covalent (hydrogen) bonds with the second chemical functionality of the “co-former” (synthon I) and the first chemical functionality of the “API” (synthon J), which are depicted by the brown dashed lines. *Supra* § VIII.A (claim construction of claim element [16b]); Ex. 1507, Ueto 2012 at 490-91.

223. For these reasons, the furosemide, nicotinamide, and water co-crystal disclosed in Ueto 2012 meets element [16b].

8. [10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [a co-crystal]

224. Ueto 2012 in combination with Martindale 2011, the '006 Publication, and Remington 2012 teaches “wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.”

225. Ueto 2012 discloses a 1:1:2 furosemide, nicotinamide, and water co-crystal. Ex. 1507, Ueto 2012 at 485-93.

226. Martindale 2011 discloses that nicotinamide is vitamin B and can be used safely at daily doses of up to 500 mg to treat vitamin B deficiency. Ex. 1506, Martindale 2011 at 2117-19. Although nicotinamide satisfies the “API” element of claim 16 of the '344 patent, nicotinamide is commonly used as an additive in pharmaceutical compositions, *see* Ex. 1509, '006 Publication, ¶ [0040], Example 8

(indicating that nicotinamide is a “GRA[S]” compound); Ex. 1531, 21 C.F.R. § 184.1535 (2000) (same); Ex. 1511, ’408 Application at 1-2 (disclosing that nicotinamide is a water-soluble B3 vitamin that “is on the list of compounds approved for safe use as additives to food products” and, because of this, it “is widely used in the co-crystallization of pharmaceutical preparations and dietary supplements”); Ex. 1507, Ueto 2012 at 486 (referring to nicotinamide as a pharmaceutically acceptable co-former), and is present in various foods, such as yeast, meat, fish, potatoes, legumes, and cereals, Ex. 1506, Martindale 2011 at 2118-19.

227. Ueto 2012 and Martindale 2011 both disclose that furosemide is a drug molecule. Ex. 1507, Ueto 2012 at 486 (disclosing that furosemide is a “loop diuretic drug”); Ex. 1506, Martindale 2011 at 1423 (disclosing that furosemide is used to treat hypertension). Martindale 2011 further discloses amounts of furosemide that are therapeutically effective to treat hypertension (*i.e.*, 40 to 80 mg daily of furosemide). Ex. 1506, Martindale 2011 at 1423.

228. The ’344 patent does not require that the therapeutically effective amount of the co-crystal in claim 16 for any given indication be based in whole or in part on the therapeutic activity of the component of the co-crystal that satisfies the “API” claim element (here, nicotinamide) when the “co-former” itself (here, furosemide) has therapeutic activity for a particular indication (here, furosemide

has therapeutic activity to treat hypertension) and the co-crystal component meeting the '344 patent's "API" definition does not have therapeutic activity for that indication.

229. I understand based on my own education and experience and with the knowledge described in the Appel Declaration that a POSA as of 2014 would have known how to formulate, and would have been capable of formulating, pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a multiple-component crystal, such as the one taught in Ueto 2012, using formulations and methods that were readily available and well known in the art such as those described in Remington 2012. *See* Ex. 1503, Appel Declaration ¶¶ 45-66; Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10. The POSA would have looked to references like Martindale 2011 for guidance in determining the therapeutically effective amount of the co-crystal to formulate into a pharmaceutical composition and would have incorporated into the co-crystal an amount of furosemide sufficient to have a therapeutic effect in hypertensive patients (*i.e.*, 40 to 80 mg daily). *See supra* ¶ 227; Ex. 1506, Martindale 2011 at 1423; Ex. 1503, Appel ¶¶ 58, 60-62.

230. Further, the inventors of the '006 Publication (which are also the named inventors of the '344 patent), citing Remington 1995 (an earlier version of Remington 2012) as support, explain that:

The multiple-component phase compositions can be formulated according to known methods for preparing pharmaceutically useful compositions. . . . 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 Pa., Mack Publishing Company, 19th ed.) [] describes formulations that can be used in connection with the subject invention.

Ex. 1509, the '006 Publication at ¶ [0051]; Ex. 1501, col. 10, ll. 6-21.

231. In view of the disclosures above, Ueto 2012 in combination with Martindale 2011, the '006 Publication, and Remington 2012 teaches element [10a].

9. Motivation to Combine Ueto 2012, Li 2011, Martindale 2011, the '006 Publication, and Remington 2012

232. A POSA would have been motivated to combine Ueto 2012 with Li 2011, Martindale 2011, the '006 Publication, and Remington 2012 to arrive at a pharmaceutical composition comprising a pharmaceutically acceptable carrier and therapeutically effective amount of the 1:1:2 co-crystal of furosemide, nicotinamide, and water taught in Ueto 2012, which meets all the co-crystal limitations of claim 16, with a reasonable expectation of success.

233. I understand based on my own education and experience and with the knowledge described in the Appel Declaration that a POSA as of 2014 would have

known that furosemide had a pharmaceutical use as a diuretic drug for hypertension and that furosemide is practically insoluble in water. Ex. 1503, Appel Declaration ¶ 58; Ex. 1506, Martindale 2011 at 1421; *see* Ex. 1507, Ueto 2012 at 486.

234. A POSA as of 2014 also would have known that co-crystals had the potential to improve physicochemical properties of an active pharmaceutical ingredient. Ex. 1507, Ueto 2012 at 485 (“[C]ocrystals have been a focus of attention as valuable API forms with the potential to improve physicochemical properties”); Ex. 1503, Appel Declaration ¶ 59; Ex. 1509, ’006 Publication ¶ [0111] (disclosing a carbamazepine/saccharin co-crystal that “has improved solubility over previously known forms of carbamazepine”); Ex. 1504, Hickey 2007 at 113-15, 117-18 (formulating co-crystals comprising carbamazepine and saccharin with α -lactose monohydrate to evaluate *in vitro* dissolution and oral bioavailability compared to the marketed form of carbamazepine).

235. As of 2014, nicotinamide was known to be a suitable additive and co-former for pharmaceutical applications. *See* Ex. 1509, ’006 Publication, ¶ [0040], Example 8 (indicating that nicotinamide is a “GRA[S]” compound); *see also* Ex. 1531, 21 C.F.R. § 184.1535 (2000) (same); Ex. 1507, Ueto 2012 at 486 (referring to nicotinamide as a pharmaceutically acceptable co-former); Ex. 1506, Martindale

2011 at 2117-19 (teaching that nicotinamide is commonly found in foods such as yeast, meat, fish, potatoes, legumes, and cereals).

236. Further, the lead author of Ueto 2012, as well as three co-authors, are associated with Chugai Pharmaceutical Co. Ltd. and/or are Faculty of Pharmaceutical Sciences at Toho University in Japan and in the publication, the authors investigate pharmaceutical co-crystals, which they recognize have the potential to improve physicochemical properties of the API, such as solubility, stability, and hygroscopicity. Ex. 1507, Ueto 2012 at 486-93. The authors' investigation in Ueto 2012 involved preparing several co-crystals, including one comprising furosemide, nicotinamide, and water. *Id.* Therefore, a POSA seeking to use furosemide for pharmaceutical uses, for example, as a diuretic in hypertensive patients would have been motivated to evaluate whether the Ueto 2012 co-crystals, including the furosemide, nicotinamide, and water co-crystal, had improved pharmaceutical properties as compared to furosemide alone. *See* Ex. 1503, Appel Declaration ¶ 59.

237. I understand based on my own education and experience and with the knowledge described in the Appel Declaration that active pharmaceutical ingredients are generally administered in a pharmaceutical composition with pharmaceutically acceptable carriers. Ex. 1503, Appel Declaration ¶¶ 34-35, 46, 50, 53, 55-56, 59, 64; Ex. 1510, Remington 2012 at 583, 606.

238. A POSA would have looked to references like Martindale 2011, which provides up-to-date information on drugs and other compounds used throughout the world, for guidance on the therapeutically effective amount of the co-crystal to formulate into a pharmaceutical composition because Martindale 2011 discloses therapeutically effective amounts of furosemide to treat hypertension, and it teaches that nicotinamide is suitable for use in a pharmaceutical composition because it is commonly found in foods such as yeast, meat, fish, potatoes, legumes, and cereals. Ex. 1506, Martindale 2011 at 1421-25, 2117-19. Nicotinamide was also known by 2014 to be a GRAS compound and common co-former used in pharmaceuticals. Ex. 1509, '006 Publication, ¶ [0040], Example 8 (indicating that nicotinamide is a “GRA[S]” compound); Ex. 1531, 21 C.F.R. § 184.1535 (2000) (same); Ex. 1507, Ueto 2012 at 486 (referring to nicotinamide as a pharmaceutically acceptable co-former); Ex. 1511, '408 Application at 1-2 (disclosing that nicotinamide is a water-soluble B3 vitamin that “is on the list of compounds approved for safe use as additives to food products”).

239. Further, as confirmed by the '006 Publication, a POSA would have looked to references like Remington 2012 that teaches “all aspects of pharmaceuticals,” Ex. 1510, Remington 2012 at Preface vii, for guidance on how to formulate a co-crystal into a pharmaceutical composition with a pharmaceutically acceptable carrier. *See* Ex. 1509, '006 Publication ¶ [0051]; *see also* Ex. 1503,

Appel Declaration ¶¶ 21, 45-56, 64; Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10.

240. And a POSA interested in preparing a pharmaceutical composition comprising the furosemide, nicotinamide, and water co-crystal taught in Ueto 2012 would have been motivated to combine Ueto 2012 with a reference like Li 2011 that concerns nicotinamide, one of the co-crystal components, and like Martindale 2011 that concerns furosemide, the other co-crystal component.

241. I understand based on my own education and experience and with the knowledge described in the Appel Declaration that a POSA would have been motivated to use and would have ascertained a therapeutically effective amount of the 1:1:2 furosemide, nicotinamide, and water co-crystal of Ueto 2012 to have a therapeutic effect in hypertensive patients, and a POSA would have confirmed that the other components of the co-crystal were present in amounts that were suitable for pharmaceutical use. Ex. 1503, Appel Declaration ¶¶ 60-62.

242. I also understand based on my own education and experience and with the knowledge described in the Appel Declaration that a POSA would have known that pharmaceutically acceptable carriers and therapeutically effective amounts of multiple-component crystals had been formulated into pharmaceutical compositions, and a POSA would have known how to formulate a pharmaceutically acceptable carrier and a therapeutically effective amount of a

multiple-component crystal into a pharmaceutical composition using formulations and methods that were readily available and well known to those in the art, as described in Remington 2012. Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10. And a POSA would have had a reasonable expectation that a pharmaceutically acceptable carrier and therapeutically effective amount of a multiple-component crystal could be formulated into a pharmaceutically useful composition. Ex. 1503, Appel Declaration ¶¶ 64-66.

243. In view of furosemide's therapeutic use as a diuretic for hypertension as taught in Ueto 2012 and Martindale 2011, and the teachings in these references as well as the '006 Publication that nicotinamide is an appropriate co-former for use in pharmaceutical compounds and compositions, a POSA would have been motivated to combine a therapeutically effective amount (to have a diuretic effect in hypertensive patients) of the 1:1:2 furosemide, nicotinamide, and water co-crystal taught in Ueto 2012 with the teachings of Remington 2012 and the '006 Publication on how to formulate a pharmaceutical composition with a pharmaceutically acceptable carrier, to arrive at the pharmaceutical composition of claim 16 of the '344 patent and would have had a reasonable expectation of success in doing so. *See* Ex. 1507, Ueto 2012 at 486; Ex. 1506, Martindale 2011 at 2117-19; Ex. 1509, '006 Publication, ¶¶ [0040], [0051], Example 8; Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10. This co-crystal taught in Ueto 2012,

as explained above, meets all the co-crystal elements of claim 16 (elements [10c] and [10e] as confirmed by Li 2011 and Martindale 2011, respectively). *See supra* §§ XI.F.1-XI.F.8 (elements [10a]-[10g], [16a]-[16b]).

244. For these reasons, claim 16 is obvious over Ueto 2012 in view of Li 2011, Martindale 2011, the '006 Publication, and Remington 2012.

XII. INVALIDITY GROUND 2: CHALLENGED CLAIM 16 IS OBVIOUS OVER THE '408 APPLICATION AND/OR SOWA 2013 IN VIEW OF MARINI 2007, LI 2011, THE '006 PUBLICATION AND REMINGTON 2012

245. Because challenged claim 16 is entitled to a priority date no earlier than 2014, it is my opinion that claim 16 is obvious over the '408 Application and/or Sowa 2013 in view of Marini 2007, Li 2011, the '006 Publication, and Remington 2012.

A. Overview of the '408 Application

246. The '408 Application, titled “A co-crystal of genistein-nicotinamide monohydrate and a method for obtaining a co-crystal of genistein-nicotinamide monohydrate,” is a patent application filed in the Polish Patent Office on October 30, 2012, and published June 10, 2013, Ex. 1586, P.401408 Patent Application Details at 1 (“General Information”; “Timeline”), 3 (“Basic Information”), 5 (“Publications”), that discloses a co-crystal comprising genistein, nicotinamide, and water having a stoichiometric molar ratio of 1:1:1, respectively, which it refers

to as “genistein-nicotinamide monohydrate.” Ex. 1511, ’408 Application at 1-9 (explaining that a co-crystal of genistein-nicotinamide monohydrate was prepared using a 1:1 stoichiometric amount of genistein and nicotinamide in water); Ex. 1586, P.401408 Patent Application Details at 1-3 (“a co-crystal of genistein-nicotinamide monohydrate”). The named inventors of the ’408 Application are Michał Sowa, Katarzyna Ślepokura and Ewa Matczak-Jon. Ex. 1586, P.401408 Patent Application Details at 1-2 (“Entities in the Case”).

247. The ’408 Application further discloses a 1:1:1 genistein-nicotinamide monohydrate co-crystal for use in the pharmaceutical and/or cosmetic industry. Ex. 1511, ’408 Application at 1.

248. The ’408 Application discloses that genistein is a major isoflavone present in soybeans and has “estrogenic activity,” “anti-inflammatory and antioxidant properties,” and “potential multidirectional application[s] in the treatment and prevention of cancer.” Ex. 1511, ’408 Application at 1-2. But the application explains that “[t]he insufficient bioavailability of genistein hinders the development of effective drugs, pharmaceutical formulations and dietary supplements and is associated with low solubility in aqueous media” and that genistein has been complexed with β -cyclodextrins in an attempt to modify genistein’s solubility. Ex. 1511, ’408 Application at 2-3.

249. The '408 Application describes co-crystallization as “one of the promising methods for modifying unfavorable physicochemical parameters of pharmaceutically active substances for several years” and notes that it has been applied to the flavonoid quercetin and the co-crystal of quercetin and caffeine resulted in a 14-fold increase in solubility and 10-fold increase in bioavailability compared to quercetin when administered alone. Ex. 1511, '408 Application at 2.

250. In addition, the '408 Application discloses that nicotinamide is a water-soluble B3 vitamin that has been used in the treatment of inflammatory skin conditions and its properties “allow the treatment of pellagra, psoriasis, schizophrenia and type I diabetes.” Ex. 1511, '408 Application at 1-2. The '408 Application also discloses that nicotinamide “is on the list of compounds approved for safe use as additives to food products” and, because of this, it “is widely used in co-crystallization of pharmaceutical preparations and dietary supplements.” *Id.* A POSA would have recognized that water is a solvent. Ex. 1572, Housecroft 2012 at UM00005304 (listing water as a solvent); Ex. 1573, Huheey 1993 at UM00005308 (same).

251. The '408 Application further discloses a method for preparing the genistein-nicotinamide monohydrate co-crystal where genistein and nicotinamide “in a stoichiometric amount of 1:1 are placed in a steel vessel of a ball mill, and then water or a mixture of acetonitrile and water in an amount of 50 μ L for every

50 mg of genistein is milled for 5-45 minutes at a vibration frequency of 50-60 Hz.” Ex. 1511, ’408 Application at 3; *see also id.* at 5 (“Example 3. Genistein (50 mg, 0.1811 mmol) and nicotinamide (21.3 mg, 0.171 mmol) were placed in a 10 mL steel vessel containing two 7 mm diameter steel balls. 100 μ L (about two drops) of distilled water was added to the mixture. The vessel was mounted in a Narva Vibrator Mill and milled for 30 minutes at a vibration frequency of 50 Hz.”). These disclosures would indicate to a POSA that genistein is a solid in pure form and at room temperature.

B. Overview of Sowa 2013

252. Like the ’408 Application, Sowa 2013, titled “Cocrystals of Fisetin, Luteolin and Genistein with Pyridinecarboxamide Coformers: Crystal Structures, Analysis of Intermolecular Interactions, Spectral and Thermal Characterization” and published in *CrystEngComm* on July 19, 2013 (Ex. 1512, Sowa 2013 at 7696-707), discloses a co-crystal comprising genistein, nicotinamide, and water having a stoichiometric molar ratio of 1:1:1, respectively, which it refers to as genistein-nicotinamide monohydrate. Ex. 1512, Sowa 2013 at 7696-707 (“genistein-nicotinamide (1 : 1) monohydrate (**GenNam**) cocrystals”), 7703 (“The asymmetric unit [of genistein-nicotinamide monohydrate] contains one genistein, one nicotinamide, and one water molecule, forming a three-component molecular assembly *via* hydrogen bonding.”).

