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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

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

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Case IPR2023-01347  
U.S. Patent No. 10,633,344

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**NOVARTIS'S PETITION FOR *INTER PARTES* REVIEW  
OF U.S. PATENT NO. 10,633,344**

## **TABLE OF CONTENTS**

|       |                                                                                                                                  |    |
|-------|----------------------------------------------------------------------------------------------------------------------------------|----|
| I.    | Introduction.....                                                                                                                | 1  |
| II.   | Grounds for Standing (37 C.F.R. §42.104(a)).....                                                                                 | 2  |
| III.  | Identification of Challenge and Statement of Precise Relief Requested (37 C.F.R. §42.104(b)).....                                | 3  |
| IV.   | Summary of the '344 Patent and Challenged Claim .....                                                                            | 3  |
| V.    | Person of Ordinary Skill in the Art.....                                                                                         | 8  |
| VI.   | Claim Construction.....                                                                                                          | 8  |
| A.    | Terms With Agreed-Upon Constructions .....                                                                                       | 9  |
| B.    | Terms Where Petitioner Will Adopt Patent Owners' Constructions Solely for Purposes of This Petition .....                        | 10 |
| VII.  | Relevant Priority Date .....                                                                                                     | 11 |
| A.    | The Priority Applications Lack Written Description Support for the Solvates of Claim 16 .....                                    | 12 |
| 1.    | The Prosecution Histories of Related Applications Further Confirm Lack of Written Description.....                               | 17 |
| B.    | The Priority Applications Fail to Enable the Solvates of Claim 16 .....                                                          | 24 |
| C.    | The Priority Applications Lack Enablement Support for Co-Crystals of Claim 16 With a Carbonyl First Chemical Functionality ..... | 29 |
| VIII. | Ground 1: Claim 16 is Obvious Over Ueto in View of Li, Martindale, the '006 Publication, and Remington .....                     | 34 |
| A.    | Ueto .....                                                                                                                       | 34 |
| B.    | Li .....                                                                                                                         | 34 |
| C.    | Martindale .....                                                                                                                 | 35 |
| D.    | '006 Publication .....                                                                                                           | 35 |

|    |                                                                                                                                                                                                                         |    |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| E. | Remington .....                                                                                                                                                                                                         | 36 |
| F. | Claim 16 Is Obvious Over Ueto in View of Li, Martindale, the<br>'006 Publication, and Remington.....                                                                                                                    | 36 |
| 1. | [10b]: a co-crystal comprising supramolecular synthons,<br>each supramolecular synthon formed from stoichiometric<br>amounts of at least one active pharmaceutical ingredient<br>(API) and at least one co-former ..... | 37 |
| 2. | [10c]: wherein the API has a first chemical functionality that<br>permits formation of API homosynthons through non-<br>covalent hydrogen bonding when the API is in its pure form<br>.....                             | 39 |
|    | [10g]: wherein the first chemical functionality is (i) a<br>carboxamide, (ii) a carbonyl, or (iii) an amine .....                                                                                                       | 39 |
| 3. | [10d]: wherein the co-former has a second chemical<br>functionality complementary to the first chemical<br>functionality via non-covalent hydrogen bonding .....                                                        | 41 |
|    | [10f]: wherein supramolecular synthons are formed via non-<br>covalent hydrogen bonding between the first chemical<br>functionality of the API and the second chemical<br>functionality of the co-former .....          | 41 |
| 4. | [10e]: wherein said co-former is a solid at room temperature<br>and atmospheric pressure when the co-former is in its pure<br>form.....                                                                                 | 43 |
| 5. | [16b]: wherein the supramolecular synthons are non-<br>covalently bonded to one another by non-covalent bonding<br>to a solvent molecule .....                                                                          | 43 |
| 6. | [10a]: A pharmaceutical composition comprising a<br>pharmaceutically acceptable carrier and a therapeutically<br>effective amount [of a co-crystal comprising supramolecular<br>synthons] .....                         | 45 |
| 7. | Motivation to Combine the Ground 1 References With a<br>Reasonable Expectation of Success.....                                                                                                                          | 49 |

|     |                                                                                                                                                                                                                |    |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| IX. | Ground 2: Claim 16 is Obvious Over the '408 Application and/OR Sowa in view of marini, Li, the '006 Publication, and Remington .....                                                                           | 51 |
| A.  | The '408 Application .....                                                                                                                                                                                     | 51 |
| B.  | Sowa .....                                                                                                                                                                                                     | 53 |
| C.  | Marini .....                                                                                                                                                                                                   | 54 |
| D.  | Li, '006 Publication, and Remington .....                                                                                                                                                                      | 54 |
| E.  | Claim 16 Is Obvious Over the '408 Application and/or Sowa in View of Li, Marini, the '006 Publication, and Remington .....                                                                                     | 54 |
| 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 ..... | 54 |
| 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 .....                              | 57 |
|     | [10g]: wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine .....                                                                                                 | 57 |
| 3.  | [10d]: wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding.....                                                      | 58 |
|     | [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 .....           | 58 |
| 4.  | [10e]: wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form.....                                                                              | 61 |
| 5.  | [16b]: wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule .....                                                                        | 61 |

|       |                                                                                                                                                                                        |    |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 6.    | [10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount [of a co-crystal comprising supramolecular synthons] ..... | 63 |
| 7.    | Motivation to Combine the Ground 2 References With a Reasonable Expectation of Success.....                                                                                            | 66 |
| X.    | There Are No Secondary Considerations of Non-Obviousness.....                                                                                                                          | 69 |
| XI.   | Trial Should Be Instituted (35 U.S.C. § 314(a)).....                                                                                                                                   | 71 |
| XII.  | Trial Should Be Instituted (35 U.S.C. § 325(d)) .....                                                                                                                                  | 73 |
| XIII. | Conclusion .....                                                                                                                                                                       | 75 |
| XIV.  | Mandatory Notices.....                                                                                                                                                                 | 75 |
| A.    | Real Party in Interest (37 C.F.R. § 42.8(b)(1)) .....                                                                                                                                  | 75 |
| B.    | Related Matters (37 C.F.R. § 42.8(b)(2)).....                                                                                                                                          | 76 |
| C.    | Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)).....                                                                                                                                  | 76 |
| D.    | Service Information (37 C.F.R. § 42.8(b)(4)).....                                                                                                                                      | 77 |
| XV.   | Payment of Fees.....                                                                                                                                                                   | 77 |
| XVI.  | Word Count .....                                                                                                                                                                       | 77 |
| XVII. | Certificate of Service .....                                                                                                                                                           | 78 |

## **TABLE OF AUTHORITIES**

### **Cases**

|                                                                                                                             |        |
|-----------------------------------------------------------------------------------------------------------------------------|--------|
| <i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH,</i><br>IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020)..... | 73     |
| <i>Amgen Inc. v. Sanofi,</i><br>143 S. Ct. 1243 (2023).....                                                                 | 28     |
| <i>Amgen Inc. v. Sanofi,</i><br>872 F.3d 1367 (Fed. Cir. 2017) .....                                                        | 17     |
| <i>Ariad Pharm., Inc. v. Eli Lilly &amp; Co.,</i><br>598 F.3d 1336 (Fed. Cir. 2010) .....                                   | 12, 17 |
| <i>Celltrion, Inc. v. Genentech, Inc.,</i><br>IPR2017-01140, Paper 31 (PTAB Jan. 25, 2018) .....                            | 75     |
| <i>Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.,</i><br>800 F.3d 1375 (Fed. Cir. 2015) .....                              | 11     |
| <i>Ericsson Inc. v. Dali Wireless Inc.,</i><br>IPR2022-01212, Paper 17 (PTAB Feb. 1, 2023).....                             | 71     |
| <i>Extractiontek Sales LLC v. Gene Pool Techs., Inc.,</i><br>IPR2022-00832, Paper 15 (PTAB Oct. 31, 2022).....              | 72     |
| <i>Fox Factory, Inc. v. SRAM, LLC,</i><br>944 F.3d 1366 (Fed. Cir. 2019) .....                                              | 69     |
| <i>FS.com Inc. v. ITC,</i><br>65 F.4th 1373 (Fed. Cir. 2023) .....                                                          | 44     |
| <i>In re Fisher,</i><br>421 F.3d 1365 (Fed. Cir. 2005) .....                                                                | 29     |
| <i>Lectrosonics, Inc. v. Zaxcom, Inc.,</i><br>IPR2018-01129, Paper 33 (PTAB Jan. 24, 2020) .....                            | 70, 71 |
| <i>McKesson Info. Solutions, Inc. v. Bridge Med., Inc.,</i><br>487 F.3d 897 (Fed. Cir. 2007) .....                          | 74     |

|                                                                                                         |        |
|---------------------------------------------------------------------------------------------------------|--------|
| <i>Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys.,</i><br>166 F.3d 1190 (Fed. Cir. 1999) ..... | 29     |
| <i>Novartis AG v. Torrent Pharm. Ltd.,</i><br>853 F.3d 1316 (Fed. Cir. 2017) .....                      | 71     |
| <i>Rasmusson v. SmithKline Beecham Corp.,</i><br>413 F.3d 1318 (Fed. Cir. 2005) .....                   | 29     |
| <i>Sotera Wireless, Inc. v. Masimo Corp.,</i><br>IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020) .....      | 72, 73 |
| <i>Trs. of Bos. Univ. v. Everlight Elecs. Co.,</i><br>896 F.3d 1357 (Fed. Cir. 2018) .....              | 33     |
| <i>Tyco Healthcare Grp. LP v. Mut. Pharm. Co.,</i><br>642 F.3d 1370 (Fed. Cir. 2011) .....              | 71     |
| <i>Yita LLC v. MacNeil IP LLC,</i><br>69 F.4th 1356 (Fed. Cir. 2023) .....                              | 71     |

## **Statutes**

|                          |    |
|--------------------------|----|
| 35 U.S.C. § 103 .....    | 3  |
| 35 U.S.C. § 112 .....    | 11 |
| 35 U.S.C. § 120 .....    | 11 |
| 35 U.S.C. § 311 .....    | 3  |
| 35 U.S.C. § 314(a) ..... | 3  |

## **Regulations**

|                             |    |
|-----------------------------|----|
| 37 C.F.R. § 42.10(b) .....  | 77 |
| 37 C.F.R. § 42.103 .....    | 77 |
| 37 C.F.R. § 42.104(a).....  | 2  |
| 37 C.F.R. § 42.104(b) ..... | 3  |
| 37 C.F.R. § 42.105(a).....  | 78 |

|                             |    |
|-----------------------------|----|
| 37 C.F.R. § 42.15(a).....   | 77 |
| 37 C.F.R. § 42.24(a).....   | 77 |
| 37 C.F.R. § 42.24(d) .....  | 77 |
| 37 C.F.R. § 42.6(e).....    | 78 |
| 37 C.F.R. § 42.8(b)(1)..... | 75 |
| 37 C.F.R. § 42.8(b)(2)..... | 76 |
| 37 C.F.R. § 42.8(b)(3)..... | 76 |
| 37 C.F.R. § 42.8(b)(4)..... | 77 |

## I. INTRODUCTION

Novartis Pharmaceuticals Corporation (“Petitioner”) petitions for *inter partes* review of claim 16 of U.S. Patent No. 10,633,344 (“the ’344 patent”) (Ex. 1501), assigned to the Regents of the University of Michigan and the University of South Florida (“Patent Owners”).

Claim 16 is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal where the co-crystal is made up of an active pharmaceutical ingredient (“API”), a co-former, and a solvent, *i.e.*, a “solvate of a co-crystal.”

Claim 16 is a broad genus claim. The claimed solvates of co-crystals contain an API selected from a broad genus of possible APIs, a co-former selected from a broad genus of possible solid co-formers, and a solvent selected from a genus of potential solvents. Notwithstanding the breadth of claim 16, there is not a single Example or even a description of a co-crystal falling within its scope in the ’344 patent’s March 1, 2002 and March 3, 2003 priority applications. As such, there is no evidence that the inventors possessed the subject matter of claim 16 when the priority applications were filed in 2002/2003. And, in view of the unpredictability of co-crystal formation and solvate formation, the breadth of claim 16, and the complete lack of guidance on how to make solvates of co-crystals within the scope of claim 16, enablement is lacking in the priority applications as well. Thus, the

earliest possible priority date for claim 16 is February 13, 2014, the filing date of U.S. Application No. 14/179,862 (“the ’862 application”), which issued as the ’344 patent.

Prior to 2014, the subject matter of claim 16 was obvious in view of the combinations of prior art references in Grounds 1 and 2, including Ueto, which disclosed a furosemide/nicotinamide/water co-crystal (Ground 1), and the ’408 Application and Sowa, which each disclosed a genistein/nicotinamide/water co-crystal (Ground 2).

The above analysis is supported by Petitioner’s solid state chemistry expert, Dr. Robin Rogers, and drug formulation expert, Dr. Leah Appel, each having extensive experience in their respective disciplines. Ex. 1502, Rogers ¶¶ 2-14; Ex. 1503, Appel ¶¶ 6-11; Ex. 1553; Ex. 1554.

Because it is more likely than not that claim 16 is unpatentable, Petitioner respectfully requests that trial be instituted.

## **II. GROUNDS FOR STANDING (37 C.F.R. §42.104(a))**

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the ’344 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting such review on the identified Grounds.

### **III. IDENTIFICATION OF CHALLENGE AND STATEMENT OF PRECISE RELIEF REQUESTED (37 C.F.R. §42.104(b))**

Petitioner requests review of claim 16 of the '344 patent under 35 U.S.C. § 311 and AIA § 6, on the following Grounds.

| <b>Ground</b> | <b>Statutory Grounds</b> | <b>Patents and Printed Publications Relied On</b>                                                                                           |
|---------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 1             | 35 U.S.C. § 103 (AIA)    | Ueto (Ex. 1507)<br>Li (Ex. 1508)<br>Martindale (Ex. 1506)<br>'006 Publication (Ex. 1509)<br>Remington (Ex. 1510)                            |
| 2             | 35 U.S.C. § 103 (AIA)    | '408 Application (Ex. 1511)<br>Sowa (Ex. 1512)<br>Li (Ex. 1508)<br>Marini (Ex. 1513)<br>'006 Publication (Ex. 1509)<br>Remington (Ex. 1510) |

There is a reasonable likelihood that Petitioner will prevail (35 U.S.C. § 314(a)) and therefore review should be instituted.

### **IV. SUMMARY OF THE '344 PATENT AND CHALLENGED CLAIM**

The '344 patent entitled "Multiple-Component Solid Phases Containing At Least One Active Pharmaceutical Ingredient" issued from the '862 application,

filed February 13, 2014. The '344 patent claims priority to provisional applications U.S. Application No. 60/360,768 (“the '768 priority application”), filed March 1, 2002, and U.S. Application No. 10/378,956 (“the '956 priority application”), filed March 3, 2003 (collectively, the “Priority Applications”). The '344 patent has expired.

Claim 16, which depends from claim 10, is the sole claim challenged in this Petition. Claims 10 and 16 are reproduced below, divided into limitations to simplify the analysis.

| Claim | Limitations                                                                                                                                                                                                                                                                                                                                         |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16    | <p>[16a] The pharmaceutical composition of claim 10 [<i>i.e.</i>, limitations [10a] – [10g], below],</p> <p>[16b] wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.</p>                                                                                                   |
| 10    | <p>[10a] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of</p> <p>[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</p> |

| Claim | Limitations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|       | <p>[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</p> <p>[10d] wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding</p> <p>[10e] wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form</p> <p>[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</p> <p>[10g] wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.</p> |

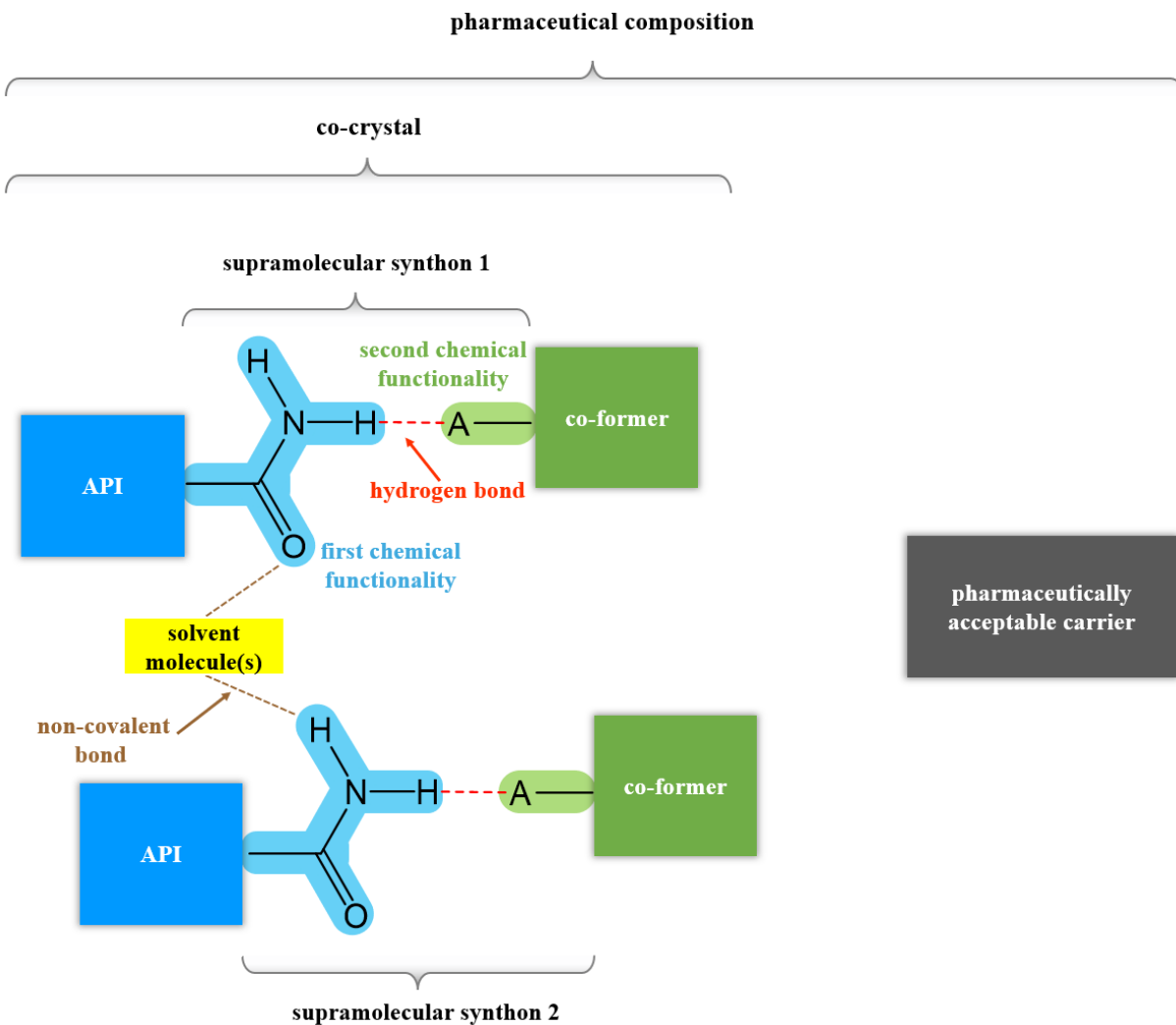
As depicted in the exemplary figure below, claim 16 is directed to a pharmaceutical composition comprising a therapeutically effective amount of a co-crystal and a pharmaceutically acceptable carrier (limitation [10a]). The claimed co-crystals comprise repeating units of an API (in blue) having a “first chemical functionality” (carboxamide is used in the figure below as an example), a co-former (in green) having a complementary “second chemical functionality,” (which can be a hydrogen bond donor or a hydrogen bond acceptor; the figure

below generically depicts an acceptor (“A”)), and a solvent (in yellow). The API’s first chemical functionality (carboxamide, carbonyl, or amine) (limitation [10g]) hydrogen bonds (shown in red) with the co-former’s second chemical functionality, forming supramolecular synthons (limitations [10b], [10d], [10f]). It is important to recognize that the supramolecular synthon is not the *entire* API and co-former; rather, it is made up of only the API’s first chemical functionality and the co-former’s second chemical functionality, and the bonds between them. Ex. 1502, Rogers ¶¶ 29, 44-46, 69; *infra* § VI.A; Ex. 1519 at 2-3.<sup>1</sup>

The supramolecular synthons must be non-covalently bonded to one another by non-covalent bonding to a solvent molecule (limitation [16b]). As shown below, supramolecular synthon 1 is non-covalently bonded to supramolecular synthon 2 by non-covalent bonding (brown dashed lines) to solvent (yellow) (an API-solvent-API connection between the two supramolecular synthons is shown below, as an example). Ex. 1502, Rogers ¶¶ 29-30, 48-51, 69-70.

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<sup>1</sup> Page cites refer to the pages of the original document, apart from prosecution histories, where page cites refer to the stamped page numbers.



In addition, claim 10, from which claim 16 depends, describes properties of the API and co-former when in their respective pure forms. The API's first chemical functionality must permit formation of API homosynthons when the API is in its pure form (*i.e.*, identical first chemical functionalities on adjacent API molecules interact with one another by hydrogen bonding (limitation [10c])), and the co-former must be solid at room temperature and atmospheric pressure (limitation [10e]). Ex. 1502, Rogers ¶ 31.