253. The authors of Sowa 2013 are the same as the inventors of the '408 Application, *i.e.*, Michał Sowa, Katarzyna Ślepokura and Ewa Matczak-Jon. *Compare* 1512, Sowa 2013 at 7696 with Ex. 1586, P.401408 Patent Application Details at 1-2 (“Entities in the Case”).

254. Sowa 2013 discloses that genistein is a flavonoid (specifically, an isoflavone) and is “the predominant flavonoid in soybean enriched food” and “exhibits a wide range of antitumor properties.” Ex. 1512, Sowa 2013 at 7696-97. Sowa 2013 also discloses that flavonoids “are of scientific interest due to health-prolonging effects attributed mainly to their antioxidant, antitumor, and anti-inflammatory properties.” Ex. 1512, Sowa 2013 at 7696. Sowa 2013 further explains that “[s]ome beneficial results of flavonoid administration were shown *in vivo*, yet their efficiency is hindered by low solubility in water and low bioavailability, therefore reducing the potential of possible applications in pharmaceutical formulations or nutritional supplements.” Ex. 1512, Sowa 2013 at 7696.

255. Sowa 2013 describes co-crystallization as “a method of obtaining novel forms of active pharmaceutical ingredients (APIs) with improved physicochemical properties (*e.g.*, solubility, stability, melting point)” that “has gained much attention in recent years.” Ex. 1512, Sowa 2013 at 7696. And Sowa 2013 further explains that co-crystallization “has been successfully employed to

modify the solubility of some APIs” and, recently, “has been applied to improve the solubility and bioavailability of a flavonoid quercetin, opening the field for improving the physicochemical properties of other compounds from this family.”

Id.

256. In addition, Sowa 2013 discloses that nicotinamide is a suitable co-former for pharmaceutical applications. *See* Ex. 1512, Sowa 2013 at 7697 (stating that nicotinamide is a “[s]uitable cocrystal former” that has been “successfully applied to cocrystallize carboxyl- and hydroxyl-derived APIs including some flavonoids”).

257. Sowa 2013 further discloses that the genistein-nicotinamide monohydrate co-crystal was prepared by dissolving 25.0 mg of genistein and 150.0 mg of nicotinamide in a 10 mL ethanol-methanol-water mixture (45:45:10 v/v/v), with stirring at ambient temperature. Ex. 1512, Sowa 2013 at 7697. Genistein was initially screened by grinding 50 mg of genistein and a 1:1 stoichiometric amount of the co-former (*i.e.*, nicotinamide) with one drop (*ca.* 25 μ L) of solvent in a 5 mL stainless steel grinding jar with two 7 mm stainless steel grinding balls for 30 minutes (3 x 10 minutes with 5 minute cooling periods) at a rate of 50 Hz and drying the resulting solids overnight at ambient conditions. *Id.* at 7697. These disclosures would indicate to a POSA that genistein is a solid in pure form and at room temperature.

C. Overview of Marini 2007

258. Marini 2007, titled “Effects of the Phytoestrogen Genistein on Bone Metabolism in Osteopenic Postmenopausal Women” and published in the *Annals of Internal Medicine*, discloses the results of a randomized, double-blind, placebo-controlled clinical trial studying the effects of genistein on bone metabolism in osteopenic postmenopausal women. Ex. 1513, Marini 2007 at 839-46.

259. In the clinical trial, the participants were randomly assigned to receive placebo (191 participants) or 54 mg of genistein (198 participants) daily for 24 months. Ex. 1513, Marini 2007 at 839-40, 844-45. The study concluded that 24 months of treatment with genistein has positive effects on bone mineral density (BMD) in osteopenic postmenopausal women. *Id.* at 839, 846.

260. Marini 2007 discloses that genistein is an “isoflavone phytoestrogen that is abundant in soybean products” and that, “[a]s a natural selective estrogen receptor modulator, genistein may positively regulate bone cell metabolism without harmful estrogenic activity in the breast and uterus.” Ex. 1513, Marini 2007 at 839.

261. Marini 2007 further states that “[e]pidemiologic data indicate that women who ingest high amounts of phytoestrogens, particularly isoflavones in soy products, have less risk for osteoporosis than do those who consume a typical

Western diet” and, as a result, “many women use phytoestrogens to maintain bone density.” Ex. 1513, Marini 2007 at 839.

D. Overview of Li 2011

262. An overview of Li 2011 is provided in section XI.B above (Invalidity Ground 1, overview of Li 2011) and is incorporated here.

E. Overview of the ’006 Publication

263. An overview of the ’006 Publication is provided in section XI.D above (Invalidity Ground 1, overview of the ’006 Publication) and is incorporated here.

F. Overview of Remington 2012

264. An overview of Remington 2012 is provided in section XI.E above (Invalidity Ground 1, overview of Remington 2012) and is incorporated here.

G. Obviousness of Claim 16 – Element by Element Claim Analysis

265. I have broken down claim 16, which depends from claim 10, into the same claim elements as I did above in paragraphs 184-185.

266. For the reasons below, claim 16 of the ’344 patent is obvious over the ’408 Application and/or Sowa 2013 in view of Marini 2007, Li 2011, the ’006 Publication, and Remington 2012. For the purpose of simplifying my analysis, I again discuss element [10a] last.

1. **[10b]: a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former**

267. The '408 Application and/or Sowa 2013 teaches “a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former.”

268. As I explained above, Petitioner’s counsel has asked me to adopt the Patent Owners’ proposed construction of co-crystal, which is “a multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.” *Supra* §§ XI.F.1 (Invalidity Ground 1, element [10b]), VIII.B (claim construction of “co-crystal”).

269. The '408 Application and Sowa 2013 disclose the same co-crystal comprising genistein, nicotinamide, and water having a fixed stoichiometric molar ratio of 1:1:1, meaning that there is one molecule of nicotinamide for every molecule of each genistein and water. Ex. 1511, '408 Application at 1-9 (explaining that a co-crystal of genistein-nicotinamide monohydrate was prepared using a 1:1 stoichiometric amount of genistein and nicotinamide in water); Ex. 1512, Sowa 2013 at 7696-707 (“genistein-nicotinamide (1 : 1) monohydrate (**GenNam**) cocrystals”), 7703 (“The asymmetric unit [of genistein-nicotinamide

monohydrate] contains one genistein, one nicotinamide, and one water molecule, forming a three-component molecular assembly *via* hydrogen bonding.”). Moreover, the co-crystal was analyzed using single crystal X-ray diffraction, Ex. 1511, ’408 Application at 4, 6; Ex. 1512, Sowa 2013 at 7696-97, 7702-03, indicating that the co-crystal is in a single crystalline phase because single crystal analysis can only be done if the material is in a single crystalline phase. Thus, the genistein, nicotinamide, and water co-crystal qualifies as a co-crystal under Patent Owners’ proposed construction because it is “a multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.”

270. The ’408 Application discloses that nicotinamide is a water-soluble B3 vitamin that has been used in the treatment of inflammatory skin conditions and its properties “allow the treatment of pellagra, psoriasis, schizophrenia and type I diabetes,” Ex. 1511, ’408 Application at 1-2, which a POSA would have understood to mean that nicotinamide is an “API” as that term is defined in the ’344 patent, *i.e.*, it is a “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.” *Supra* § VIII.A (claim construction of “API”); Ex. 1501, col. 9, ll. 27-34.

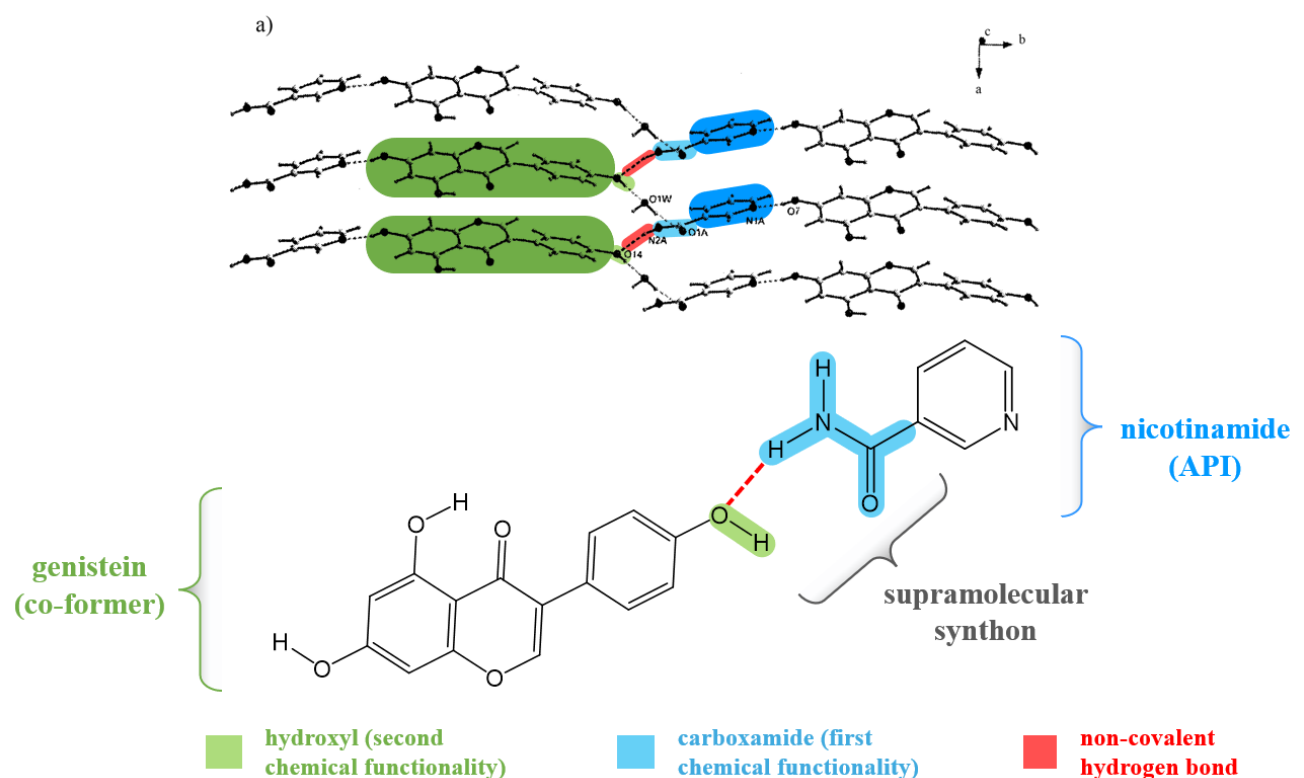
271. Additionally, the ’408 Application and Sowa 2013 each discloses that genistein has pharmaceutical uses. Specifically, the ’408 Application discloses that

genistein is a major isoflavone present in soybeans and has “estrogenic activity,” “anti-inflammatory and antioxidant properties,” and “potential multidirectional application[s] in the treatment and prevention of cancer.” Ex. 1511, ’408 Application at 1. Sowa 2013 similarly discloses that genistein is a flavonoid (specifically, an isoflavone), is “the predominant flavonoid in soybean enriched food,” and “exhibits a wide range of antitumor properties, involving influence on cell proliferation, cell cycle progression, and apoptosis.” Ex. 1512, Sowa 2013 at 7696-97. Sowa 2013 also discloses that most flavonoids “are of scientific interest due to health-prolonging effects attributed mainly to their antioxidant, antitumor, and anti-inflammatory properties.” Ex. 1512, Sowa 2013 at 7696. The ’344 patent provides that the co-former can be, for example, “*other drug molecules*, GRAS compounds, or approved food additives,” Ex. 1501, col. 3, ll. 35-37 (emphasis added), and that a GRAS compound is one that is “Generally Regarded as Safe by the Food and Drug Administration (FDA).” Ex. 1501, col. 9, ll. 21-26. Thus, a POSA would have understood that genistein qualifies as a “co-former” according to the ’344 patent based on the above characterizations.

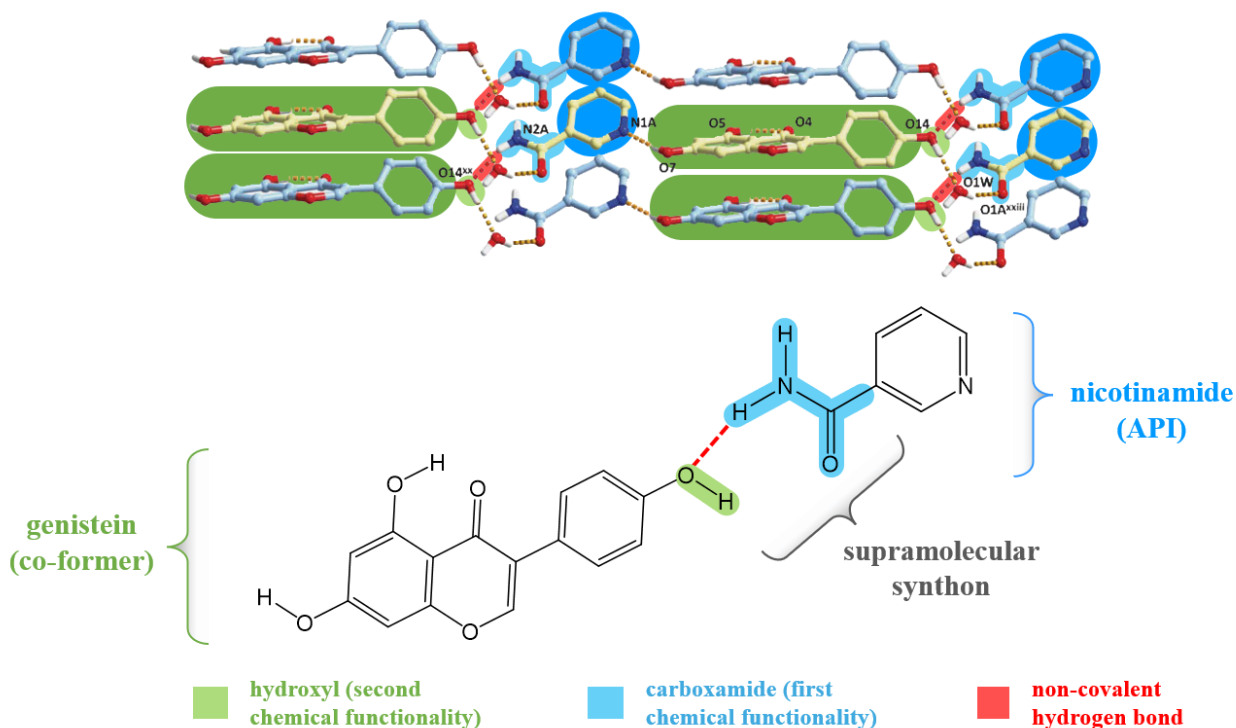
272. The ’408 Application and Sowa 2013 each discloses that the second chemical functionality of genistein is complementary to, and forms a co-crystal with, the first chemical functionality of nicotinamide (*infra* § XII.G.3, claim element [10d]).

273. An image from the single crystal structure of the 1:1:1 genistein, nicotinamide, and water co-crystal is depicted in Figure 3(a) of the '408 Application and Figure 9(b) of Sowa 2013. Ex. 1511, '408 Application at 4, 9; 1512, Sowa 2013 at 7702-03. I have annotated both figures in this paragraph to point out certain aspects of the co-crystal that are relevant to my analysis of claim 16.

'408 Application (Figure 3(a)):



Sowa 2013 (Figure 9(b)):



274. Nicotinamide, the “API” according to the ’344 patent, has a first chemical functionality that is a carboxamide (shaded light blue), which the Parties agree covers “-C(=O)NH₂.” *Supra* § VIII.A (claim construction of “carboxamide”). Genistein, which meets the requirements of a “co-former” according to the ’344 patent, has a second chemical functionality that is a hydroxyl (“-OH” group) (shaded light green).

275. The carboxamide of nicotinamide interacts with the hydroxyl of genistein via non-covalent hydrogen bonding (shown by the dashed line shaded red), forming a supramolecular synthon (shown by the gray bracket). As I

explained above, the term “supramolecular synthon” is defined in the ’344 patent and collectively refers to two or more chemical functionalities and the non-covalent bond(s) between them, here, the carboxamide of nicotinamide, the hydroxyl of genistein, and the non-covalent hydrogen bond between them. *See supra* § VIII.A (claim construction of “supramolecular synthon”); *see also* Ex. 1501, col. 3, ll. 37-59, col. 9, l. 43 – col. 10, l. 5. Thus, the genistein, nicotinamide, and water co-crystal taught in each of the ’408 Application and Sowa 2013 comprises supramolecular synthons.

276. Consistent with the figures in paragraph 273 above, Sowa 2013 explains that “[a]nalysis of interactions within the structure of **GenNam** reveals the presence of Gen-Nam-H₂O [genistein-nicotinamide-water] chains running along the [110] direction, hydrogen bon[d]ed *via* . . . O14-H14 [of genistein]⋯O1W²² [of water]. . . and O1W-H2W [of water]⋯O1A^{xxiii} [of nicotinamide] . . . contacts (Fig. 9a²³).” Ex. 1512, Sowa 2013 at 7703. Further, “Gen-Nam-H₂O chains are arranged in stacks running along the *a* direction, combined *via* interactions between the amide moieties of Nam and the O14 hydroxyl substituent in Gen,

²² The atom numbering of oxygen and nitrogen atoms is shown in Figures 9(a)-(c) of Sowa 2013.