## **V. PERSON OF ORDINARY SKILL IN THE ART**

A person of ordinary skill in the art (“POSA”) of the ’344 patent 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. Alternatively, a POSA 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. These two alternate POSAs can also work together as part of a team, and consult with others having ordinary experience in other disciplines. Ex. 1502, Rogers ¶ 19; Ex. 1503, Appel ¶ 30; Ex. 1553; Ex. 1554.

## **VI. CLAIM CONSTRUCTION**

Petitioner sets forth constructions of the terms below, which it believes will assist the Board in understanding and resolving disputed issues. The terms are grouped in two categories: (A) terms with agreed-upon constructions (or agreed-upon portions of constructions, where the disputed portions are not relevant to issues raised in this Petition), and (B) terms currently disputed in parallel litigation between the parties; however, because claim 16 is unpatentable under Patent

Owners' constructions, Petitioner adopts those constructions solely for the purpose of this Petition to minimize the issues the Board must decide. For each of the terms below, it is Petitioner's position that the terms would have been construed by the POSA the same way as of 2002/2003 and 2014.

**A. Terms With Agreed-Upon Constructions**

**“active pharmaceutical ingredient (API)”/“API”:** “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. 1519 at 21.

**“API homosynthons”:** “synthons formed between identical and complementary chemical functionalities of the API.” Ex. 1518, Ex. A at 6-7.

**“carbonyl”:** “-C(=O)-; for clarity, ‘carbonyl’ does not refer to the -C(=O)-portion of another functional group such as carboxylic acid or carboxamide.” *Id.* at 1.

**“carboxamide”:** The parties dispute the meaning of “carboxamide” as used in the '344 patent, but agree that it encompasses -C(=O)NH<sub>2</sub>. Ex. 1519 at 22; Ex. 1502, Rogers ¶ 59.

**“co-former”:** The parties agree that co-former is used synonymously with co-crystal former and that a co-former is a component of a co-crystal. Ex. 1518, Ex. A at 5-6; Ex. 1502, Rogers ¶ 60. Petitioner describes the co-crystal as a

“molecular *component*” whereas Patent Owner describes it as a “*component* compound;” however, that dispute is not pertinent to any issue in this Petition. Ex. 1518, Ex. A at 5-6.

**“supramolecular synthon”**: “[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.” *Id.* at 1. *See also* Ex. 1519 at 2-3 (“[A] supramolecular synthon consists of two or more chemical functionalities and the noncovalent bond(s) between them.”).

**“wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule”**: “[p]lain and ordinary meaning, which is ‘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 at 1.

**B. Terms Where Petitioner Will Adopt Patent Owners’ Constructions Solely for Purposes of This Petition**

**“co-crystal”**: Although Petitioner disagrees with Patent Owners’ construction of the term “co-crystal,” solely for purposes of this Petition, Petitioner adopts Patent Owners’ proposal: “A multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.” *Id.* Ex. A at 1-5; Ex. 1502, Rogers ¶ 63.

## VII. RELEVANT PRIORITY DATE

In Grounds 1 and 2, Petitioner relies on art dated after the 2002/2003 filing dates of the Priority Applications. Patent Owners will be unable to meet their burden of production of showing written description and enablement support for claim 16 as of the 2002/2003 filing dates of the Priority Applications, as required by 35 U.S.C. §§ 112 and 120 (pre-AIA). *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378-81 (Fed. Cir. 2015).

Patent Owners claimed broadly in claim 16, notwithstanding that the Priority Applications included nothing more than a general research plan (not directed to solvates of co-crystals) and several specific and limited co-crystal Examples, none of which falls within the scope of claim 16. Ex. 1502, Rogers ¶¶ 29-33, 73. Claim 16 is a broad genus claim where the API may be selected from a large genus of potential APIs, the complementary co-former selected from a large genus of potential solid co-formers, and the solvent selected from a genus of potential solvents, providing an essentially limitless number of options. *Id.* ¶¶ 125-29. The Priority Applications do not include written description or enablement support commensurate with the subject matter of claim 16 for at least three independent reasons.

In particular, the Priority Applications lack: (A) written description support for the full scope of solvates of co-crystals encompassed by claim 16, (B)

enablement support for the full scope of those solvates of co-crystals, and (C) enablement support for the solvates of co-crystals where the first chemical functionality is a carbonyl. As a result, the earliest possible priority date is the February 13, 2014 filing date of the '862 application.

**A. The Priority Applications Lack Written Description Support for the Solvates of Claim 16**

Adequate written description requires that the patent specification “clearly allow persons of ordinary skill in the art to recognize that [the inventors] invented what is claimed,” *i.e.*, it must “reasonably convey[] to those skilled in the art that the inventor[s] had possession of the claimed subject matter as of the filing date.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). Written description of a genus claim such as claim 16, requires disclosure of either (1) structural features common to all members of the genus allowing a POSA to “visualize or recognize” the members of the genus, or (2) a representative number of species within the genus, neither of which is present here. *Ariad*, 598 F.3d at 1350.

The Priority Applications are devoid of written description support for claim 16, particularly claim limitation [16b], “wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.” Nowhere do the Priority Applications disclose, teach, or suggest co-

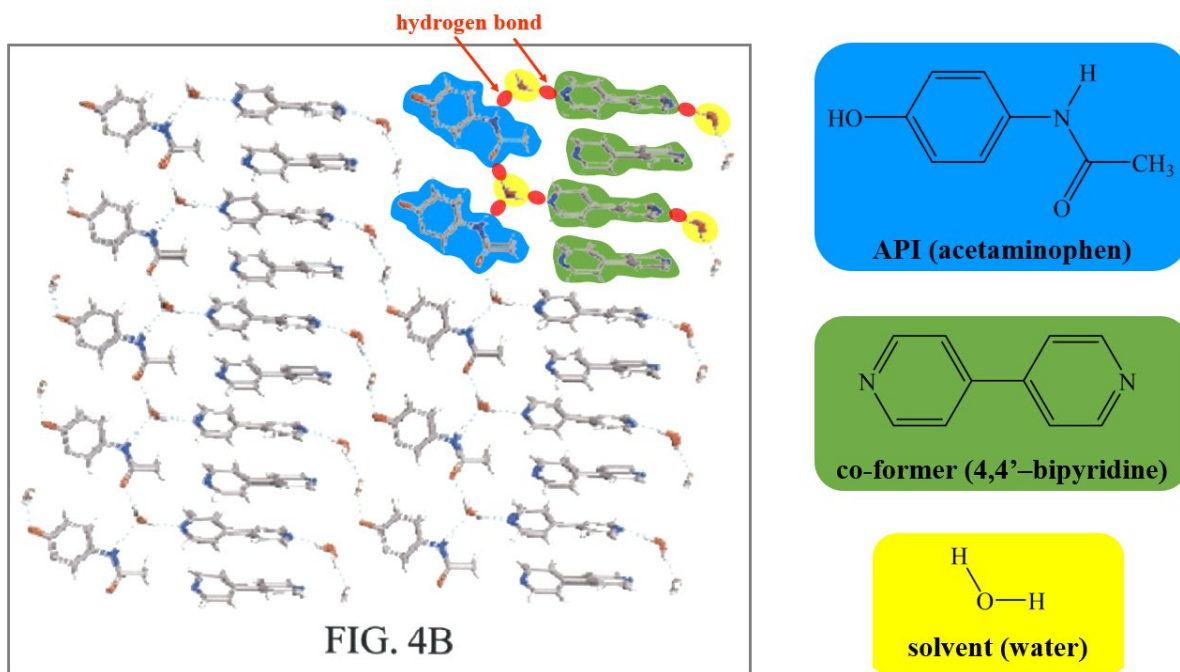
crystals where solvent molecules non-covalently link the claimed supramolecular synthons. Ex. 1502, Rogers ¶¶ 65-71.

**No common structural features.** Because claim 16 does not limit the structure of the API (beyond specifying the first chemical functionality), co-former, or solvent components of the claimed co-crystals, let alone their structures when combined into a co-crystal, the common structural features test for establishing written description does not apply; there are no structural features common to all embodiments of the challenged claim. *Id.* ¶¶ 68, 72.

**No representative examples.** None of the Examples in the Priority Applications describes a co-crystal within the scope of claim 16. Because all of the Examples and disclosures in the 2002 '768 priority application are included in the 2003 '956 priority application, the discussion below focuses on the '956 priority application. Of the 19 Examples in the '956 priority application, Examples 1, 3, and 11 are the only ones that reference an API, solid co-former, and solvent in the final product, and thus the only Examples that could potentially fall within the scope of claim 16. *Id.* ¶¶ 71, 73-90. None does.

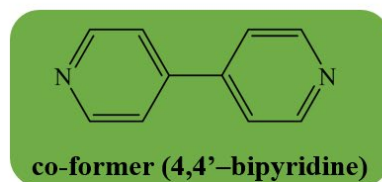
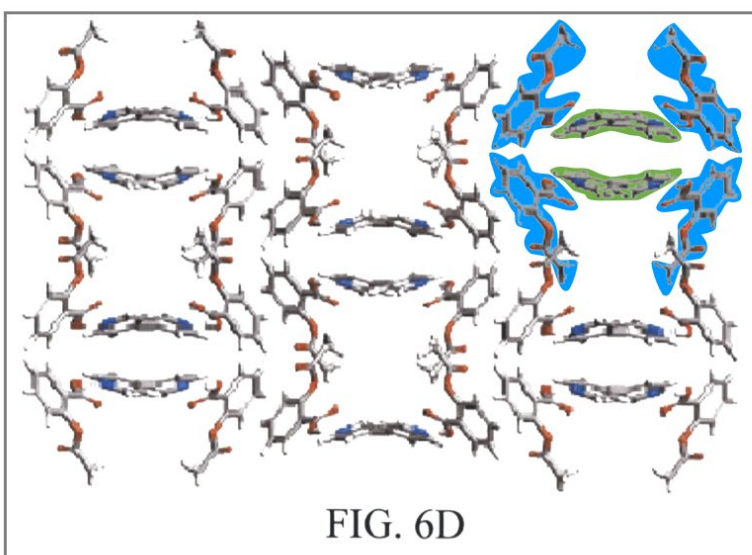
**Example 1** does not have the supramolecular synthons required by claim limitation [10f], “formed via noncovalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.” In Example 1’s “1:1:1 acetaminophen/4,4’-bipyridine/water co-crystal, as

shown in FIG. 4B” (Ex. 1515 at 16, Fig. 4B), there is no hydrogen bonding between the first chemical functionality of the API (shaded blue in the annotated Figure 4B, below) and the second chemical functionality of the co-former (shaded green). Ex. 1502, Rogers ¶¶ 74, 76-77. Without such hydrogen bonding, the supramolecular synthon limitation [10f] is not met and therefore limitation [16b] cannot be met. *Id.* ¶¶ 74, 76-78. The only dashed lines (which typically show hydrogen bonding) in the figure are between the API (acetaminophen, shaded blue) and solvent (water, shaded yellow), or between the co-former (4,4'-bipyridine, shaded green) and solvent (water, shaded yellow). *Id.* ¶ 77; Ex. 1515 at Fig. 4B.



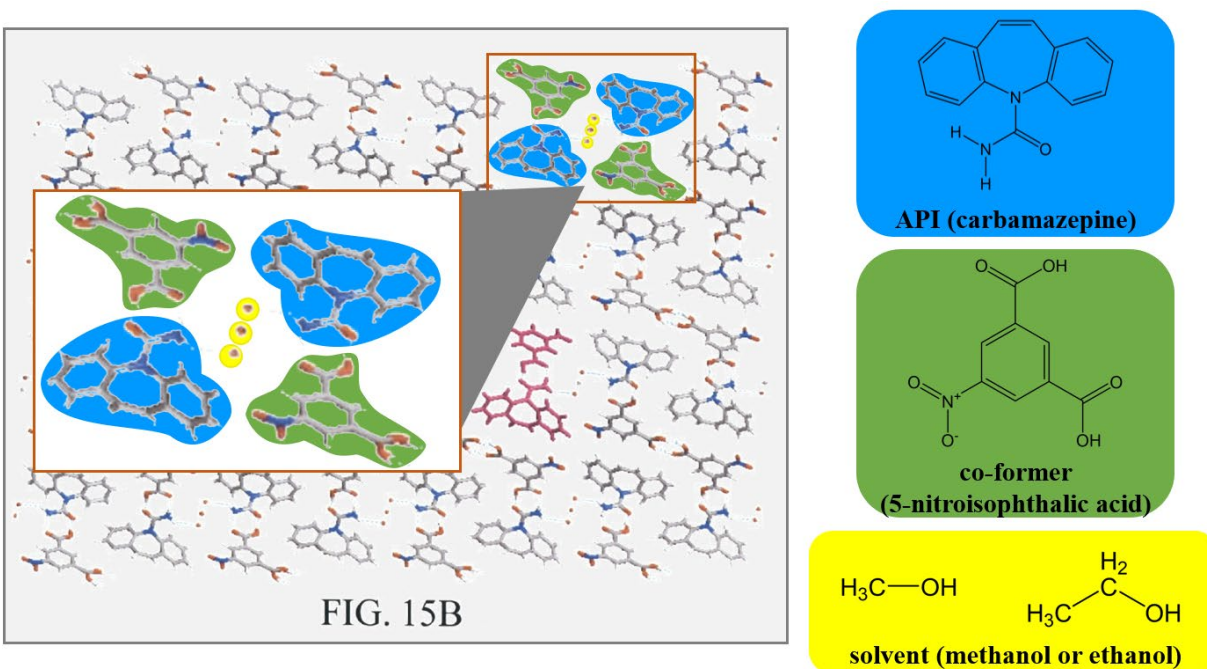
**Example 3’s** co-crystal (“2:1 aspirin/4,4'-bipyridine”) shown in Figure 6D is described as “an inclusion compound containing disordered solvent in the

channels.” Ex. 1515 at 18, Fig. 6D. A POSA would understand that the solvent was trapped (included) in voids within the crystal structure and not non-covalently linking the claimed supramolecular synthons. Ex. 1502, Rogers ¶¶ 80-84. Solvent is not even depicted in Figure 6D (shown below, with annotations) and there is no evidence that solvent links the supramolecular synthons as required by limitation [16b]. *Id.*



**Example 11**’s co-crystal (“1:1 carbamazepine/5-nitroisophthalic acid”) shown in Figure 15B (reproduced below with annotations) is described as having “solvent hydrogen bonded to an additional N—H donor from the carbamazepine

moiety.” Ex. 1515 at 26-27, Fig. 15B. Based on this description and Figure 15B,<sup>2</sup> a POSA would understand that the solvent (methanol (CH<sub>3</sub>OH) or ethanol (CH<sub>3</sub>CH<sub>2</sub>OH)) interacts only with one carbamazepine, and does not link supramolecular synthons as required by limitation [16b]. Ex. 1502, Rogers ¶¶ 85-90.



Therefore, the Priority Applications do not include any examples, let alone a representative number of examples, to support the full scope of claim 16. *Id.* ¶¶ 73-75, 79, 84, 90-93.

<sup>2</sup> A POSA would not understand the three circles shaded in yellow in Figure 15B to be atoms of a single solvent molecule because they are not connected to one another and they are too close together. Ex. 1502, Rogers ¶¶ 87-88.

Even if one or more of the co-crystals of Examples 1, 3, and/or 11 fell within claim 16 (Petitioner disagrees), the Priority Applications do not provide any information that would allow a POSA to extrapolate them to the full scope of the claimed genus. *Id.* ¶ 91. Disclosure of at most three species is insufficient to reasonably convey that the patentees had possession of the broad genus of solvates of co-crystals encompassed by claim 16. *Ariad*, 598 F.3d at 1350-52. A diverse range of solvates of co-crystals fall within the scope of claim 16, including those disclosed in Ex. 1507, Ueto (furosemide/nicotinamide/water); Ex. 1512, Sowa and Ex. 1511, the '408 Application (genistein/nicotinamide/water); and Ex. 1574, Das (isonicotinamide/dipicolinic acid/water); Ex. 1502, Rogers ¶ 92.<sup>3</sup> The co-crystals of Examples 1, 3, and 11 are not representative of that diverse class and are thus insufficient to provide written description. Ex. 1502, Rogers ¶¶ 65-66, 73-75, 92-93.

**1. The Prosecution Histories of Related Applications Further Confirm Lack of Written Description**

That claim 16 lacks written description support in the Priority Applications is further confirmed by the prosecution histories of related patent applications,

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<sup>3</sup> Evidence that a patent specification does not disclose a representative number of species of a claimed genus may include evidence that post-dates the priority date. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017).

including U.S. Patent Application No. 15/639,223 (“the ’223 application”) and U.S. Patent Application No. 10/660,202, which issued as U.S. Patent No. 7,927,613 (“Almarsson”). The examiners of these applications, unlike the ’344 patent examiner, expressly considered written description and rejected overbroad application claims similar to claim 16 of the ’344 patent on those bases. Unfortunately, the ’344 patent examiner did not have the benefit of reviewing these rejections, including those dated before the ’344 patent issued.

**’223 application:** The ’223 application shares a common specification with the 2003 ’956 priority application and names the same three ’344 patent inventors. Ex. 1502, Rogers ¶¶ 95-96. There are significant similarities between ’223 application claim 37 (the sole independent claim when the application was abandoned) and claim 16 of the ’344 patent, shown below (differences are underlined and comments added in italics). *Id.* ¶ 107.

| <b>’223 Application Claim 37</b>                                                  | <b>’344 Patent Claim 16</b>                                                                                                              |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| [ <i>See rows below corresponding to ’344 patent claim elements [10a]-[10g]</i> ] | [16a] <u>The pharmaceutical composition of claim 10,</u>                                                                                 |
|                                                                                   | [16b] <u>wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.</u> |

| '223 Application Claim 37                                                                                                                                                                                              | '344 Patent Claim 16                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 <sup>4</sup> | [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 (Ex. 1502, Rogers ¶ 107)</i> ]                            |

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<sup>4</sup> As the parties agree that “co-former” and “co-crystal former” are used synonymously in the '344 patent (*supra* p. 9), these differences are not underlined.

| '223 Application Claim 37                                                                                                                                                        | '344 Patent Claim 16                                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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, <u>and</u> | [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,                                                          |
| wherein the first chemical functionality is <u>selected from carboxylic acid, amide, N-heterocycle, and alcohol</u> ;                                                            | [10g] <sup>5</sup> wherein the first chemical functionality is (i) <u>a carboxamide</u> , (ii) <u>a carbonyl</u> , or (iii) <u>an amine</u> .<br><br>[“ <i>carboxamide</i> ” is a type of “ <i>amide</i> ” (Ex. 1502, Rogers ¶ 107)] |
| wherein the co-crystal former has a second chemical functionality complimentary [ <i>sic</i> ] 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,                                                                               |

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<sup>5</sup> Limitation [10g] is listed out of order to facilitate the comparison.

| '223 Application Claim 37                                                                                                                                                                                                                                                                        | '344 Patent Claim 16                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>[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, nearly all of which will be solids at room temperature and atmospheric pressure (Ex. 1502, Rogers ¶ 107; Ex. 1521, ¶ [0042])]</i></p> | <p>[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></p>                                                                    |
| <p>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</p>                                                                                     | <p>[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,</p> |
| <p><u>wherein the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol;</u></p>                                                                                                                                                                                           | <p><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 (Ex. 1502, Rogers ¶ 107)]</i></p> |

Ex. 1522, p. 368; Ex. 1501, claims 10, 16.

During prosecution of the '223 application, application claim 37 was rejected for lack of written description. The examiner commented that the claims were “broad and generic, with respect to all possible compounds encompassed by the claims” and “[t]he possible structural variations are limitless to any [] pharmaceutical composition comprising an API and a co-crystal former that are associated through non-covalent hydrogen binding.” Ex. 1522, p. 394; *id.* p. 317; Ex. 1502, Rogers ¶¶ 97-100. Further, the '223 examiner stated that in the '223 specification (which is the same as the '956 priority application), “there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the [E]xamples,” the specification “lacks sufficient variety of species to reflect th[e] variance in the [claimed] genus,” and the specification “does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.” Ex. 1522, pp. 394-95; *id.* p. 317; Ex. 1502, Rogers ¶¶ 97-106, 108. Thus, the '223 application examiner recognized that the '223 specification (which is the same as the '956 priority application here, Ex. 1502, Rogers ¶¶ 96, 98, 108) had limited disclosures and those disclosures could not be extrapolated to non-exemplified species. *Id.* ¶¶ 97-100, 103-04, 108-09.

**Almarsson:** Almarsson was filed as a continuation-in-part of the 2003 '956 priority application. Ex. 1505 at cover. Almarsson includes many of the '956

priority application's 19 Examples as well as additional teachings, Examples, and tables, and includes as inventors the '344 patent inventors. Ex. 1502, Rogers ¶¶ 110-11.

During prosecution, the Almarsson examiner issued a written description rejection against broad co-crystal claims because the specification failed to “describe[] or show[] how the numerous and diverse different co-crystals could be obtained.” *See* Ex. 1523, p. 803; *id.* p. 747; Ex. 1502, Rogers ¶¶ 112-17, 120.

Ultimately, the Almarsson applicants limited the application claims to only those that specifically recited the co-crystals in the Examples. Ex. 1523, pp. 807-13; Ex. 1502, Rogers ¶¶ 118-20.