²³ These interactions can also be seen in Figure 9(b) of Sowa 2013.

namely N2A-H2A1 [of nicotinamide]···O14^{xx} [of genistein] . . . (Fig. 9b).” *Id.* at 7702 (Figures 9(a)-(c)), 7703; *see also* Ex. 1511, ’408 Application, Figures 2 and 3(a)-(c)).

277. For these reasons, the co-crystal disclosed in each of the ’408 Application and Sowa 2013 meets element [10b].

2. [10c]: 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

278. By disclosing nicotinamide, which has a carboxamide group (*see* Ex. 1511, ’408 Application at 4, 9; Ex. 1512, Sowa 2013 at 7702-03) and which forms API homosynthons in its pure form, the ’408 Application and Sowa 2013 each inherently discloses “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,” element [10c]. Further, Li 2011 expressly discloses this claim element as I explained in detail above in section XI.F.2 (Invalidity Ground 1, claim element [10c]), and I incorporate that discussion here.

3. [10d]: wherein the co-former has a second chemical functionality compl[e]mentary to the first chemical functionality via non-covalent hydrogen bonding

279. The ’408 Application and Sowa 2013 each discloses “wherein the co-former has a second chemical functionality compl[e]mentary to the first chemical functionality via non-covalent hydrogen bonding.”

280. The second chemical functionality of genistein interacts with the first chemical functionality of nicotinamide to form a co-crystal and, therefore, the second chemical functionality of genistein is complementary to the first chemical functionality of nicotinamide via non-covalent hydrogen bonding. Specifically, as shown in annotated Figure 3(a) of the '408 Application and Figure 9(b) of Sowa 2013 (in paragraph 273 above, claim element [10b]), the 1:1:1 genistein, nicotinamide, and water co-crystal has (i) an “API” (nicotinamide) that has a first chemical functionality (a carboxamide, shaded light blue), and (ii) a “co-former” (genistein) that has a second chemical functionality (a hydroxyl, shaded light green). Ex. 1511, '408 Application at 8-9 (Figures 2, 3(a)-(c)); Ex. 1512, Sowa 2013 at 7702 (Figures 9(a)-(c)), 7703 (“Gen-Nam-H₂O chains are arranged in stacks running along the *a* direction, combined *via* interactions between the amide moieties of Nam and the O14 hydroxyl substituent in Gen, namely N2A-H2A1 [of nicotinamide]···O14^{xx} [of genistein] . . . (Fig. 9b).”); 7703 (“The asymmetric unit [of genistein-nicotinamide monohydrate] contains one genistein, one nicotinamide, and one water molecule, forming a three-component molecular assembly *via* hydrogen bonding.”). The carboxamide of nicotinamide interacts with the hydroxyl of genistein via non-covalent hydrogen bonding, forming a supramolecular synthon. Ex. 1511, '408 Application at 9; Ex. 1512, Sowa 2013 at 7702-03. As a result of this non-covalent hydrogen bonding interaction, a POSA would have

understood that the genistein, nicotinamide, and water co-crystal taught in each of the '408 Application and Sowa 2013 meets element [10d].

4. [10e]: wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form

281. By disclosing genistein, the '408 Application and Sowa 2013 each inherently discloses “wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form.”

282. The '408 Application discloses a method for preparing the genistein-nicotinamide monohydrate co-crystal where genistein and nicotinamide “in a stoichiometric amount of 1:1 are placed in a steel vessel of a ball mill, and then water or a mixture of acetonitrile and water in an amount of 50 μ L for every 50 mg of genistein is milled for 5-45 minutes at a vibration frequency of 50-60 Hz.” Ex. 1511, '408 Application at 3; *see also id.* at 5 (Example 3 disclosing milling a mixture of genistein (50 mg) and nicotinamide (21.3 mg) and 100 μ L of water in a steel vessel with steel balls); Ex. 1512, Sowa 2013 at 7696-97 (disclosing that genistein-nicotinamide monohydrate was prepared by dissolving 25.0 mg of genistein and 150.0 mg of nicotinamide in a 10 mL ethanol-methanol-water mixture (45:45:10 v/v/v) with stirring at ambient temperature; disclosing that genistein was screened by grinding 50 mg of genistein and a 1:1 stoichiometric amount of the co-former (*i.e.*, nicotinamide) with one drop of solvent in a grinding

jar with two stainless steel grinding balls). Based on disclosures that 25 or 50 *mg* of genistein was *dissolved* and that the genistein was *milled* or *ground*, a POSA would have understood that genistein is a solid at room temperature and atmospheric pressure in its pure form. *See also* Ex. 1579, 2006 Merck Index at 756-57 (entry 4391) (disclosing that genistein alone (*i.e.*, when in pure form) has a melting point of 297-298 °C, which is above room temperature, which a POSA would have understood to mean that genistein is a solid at room temperature and atmospheric pressure).

283. Therefore, the genistein, nicotinamide, and water co-crystal taught in each of the '408 Application and Sowa 2013 inherently meets element [10e] (which is expressly confirmed by the 2006 Merck Index).

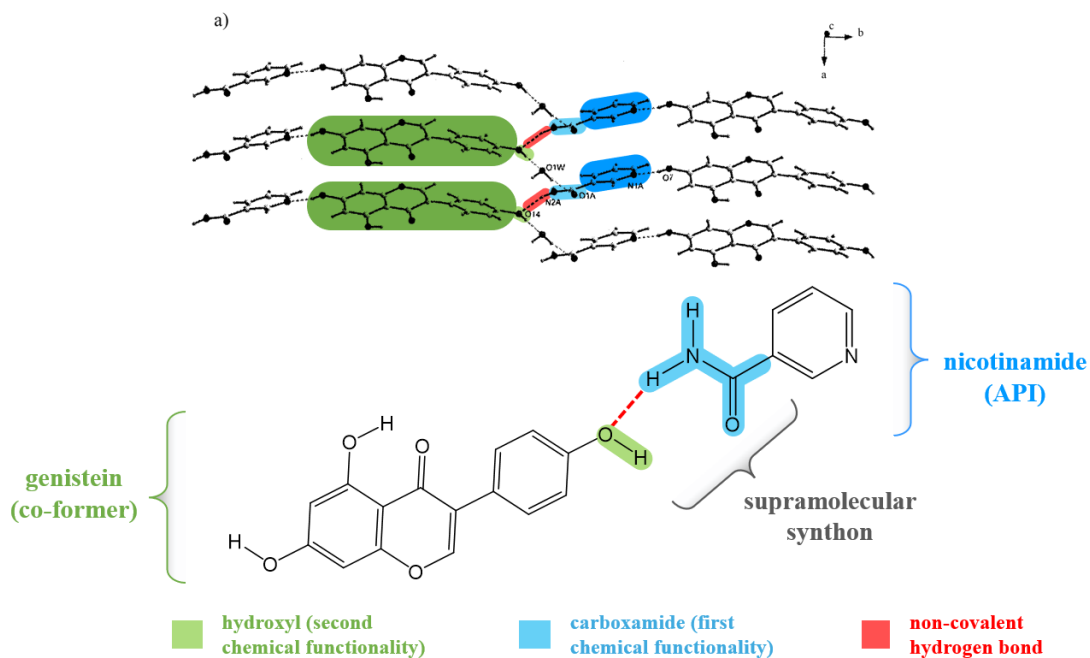
5. [10f]: wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former

284. The '408 Application and Sowa 2013 each discloses “wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.”

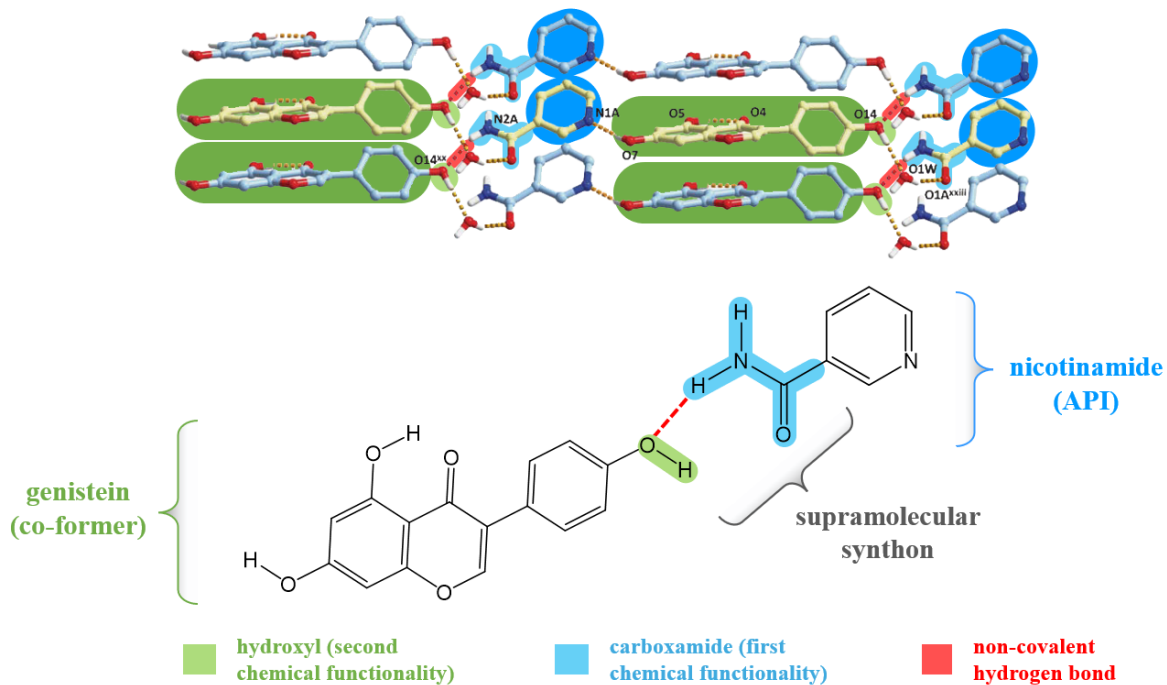
285. Figure 3(a) of the '408 Application and Figure 9(b) of Sowa 2013 (in paragraph 273 above, claim element [10b]), which I reproduce again in this

paragraph, each shows that the 1:1:1 genistein, nicotinamide, and water co-crystal has (i) an “API” (nicotinamide) that has a first chemical functionality (a carboxamide, shaded light blue), and (ii) a “co-former” (genistein) that has a second chemical functionality (a hydroxyl, shaded light green). Ex. 1511, ’408 Application at 8-9 (Figures 2, 3(a)-(c)); Ex. 1512, Sowa 2013 at 7702 (Figures 9(a)-(c)). The carboxamide of nicotinamide and the hydroxyl of genistein interact via non-covalent hydrogen bonding, which is shown by the dashed line shaded red, Ex. 1511, ’408 Application at 9; Ex. 1512, Sowa 2013 at 7702, resulting in the formation of a supramolecular synthon, *i.e.*, the carboxamide and hydroxyl chemical functionalities and the non-covalent hydrogen bond interaction between them. *See supra* § VIII.A (claim construction of “supramolecular synthon”); *see also* Ex. 1501, col. 3, ll. 37-59, col. 9, l. 43 – col. 10, l. 5.

'408 Application (Figure 3(a)):



Sowa 2013 (Figure 9(b)):



286. Consistent with Figure 3(a) of the '408 Application and Figure 9(b) of Sowa 2013, Sowa 2013 explains that “Gen-Nam-H₂O chains are arranged in stacks running along the *a* direction, combined *via* interactions between the amide moieties of Nam and the O14 hydroxyl substituent in Gen, namely N2A-H2A1 [of nicotinamide]···O14^{xx} [of genistein] . . . (Fig. 9b).” Ex. 1512, Sowa 2013 at 7703, *id.* at 7703 (“The asymmetric unit [of genistein-nicotinamide monohydrate] contains one genistein, one nicotinamide, and one water molecule, forming a three-component molecular assembly *via* hydrogen bonding.”)).

287. Therefore, the genistein, nicotinamide, and water co-crystal taught in each of the '408 Application and Sowa 2013 meets element [10f].

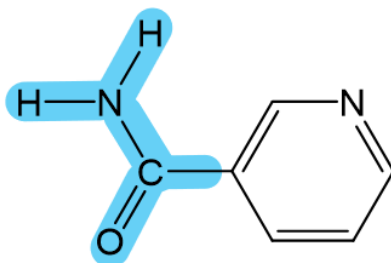
6. [10g]: wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine

288. The '408 Application and Sowa 2013 each discloses “wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.”

289. Nicotinamide (its chemical structure is shown below in this paragraph), the “API” in the 1:1:1 genistein, nicotinamide, and water co-crystal taught in the '408 Application and Sowa 2013, has a first chemical functionality that is a carboxamide (shaded light blue), which the Parties agree covers “-C(=O)NH₂,” meeting element [10g]. Ex. 1511, '408 Application at 9; Ex. 1512,

Sowa 2013 at 7702-03; *see also id.* Figure 11(a); *supra* § VIII.A (claim construction of “carboxamide”).

nicotinamide (API)



7. [16b]: wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule

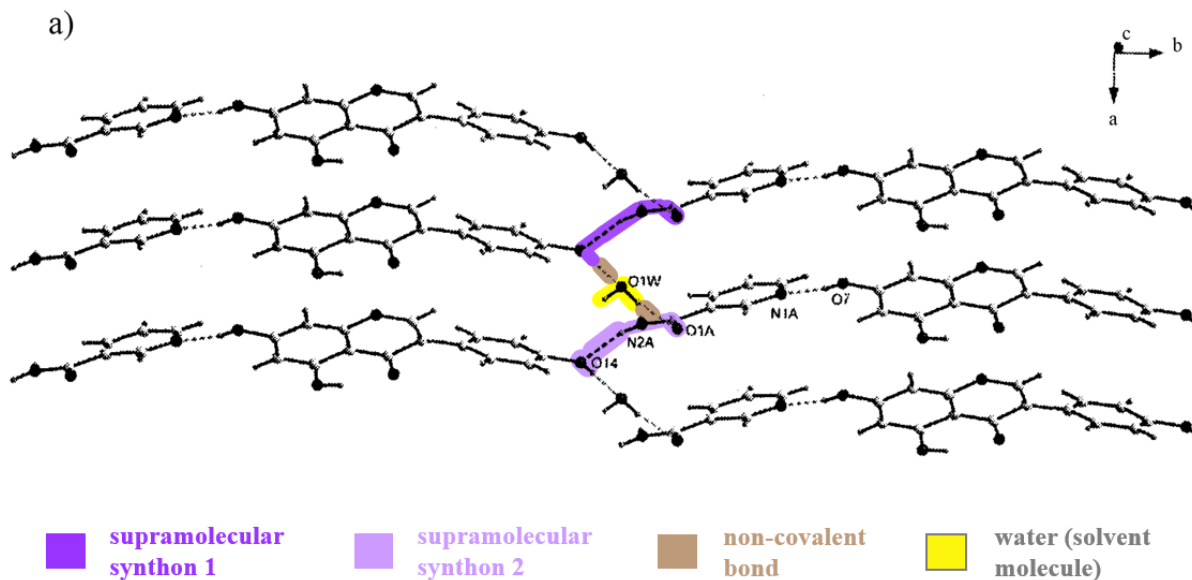
290. The '408 Application and Sowa 2013 each discloses “wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.”

291. As I explained above, the Parties in the district court litigation agree that limitation [16b] means “wherein one or more solvent molecules are non-covalently bonded to two or more supramolecular synthons, linking the supramolecular synthons to one another.” *Supra* § VIII.A (claim construction of claim element [16b]). A POSA would have understood water to be a solvent. Ex. 1572, Housecroft 2012 at UM00005304 (listing water as a solvent); Ex. 1573, Huheey 1993 at UM00005308 (same).

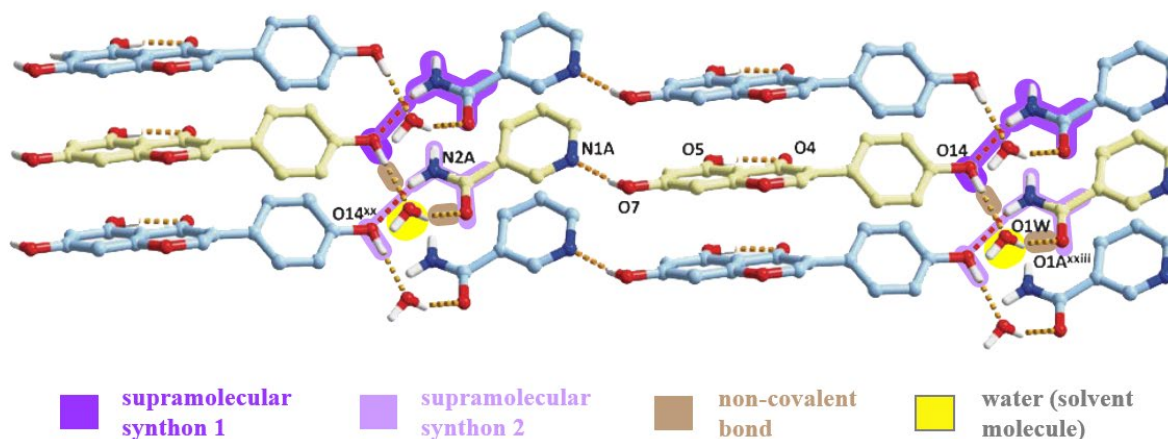
292. The '408 Application and Sowa 2013 both disclose the same 1:1:1 genistein, nicotinamide, and water co-crystal where nicotinamide is the “API”, genistein is the “co-former,” and water is the solvent. Ex. 1511, '408 Application at 1-9; Ex. 1512, Sowa 2013 at 7696-707. Nicotinamide has a first chemical functionality that is a carboxamide and genistein has a second chemical functionality that is a hydroxyl. The carboxamide of nicotinamide interacts with the hydroxyl of genistein via non-covalent hydrogen bonding. This interaction forms supramolecular synthons. *Supra* § XII.G.5 (claim element [10f]).