**Conclusion based on related applications:** In the prosecution of the related applications, the patent examiners (who were different from the '344 patent examiner, Ex. 1502, Rogers ¶¶ 95, 111) found written description lacking for claims encompassing more than the Examples in the specifications—specifications that were the same as, or contained similar disclosures to, the Priority Applications here. Further, the application claims discussed above in the '223 application and Almarsson did not include claim 16's limitation [16b], requiring a non-covalent interaction between supramolecular synthons and solvent, which is not described anywhere in the Priority Applications and is a further basis for finding lack of written description here. *Id.* ¶¶ 96, 108-10, 120-21.

## **B. The Priority Applications Fail to Enable the Solvates of Claim 16**

As reflected in the *Wands* factor analysis below, a POSA in 2002/2003 could not have practiced the full scope of claim 16 without undue experimentation. *Id.* ¶ 123.

**(1) Breadth of the Claim:** Claim 16 is broad. The co-crystals encompassed by claim 16 can be made up of (a) any API having one of the three first chemical functionalities recited in claim 10, (b) any solid co-former having a second chemical functionality complementary to the API's first chemical functionality, and (c) any pharmaceutically acceptable solvent, where the solvent links supramolecular synthons in any manner by any type of non-covalent bond. *Id.* ¶¶ 125-29. This factor supports non-enablement.

**(2) Nature of the Invention, (3) State of the Art, (4) Predictability of the Art:** Claim 16 is directed to pharmaceutical compositions comprising solvates of co-crystals with specific non-covalent interactions. *Id.* ¶ 130.

As of 2002/2003, it was not possible to predict with reasonable certainty whether any solvate would form, or whether any co-crystal would form, let alone a solvate of a co-crystal comprising an API, co-former, and solvent, and having the specific non-covalent interactions required by claim 16. *Id.* ¶ 131. "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.” Ex. 1575 at 18 (emphasis added). A POSA would have understood that this unpredictability with respect to forming solvates of “compounds” was equally (if not more so) applicable to solvates of “co-crystals,” which include an additional co-former component. Ex. 1502, Rogers ¶ 131.

Separate from the unpredictability associated with solvate formation, there was unpredictability associated with co-crystal formation (generally). Ex. 1524 at 398-400 (“[I]n 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.”); Ex. 1525 at 164; Ex. 1526 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.” (emphasis in original)); Ex. 1502, Rogers ¶ 132. Further, the art includes many examples of failures to predict whether co-crystals would form at all, or what interactions they would have if they formed. *See, e.g.*, Ex. 1527 at 90; Ex. 1525 at 160; Ex. 1507, Ueto at 487; Ex. 1520, 18:2-17, 27:5-9; Ex. 1502, Rogers ¶ 133.

Even the ’344 patent applicants acknowledged the complexity and unpredictability of co-crystal formation (generally) during prosecution of the ’956

application, stating: “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 (emphasis added). While the applicants purported to set themselves apart from the unpredictable state of the prior art on the basis 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,” that statement is misleading at best,<sup>6</sup> and certainly not applicable to claim 16 for which no Examples are provided in the Priority Applications. Ex. 1502, Rogers ¶ 134.

Further, the Priority Applications’ Examples confirm that it is unpredictable whether co-crystals prepared using solvent-based methods will incorporate solvent into the co-crystal. Of the 13 Examples where an API and solid co-former were

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<sup>6</sup> The inventors’ own work reported in Fleischman confirms the unpredictability of co-crystal formation (generally). Fleischman discusses attempts to synthesize co-crystals of carbamazepine (the API in 13 of the ’956 priority application Examples) with about 50 different co-formers, and even with this relatively simple API having few potential hydrogen-bonding sites, the “success ratio” was only 20%. Ex. 1528 at 911; Ex. 1502, Rogers ¶ 135.

dissolved in a solvent to prepare the co-crystal, only three resulted in a final product that includes a solvent (Examples 1, 3, and 11, discussed *supra* § VII.A), and none falls within claim 16. Ex. 1502, Rogers ¶¶ 136-38. These factors support non-enablement.

**(5) Relative Skill of Those in the Art:** This factor is neutral with respect to enablement because although the level of skill is high, the art is unpredictable. *Supra* § V; Ex. 1502, Rogers ¶ 139.

**(6) Presence or Absence of Working Examples, (7) Amount of Direction or Guidance:** The Priority Applications do not include *any* Examples or other guidance that would allow a POSA to practice claim 16. *See supra* § VII.A; Ex. 1502, Rogers ¶¶ 140-43.

In addition, a POSA would understand that solvent can *disrupt* hydrogen bonding, interfering with co-crystal formation, and the Priority Applications offer no guidance on this issue. Ex. 1530 at 192; Ex. 1502, Rogers ¶¶ 144-45.

The specification is completely lacking in instructions on how to make solvates of co-crystals of claim 16, supporting non-enablement. Ex. 1502, Rogers ¶¶ 143, 145.

**(8) Quantity of Experimentation:** Because solvate formation is not predictable, and co-crystal formation is not predictable, incorporation of a solvent into a co-crystal with the bonding pattern required by claim 16 was certainly not

predictable and significant experimentation would be required to prepare such co-crystals. *Id.* ¶¶ 146-48. In view of the unpredictability in the art (factor 4) and lack of guidance in the Priority Applications (factors 6, 7), a POSA would have to engage in an iterative trial and error process involving the manipulation of numerous variables (*e.g.*, API, co-former, solvent, reaction time, temperature, concentration), in which many failures could result, to practice the full scope of claim 16, which is broad (factor 1). *Id.* ¶ 148. This factor supports non-enablement.

**Conclusion:** Seven of the eight *Wands* factors suggest undue experimentation is required to practice the full scope of claim 16, and one factor is neutral. *Id.* ¶ 149. Thus, the *Wands* factors overwhelmingly support a finding of non-enablement for claim 16 as of the 2002/2003 filing dates of the Priority Applications. *Amgen Inc. v. Sanofi*, 143 S. Ct. 1243, 1254 (2023).

This conclusion is further confirmed by the prosecution history of the related Almarsson patent discussed above (*supra* § VII.A.1). The Almarsson patent examiner rejected for lack of enablement application claims covering co-crystals beyond “the particular co-crystals” in the Almarsson Examples. Ex. 1523, p. 803; *see also id.* pp. 747-53, 777. The Almarsson patent examiner rejected the applicants’ arguments that experimentation was routine and “the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *Id.* p. 777. Because “the formation and

structure of crystals is unpredictable,” the examiner maintained the enablement rejection, leading the Almarsson applicants to limit their claims to the specific co-crystals exemplified in the Almarsson Examples. *Id.*; Ex. 1502, Rogers ¶¶ 132, 151-59.

Like the Almarsson specification, the Priority Applications fail to enable a POSA to make co-crystals beyond those specifically disclosed in the Examples (none of which falls within the scope of claim 16) without undue experimentation and therefore claim 16 lacks enablement. Ex. 1502, Rogers ¶ 159.

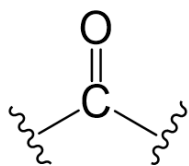
**C. The Priority Applications Lack Enablement Support for Co-Crystals of Claim 16 With a Carbonyl First Chemical Functionality**

Claim 16 also lacks enablement support in the Priority Applications because it encompasses pharmaceutical compositions containing solvates of a co-crystal where the API’s first chemical functionality is a carbonyl. All such embodiments are inoperative and thus lack utility because they cannot form API homosynthons by hydrogen bonding, as required by limitation [10c]. *Id.* ¶¶ 160-68; *In re Fisher*, 421 F.3d 1365, 1371, 1378–79 (Fed. Cir. 2005) (inoperative invention lacks enablement); *Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys.*, 166 F.3d 1190, 1196-97 (Fed. Cir. 1999); *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1322-25 (Fed. Cir. 2005).

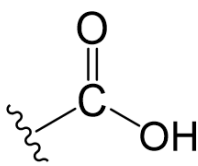
Claim 10 requires a “first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form . . . wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.” Dependent claim 16 incorporates this limitation, and as such, includes co-crystals where the first chemical functionality of the API is a carbonyl. Ex. 1502, Rogers ¶ 160.

The parties agree that “carbonyl” means -C(=O)-, and not the -C(=O)- portion of a larger functional group (*e.g.*, the C=O portion of a carboxylic acid or carboxamide). *Supra* § VI.A. The parties’ agreement is consistent with the ’344 applicants’ prosecution statements wherein they used “carbonyl” to refer to a carbonyl group on its own and not the carbonyl portion of a larger functional group. Ex. 1502, Rogers ¶¶ 58, 161-62. For example, the applicants stated that the application claims had been amended “to ***exclude*** supramolecular heterosynthons formed by hydrogen bonding involving a ***first chemical functionality comprising a carboxylic acid***.” Ex. 1516, pp. 256-58, 261-63 (emphasis added). At the time, pending application claim 57 recited: “The pharmaceutical composition of claim 52, wherein the ***first chemical functionality is a carbonyl***.” *Id.* pp. 256-58 (emphasis added). Because the applicants stated that the application claims had been amended to exclude carboxylic acid first chemical functionalities but continued to pursue “carbonyl” as a first chemical functionality, “carbonyl” cannot

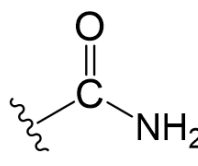
refer to the carbonyl portion of a larger functional group, such as a carboxylic acid or carboxamide (all pictured below). Ex. 1502, Rogers ¶ 163.



carbonyl



carboxylic acid



carboxamide

That “carbonyl,” as used in the ’344 patent, does not encompass the carbonyl portion of larger functional groups is also consistent with the fact that the claims separately claim “carboxamide” (claim 18) and “carbonyl” (claim 19) as first chemical functionalities, and the patent claims separately recite “carbonyl” and “carboxamide” (claim 10), or “carbonyl,” “carboxamide” and “carboxylic acid” (claim 21). Ex. 1501, claims 10, 18, 19, 21; Ex. 1502, Rogers ¶ 164.

Because the parties agree that “carbonyl” means a carbon double-bonded to an oxygen, and does not include additional atoms (*supra* p. 9), a POSA would understand that this group cannot form API homosynthons. Ex. 1502, Rogers ¶¶ 58, 161, 166-68.

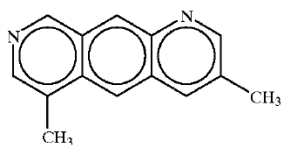
The claimed API homosynthons (limitation 10[c]) are formed when two identical functional groups interact with one another by hydrogen bonding. *See supra* p. 7. During prosecution of the ’956 application, the applicants explained

that to be capable of forming a homosynthon, a chemical functionality must have both a hydrogen bond donor and acceptor:

This composition found in example 9 of Zaworotko [U.S. Patent No. 5,994,365] *does not teach an API that has a first supramolecular synthon comprising a hydrogen bond, as recited in amended 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)<sub>2</sub>,<sup>[7]</sup> which although possessing a pair of hydrogen [bond] acceptors, lacks any hydrogen bond donors.*

Ex. 1517, p. 3464 (emphasis added); *see also* Ex. 1515 at 4, ¶ [0009]; Ex. 1558, 16:25-36; Ex. 1502, Rogers ¶¶ 165-67.