293. The supramolecular synthons formed by a non-covalent hydrogen bond between the carboxamide of nicotinamide and the hydroxyl of genistein are non-covalently bonded to one another by non-covalent bonding to a water (solvent) molecule. This is shown in Figure 3(a) of the '408 Application and Figure 9(b) of Sowa 2013, which I annotate in this paragraph. Ex. 1511, '408 Application at 9; Ex. 1512, Sowa 2013 at 7702.

'408 Application (Figure 3(a)):



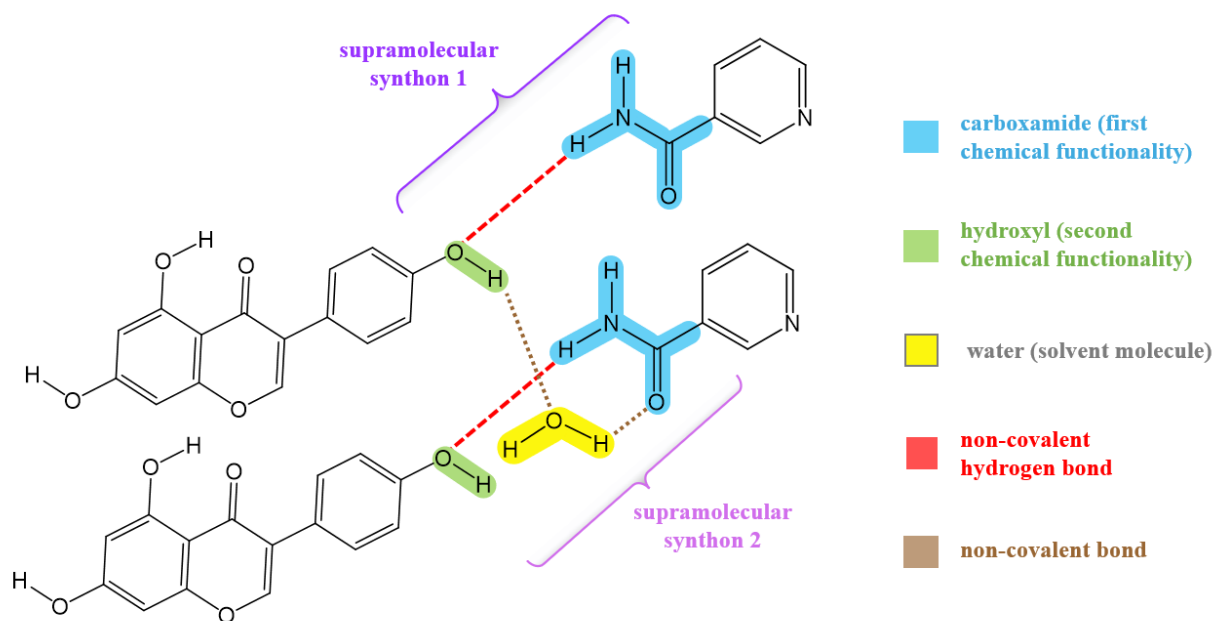
Sowa 2013 (Figure 9(b)):



294. Specifically, a water molecule (labeled “O1W” and shaded yellow) links via non-covalent hydrogen bonding (shaded brown) one supramolecular synthon (on the top shaded dark purple) to an adjacent supramolecular synthon (on

the bottom shaded light purple). Ex. 1511, '408 Application at 9; Ex. 1512, Sowa 2013 at 7702.

295. I also provide a simplified figure below in this paragraph illustrating how the genistein, nicotinamide, and water co-crystal in the '408 Application and Sowa 2013 meets the limitations of element [16b].



296. As shown in the figure in paragraph 295, each supramolecular synthon (supramolecular synthon 1, shown by the dark purple bracket, and supramolecular synthon 2, shown by the light purple bracket) is formed by the first chemical functionality of the “API” (the carboxamide of nicotinamide, shaded light

blue), the second chemical functionality of the “co-former” (the hydroxyl of genistein, shaded light green), and the non-covalent hydrogen bond between them (shown by the red dashed line). *Supra* § VIII.A (claim construction of “supramolecular synthon”).

297. As also shown in the figure in paragraph 295, the solvent molecule (water, shaded yellow) is non-covalently (hydrogen) bonded (shown by the brown dashed lines) to two supramolecular synthons (supramolecular synthon 1 and supramolecular synthon 2), linking the supramolecular synthons to one another. *Supra* § VIII.A (claim construction of claim element [16b]). Specifically, the solvent links the second chemical functionality of the “co-former” of one supramolecular synthon (supramolecular synthon 1) to the first chemical functionality of the “API” of an adjacent supramolecular synthon (supramolecular synthon 2). Ex. 1511, ’408 Application at 9; Ex. 1512, Sowa 2013 at 7702.

298. Consistent with Figure 3(a) of the ’408 Application, Figure 9(b) of Sowa 2013 and my illustration in paragraph 295 above, Sowa 2013 states that “[a]nalysis of interactions within the structure of **GenNam** reveals the presence of Gen-Nam-H₂O chains running along the [110] direction, hydrogen bon[d]ed *via* . .

. O14-H14 [of genistein]···O1W²⁴ [of water]. . . and O1W-H2W [of water]···O1A^{xxiii} [of nicotinamide] . . . contacts (Fig. 9a²⁵).” Ex. 1512, Sowa 2013 at 7703.

299. For these reasons, the genistein, nicotinamide, and water co-crystal disclosed in each of the ’408 Application and Sowa 2013 meets element [16b].

8. [10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [a co-crystal]

300. The ’408 Application and/or Sowa 2013 in combination with Marini 2007, the ’006 Publication, and Remington 2012 teaches “a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [a co-crystal].”

301. The ’408 Application and Sowa 2013 each disclose the same 1:1:1 genistein, nicotinamide, and water co-crystal. Ex. 1511, ’408 Application at 1-9; Ex. 1512, Sowa 2013 at 7696-707.

302. The ’408 Application discloses that nicotinamide is a water-soluble B3 vitamin that has been used in the treatment of inflammatory skin conditions and

²⁴ The atom numbering of oxygen and nitrogen atoms is shown in Figures 9(a)-(c) of Sowa 2013.

²⁵ The interactions can also be seen in Figure 9(b) of Sowa 2013.

its properties “allow the treatment of pellagra, psoriasis, schizophrenia and type I diabetes.” Ex. 1511, ’408 Application at 1-2.

303. Although nicotinamide satisfies the “API” element of claim 16 of the ’344 patent, the ’408 Application and Sowa 2013 each also explains that nicotinamide is a suitable additive for pharmaceutical applications. Ex. 1511, ’408 Application at 2 (disclosing that nicotinamide “is on the list of compounds approved for safe use as additives to food products” and, because of this, it “is widely used in the co-crystallization of pharmaceutical preparations and dietary supplements”); Ex. 1512, Sowa 2013 at 7697 (stating that nicotinamide is a “[s]uitable cocrystal former” that has been “successfully applied to cocrystallize carboxyl- and hydroxyl-derived APIs including some flavonoids”); *see also* Ex. 1509, ’006 Publication, ¶ [0040], Example 8 (indicating that nicotinamide is a “GRA[S]” compound); Ex. 1531, 21 C.F.R. § 184.1535 (2000) (same); *see also* Ex. 1506, Martindale 2011 at 2117-19 (disclosing that nicotinamide is present in various foods, such as yeast, meat, fish, potatoes, legumes, and cereals and can be safely administered at daily doses of up to 500 mg to treat vitamin B deficiency).

304. The ’408 Application and Sowa 2013 each provides several pharmaceutical uses for genistein. Specifically, the ’408 Application discloses that genistein has “estrogenic activity,” “anti-inflammatory and antioxidant properties,” and “potential multidirectional application[s] in the treatment and prevention of

cancer.” Ex. 1511, ’408 Application at 1. Sowa 2013 similarly discloses that genistein “exhibits a wide range of antitumor properties, involving influence on cell proliferation, cell cycle progression, and apoptosis.” Ex. 1512, Sowa 2013 at 7696-97; *see also id.* at 7696 (disclosing that most flavonoids “are of scientific interest due to health-prolonging effects attributed mainly to their antioxidant, antitumor, and anti-inflammatory properties”); Ex. 1513, Marini 2007 at 839-40, 844-45 (disclosing that 54 mg of genistein daily for 24 months had positive effects on bone mineral density (BMD) in osteopenic postmenopausal women).

305. The ’344 patent does not require that the therapeutically effective amount of the co-crystal in claim 16 for any given indication be based in whole or in part on the therapeutic activity of the component of the co-crystal that satisfies the “API” claim element (here, nicotinamide) when the “co-former” itself (here, genistein) has therapeutic activity for a particular indication (here, genistein has estrogenic activity, specifically, reducing bone loss in osteopenic postmenopausal women) and the co-crystal component meeting the ’344 patent’s “API” definition does not have therapeutic activity for that indication.

306. I understand based on my own education and experience and with the knowledge described in the Appel Declaration that a POSA as of 2014 would have known how to formulate, and would have been capable of formulating, pharmaceutical compositions comprising a pharmaceutically acceptable carrier and

a therapeutically effective amount of a multiple-component crystal, such as the one taught in the '408 Application and Sowa 2013, using formulations and methods that were readily available and well known in the art such as those described in Remington 2012. *See* Ex. 1503, Appel Declaration ¶¶ 45-56, 67-77; Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10. The POSA would have looked to a reference like Marini 2007, for guidance in determining the therapeutically effective amount of the co-crystal to formulate into a pharmaceutical composition and would have incorporated into the co-crystal an amount of genistein sufficient to have a therapeutic effect of reducing bone loss in osteopenic postmenopausal women (*i.e.*, 54 mg daily). *See supra* ¶ 304; Ex. 1513, Marini 2007; Ex. 1503, Appel ¶¶ 68, 71-73.

307. Further, the inventors of the '006 Publication (which are also the named inventors of the '344 patent), citing Remington 1995 (an earlier version of Remington 2012) as support, explain that:

The multiple-component phase compositions can be formulated according to known methods for preparing pharmaceutically useful compositions. . . . 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 Pa., Mack

Publishing Company, 19th ed.) [] describes formulations that can be used in connection with the subject invention.

Ex. 1509, the '006 Publication at ¶ [0051]; Ex. 1501, col. 10, ll. 6-21.

308. In view of the disclosures above, the '408 Application and/or Sowa 2013 in combination with Marini 2007, the '006 Publication, and Remington 2012 teaches element [10a].

9. Motivation to Combine the '408 Application and/or Sowa 2013 with Marini 2007, Li 2011, the '006 Publication, and Remington 2012

309. A POSA would have been motivated to combine the '408 Application and/or Sowa 2013 with Marini 2007, Li 2011, the '006 Publication, and Remington 2012 to arrive at a pharmaceutical composition comprising a pharmaceutically acceptable carrier and therapeutically effective amount of the 1:1:1 co-crystal of genistein, nicotinamide, and water taught in the '408 Application and Sowa 2013, which meets all the co-crystal limitations of claim 16, with a reasonable expectation of success.

310. A POSA as of 2014 would have known that genistein had a number of pharmaceutical applications, including estrogenic activity. *E.g.*, 1511, '408 Application at 1 (disclosing that genistein has “estrogenic activity,” “anti-inflammatory and antioxidant properties,” and “potential multidirectional application[s] in the treatment and prevention of cancer.”); Ex. 1513, Marini 2007

at 839 (disclosing that genistein is an “isoflavone phytoestrogen that is abundant in soybean products” and that, “[a]s a natural selective estrogen receptor modulator, genistein may positively regulate bone cell metabolism without harmful estrogenic activity in the breast and uterus”); Ex. 1503, Appel Declaration ¶ 68.

311. The ’408 Application and Sowa 2013 each teaches the POSA that genistein has low aqueous solubility and low bioavailability, hindering its use as an effective drug. Ex. 1511, ’408 Application at 2 (“The insufficient bioavailability of genistein hinders the development of effective drugs, pharmaceutical formulations and dietary supplements and is associated with low solubility in aqueous media); *see* Ex. 1512, Sowa 2013 at 7696 (“Some beneficial results of flavonoid administration were shown *in vivo*, yet their efficiency is hindered by low solubility in water and low bioavailability, therefore reducing the potential of possible applications in pharmaceutical formulations or nutritional supplements.”); *see also* Ex. 1503, Appel Declaration ¶ 68.

312. And the ’408 Application and Sowa 2013 each teaches that co-crystals have the potential to improve therapeutic activity of APIs. *E.g.*, Ex. 1511, ’408 Application at 2 (describing co-crystallization as “one of the promising methods for modifying unfavorable physicochemical parameters of pharmaceutically active substances for several years”; noting that co-crystallization has been applied to the flavonoid quercetin and the co-crystal of quercetin and caffeine resulted in a 14-

fold increase in solubility and 10-fold increase in bioavailability compared to quercetin when administered alone); Sowa 2013 at 7696 (describing co-crystallization as “a method of obtaining novel forms of active pharmaceutical ingredients (APIs) with improved physicochemical properties (e.g., solubility, stability, melting point)” that “has gained much attention in recent years” and “has been successfully employed to modify the solubility of some APIs”; explaining that co-crystallization “has been applied to improve the solubility and bioavailability of a flavonoid quercetin, opening the field for improving the physicochemical properties of other compounds from this family”); Ex. 1503, Appel Declaration ¶ 69; Ex. 1509, ’006 Publication ¶ [0111] (disclosing a carbamazepine/saccharin co-crystal that “has improved solubility over previously known forms of carbamazepine”); Ex. 1504, Hickey 2007 at 113-15, 117-18 (formulating co-crystals comprising carbamazepine and saccharin with α -lactose monohydrate to evaluate *in vitro* dissolution and oral bioavailability compared to the marketed form of carbamazepine).

313. As of 2014, nicotinamide was known to be a suitable additive and co-former for pharmaceutical applications. *E.g.*, Ex. 1511, ’408 Application at 1 (disclosing a genistein-nicotinamide monohydrate co-crystal for use in the pharmaceutical and/or cosmetic industry), 1-2 (disclosing that nicotinamide is a water-soluble B3 vitamin that “is on the list of compounds approved for safe use as

additives to food products” and, because of this, it “is widely used in the co-crystallization of pharmaceutical preparations and dietary supplements”); Ex. 1512, Sowa 2013 at 7697 (stating that nicotinamide is a “[s]uitable cocrystal former” that has been “successfully applied to cocrystallize carboxyl- and hydroxyl-derived APIs including some flavonoids”); *see also* Ex. 1509, ’006 Publication, ¶ [0040], Example 8 (indicating that nicotinamide is a “GRA[S]” compound); Ex. 1531, 21 C.F.R. § 184.1535 (2000) (same); Ex. 1506, Martindale 2011 at 2117-19 (teaching that nicotinamide is commonly found in foods such as yeast, meat, fish, potatoes, legumes, and cereals).

314. Further, the Applicants of the ’408 Application and authors of Sowa 2013, which are the same, *supra* ¶ 253 (overview of Sowa 2013), recognized that the low water solubility of flavonoids, like genistein, could potentially be improved by co-crystallizing it with a co-former, such as nicotinamide, a water-soluble B3 vitamin. *See* Ex. 1511, ’408 Application at 1-2 (disclosing that nicotinamide is a water-soluble B3 vitamin that “is on the list of compounds approved for safe use as additives to food products” and, because of this, it “is widely used in the co-crystallization of pharmaceutical preparations and dietary supplements”; noting that co-crystallization has been applied to a different flavonoid and the obtained co-crystal (with caffeine as the co-former) increased solubility and bioavailability compared to that flavonoids when administered alone), 3 (disclosing an attempt to

modify the solubility of genistein by complexing it with β -cyclodextrins); *see also* Ex. 1512, Sowa 2013 at 7697 (stating that nicotinamide is a “[s]uitable cocrystal former” that has been “successfully applied to cocrystallize carboxyl- and hydroxyl-derived APIs including some flavonoids”).

315. I understand based on my own education and experience and with the knowledge described in the Appel Declaration that active pharmaceutical ingredients are generally administered in a pharmaceutical composition with pharmaceutically acceptable carriers, Ex. 1503, Appel Declaration ¶¶ 34-35, 46, 50, 53, 55-56, 69, 75; Ex. 1510, Remington 2012 at 583, 606, and therefore, a POSA seeking to use genistein for pharmaceutical uses such as to reduce bone loss in osteopenic postmenopausal women, would have been motivated to consider the genistein, nicotinamide, and water co-crystal to evaluate whether it improved the physicochemical properties (e.g., solubility, bioavailability) of genistein compared to genistein alone. Ex. 1503, Appel Declaration ¶ 70.

316. A POSA would have been motivated to combine the ’408 Application and/or Sowa 2013 with a reference like Marini 2007 because all those references concern genistein, and Marini 2007 discloses therapeutically effective amounts of genistein to reduce bone loss in osteopenic postmenopausal women, Ex. 1513, Marini 2007 at 839-40, 844-45 (disclosing that 54 mg of genistein daily for 24

months had positive effects on bone mineral density (BMD) in osteopenic postmenopausal women).

317. Further, a POSA would have been motivated to combine the '408 Application and/or Sowa 2013 with a reference like Li 2011 because Li 2011 concerns nicotinamide, one of the co-crystal components of the co-crystal taught in the '408 Application and/or Sowa 2013.

318. Further, as confirmed by the '006 Publication, a POSA would have looked to a reference like Remington 2012 that teaches “all aspects of pharmaceuticals,” Ex. 1510, Remington 2012 at Preface vii, for guidance on how to formulate a co-crystal into a pharmaceutical composition with a pharmaceutically acceptable carrier. *See* Ex. 1509, '006 Publication ¶ [0051]; *see also* Ex. 1503, Appel Declaration ¶¶ 21, 45-56, 75; Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10.

319. I understand based on my own education and experience and with the knowledge described in the Appel Declaration that a POSA would have been motivated to use, and would have ascertained, a therapeutically effective amount of the 1:1:1 genistein, nicotinamide, and water co-crystal of the '408 Application and Sowa 2013 for reducing bone loss in osteopenic postmenopausal women and a POSA would have confirmed that the other components of the co-crystal were

present in amounts that were suitable for pharmaceutical use. Ex. 1503, Appel Declaration ¶¶ 71-73.

320. I further understand based on my own education and experience and with the knowledge described in the Appel Declaration that a POSA would have known that pharmaceutically acceptable carriers and therapeutically effective amounts of multiple-component crystals had been formulated into pharmaceutical compositions, and a POSA would have known how to formulate a pharmaceutically acceptable carrier and a therapeutically effective amount of a multiple-component crystal into a pharmaceutical composition using formulations and methods that were readily available and well known to those in the art, as described in Remington 2012. And a POSA would have had a reasonable expectation that a pharmaceutically acceptable carrier and therapeutically effective amount of a multiple-component crystal could be formulated into a pharmaceutically useful composition. Ex. 1503, Appel Declaration ¶¶ 75-77; Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10.

321. In view of genistein's estrogenic activity in reducing bone loss in osteopenic postmenopausal women as taught in the '408 Application and Marini 2007, and the teachings in the '408 Application, Sowa 2013, and the '006 Publication that nicotinamide is an appropriate co-former for use in pharmaceutical compounds and compositions, a POSA would have been motivated to combine a

therapeutically effective amount (to reduce bone loss in osteopenic women) of the 1:1:1 genistein, nicotinamide, and water co-crystal taught in the '408 Application and Sowa 2013 with the teachings of Remington 2012 and the '006 Publication on how to formulate a pharmaceutical composition with a pharmaceutically acceptable carrier, to arrive at the pharmaceutical composition of claim 16 of the '344 patent and would have had a reasonable expectation of success in doing so. *See* Ex. 1511, '408 Application at 1-3; Ex. 1512, Sowa 2013 at 7696-97; Ex. 1513, Marini 2007 at 839-40, 844-46; Ex. 1509, '006 Publication, ¶¶ [0040], [0051], Example 8; Ex. 1510, Remington 2012 at 586-87, 592-93, 604-10. This co-crystal taught in the '408 Application and Sowa 2013, as explained above, meets all the co-crystal elements of claim 16 (element [10c] as confirmed by Li 2011). *See supra* §§ XII.G.1-XII.G.8 (elements [10a]-[10g], [16a]-[16b]).

322. For these reasons, claim 16 is obvious over the '408 Application and Sowa 2013 in combination with Marini 2007, Li 2011, the '006 Publication, and Remington 2012.

* * *

323. For the reasons I have discussed above, it is my opinion that claim 16 would have been obvious over the prior art as of 2014.

XIII. OBVIOUSNESS - SECONDARY CONSIDERATIONS

324. Petitioner's counsel has informed me that one of the factual inquiries relevant to an obviousness analysis is objective indicia of non-obviousness, also called secondary considerations of non-obviousness, which include unexpected results, commercial success, long felt but unmet need, failure of others, copying by others, and skepticism of experts. The legal principles provided to me by Petitioner's counsel with respect to secondary considerations are in **Appendix B**, ¶¶ 10-12.

325. Below I address certain statements made by Applicants in either the '344 patent or the prosecution history of the '344 patent or '956 application that were potentially directed to secondary considerations of non-obviousness and their applicability to either Ground 1 or Ground 2. For the reasons I explain below, the evidence from the intrinsic record, considered in connection with my analysis of Grounds 1 and 2 above, does not change my opinion that challenged claim 16 is obvious.

326. The intrinsic evidence does not establish any secondary considerations. Any alleged secondary considerations (1) lack the required nexus to the full scope of claim 16 and (2) do not overcome the clear showing that claim 16 is obvious for the reasons I explained in sections XI-XII above (Invalidity Grounds 1 and 2).

327. I reserve the right to address any secondary considerations put forth by the Patent Owners in any later response to this declaration or the petition.

A. There is No Evidence of Any Unexpected or Surprising Results Commensurate in Scope With the Challenged Claim 16

328. I understand from Petitioner’s counsel that evidence of unexpected results may support a showing of non-obviousness if the results are unexpected in view of the prior art. I also understand that evidence of unexpected results must be commensurate in scope with (*i.e.*, must correspond to the full scope of) the claimed invention and must be based on a POSA’s knowledge as of the relevant priority date (here, no earlier than 2014). In addition, any unexpected or surprising results must be directed to a novel aspect of the claim, not something known in the prior art.

329. In my opinion, there is nothing in the ’344 patent or the prosecution history of the ’344 patent or ’956 application that supports finding unexpected results of claim 16.

330. The ’344 patent states that the multiple-component crystals described in the specification “*can* afford improved drug solubility, dissolution rate, stability and bioavailability” compared to the parent pharmaceutical ingredient. Ex. 1501, col. 3, ll. 12-28 (emphasis added), *see also* col. 7, ll. 23-41, col. 8, ll. 57-61. The ’344 patent also states in connection with Example 9, which discloses a 1:1

carbamazepine/saccharin co-crystal, that “[s]olubility measurements indicated that this multiple-component crystal of carbamazepine has improved solubility over previously known forms of carbamazepine (e.g., increased molar solubility and longer solubility in aqueous solutions).” Ex. 1501, col. 17, ll. 50-58. During prosecution of the ’344 patent, Applicants alleged that “the teachings of the instant application demonstrate the unpredictable finding that APIs could not only be used in co-crystals, but that the co-crystals exhibit improved characteristics as compared to the API alone.” Ex. 1516, p. 359, ’344 patent file history, April 1, 2016 Amendment in Response to Office Action at 14 (emphasis added); *id.*, pp. 445-46, August 10, 2017 Appeal Brief at 21-22 (same); *id.*, p. 561, February 7, 2018 Reply Brief at 6 (same). However, none of these statements supports finding unexpected results of claim 16.

331. First, co-crystals falling within the scope of the co-crystal elements of challenged claim 16 were known in the art by 2014. *See supra* §§ XI-XII (Invalidity Grounds 1 and 2). Thus, any unexpected properties of a co-crystal do not provide evidence of non-obviousness of any novel feature of claim 16.

332. Second, none of the ’344 patent, its prosecution history, or the prosecution history of the ’956 application provides any evidence (in the form of data) that the alleged co-crystal invention of challenged claim 16 in fact improved the drug solubility, dissolution rate, stability and/or bioavailability of *any* API in a

co-crystal as compared to the API alone, much less of carbamazepine as Applicants alleged in Example 9 of the '344 patent. Even if Applicants had shown some unexpected property for *a particular co-crystal*, such as the carbamazepine/saccharin co-crystal of Example 9, this co-crystal does not fall within the scope of challenged claim 16, and such evidence is not commensurate in scope with the broad genus of co-crystals covered by the claim, much less the claimed pharmaceutical *composition* containing them. A POSA as of 2014 would have understood that the properties of a single co-crystal relative to its individual components are not representative of that which would be expected for an entire genus of co-crystals relative to the individual components of those co-crystals.

333. Additionally, Patent Owners cannot argue that any of the alleged unexpected results set forth in the '344 patent specification were unexpected as of 2014 because the '006 Publication (the publication of the '956 application) was publicly available as of December 4, 2003, Ex. 1509, '006 Publication, at cover, and included all the statements in the '344 patent specification, including that the subject matter of challenged claim 16 “*can* afford improved drug solubility, dissolution rate, stability and bioavailability” compared to the parent pharmaceutical ingredient, *see* Ex. 1501, col. 3, ll. 12-28, and that the 1:1 carbamazepine and saccharin co-crystal disclosed in the '344 patent has improved solubility over carbamazepine alone, *see* Ex. 1501, col. 17, ll. 50-58. Ex. 1509,

'006 Publication, ¶¶ [0009] (The multiple-component crystals “can afford improved drug solubility, dissolution rate, stability and bioavailability.”), [0040], [0045], [0111] (“Solubility measurements indicate that this multiple-component crystal of carbamazepine has improved solubility over previously known forms of carbamazepine (e.g., increased molar solubility and in aqueous solutions).”).

334. For these reasons, there are no unexpected or surprising results commensurate in scope with challenged claim 16 or directed to a novel feature of claim 16 that supports a showing of non-obviousness.

B. There is No Evidence that There Was a Long Felt But Unmet Need for the Purported Invention of Challenged Claim 16 Commensurate in Scope With Claim 16

335. I understand from Petitioner’s counsel that evidence showing a long felt but unmet need in the industry for the solution offered by the claimed invention may support a finding of non-obviousness.

336. The '344 patent discloses that “crystal structure prediction . . . remains a largely unmet goal.” Ex. 1501, col. 2, ll. 18-20. During prosecution of the '344 patent, Applicants explained that the problem the claimed inventions allegedly solved was the “rational design of crystalline pharmaceuticals, which is hampered by the multiple phases, polymorphs, and solvates formed by drugs.” Ex. 1516, p. 434, '344 patent file history, August 10, 2017 Appeal Brief at 10. And during prosecution of the '956 parent application, Applicants explained that “there was a

long-felt but unsolved need for predictable crystal engineering technology at the time of the present invention.” Ex. 1517, p. 4416, ’956 application file history, July 25, 2016 Response at 10; *see also* Ex. 1517, p. 4416, ’956 application file history, July 25, 2016 Response at 10:

As further support of the non-obviousness of the claimed invention, there was a long-felt but unsolved need for predictable crystal engineering technology at the time of the present invention. Indeed, as disclosed at paragraph [0003] of the instant application:

“Physical properties of crystalline solids are critically dependent on the internal arrangement of molecules or ions, making prediction of composition, crystal structure and morphology from knowledge of molecular structure a scientific challenge of the highest order. However, crystal structure prediction and even prediction of composition remains a largely unmet goal.” (WO2003/074474, paragraph [0003] [which corresponds to Ex. 1501, col. 2, ll. 13-20]).

Prior to the present invention, cocrystal engineering relied heavily on *empirical* determination of structures. The instant application teaches an expectation that pharmaceutical compounds will form pharmaceutical co-crystals if (a) the pharmaceutical will form a homosynthon and (b) one selects a co-crystal co-former that will form a supramolecular synthon with the pharmaceutical via non-covalent hydrogen bonding Thus, the instant application provided a

transformative technology which allowed predictable crystal engineering, which was previously lacking in the art.

337. The '344 patent explains that the claimed inventions (i) “concern[] multiple-component compositions, and it is demonstrated herein that the concepts of crystal engineering and supramolecular synthons can be applied to prepare a wide range of novel pharmaceutical materials that are based on rational design,” Ex. 1501, col. 10, ll. 51-55, and (ii) “ha[ve] the following implications from a scientific perspective: (a) protocols are now available for the rational design of a new generation of pharmaceutical phases that contain at least two components that are sustained by supramolecular synthons . . . ”. Ex. 1501, col. 11, ll. 22-26.

338. First, the statements made by Applicants in the '344 patent and during prosecution of the '344 patent and '956 application do not explain how the *challenged claim* (as opposed to other claims in the '344 patent, including the application claims pursued during prosecution of the '344 patent or its parent) achieved the previously unmet goal of, and satisfied a long-felt need for, “crystal structure prediction,” “prediction of composition,” and/or “rational design of crystalline pharmaceuticals” in the field of crystal engineering. Claim 16 is directed to a *pharmaceutical composition* comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal that includes an API, co-former, and solvent, not *methods* or *protocols* or *procedures*

for crystal structure prediction, prediction of composition, or the rational design of crystalline pharmaceuticals.

339. Second, there is no evidence that the subject matter of challenged claim 16 solved the problems of crystal structure prediction and/or rationally designing crystalline pharmaceuticals and enabled a POSA to predict crystal structures or rationally design crystalline pharmaceuticals. Furthermore, even if challenged claim 16 solved the problems of crystal structure prediction and/or rationally designing crystalline pharmaceuticals, these problems were not solved by any novel feature of claim 16. Thus, there is no nexus (*i.e.*, connection) between the secondary indicia of non-obviousness and the subject matter of claim 16.

340. Furthermore, Patent Owners cannot argue that the purported invention of challenged claim 16 provided a solution to a long felt but unmet need in the industry for crystal structure prediction and/or rationally designing crystalline pharmaceuticals because the '006 Publication (the publication of the '956 application) was publicly available as of December 4, 2003, Ex. 1509, '006 Publication, at cover, and provides the same disclosures as the '344 patent specification. Thus, any need that was met by the purported invention of claim 16 (if properly supported) would have been met by the '006 Publication in 2003.

341. For these reasons, there is no evidence of any long-felt but unmet need for the purported invention of claim 16 that supports a finding of non-obviousness of claim 16.

* * *

342. In conclusion, I am not aware of any evidence of secondary considerations supporting non-obviousness of claim 16.

XIV. THE PETITION SHOULD NOT BE DISCRETIONARILY DENIED

343. I understand from Petitioner's counsel that the Board may elect not to institute a proceeding (and discretionarily deny an IPR petition) if the challenge to the patent is based on the same or substantially the same prior art or arguments previously presented to the Patent Office during prosecution. I further understand that this decision is based on a factual inquiry which considers the following, non-exclusive factors:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

344. Petitioner's counsel has informed me that these factors are considered in a two-part framework. First, factors (a), (b), and (d) above are considered to determine whether the art or arguments presented in the petition are the same or substantially the same as those previously presented to the Patent Office during prosecution. If the Board determines that the same or substantially the same art or arguments were previously presented to the Patent Office during prosecution, then factors (c), (e), and (f) above are considered to determine whether the Petitioner has demonstrated a material error by the Patent Office.

A. Part 1: The Same or Substantially the Same Art and Arguments Were Not Previously Presented to the Patent Office

345. The art and arguments discussed in Grounds 1 and 2 above are not the same or substantially the same as those previously presented to the Patent Office during prosecution. In reaching this conclusion, I considered factors (a), (b), and (d) above.

1. Factor (a): The Similarities and Material Differences Between the Asserted Art and the Prior Art Involved During Examination

346. The prior art addressed by the examiner on the merits during prosecution of the '344 patent (and its parent application, the '956 application) is materially different from the art discussed in connection with Grounds 1 and 2 above. Further, the combinations of references discussed in Grounds 1 and 2 were not addressed by the examiner on the merits during prosecution of the '344 patent or the '956 application.

347. At the outset, no primary reference (*i.e.*, Ueto 2012 (Ground 1) or '408 Application or Sowa 2013 (Ground 2)) was cited by the examiner during prosecution of the '344 patent or the '956 application or disclosed by Applicants in connection with the '344 patent or '956 application.

348. The primary references evaluated by the patent examiner on the merits during prosecution of the '344 patent (and '956 application) are materially different from the art discussed in Grounds 1 and 2 above, including that the primary references evaluated by the patent examiner on the merits do not teach the co-crystals taught by the primary references in Grounds 1 and 2.

a. GB 2169601 (Jackson)

349. During prosecution of the '344 patent and '956 application, the examiner rejected the then-pending application claims as anticipated ('344 patent

and '956 application) and/or obvious ('956 application) over Jackson. The examiner said that Jackson “teaches sucralose co-crystallized with an aliphatic or cyclic secondary or tertiary amine, specifically niacinamide (claims 1-11), meeting the limitations of the instant claims.” Ex. 1516, p. 198, '344 patent file history, April 11, 2014 Office Action at 4; Ex. 1517, p. 4022, '956 application file history, August 2, 2013 Office Action at 3 (similar); Ex. 1517, pp. 4156-57, '956 application file history, July 15, 2014 Office Action at 3-4 (similar); *see* Ex. 1561, Jackson at 1-5.

350. The examiner also stated that Jackson “does not specifically teach a working example of a co-crystal in stoichiometric ratios,” but “[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned the co-crystals of niacinamide with that of sucralose as taught by Jackson to be in stoichiometric amounts. It is common practice to the ordinary artisan to form specific ratios (i.e., 1:1, 1:2, etc.) between the two entities in order to get optimal results.” Ex. 1517, pp. 4156-57, '956 application file history, July 15, 2014 Office Action at 3-4.