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Ex. 1558, 5:53-65.

Like the diazaanthracene discussed during prosecution, a carbonyl (-C(=O)-) has a hydrogen bond acceptor, but no hydrogen bond donors.<sup>8</sup> Accordingly, a carbonyl cannot form API homosynthons. Ex. 1502, Rogers ¶ 167. All embodiments where the first chemical functionality is a carbonyl are therefore inoperable. *Id.* ¶ 168. Because a POSA cannot practice the full scope of claim 16, including one of the three specifically enumerated first chemical functionalities in claim 10 (from which claim 16 depends), claim 16 is not enabled by the Priority Applications. *Id.* ¶¶ 167-68. Because “carbonyl” is specifically enumerated in claim 10 from which claim 16 depends, the carbonyl group must be enabled. *Trs. of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362, 1363-64 (Fed. Cir. 2018) (claims not enabled where one of six possible embodiments was physically impossible).

In addition, if Patent Owners argue the prior art does not provide a reasonable expectation of formulating a solvate of a co-crystal into a

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<sup>8</sup> See, e.g., Ex. 1576 at 22-23 (“[T]here are molecules with oxygen or nitrogen but without O-H and N-H bonds such as aldehydes, ketones, ethers, esters . . . which can accept H-bonds but cannot donate them.”); Ex. 1577 at 489 (“A hydrogen-bond donor must have a hydrogen atom bonded to F, O, or N.”); Ex. 1502, Rogers ¶ 167 n. 21.

pharmaceutical composition in a therapeutically effective amount, along with a pharmaceutically acceptable carrier, claim 16 lacks enablement support in the Priority Applications for this additional reason. The Priority Applications provide no examples, direction, or guidance in this regard. Ex. 1502, Rogers ¶ 150.

### **VIII. GROUND 1: CLAIM 16 IS OBVIOUS OVER UETO IN VIEW OF LI, MARTINDALE, THE '006 PUBLICATION, AND REMINGTON**

Because claim 16 lacks written description or enablement support in the Priority Applications and is therefore not entitled to a priority date before February 2014, claim 16 is obvious over Ueto in view of Li, Martindale, the '006 Publication, and Remington. Ex. 1502, Rogers ¶¶ 170-73.

#### **A. Ueto**

Ueto, “Polymorphs and a Hydrate of Furosemide–Nicotinamide 1:1 Cocystal,” published in *Crystal Growth & Design* in 2012, is a pharmaceutical co-crystal reference that discloses a 1:1:2 co-crystal of furosemide (“FS”), nicotinamide (“NCT”), and water. Ex. 1507, Ueto at 485-93 (“The asymmetric unit of the hydrate consists of one FS molecule, one NCT molecule, and two water molecules.”); Ex. 1502, Rogers ¶ 174. Ueto discloses that furosemide is a “loop diuretic drug.” Ex. 1507, Ueto at 486.

#### **B. Li**

Li, “New polymorphs of isonicotinamide and nicotinamide,” published in *Chemical Communications* in 2011, discloses that in its pure form, nicotinamide

forms hydrogen bonds between the carboxamide groups of adjacent nicotinamide molecules. *See, e.g.*, Ex. 1508, Li at 1531 (Figure 6, Nic2); Ex. 1502, Rogers ¶¶ 176-77.

### **C. Martindale**

Martindale, “The Complete Drug Reference” summarizes clinically useful information on drugs and other compounds, including their indications and dosage information. Ex. 1506, Martindale at preface v-vi; Ex. 1502, Rogers ¶ 178.

Martindale discloses that nicotinamide is also known as vitamin B and is used in the treatment and prevention of nicotinic acid deficiency, administered orally at doses of up to 500 mg daily in divided doses. Ex. 1506, Martindale at 2117, 2119; Ex. 1502, Rogers ¶ 179.

Martindale further discloses that furosemide is a “crystalline powder” (*i.e.*, a solid in pure form) and is used in the treatment of hypertension, administered orally at doses of 40 to 80 mg daily. Ex. 1506, Martindale at 1421-25; Ex. 1502, Rogers ¶ 180.

### **D. '006 Publication**

The '956 priority application published as the '006 Publication on December 4, 2003. Ex. 1514, '006 Publication, cover. The '006 Publication, therefore, discloses the same 19 co-crystal Examples as the '956 priority application and 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’s (1995). Ex. 1514, ’006 Publication ¶¶ 51, 58-179; Ex. 1502, Rogers ¶ 181.

#### **E. Remington**

Remington, “*Essentials of Pharmaceutics*,” 2012, is a well-known textbook directed to the science and practice of pharmacy, including pharmaceutical manufacturing and preparations, as the ’344 patent and ’006 Publication recognize (citing 1995 edition) (Ex. 1501, 10:15-21; Ex. 1509, [0051]). Ex. 1510, Remington at preface xvii-xxii; Ex. 1502, Rogers ¶¶ 182-83; Ex. 1503, Appel ¶¶ 21, 64, 75. Remington discloses methods for formulating pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more drug substances. Ex. 1510, Remington at 581-610; Ex. 1502, Rogers ¶ 183.

#### **F. Claim 16 Is Obvious Over Ueto in View of Li, Martindale, the ’006 Publication, and Remington**

For purposes of the analysis in Grounds 1 and 2, the claims are divided into limitations [10a] – [10g] (which collectively make up limitation [16a]), and limitation [16b]) (*supra* § IV), and certain limitations will be addressed together or out of order.

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**

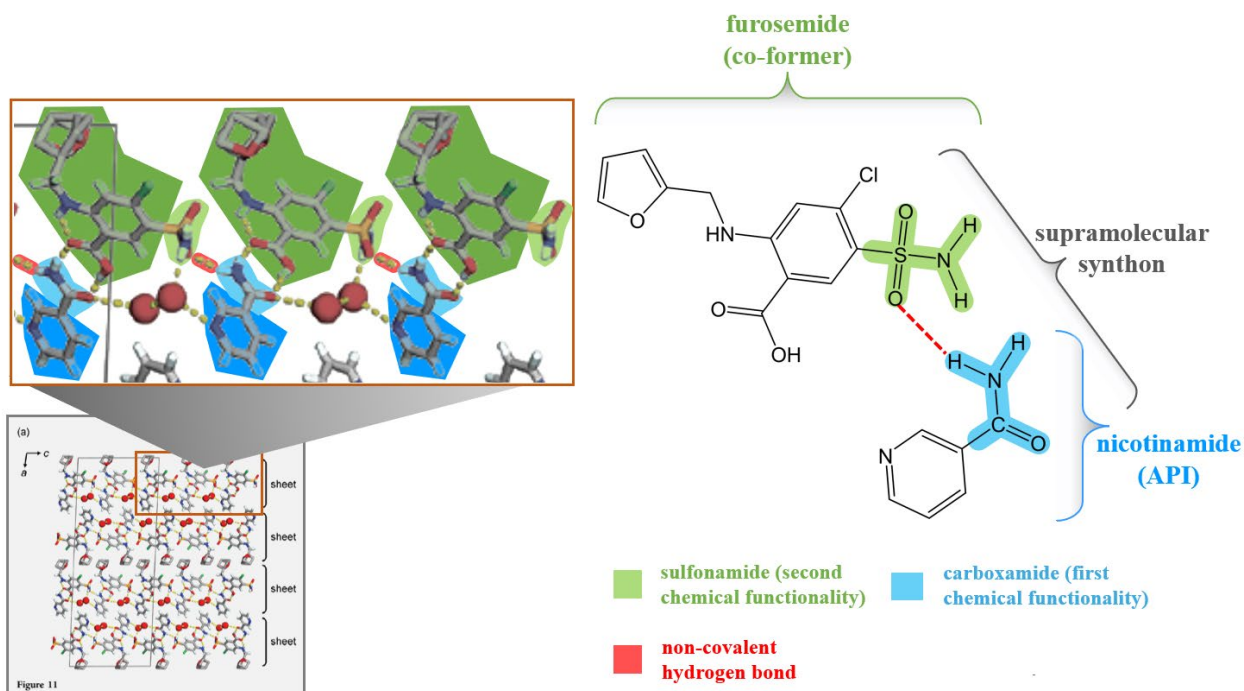
Ueto discloses a “hydrate of furosemide–nicotinamide 1:1 cocrystal,” which contains furosemide (FS), nicotinamide (NCT), and water in **stoichiometric amounts** of 1:1:2: “[t]he asymmetric unit of the hydrate consists of one FS molecule, one NCT molecule, and two water molecules.” Ex. 1507, Ueto at 485-93; Ex. 1502, Rogers ¶¶ 187-89. This “hydrate” qualifies as a **co-crystal** under the ’344 patent as it is “[a] multiple component, single crystalline phase, having a fixed stoichiometry of its component compounds,” wherein the components are furosemide, nicotinamide, and water in a fixed 1:1:2 stoichiometry, and they are present as a single crystalline phase as evidenced by the fact that the Ueto authors prepared and evaluated a single crystal. *See supra* § VI.B (construction of co-crystal); Ex. 1507, Ueto at 485-93; Ex. 1502, Rogers ¶¶ 188-89.

A POSA would have understood that nicotinamide qualifies as an “**API**” *supra* § VI.A (construction of “API”) because it was indicated to treat vitamin B3 deficiency, and is therefore a “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition.” Ex. 1506, Martindale at 2119; Ex. 1502, Rogers ¶ 190.

Furosemide qualifies as a “**co-former**” under the ’344 patent, which provides that “co-formers can be . . . drug molecules.” Ex. 1501, 3:35-37. Ueto

discloses that furosemide is a loop diuretic and Martindale discloses that furosemide is used in the treatment of hypertension. Ex. 1506, Martindale at 1421-25; Ex. 1507, Ueto at 486. A POSA would therefore understand that furosemide is a drug molecule that forms a co-crystal with nicotinamide, as disclosed in Ueto, and thus qualifies as a “co-former.” Ex. 1507, Ueto at 485-93; Ex. 1502, Rogers ¶¶ 191, 202-03.

The Ueto co-crystal contains **supramolecular synthons**. As shown below, the first chemical functionality (carboxamide, shaded light blue) of the “API” (nicotinamide) interacts with the second chemical functionality (sulfonamide, shaded light green) of the “co-former” (furosemide) via non-covalent hydrogen bonds (shaded red) to form a supramolecular synthon. Ex. 1507, Ueto at 490, 492; Ex. 1502, Rogers ¶¶ 192-95.