351. In response, Applicants argued that Jackson “is not a co-crystal” (with stoichiometric proportions of API and co-former) and “does not disclose an API comprising a first chemical functionality that is a carboxamide, carbonyl or an amine.” Ex. 1516, pp. 260-61, '344 patent file history, July 10, 2014 Amendment at 10-11; Ex. 1517, pp. 4174-75, '956 application file history, January 15, 2015

Response to Office Action at 7-8 (similar); *see also* Ex. 1517, p. 4073, '956 application file history, January 14, 2014 Response to Office Action at 10 (arguing that Jackson does not teach “preparing a co-crystal comprising *stoichiometric* [] proportions of said API and said selected co-crystal former” as claimed because “the alleged ‘co-crystals’ provided by Jackson are a.) formed over and b.) demonstrate the desired effect over a *broad range* of compound ratios” (emphasis in original)).

352. Applicants further argued that to the extent Jackson does disclose a co-crystal, it does not have the specific hydrogen bonding required by the claims, instead “forming a hydroxyl:pyridine bond.” Ex. 1516, p. 260, '344 patent file history, July 10, 2014 Amendment at 10; Ex. 1517, pp. 4174-75, '956 application file history, January 15, 2015 Response to Office Action at 7-8 (same).

353. The primary references in Grounds 1 and 2 (*supra* §§ XI-XII) each discloses at least one co-crystal having a fixed stoichiometric molar ratio of its components, *i.e.*, a 1:1:2 furosemide, nicotinamide, and water co-crystal (Ueto 2012, Ground 1) and a 1:1:1 genistein, nicotinamide, and water co-crystal ('408 Application and Sowa 2013, Ground 2). In addition, the co-crystals in the primary references of Grounds 1 and 2 comprise an API having a first chemical functionality that is a carboxamide. Neither co-crystal comprises a supramolecular synthon formed by hydrogen bonds between a hydroxyl group (an “-OH” group)

and a pyridine group that also has the interactions between the supramolecular synthons and solvent as required by claim 16. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2). Moreover, a supramolecular synthon formed by hydrogen bonds between a hydroxyl and a pyridine group does not fall within the scope of challenged claim 16, which requires the first chemical functionality of the API to be a carboxamide, carbonyl, or amine.

b. Caira, *Molecular Complexes of Sulfonamides. 3. Structure of 5-methoxysulfadiazine (Form II) and its 1:1 Complex with Acetylsalicylic Acid*, 24 JOURNAL OF CHEMICAL CRYSTALLOGRAPHY 695-701 (1994) (Caira 1994)

354. Caira 1994 was cited by the examiner as an anticipatory reference during prosecution of both the '344 patent and the '956 application. The examiner said that Caira 1994 “teaches [] 1:1 complexation of 5-methoxysulfadiazine with acetylsalicylic acid (abstract; page 700, figure 4)” and “discloses that the crystal structures were determined by X-ray diffraction (page 696), meeting the limitations of the instant claims.” Ex. 1516, p. 199, '344 patent file history, April 11, 2014 Office Action at 5; Ex. 1517, pp. 4022-23, '956 application file history, August 2, 2013 Office Action at 3-4 (similar); *see* Ex. 1564, Caira 1994 at 700.

355. Applicants argued in response that Caira 1994 “does not disclose an API comprising a first chemical functionality that is a carboxamide, carbonyl, or an amine,” Ex. 1516, p. 263, '344 patent file history, July 10, 2014 Amendment at

13, but rather, it discloses “a co-crystal comprising 5-methoxysulfadiazine (SMD) with acetylsalicylic acid that forms a supramolecular synthon comprising heterosynthons formed by hydrogen bonds between the sulfonamide group of the SMD and the carboxylic acid group of the acetylsalicylic acid.” Ex. 1516, pp. 262-63, ’344 patent file history, July 10, 2014 Amendment at 12-13. Applicants overcame the examiner’s rejection over Caira 1994 by a claim amendment requiring that the co-former not be an API. Ex. 1517, p. 4065, ’956 application file history, January 14, 2014 Response to Office Action at 2, 10.

356. In contrast to the limitation added by Applicants during prosecution of the ’956 application that the co-former not be an API, this limitation is not a requirement of claim 16, which permits the co-former to be a drug substance. However, challenged claim 16 requires that the API have a first chemical functionality that is a carboxamide, carbonyl, or amine and thus Caira 1994 does not fall within the scope of claim 16. *See* Ex. 1564, Caira 1994 at 700. The primary references in Grounds 1 and 2 each discloses a co-crystal where the API has a first chemical functionality that is a carboxamide, meeting the first chemical functionality limitation of claim 16. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

c. U.S. Patent No. 3,664,858 (Huffman)

357. During prosecution, the examiner rejected the application claims of both the ’344 patent and the ’956 application as obvious over Huffman. The

examiner said that Huffman teaches “co-crystal complexes or adducts of amines with aromatic hydroxy compounds” and that “substantially stoichiometric portions of amine and acid are normally preferred.” Ex. 1516, pp. 287-89, ’344 patent file history, December 19, 2014 Office Action at 5-7; Ex. 1516, pp. 334-37, ’344 patent file history, October 5, 2015 Office Action at 9-12 (same); Ex. 1516, pp. 394-96, ’344 patent file history, July 12, 2016 Office Action at 11-13 (same); Ex. 1516, pp. 547-49, ’344 patent file history, December 8, 2017 Examiner’s Answer at 7-9 (same); Ex. 1517, pp. 4195-97, ’956 application file history, June 16, 2015 Office Action at 8-10 (same); Ex. 1517, pp. 4373-76, ’956 application file history, February 25, 2016 Office Action at 10-13 (same); *see* Ex. 1556, Huffman at col. 1, ll. 19-21, col. 2, ll. 44-45.

358. Applicants responded that Huffman “provides no teaching or suggestion to make co-crystals, as recited in the present claims. Huffman makes salts rather than co-crystals. . . . Indeed, one of ordinary skill in the art will readily appreciate that the amines disclosed in Huffman will deprotonate the carboxylic acids disclosed in Huffman to make salts. The present claims recite co-crystals.” Ex. 1516, pp. 357-58, ’344 patent file history, April 1, 2016 Amendment at 12-13; Ex. 1516, pp. 443-44, ’344 patent file history, August 10, 2017 Appeal Brief at 19-20 (same); Ex. 1516, p. 560, ’344 patent file history, February 7, 2018 Reply Brief

at 5 (same); Ex. 1517, p. 4229, '956 application file history, October 20, 2015 Amendment at 12 (same).

359. The primary references in Grounds 1 and 2, on the other hand, each discloses at least one co-crystal (*i.e.*, not a salt). *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

d. CA 1148020A1 (McCoy)

360. The '956 application claims were rejected by the patent examiner during prosecution as both anticipated and obvious over CA 1148020A1 (McCoy). The application claims of the '344 patent were also rejected as obvious over McCoy. The examiner said that McCoy teaches “improved amino acid food additive[s] comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an ‘effective amount of a soluble edible cocrystallizer material...[’].” Ex. 1516, p. 332, '344 patent file history, October 5, 2015 Office Action at 7; Ex. 1516, pp. 545-56, '344 patent file history, December 8, 2017 Examiner’s Answer at 5-6 (same); Ex. 1517, p. 4194, '956 application file history, June 16, 2015 Office Action at 7 (similar); Ex. 1517, pp. 4436-37, '956 application file history, January 5, 2017 Office Action at 7-8 (same); *see* Ex. 1560, McCoy at Abstract, 6-8.

361. The examiner further said that “an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the

amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of amino acid and crystallizer are used.” Ex. 1516, p. 333, ’344 patent file history, October 5, 2015 Office Action at 8 (underlining in original); Ex. 1516, pp. 391-92, ’344 patent file history, July 12, 2016 Office Action at 8-9 (same); Ex. 1517, pp. 4192-93, ’956 application file history, June 16, 2015 Office Action at 5-6 (same); Ex. 1517, p. 4371, ’956 application file history, February 25, 2016 Office Action at 8 (similar); Ex. 1517, pp. 4436-37, ’956 application file history, January 5, 2017 Office Action at 7-8 (same); *see also* Ex. 1516, pp. 385-86, ’344 patent file history, July 12, 2016 Office Action at 2-3 (noting that “the range disclosed for the ratio between co[-]crystallizer and edible amino acid salt would encompass a co-crystal that is also stoichiometrically proportional” (underlining in original)); Ex. 1516, pp. 550-51, ’344 patent file history, December 8, 2017 Examiner’s Answer at 10-11 (same); Ex. 1517, pp. 4365-66, 4371, ’956 application file history, February 25, 2016, Office Action at 2-3, 8 (same); Ex. 1517, pp. 4432-33, 4437-38, ’956 application file history, January 5, 2017 Office Action at 3-4, 8-9 (same); *see* Ex. 1560, McCoy at Abstract, 7, 10, 22, 23.

362. Applicants argued in response that McCoy “discloses physical mixtures of multiple components in *non-stoichiometric* ratios” because “[t]he equal amounts of co[-]crystallizer disclosed by McCoy are equal amount by *weight*, not equal amount by *moles*.” Ex. 1516, pp. 353-54, ’344 patent file history, April 1,

2016 Amendment at 8-9 (emphasis in original); Ex. 1517, pp. 4224-25, '956 application file history, October 20, 2015 Amendment at 7-8 (same); Ex. 1517, pp. 4412-13, '956 application file history, July 25, 2016 Amendment at 6-7 (similar).

363. Applicants further argued that “stoichiometric amounts are important for intermolecular interactions between two or more independent molecular entities in a co-crystal.” Ex. 1516, p. 354, '344 patent file history, April 1, 2016 Amendment at 9; Ex. 1516, p. 439, '344 patent file history, August 10, 2017 Appeal Brief at 15 (same); Ex. 1517, pp. 4425-27, '956 application file history, October 20, 2015 Amendment at 8-10 (similar) Ex. 1517, pp. 4414-15, '956 application file history, July 25, 2016 Amendment at 8-9 (similar); *see also* Ex. 1516, pp. 439-4, '344 patent file history, August 10, 2017 Appeal Brief at 15-17 (arguing that McCoy does not “suggest that it would be advantageous to select a stoichiometric ratio from the range of weight ratios”); Ex. 1516, pp. 557-58, '344 patent file history, February 7, 2018 Reply Brief at 2-3 (same).

364. Unlike McCoy, the primary references in Grounds 1 and 2 each discloses at least one co-crystal comprising stoichiometric amounts of the components by *moles*. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

e. U.S. Patent No. 6,559,293 (the '293 patent)

365. During prosecution of the '956 application, the examiner rejected the then-pending application claims as anticipated by the '293 patent. The examiner

said that the '293 patent teaches, among other things, co-crystals of topiramate with caffeine, methods of making a topiramate-caffeine co-crystal composition, and that “topiramate has an acidic proton, [for which] the acidity can be exploited to make salts and/or co-crystals (such as when complexed with caffeine).” Ex. 1517, pp. 146-48, '956 application file history, March 22, 2006 Office Action at 4-6 (citing column 14, line 14 through column 15, line 20 of the '293 patent which states that “[t]he present invention involved the unexpected discovery that the sulfamate [-OSO₂NH₂] group of topiramate is slightly acidic and thus may be a handle for the generation of salts, co-crystals, and complexes with basic compounds such as, but not limited to, caffeine....”); Ex. 1517, pp. 2956-58, '956 application file history, November 15, 2006 Office Action at 6-8 (same); *see* Ex. 1558, '293 patent at col. 14, l. 14 – col. 15, l. 20; *see* Ex. 1559, '293 patent, col. 14, l. 14 – col. 15, l. 20.

366. In response, Applicants argued that the passage cited by the examiner in the '293 patent “relates to the formation of salts, not crystals comprising at least one active pharmaceutical ingredient (API) and a co-crystal former” and, therefore, “does not anticipate the presently claimed method of forming a crystal comprising at least one API and a co-crystal former.” Ex. 1517, pp. 3021-23, '956 application file history, August 3, 2007 Response to Office Action at 5-7.

367. The primary references in Grounds 1 and 2, on the other hand, each discloses at least one co-crystal (*i.e.*, not a salt) comprising at least one API and at least one co-former. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

f. U.S. Patent No. 5,023,092 (DuRoss)

368. The application claims of the '956 application were rejected by the examiner during prosecution as anticipated and obvious over DuRoss. The examiner said that DuRoss “teaches gamma sorbitol co-crystallized therewith mannitol in the gamma sorbitol polymorph” as well as how to carry out the co-crystallization. Ex. 1517, pp. 3165-66, '956 application file history, October 14, 2008 Office Action at 3-4; *see* Ex. 1557, DuRoss at Abstract, col. 6, ll. 8-44.

369. Applicants responded that DuRoss does not disclose all the elements of the claimed method (a method for identifying complementary chemical functionalities to form a desired supramolecular synthon), does not teach them as arranged or combined in the claim, and “does not contemplate mannitol or sorbitol as an active pharmaceutical ingredient.” Ex. 1517, pp. 3193-94, '956 application file history, January 21, 2009 Response to Office Action at 7-8.

370. Challenged claim 16 of the '344 patent is directed to a pharmaceutical composition, regardless of how it is made, not a method like the '956 application claims, so whether DuRoss discloses elements of a particular method arranged or combined in a certain way is not relevant to the challenged claim.

371. Additionally, the mannitol and sorbitol components disclosed in DuRoss have only hydroxyl groups and therefore neither has a first chemical functionality that is a carboxamide, carbonyl, or amine, as required by challenged claim 16. In contrast to DuRoss, the primary references of Grounds 1 and 2 each involves a co-crystal with an API having a carboxamide first chemical functionality. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

- g. Ammar, *Effect of Aromatic Hydrotropes on the Solubility of Carbamazepine. Part II: Effect of Nicotinamide, Sodium Salts of Benzoic, Naphthoic and Nicotinic Acids*, 35 EGYPTIAN JOURNAL PHARMACEUTICAL SCIENCES 209-23 (1994) (Ammar 1994)**

372. The examiner rejected the application claims of the '956 application during prosecution as obvious over Ammar 1994. The examiner said that Ammar 1994 “teaches that carbamazepine forms a 2:1 complex with nicotinamide” but “does not specifically recite Applicant’s steps as set forth in [the claim].” Ex. 1517, p. 3265, '956 application file history, October 5, 2009 Office Action at 4; *see* Ex. 1563, Ammar at 209-22.

373. In response, Applicants argued that Ammar 1994 does not disclose a multiple-component solid phase composition as recited in the '956 application claims because Ammar 1994 discloses only the “possible existence of ‘complexes’ in solution” and “the existence of a complex in solution does not convey to one of

ordinary still in the art that the complex can be isolated as a crystalline solid.” Ex. 1517, pp. 3356-57, ’956 application file history, March 5, 2010 Response to Office Action at 10-11. According to Applicants:

The existence of a complex in solution does not inform one of ordinary skill in the art what forces may be holding the complex together (*i.e.*, supramolecular synthons, or other forces). The existence of a complex in solution for an individual pair of molecules does not impart to persons of ordinary skill in the art a reasonable expectation that they can extrapolate that pair into a genus of related compounds, as the subject specification demonstrates. Thus, even if a 1:2 complex of carbamazepine and nicotinamide does exist in the Ammar *et al.* publication, it has little bearing on the existence of groups of multiple-component crystalline compositions, nor does it convey a reasonable expectation of success in deliberately and rationally producing such multiple-component crystalline compositions in accordance with the methods of the invention.

Ex. 1517, p. 3357, ’956 application file history, March 5, 2010 Response to Office Action at 11.

374. Unlike Ammar 1994, the primary references in Grounds 1 and 2 each discloses at least one co-crystal, not merely its “possible existence.” *Supra* §§ XI-XII (Invalidity Grounds 1 and 2). In particular, Ueto 2012 discloses a co-crystal comprising an API (nicotinamide), a co-former (furosemide), and a solvent (water) having a stoichiometric molar ratio of 1:1:2 that was confirmed by single crystal

X-ray analysis. *Supra* § XI (Invalidity Ground 1). The '408 Application and Sowa 2013 also each discloses a co-crystal comprising an API (nicotinamide) and a co-former (genistein) having a stoichiometric molar ratio of 1:1:1 that was confirmed by single crystal X-ray analysis. *Supra* § XII (Invalidity Ground 2).

**h. Desiraju, *Supramolecular Synthons in Crystal Engineering-A New Organic Synthesis*, 34
ANGEWANDTE INTERNATIONAL EDITION IN ENGLISH
2311-27 (1995) (Desiraju 1995)**

375. Desiraju 1995 was cited by the examiner during prosecution of the '956 application as a secondary obviousness reference used in combination with DuRoss (*supra* § XIV.A.1.f) and in combination with Ammar 1994 (*supra* § XIV.A.1.g). The examiner said that Desiraju 1995 “teaches that hydrogen bonding, the master key for molecular recognition, is the most reliable directional interaction in supramolecular construction, and its significance in crystal engineering can scarcely be underestimated.” Ex. 1517, p. 3168, '956 application file history, October 14, 2008 Office Action at 6; Ex. 1517, p. 3265, '956 application file history, October 5, 2009 Office Action at 4 (same); *see* Ex. 1565, Desiraju 1995 at 2324.

376. The examiner concluded that because Desiraju 1995 “teaches that [] pharmaceutical molecules are all capable of hydrogen bonding and would therefore obviously be capable of forming these supramolecular synthons. . . , one in the art

would expect, with a reasonable degree of certainty, that it would be possible to form co-crystals of the instant pharmaceutical agents [taught in each DuRoss and Ammar 1994] as they possess all the prerequisites (i[.]e[.], hydrogen bonding) inherently.” Ex. 1517, pp. 3168-69, ’956 application file history, October 14, 2008 Office Action at 6-7 (discussing DuRoss); Ex. 1517, pp. 3265-66, ’956 application file history, October 5, 2009 Office Action at 4-5 (similar, discussing Ammar 1994).

377. Applicants argued in response to the rejection that Desiraju 1995 “fail[s] to teach any of aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin, or acetaminophen as pharmaceutical molecules (active pharmaceutical ingredients) and no discussion or teaching of co-crystal formers that are to be used to construct a crystal comprising an active pharmaceutical ingredient and one of the co-crystal formers identified in the method steps [of the application claim] is identified in the Office Action.” Ex. 1517, pp. 3195-96, ’956 application file history, January 21, 2009 Response to Office Action at 9-10.

378. Unlike Desiraju 1995, the primary references in Ground 1 and 2 each teaches at least one co-crystal that includes an API, co-former, and solvent that falls within the scope of the challenged claim, not merely components having a possibility of interacting to form a co-crystal. Specifically, Ueto 2012 (Ground 1) teaches a 1:1:2 furosemide, nicotinamide, and water co-crystal, and the ’408

Application and Sowa 2013 (Ground 2) teaches a 1:1:1 genistein, nicotinamide, and water co-crystal.

i. U.S. Patent No. 2,665,277 (Homeyer)

379. During prosecution of the '956 application, the examiner rejected the then-pending application claims as anticipated and obvious over Homeyer. The examiner said that Homeyer “describes a method of making morphine phosphate hemihydrate. The said crystal contains a salt of an active agent (morphine phosphate) and a guest (water).” Ex. 1517, p. 3264, '956 application file history, October 5, 2009 Office Action at 3; *see* Ex. 1555, Homeyer at col. 1, l. 1 – col. 2, l. 48.

380. In response, Applicants amended the application claims to require that the co-former be a solid at room temperature and atmospheric pressure and argued that Homeyer does not teach a multiple-component solid phase composition wherein the co-former is a solid at room temperature and under atmospheric pressure. Ex. 1517, pp. 3348-53, '956 application file history, March 5, 2010 Response to Office Action at 2-7.

381. The primary references in Grounds 1 and 2, on the other hand, each discloses at least one co-crystal comprising at least one API and at least one co-former, wherein the co-former is a solid at room temperature and under atmospheric pressure. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

j. U.S. Patent No. 5,994,365 (the '365 patent)

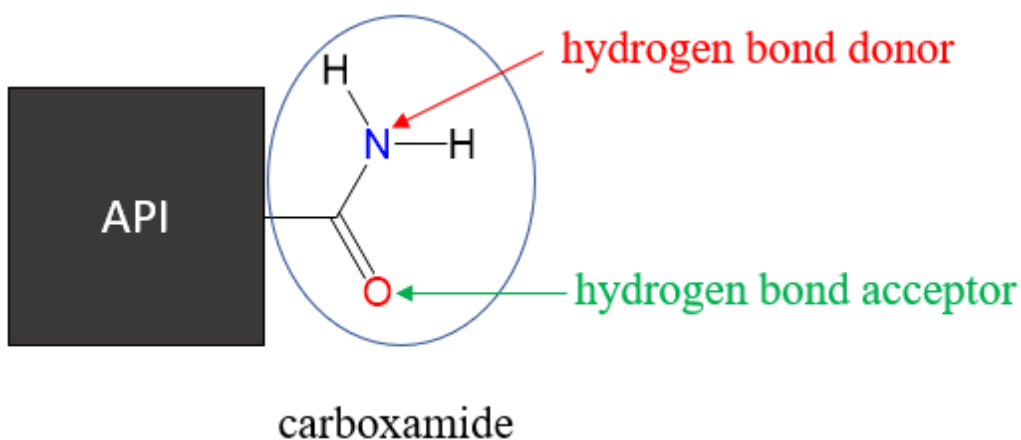
382. The examiner cited the '365 patent as an anticipatory reference during prosecution of the '956 application. The examiner explained that the '365 patent teaches a 1:2 co-crystal of fumaric acid and 1,8-DAA-3,6-(Me)₂ hemiacetone and a method of preparing it. Ex. 1517, p. 3369, '956 application file history, June 24, 2010 Office Action at 3; *see* Ex. 1558, '365 patent at col. 16, ll. 15-36.

383. Applicants responded that the '365 patent “does not teach an API that has a first supramolecular synthon comprising a hydrogen bond, as recited in amended [application] claim 25, as the API has no hydrogen bond donor.” Ex. 1517, p. 3464, '956 application file history, October 22, 2010 Response to Office Action at 8. According to Applicants,

Homosynthons are disclosed, for example in paragraph [0009], page 4 of the specification with examples thereof given in Examples 1-19 and Figures 4A, 5A, 6C, 7B, 8B, 10A, 14A, 15A, 16A, 17A, 18A, 19A, 20A, 21A, 22A, and 23A. These *homosynt[h]on functionalities are those that contain hydrogen bond donors and hydrogen bond acceptors*, as would be appreciated upon inspection by those skilled in the art. The ability to form a homosynthon is lacking in 1,8-DAA-3[,]6-(Me)₂, which although possessing a pair of hydrogen acceptors, lacks any hydrogen bond donors.

Ex. 1517, p. 3464, '956 application file history, October 22, 2010 Response to Office Action at 8 (emphasis added).

384. The primary references in Grounds 1 and 2 each teach at least one co-crystal comprising an API and a co-former wherein the API has a first chemical functionality—a carboxamide—that has both a hydrogen bond donor and acceptor, and that was shown by single crystal X-ray analysis to form API homosynthons. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2). The carboxamide’s hydrogen bond donor (*i.e.*, an atom or functional group that can form a hydrogen bond by donating a hydrogen) and hydrogen bond acceptor (*i.e.*, an atom or functional group that can form a hydrogen bond by accepting a hydrogen) are shown in the figure below.



385. Unlike the '365 patent, which, according to Applicants, teaches 1,8-DAA-3[,]6-(Me)₂ which “lacks any hydrogen bond donors” and therefore lacks the ability to form API homosynthons, the art cited in Grounds 1 and 2 establishes by single crystal X-ray analysis that the API taught in each primary reference forms API homosynthons at the carboxamide by hydrogen bonding between the

carboxamide's hydrogen bond donor and hydrogen bond acceptor. *See supra* §§ XI-XII (Invalidity Grounds 1 and 2).

k. JP-B-46-33588 (Sanzu)

386. During prosecution of the '956 application, the examiner rejected the then-pending application claims as anticipated by JP-B-46-33588 (Sanzu). The examiner said that Sanzu teaches, among other things, a phenazone paracetamol complex “in a molar ratio of approximately 1:1 or a weight percentage of phenazone [of] approximately 59-53%, [and] paracetamol [of] approximately 41-47% . . . meeting the limitations of the instant claims.” Ex. 1517, pp. 3370-71, '956 application file history, June 24, 2010 Office Action at 4-5; *see* Ex. 1562, Sanzu at 1.

387. In response, Applicants argued that “Sanzu does not teach a co-crystal” because “a co-crystal, being a single crystalline entity, has a fixed stoichiometry of component molecules” and Sanzu teaches that the composition of a co-crystal can vary in stoichiometry by $\pm 10\%$. Ex. 1517, pp. 3465-66, '956 application file history, October 22, 2010 Response to Office Action at 9-10.

388. The primary references in Grounds 1 and 2, on the other hand, each discloses at least one co-crystal having a fixed stoichiometric molar ratio of its components. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

I. Freemont et al., *Cocrystal Structure of an Editing Complex of Klenow Fragment with DNA*, 85 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 8924-28 (1998) (Freemont 1998)

389. Freemont 1998 was also cited by the examiner as an anticipatory reference during prosecution of the '956 application. The examiner said that Freemont 1998 “discloses complexes of both duplex and single-stranded DNA bound to Escherichia coli DNA polymerase I large fragment (Klenow fragment) [which] show four nucleosides of single-standard DNA bound to the 3'5' exonuclease active site and extending towards the polymerase active site, meeting the limitations of claim 25.” Ex. 1517, p. 4023, '956 application file history, August 2, 2013 Office Action at 4; *see* Ex. 1566, Freemont 1998 at 8924-28.

390. Applicants responded that the duplex or single stranded DNA in Freemont 1998, “does not possess a chemical functionality that forms API homosynthons comprising a hydrogen bond” and Freemont 1998 “does not explicitly teach or address forming a homosynthon. Nor does Freemont inherently disclose such a capability . . .” Ex. 1517, p. 4074, '956 application file history, January 14, 2014 Response to Office Action at 11.

391. Unlike Freemont 1998, which, according to Applicants, “does not possess a chemical functionality that forms API homosynthons comprising a hydrogen bond” and “does not explicitly teach or address forming a

homosynthon,” the art cited in Grounds 1 and 2 establishes by single crystal X-ray analysis that the API in the co-crystal taught in each primary reference has a first chemical functionality (a carboxamide) that forms API homosynthons. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

- m. **Smith et al., *The Utility of 4-Aminobenzoic Acid in Promotion of Hydrogen Bonding in Crystallization Processes: The Structures of the Cocrystals with Halo and Nitro Substituted Aromatic Compounds, and the Crystal Structures of the Adducts with 4-nitroaniline (1:1), 4-(4-nitrobenzyl)pyridine (1:2), and (4-nitrophenyl)acetic acid (1:1)*, 27 JOURNAL OF CHEMICAL CRYSTALLOGRAPHY 307-17 (1997) (Smith 1997)**

392. During prosecution of the '956 application, the examiner rejected the then-pending application claims as obvious over Smith 1997. The examiner said that Smith 1997 teaches co-crystals of 4-aminobenzoic acid with 4-nitroaniline, 4-(4-nitrobenzyl)pyridine, and (4-nitrophenyl)acetic acid, all having a stoichiometric ratio of either 1:1 or 1:2. Ex. 1517, pp. 4376-77, '956 application file history, February 25, 2016 Office Action at 13-14; Ex. 1517, p. 4434, '956 application file history, January 5, 2017 Office Action at 10 (same); *see* Ex. 1567, Smith 1997 at 307-17.

393. The examiner acknowledged that Smith 1997 does not teach that 4-aminobenzoic acid is an API but said that such limitation is taught by a secondary reference (Evgen'ev) and as such, it would have been obvious to a POSA “to have

envisioned that the cocrystals taught by Smith [would] be employed in the pharmaceutical art.” Ex. 1517, p. 4376, ’956 application file history, February 25, 2016 Office Action at 14; Ex. 1517, p. 4440, ’956 application file history, January 5, 2017 Office Action at 11 (same).

394. Applicants argued in response that unlike the then-pending ’956 application claims, Smith 1997 does not disclose a method that includes the claimed method steps of “(a) providing an API that will form a homosynthon, and (b) selecting a co-crystal co-former that will form a supramolecular synthon with the API via non-covalent hydrogen bonding.” Ex. 1517, pp. 4417-18, ’956 application file history, July 25, 2016 Response to Office Action at 11-12.

395. In contrast to Smith 1997, challenged claim 16 of the ’344 patent is directed to a pharmaceutical composition, regardless of how it is made, not a method like the ’956 application claims, so whether Smith 1997 discloses elements of a particular method arranged or combined in a certain way is not relevant to the analysis. *Supra* §§ XI-XII (Invalidity Grounds 1 and 2).

* * *

396. For the reasons above, the prior art substantively considered and evaluated by the patent examiner during prosecution of the ’344 patent and the ’956 application is materially different from the art discussed above in Grounds 1 and 2. Therefore, factor (a) weighs against discretionarily denying the petition.

2. Factor (b): The Cumulative Nature of the Asserted Art and the Prior Art Evaluated During Examination

397. In view of the substantive differences between the primary references evaluated by the patent examiner during prosecution of the '344 patent (and the '956 application) that I discussed above with respect to factor (a), *supra* § XIV.A.1, the art asserted in Grounds 1 and 2 above is not cumulative of the prior art evaluated during prosecution of the '344 patent (or the '956 application). Therefore, factor (b) weighs against discretionarily denying the petition.

3. Factor (d): The Extent of the Overlap Between the Arguments Made During Examination and the Manner in Which Petitioner Relies on the Prior Art or Patent Owners Distinguish the Prior Art

398. Since no primary reference of Ground 1 or Ground 2 (or any reference in the combinations in those Grounds) was the basis for any rejection during prosecution of either the '344 patent (or '956 application), *supra* § XIV.A.1 (factor (a)), or cumulative of the prior art evaluated by the examiner during prosecution, *supra* § XIV.A.2 (factor (b)), there is no overlap between the arguments made by the examiner during examination of the '344 patent (or '956 application) and those in Grounds 1 and 2.

399. Further, because the primary art references asserted in Grounds 1 and 2 teach limitations of challenged claim 16 that the Patents Owners alleged were lacking in the prior art evaluated by the examiner, *see supra* §§ XIV.A.1 (factor

(a)); XI-XII (Invalidity Grounds 1 and 2), there is no overlap between the arguments made by the examiner and those made by the Patent Owners distinguishing the evaluated prior art during prosecution. Therefore, factor (d) weighs against discretionarily denying the petition.

**a. Lack of Written Description and Enablement
Rejections During Prosecution of the '344 Patent and
'956 Application**

400. The examiner did not address written description or enablement at any time during prosecution of the '344 patent or '956 application. Nor did the examiner address whether the claims in either the '344 patent or '956 application were in fact entitled to claim priority to an earlier application. *See* Ex. 1516, p. 10, '344 patent file history, February 13, 2014 Application Data Sheet at 4 (claiming priority to the '768 application, filed March 1, 2002, and the '956 application, filed March 3, 2003); Ex. 1516, p. 189, '344 patent file history, April 1, 2014 Application Data Sheet at 4 (same); Ex. 1517, p. 4, '956 application file history, '956 application at 1 (claiming priority to the '768 application, filed March 1, 2002). Therefore, there is no evidence that the examiner considered the lack of written description and lack of enablement arguments discussed above, and these arguments are materially different from, and not cumulative of, arguments considered by the examiner.

401. In contrast to the '344 patent and '956 application examiner, the examiners of the related Almarsson patent and '223 application substantively addressed priority claims to earlier-filed applications (including the Priority Applications) on the basis of written description and enablement and found that support in those earlier-filed applications was lacking for application claims covering co-crystals beyond those specifically exemplified in the Examples. Ex. 1523, pp. 647-48, Almarsson file history, March 30, 2007 Non-Final Office Action at 3-4 ("The disclosure of the prior-filed applications, including application nos. 10/378,956, 10/367,829, 10/449,307 and 10/601,092, as well as the provisional and non-provisional applications to which they claim priority, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application . . . Accordingly, the instant claims do not receive benefit of the filing dates of these prior applications or the provisional and non-provisional application to which the claim priority."); Ex. 1522, p. 244, '223 application file history, November 5, 2019 Non-Final Office Action at 2 ("The disclosure of the prior-field application, Application No. 10/378956 fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph for one or more claims of this application . . . Based on this analysis the effective filing of the

instant application is 30 April 2017.’). *Supra* §§ IX.A.3 (lack of priority: written description), IX.B.2 (lack of priority: enablement).

402. The Examiner did not consider the patentability of the claims during prosecution of the ’344 patent or ’956 application as of 2014 and never specifically discussed the patentability of claim 16 of the ’344 patent during prosecution. Therefore, Petitioner’s argument that the Priority Applications do not adequately describe or enable claim 16 such that the claim is not entitled to claim priority to the 2002/2003 applications (and thus Ueto 2012, the ’408 Application, and Sowa 2013 are prior art), does not overlap with any argument made by the examiner during prosecution of the ’344 patent (or ’956 application).

4. Part 1 Conclusion

403. For the reasons explained above, the art and arguments in this declaration are not the same or substantially the same as those evaluated on the merits during prosecution of the ’344 patent (or the ’956 application). Therefore, the Board should not discretionarily deny the petition.

404. Since Ueto 2012, the ’408 Application, and Sowa 2013 were not cited by the examiner or by Applicants in an IDS during prosecution of the ’344 patent or the ’956 application, nor were they evaluated on the merits during prosecution of the ’344 patent or the ’956 application, I understand that the Board need not reach Part 2 of the discretionary denial analysis in this petition.

XV. AVAILABILITY FOR CROSS EXAMINATION

405. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, and with reasonable notice, I will appear for cross examination within the United States during the time allotted for cross examination.

* * *

406. 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, 2023



Robin D. Rogers, Ph.D.