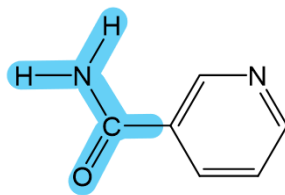
Therefore, Ueto and Martindale teach limitation [10b]. Ex. 1502, Rogers

¶ 196.

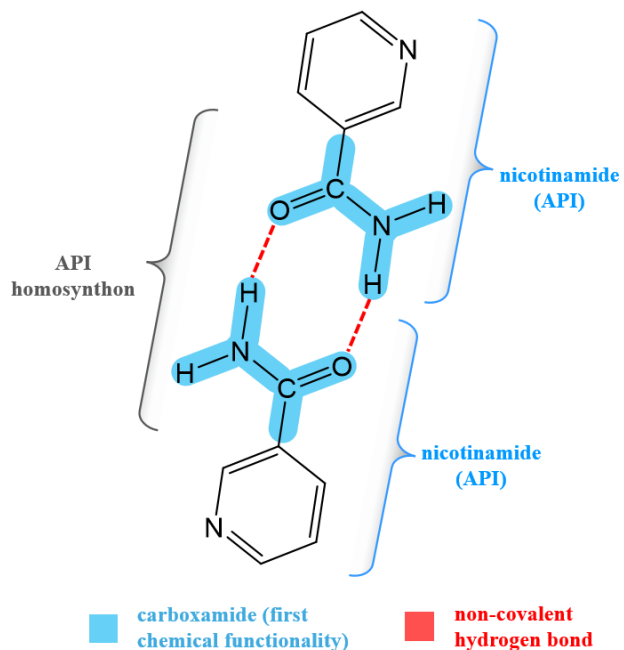
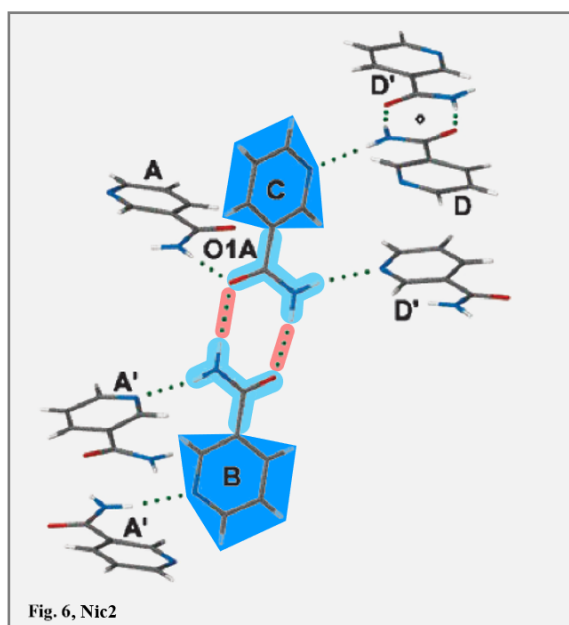
2. [10c]: wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form

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

Nicotinamide (the “API”) has a  $-C(=O)NH_2$  chemical functionality (shaded light blue in the figure below), *i.e.*, a carboxamide (*see supra* § VI.A, claim construction), therefore meeting limitation [10g]. Ex. 1507, Ueto at 485; Ex. 1502, Rogers ¶¶ 197, 199, 211-12.



As for limitation [10c], when nicotinamide is in its pure form, the carboxamide of one nicotinamide interacts with the identical carboxamide on an adjacent nicotinamide through non-covalent hydrogen bonding thereby forming “API homosynthons,” as shown in the figure below from Li with annotations added. *See, e.g.*, Ex. 1508, Li at 1531 (Figure 6, Nic2); Ex. 1502, Rogers ¶¶ 197-200.



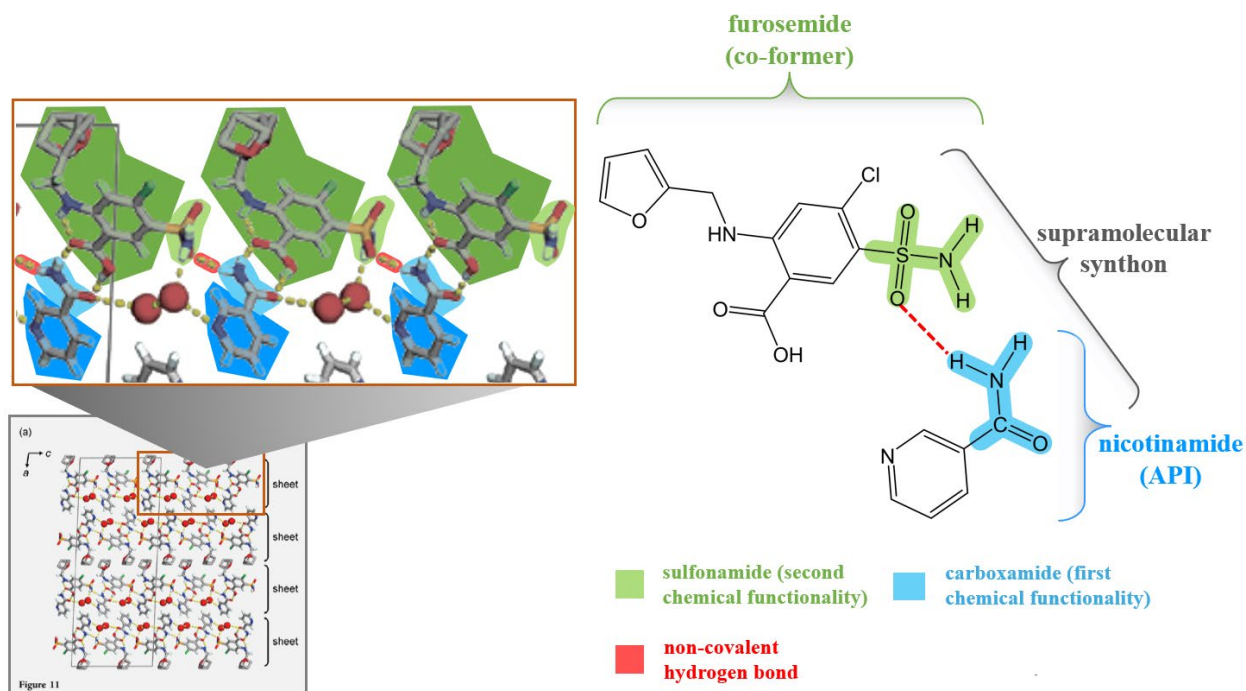
Therefore, Ueto inherently discloses, and Li expressly discloses, limitation [10c]. Ex. 1502, Rogers ¶ 201.

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

**[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**

In the Ueto co-crystal (shown below with annotations), furosemide (the “co-former”) has a second chemical functionality (sulfonamide, shaded light green) that interacts with the first chemical functionality (carboxamide, shaded light blue) of nicotinamide (the “API”) via non-covalent hydrogen bonding (shaded red) thereby forming supramolecular synthons, meeting limitation [10f]. Ex. 1502, Rogers ¶¶ 192-95, 207-10.

Specifically, pairs of furosemide and nicotinamide “form corrugated sheets *stabilized by sulfonamide...amide hydrogen bonds (synthon D)*”; Ex. 1507, Ueto 2011 at 490, 492 (emphasis added); *see also* 486; Ex. 1502, Rogers ¶¶ 192-95, 208-09. These hydrogen bonds are depicted below (shaded red):



Ex. 1507, Ueto at 492, Fig 11(a); Ex. 1502, Rogers ¶ 208.

As for limitation [10d], because the first chemical functionality of the API and the second chemical functionality of the co-former form a non-covalent hydrogen bond, a POSA would understand that the chemical functionalities are *complementary* to each other. Ex. 1502, Rogers ¶¶ 191-95, 202-03, 208-09.

Therefore, Ueto discloses or teaches that the “co-former” furosemide has a second chemical functionality complementary to the first chemical functionality (carboxamide) of the “API” nicotinamide via non-covalent hydrogen bonding, limitation [10d]. Ex. 1502, Rogers ¶¶ 202-03.

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

Martindale discloses that furosemide is a “crystalline powder,” which a POSA would understand means that it is a solid at room temperature and atmospheric pressure when in its pure form, meeting limitation [10e]. Ex. 1506, Martindale at 1421; *see also* Ex. 1579 at 740 (furosemide’s melting point in pure form is 206 °C, which is above room temperature); Ex. 1502, Rogers ¶¶ 204-06.

**5. [16b]: wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule**

In Ueto’s furosemide/nicotinamide/water co-crystal, supramolecular synthons are formed between the carboxamide (first chemical functionality) of nicotinamide (the “API”) and the sulfonamide (second chemical functionality) of furosemide (the “co-former”). *Supra* § VIII.F.3; Ex. 1502, Rogers ¶¶ 207-10, 215.

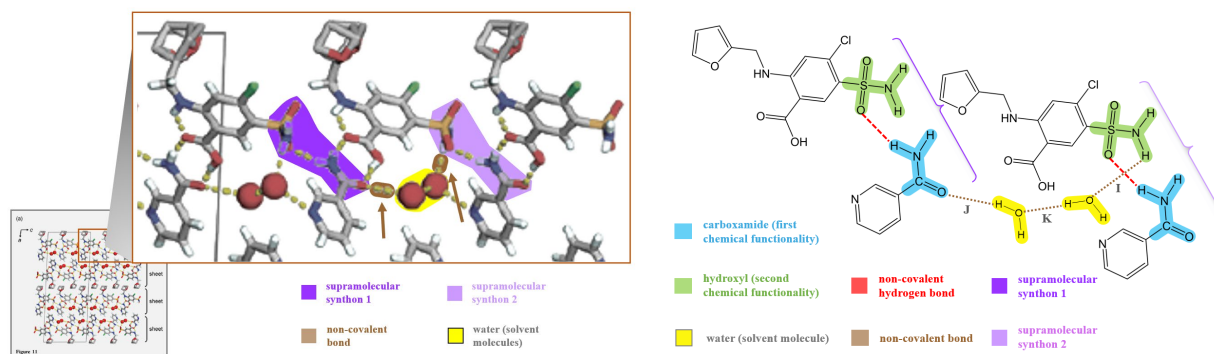
These furosemide/nicotinamide supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to water, which a POSA would understand is a solvent. *See* Ex. 1502, Rogers ¶¶ 213-14, 216-17; Ex. 1573,

UM00005308. As shown in the annotated Figure 11a below, two water molecules<sup>9</sup> (red spheres, shaded yellow) link via non-covalent bonding (shaded brown and identified with arrows) one supramolecular synthon (shaded dark purple) to an adjacent supramolecular synthon (shaded light purple). Ex. 1507, Ueto at 491; Ex. 1502, Rogers ¶¶ 216-17. Ueto also explains this interaction: “*The 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).*” Ex. 1512, Ueto at 491 (emphases added); Ex. 1502, Rogers ¶¶ 218-19.