APPENDIX A

Appendix A: Materials Considered

Exhibit	Description	Abbreviation
1501	U.S. Patent No. 10,633,344	'344 patent
1503	Declaration of Dr. Leah Appel, Ph.D.	Appel Declaration
1504	Hickey et al., <i>Performance Comparison of a Co-crystal of Carbamazepine with Marketed Product</i> , 67 EUR. J. PHARM. & BIOPHARM. 112–19 (2007)	Hickey 2007
1505	U.S. Patent No. 7,927,613	Almarsson
1506	MARTINDALE: THE COMPLETE DRUG REFERENCE, at v-x (preface), 1421–25 (entry for furosemide), 2117–19 (entry for nicotinamide) (37 th ed. 2011)	Martindale 2011
1507	Ueto et al., <i>Polymorphs and a Hydrate of Furosemide–Nicotinamide 1:1 Cocrystal</i> , 12 CRYST. GROWTH DES. 485-94 (2012)	Ueto 2012
1508	Li et al., <i>New Polymorphs of Isonicotinamide and Nicotinamide</i> , 47 CHEM. COMM. 1530-32 (2011)	Li 2011
1509	U.S. Patent Publication No. 2003/0224006 (published '956 priority application)	'006 Publication
1510	Loyd, <i>Oral Solid Dosage Forms</i> , in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (22 nd ed. 2012) vii (Preface), 581-610 (Chapter 30: Oral Solid Dosage Forms)	Remington 2012
1511	P.401408 Specification, Claims, Drawings & State of the Art Report (with translation), “Documents from the filing date,” available at https://ewyszukiwarka.pue.uprp.gov.pl/search/pwp-details/P.401408?lng=en (accessed May 4, 2023) (last accessed August 27, 2023)	'408 Application
1512	Sowa et al., <i>Cocrystals of Fisetin, Luteolin and Genistein with Pyridinecarboxamide Coformers: Crystal Structures, Analysis of Intermolecular Interactions, Spectral and Thermal Characterization</i> , 15 CRYSENGCOMM 7696-7708 (2013)	Sowa 2013
1513	Marini et al., <i>Effects of the Phytoestrogen Genistein on Bone Metabolism in Osteopenic</i>	Marini 2007

Exhibit	Description	Abbreviation
	<i>Postmenopausal Women</i> , 146 ANN. INTERNAL MED. 839–47 (2007)	
1514	U.S. Patent Application No. 60/360,768	'768 application
1515	U.S. Patent Application No. 10/378,956	'956 application
1516	Prosecution history of U.S. Patent No. 10,633,344 (filed as U.S. Patent Application No. 14/179,862) (foreign references removed)	'344 patent file history
1517	Prosecution history of U.S. Patent Application No. 10/378,956 (foreign references removed)	'956 application file history
1518	Joint Claim Construction & Prehearing Statement and Exhibit A (dated June 6, 2023); 3:22-cv-04913-AMO, D.I. 73	Joint Claim Construction & Prehearing Statement
1519	Plaintiffs' Opening Claim Construction Brief (dated August 1, 2023); 3:22-cv-04913-AMO, D.I. 77	Plaintiffs' Opening Claim Construction Brief
1521	U.S. Patent Application No. 15/639,223	'223 application
1522	Prosecution history of U.S. Patent Application No. 15/639,223 (foreign references removed)	'223 application file history
1523	Prosecution history of U.S. Patent No. 7,927,613 (filed as U.S. Patent Application No. 10/660,202) (foreign references removed)	Almarsson file history
1524	Desiraju, <i>Chemistry Beyond the Molecule</i> , 412 NATURE 397-400 (2001)	Desiraju 2001
1525	Aakeröy et al., <i>Do Polymorphic Compounds Make Good Cocrystallizing Agents? A Structural Case Study that Demonstrates the Importance of Synthon Flexibility</i> , 3 CRYST. GROWTH DES. 159-65 (2003)	Aakeröy 2003
1526	Dunitz, <i>Are Crystal Structures Predictable?</i> , 5 CHEM. COMMUN. 545-48 (2003)	Dunitz 2003
1527	Reddy et al., <i>Phenyl-Perfluorophenyl Synthon Mediated Cocrystallization of Carboxylic Acids and Amides</i> , 4 CRYST. GROWTH DES. 89-94 (2004)	Reddy 2004
1528	Fleischman et al., <i>Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving</i>	Fleischman 2003

Exhibit	Description	Abbreviation
	<i>Carbamazepine</i> , 3 CRYST. GROWTH DES. 909-19 (2003)	
1529	Aitipamula et al., <i>Polymorphs and Solvates of a Cocrystal Involving an Analgesic Drug, Ethenzamide, and 3,5-Dinitrobenzoic Acid</i> , 10 CRYST. GROWTH DES. 2229-38 (2010)	Aitipamula 2010
1530	Guillory, <i>Generation of Polymorphs. Hydrates, Solvates, and Amorphous Solids</i> , in POLYMORPHISM IN PHARMACEUTICAL SOLIDS (1999) 183-226	Guillory 1999
1531	21 C.F.R. § 184 (2000), Direct Food Substances Affirmed as Generally Recognized as Safe	21 C.F.R. § 184 (2000)
1532	Moss et al., <i>Glossary of Class Names of Organic Compounds and Reactive Intermediates Based on Structure (IUPAC Recommendations 1995)</i> , 67 PURE & APPL. CHEM. 1307–75 at 1307–10, 1316, 1341 (1995)	Moss 1995
1533	Leigh et al., PRINCIPLES OF CHEMICAL NOMENCLATURE: A GUIDE TO IUPAC RECOMMENDATIONS 14, 85 (1998)	IUPAC 1998
1534	Gavezzotti, <i>Are Crystal Structures Predictable?</i> 27 ACC. CHEM. RES. 309–14 (1994)	Gavezzotti 1994
1535	PHYSICIANS' DESK REFERENCE, at 1048–52 (entry for Coumadin®), 1427–31 (entry for Amoxil®), 2665–68 (entry for Vibramycin® Hyclate) (58 th ed. 2004)	Physicians' Desk Reference 2004
1536	Hilton & Deasy, <i>Use of Hydroxypropyl Methylcellulose Acetate Succinate in an Enteric Polymer Matrix To Design Controlled-Release Tablets of Amoxicillin Trihydrate</i> , 82 J. PHARM. SCI. 737–43 (1993)	Hilton 1993
1537	Coumadin® Label Revised October 2011	Coumadin® Label
1538	Vibramycin® Label Revised December 2022	Vibramycin® Label
1539	Amoxil® Label Revised September 2015	Amoxil® Label
1540	MARTINDALE: THE COMPLETE DRUG REFERENCE, at vii-viii (preface) (32 nd ed. 1999)	Martindale 1999

Exhibit	Description	Abbreviation
1548	Aakeröy, <i>Crystal Engineering: Strategies and Architectures</i> , B53 ACTA CRYST. 569-86 (1997)	Aakeröy 1997
1549	THE MERCK INDEX: AN ENCYCLOPEDIA OF CHEMICALS, DRUGS, AND BIOLOGICALS (13 th ed. 2001) Foreword, 6-7, 43, 49, 70, 80-81, 116, 147, 205, 234, 268-69, 298, 317-18, 326, 330-31, 333, 335, 337, 340, 341, 379, 413-14, 495, 507, 591-92, 606-07, 638, 665, 887, 978, 1032, 1095, 1101, 1112, 1128, 1205, 1242-43, 1249, 1292, 1297, 1335, 1342, 1344, 1391, 1479, 1501-02, 1614, 1630, 1631, 1764, 1766, 1782 (2001)	2001 Merck Index
1551	USPTO Assignment Database Entry for U.S. Patent No. 10,633,344, available at https://assignment.uspto.gov/patent/index.html#/patent/search/resultAbstract?id=10633344&type=patNum (accessed June 8, 2023)	USPTO Assignment Database Entry for '344 patent
1552	USPTO Assignment Database Entry for U.S. Patent Application No. 15/639,223, available at https://assignment.uspto.gov/patent/index.html#/patent/search/resultAbstract?id=15639223&type=applNum (accessed June 8, 2023)	USPTO Assignment Database Entry for '223 application
1553	Curriculum Vitae of Robin D. Rogers, Ph.D.	
1555	U.S. Patent No. 2,665,277	Homeyer
1556	U.S. Patent No. 3,664,858	Huffman
1557	U.S. Patent No. 5,023,092	DuRoss
1558	U.S. Patent No. 5,994,365	'365 patent
1559	U.S. Patent No. 6,559,293	'293 patent
1560	CA 1148020A1	McCoy
1561	GB 2169601	Jackson
1562	JP-B-46-33588 (UM00014569-71)	Sanzu
1563	Ammar, <i>Effect of Aromatic Hydrotropes on the Solubility of Carbamazepine. Part II: Effect of Nicotinamide, Sodium Salts of Benzoic, Naphthoic and Nicotinic Acids</i> , 35 EGYPT J. PHARMACEUT. SCI. 209-23 (1994)	Ammar 1994
1564	Caira, <i>Molecular Complexes of Sulfonamides. 3. Structure of 5-methoxysulfadiazine (Form II) and</i>	Caira 1994

Exhibit	Description	Abbreviation
	<i>its 1:1 Complex with Acetylsalicylic Acid</i> , 24 J. CHEM. CRYSTALLOGR. 695-701 (1994)	
1565	Desiraju, <i>Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis</i> , 34 ANGEW. CHEM. INT. ED. ENGL. 2311-27 (1995)	Desiraju 1995
1566	Freemont et al., <i>Cocrystal Structure of an Editing Complex of Klenow Fragment with DNA</i> , 85 PROC. NATL. ACAD. SCI. 8924-28 (1998)	Freemont 1998
1567	Smith et al., <i>The Utility of 4-Aminobenzoic Acid in Promotion of Hydrogen Bonding in Crystallization Processes: The Structures of the Cocrystals with Halo and Nitro Substituted Aromatic Compounds, and the Crystal Structures of the Adducts with 4-nitroaniline (1:1), 4-(4-nitrobenzyl)pyridine (1:2), and (4-nitrophenyl)acetic acid (1:1)</i> , 27 J. CHEM. CRYSTALLOGR. 307-17 (1997)	Smith 1997
1572	Housecroft & Sharpe, INORGANIC CHEMISTRY (4 th ed. 2012) 270 (UM00005301-04)	Housecroft 2012
1573	Huheey et al., INORGANIC CHEMISTRY: PRINCIPLES OF STRUCTURE AND REACTIVITY (4 th ed. 1993) 370 (UM00005305-08)	Huheey 1993
1574	Das & Baruah, <i>Supramolecular Synthons and Hydrates in Stabilization of Multicomponent Crystals of Nicotinamide and Isonicotinamide with N-Containing Aromatic Dicarboxylic Acids</i> , 11 CRYST. GROWTH DES. 5522-32 (2011)	Das 2011
1575	Vippagunta et al., <i>Crystalline Solids</i> , 48 ADVANCED DRUG DELIVERY REVIEWS 3-26 (2001)	Vippagunta 2001
1576	Palleros, <i>Basic Concepts</i> , in EXPERIMENTAL ORGANIC CHEMISTRY (2000) 19-44	Palleros 2000
1577	Olmsted & Williams, <i>Effect of Intermolecular Forces</i> , in CHEMISTRY, THE MOLECULAR SCIENCES (2 nd ed. 1997) 449-511	Olmstead 1997
1579	THE MERCK INDEX, at v–xiv (foreword, acknowledgments, explanatory notes), 740 (entry 4309, furosemide), 756–57 (entry 4391, genistein) (14 th ed. 2006)	2006 Merck Index

Exhibit	Description	Abbreviation
1586	P.401408 Patent Details (with translation), available at https://ewyszukiwarka.pue.uprp.gov.pl/search/pwp-details/P.401408?lng=en (accessed May 4, 2023) (last accessed August 27, 2023)	P.401408 Patent Details

APPENDIX B

Appendix B: Relevant Legal Standards

Below are the relevant legal principles of U.S. patent law provided to me by Petitioner's counsel.

1. Petitioner has the burden of proving that the challenged claim is unpatentable by a preponderance of the evidence, *i.e.*, Petitioner must show that the claim is more likely than not unpatentable.

A. Claim Construction

2. Patent claim terms are construed as they would be understood by a POSA as of the priority date of the patent at issue. Here, I have been asked to use 2002/2003 and 2014 as the relevant dates.

3. Claim terms must be interpreted in light of the intrinsic evidence, which includes the patent claims, the patent specification, and the patent's prosecution history. The prosecution history of any parent patent application (here, the '956 application) also constitutes intrinsic evidence.

4. Patent claim terms should be given their plain and ordinary meaning in view of the intrinsic record. Further, claims should be construed to give claims their full scope unless there is an explicit statement to the contrary by the patentee in the specification (*e.g.*, an explicit definition) or there was an explicit disavowal of claim scope during prosecution.

5. The Board may consider extrinsic evidence that was publicly available as of the priority date of the patent provided that it is not used to alter or contradict the meaning established by the intrinsic evidence. Where a claim term's meaning is clear in view of the intrinsic evidence, there is no need to consider any extrinsic evidence.

B. Obviousness

6. A patent claim is obvious if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious as of the priority date to which the claim is entitled.

7. When analyzing obviousness, the following must be considered:

- (1) the scope and content of the prior art;
- (2) the differences between the claimed invention and the prior art;
- (3) the level of ordinary skill in the art; and
- (4) any objective indicia of non-obviousness, such as unexpected results, commercial success, long-felt but unmet need, failure of others, copying by others, and skepticism of experts.

8. A single prior art reference can render a patent claim obvious if any differences between that prior art reference and the claim would have been obvious

to a POSA. A prior art reference may be combined with other references to disclose each element of the invention.

9. There must be some rationale for combining references or modifying a reference to show obviousness of the claimed subject matter and a reasonable expectation of success in doing so. Rationales can include:

- (1) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention;
- (2) combining prior art elements according to known methods to yield predictable results;
- (3) simple substitution of one known element for another to obtain predictable results;
- (4) use of a known technique to improve a similar device (method, or product) in the same way;
- (5) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; and
- (6) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

1. Objective Indicia (Secondary Considerations) of Non-Obviousness

10. The burden is on the Patent Owners to come forward with real-world evidence showing that an invention is non-obvious, *i.e.*, objective indicia (also called secondary considerations) of non-obviousness.

11. Secondary considerations will only be considered if the Patent Owners establish a nexus (*i.e.*, a connection) between the secondary considerations of non-obviousness and the novel features of the claim.

12. Any secondary considerations must be commensurate in scope with the claim, meaning that the evidence of non-obviousness must correspond to the full scope of the claimed subject matter.

C. Priority Date for Obviousness

13. Obviousness is analyzed as of the patent's priority date. Here, I have been asked to assess obviousness as of 2014.

14. A patentee may claim the benefit of the date of an earlier-filed application if the patentee shows that the earlier-filed application adequately discloses and enables the claimed subject matter. Here, I have been asked to assess whether Patent Owners are entitled to the benefit of the 2002/2003 filing dates of the Priority Application.

1. Written Description

15. To adequately describe the claimed subject matter, the earlier-filed application must reasonably convey to a POSA that as of the priority date, the patentee had possession of the full scope of the claimed subject matter.

16. Whether possession of the invention is shown is an objective inquiry limited to what is disclosed in the four corners of the patent specification.

17. A description that merely renders a claim limitation obvious is not sufficient to provide adequate written description support for that limitation.

18. A sufficient written description of a genus requires the disclosure of either structural features common to all members of the genus so that one of skill in the art can visualize or recognize all members of the genus, or a representative number of species falling within the scope of the genus.

19. Post-priority-date evidence may be relevant to determining whether the application discloses a representative number of species of the claimed genus.

2. Enablement

20. If a patentee wishes to obtain the benefit of an earlier priority date, the earlier-filed application must teach a POSA how to make and use the full scope of the claimed invention without undue experimentation as of the date of the earlier-filed application, *i.e.*, it must enable the claimed invention.

21. The following factors may be relevant for assessing whether undue experimentation is required:

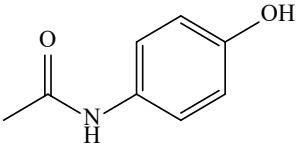
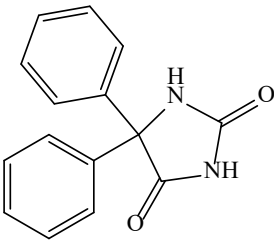
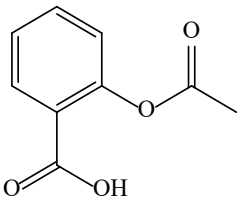
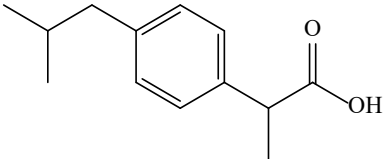
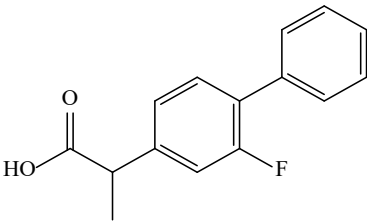
- (1) the quantity of experimentation necessary;
- (2) the amount of direction or guidance presented;
- (3) the presence or absence of working examples;
- (4) the nature of the invention;
- (5) the state of the prior art;
- (6) the relative skill of those in the art;
- (7) the predictability or unpredictability of the art; and
- (8) the breadth of the claims.

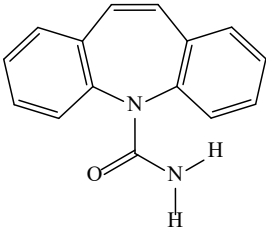
22. Even if an individual experiment is routine, the amount of experimentation required to practice the full scope of the claimed invention can be undue.

23. Post-priority-date evidence can be relevant to determining if the claim was enabled as of the priority date.

APPENDIX C

**Appendix C: Chemical Structures of APIs
Disclosed in the Priority Applications**

Name of API	Chemical structure
acetaminophen	
phenytoin	
aspirin	
ibuprofen	
flurbiprofen	

Name of API	Chemical structure
carbamazepine	 The chemical structure of carbamazepine is shown. It consists of a tricyclic system: a central six-membered ring with a double bond, fused to two benzene rings. A carbonyl group (C=O) is attached to the central ring, and a nitrogen atom (N-H) is attached to the carbonyl carbon.