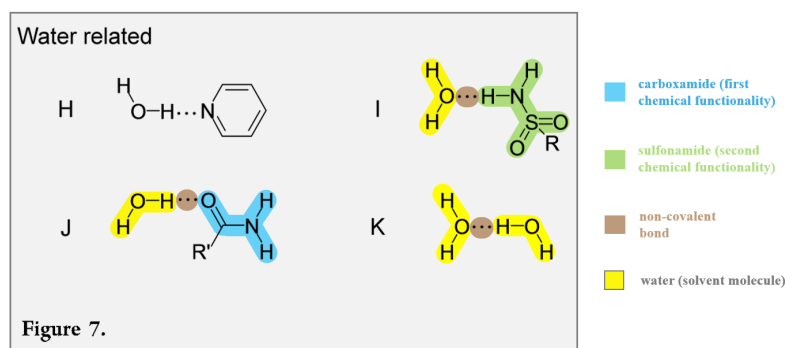
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<sup>9</sup> While claim 16 refers to “a” solvent molecule, “[g]enerally, the terms ‘a’ or ‘an’ in a patent claim mean ‘one or more,’ unless the patentee evinces a clear intent to limit ‘a’ or ‘an’ to ‘one.’” *See FS.com Inc. v. ITC*, 65 F.4th 1373, 1377 (Fed. Cir. 2023). Because there is no evidence to limit “a” to “one” solvent molecule, Ueto’s two water molecules satisfy limitation [16b]. *See supra* § VI.A (claim construction).

**Figure 11a**



Ex. 1502, Rogers ¶¶ 218-22. Supramolecular synthons H, I, J, and K are depicted in Ueto's Figure 7 (annotated below). Ex. 1507, Ueto at 490, Fig. 7; Ex. 1502, Rogers ¶¶ 218-19.



Therefore, Ueto discloses claim limitation [16b]. Ex. 1502, Rogers ¶ 223.

6. **[10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount [of a co-crystal comprising supramolecular synthons]**

As of 2014, and a year before 2014, a POSA would have been capable of formulating a pharmaceutical composition comprising a pharmaceutically

acceptable carrier and a therapeutically effective amount of the Ueto furosemide/nicotinamide/water co-crystal in view of the teachings of well-known references such as Remington. Ex. 1503, Appel ¶¶ 57, 66; Ex. 1502, Rogers ¶¶ 228-30.

The '006 Publication (as well as the '344 patent itself) admits that formulating multiple-component phase compositions of the invention (*e.g.*, co-crystals) with a pharmaceutically acceptable carrier can be done using known methods, citing Remington's (albeit the earlier 1995 version) as support:

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 EW [1995] Eastone Pa., Mack Publishing Company, 19<sup>th</sup> ed.) [] describes formulations that can be used in connection with the subject invention.

Ex. 1509, '006 Publication ¶ 51; Ex. 1501, 10:6-21; *see also* Ex. 1510, Remington at 581-610 (teaching formulation of pharmaceutical compositions containing a pharmaceutically acceptable carrier by methods such as dry granulation and direct

compression); *supra* §§ VIII.D, VIII.E. These formulation methods were well known to a POSA by 2014. Ex. 1503, Appel ¶¶ 21-24, 34-56; Ex. 1502, Rogers ¶¶ 229-30; *see also* Ex. 1510, Remington at 581-84, 586-87, 592-93, 604-10; Ex. 1543 at x.

Therefore, it would be well within the POSA's knowledge to formulate the Ueto co-crystal into a pharmaceutical composition. Ex. 1503, Appel ¶ 65.

To determine a therapeutically effective amount of the co-crystal to include in that composition, a POSA would look at the co-crystal's components and consult references such as Martindale. *Id.* ¶¶ 58, 60-63, 66; Ex. 1502, Rogers ¶¶ 227, 229. Martindale teaches that furosemide has therapeutic activity in amounts of 40-80 mg/day to treat hypertension. Ex. 1506, Martindale at 1423; Ex. 1502, Rogers ¶¶ 227, 229; *see also* Ex. 1580 at 2411-12 (crystalline furosemide for various indications, including hypertension at doses of 40 mg twice-daily).

Martindale further teaches that nicotinamide is present in various foods (yeast, meat, milk, green vegetables), commonly added to cereals and other foods, and can be used safely at daily doses of up to 500 mg to treat vitamin B deficiency. Ex. 1506, Martindale at 2118-19. Consistent with these teachings, the '006 Publication taught the use of nicotinamide as a co-former, describing it as a GRAS compound. Ex. 1509, '006 Publication ¶ [0040], Example 8; Ex. 1502, Rogers ¶ 226.

Although nicotinamide satisfies the parties' agreed upon definition of "API," which merely requires some therapeutic effect against some pathological condition in a human or animal (*see supra* § VI.A), the '344 patent nowhere indicates that pharmaceutical composition must be used for that condition. Nor does the patent require that the claimed therapeutically effective amount of the co-crystal be derived in whole or in part from the activity of the "API" (nicotinamide) when the "co-former" itself has therapeutic activity for a sought after indication (here, *e.g.*, hypertension) and the "API" does not have activity for that particular indication. A POSA looking to prepare a pharmaceutical composition for hypertension would not have been concerned with whether the co-crystal's therapeutic activity comes from the component that technically qualifies as the "API" or the "co-former" under the '344 patent's use of those terms. Ex. 1502, Rogers ¶¶ 226-28.

Rather, considering the known uses and therapeutic properties of furosemide and nicotinamide, a POSA would prepare a pharmaceutical composition comprising a therapeutically effective amount of the Ueto co-crystal for use in, for example, hypertension. In doing so, the POSA would rely on information about the therapeutically effective amount of furosemide as taught in Martindale to determine the therapeutically effective amount of the co-crystal. The POSA would incorporate amounts of the Ueto co-crystal sufficient to provide furosemide at 40-

80 mg/day, a therapeutically effective amount for use in hypertension.<sup>10</sup> Ex. 1503, Appel ¶¶ 58, 60-62; Ex. 1502, Rogers ¶¶ 225-30.

Therefore, Ueto, Martindale, the '006 Publication, and Remington teach all the features of limitation [10a]. Ex. 1502, Rogers ¶ 231.

## **7. Motivation to Combine the Ground 1 References With a Reasonable Expectation of Success**

A POSA would have been motivated to combine Ueto with Li, Martindale, the '006 Publication, and Remington. Ueto, lead authored by a scientist at the pharmaceutical company Chugai Pharmaceutical Co. Ltd., investigated pharmaceutical co-crystals (including several furosemide-containing co-crystals), noting that they have been a “focus of attention” with the potential to improve physicochemical properties of the co-crystal components. Ex. 1507, Ueto at 485. In particular, furosemide was known as of 2014 to have low water solubility (Ex. 1506, Martindale at 1421; Ex. 1503, Appel ¶ 58; Ex. 1502, Rogers ¶¶ 232-34, 236), and water solubility, along with bioavailability, were properties that co-crystals had the potential to improve. Ex. 1507, Ueto at 485; Ex. 1503, Appel ¶ 59; Ex. 1502, Rogers ¶¶ 234, 236. As such, a POSA would have been motivated to pursue studies with the Ueto co-crystals, including the furosemide/nicotinamide/water co-crystal.

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<sup>10</sup> This approach for determining a therapeutically effective amount was used by '344 patent inventor, Dr. Zaworotko, in Ex. 1504.

Because drugs are not typically administered to animals and humans on their own, a POSA would have been motivated to formulate the furosemide-containing Ueto co-crystal into a pharmaceutical composition and evaluate whether the co-crystal had improved pharmaceutical properties as compared to furosemide alone; the POSA would have looked to Martindale for guidance on determining a therapeutically effective amount of the co-crystal as it specifically discusses therapeutically effective amounts of furosemide and indicates that nicotinamide is commonly used as a food additive. Ex. 1503, Appel ¶¶ 34, 58-62, 66; Ex. 1502, Rogers ¶¶ 233-39, 241. A POSA also would have looked to references like Remington and the '006 Publication for guidance on how to formulate the co-crystal into a pharmaceutical composition with a pharmaceutically acceptable carrier in view of Remington's teachings about formulating pharmaceutical compositions of multiple-component solids. Ex. 1510, Remington at 581-610; Ex. 1503, Appel ¶¶ 64-66; Ex. 1502, Rogers ¶¶ 237, 239, 242.

Further, a POSA would have been motivated to combine Ueto with Li, as both concern nicotinamide, and Ueto with Martindale as both concern furosemide. Ex. 1502, Rogers ¶ 240.

In view of the teachings discussed above, a POSA would have had a reasonable expectation of successfully formulating a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective

amount of a 1:1:2 co-crystal of furosemide, nicotinamide, and water, which meets all the limitations of claim 16. Ex. 1502, Rogers ¶¶ 232, 242-44; Ex. 1503, Appel ¶¶ 65-66.

Indeed, if Patent Owners were to argue that there was no reasonable expectation of success, the Priority Applications would lack enablement as they fail to provide any specific guidance on how to formulate any of the disclosed or claimed co-crystals into a pharmaceutical composition in a therapeutically effective amount. Ex. 1502, Rogers ¶ 150. As a result, claim 16 is obvious over Ueto in view of Li, Martindale, the '006 Publication, and Remington. *Id.* ¶ 244.

**IX. GROUND 2: CLAIM 16 IS OBVIOUS OVER THE '408 APPLICATION AND/OR SOWA IN VIEW OF MARINI, LI, THE '006 PUBLICATION, AND REMINGTON**

Because claim 16 lacks written description and enablement support in the 2002/2003 Priority Applications and is therefore not entitled to a priority date before February 2014, claim 16 is obvious over the '408 Application and/or Sowa in view of Li, the '006 Publication, and Remington. Ex. 1502, Rogers ¶ 245.

**A. The '408 Application**

The '408 Application is entitled “A co-crystal of genistein-nicotinamide monohydrate and a method for obtaining a co-crystal of genistein-nicotinamide monohydrate.” Ex. 1511 at 1; Ex. 1502, Rogers ¶ 246; Exhibit 1511 includes the originally filed '408 Application, and Exhibit 1586 includes the bibliographic

information from the Polish Patent Office. *See also* Exs. 1589, 1588, 1587. The '408 Application was filed with the Polish Patent Office on October 30, 2012 and has a "Patent Office Bulletin Publication Date" of June 10, 2013. Ex. 1586 at 1. *See also* Exs. 1589, 1588, 1587. Thus, the '408 Application is prior art under 35 U.S.C. § 102(a)(2) (AIA) as of its October 30, 2012 effective filing date and also as of its June 10, 2013 publication date.

The '408 Application discloses a 1:1:1 genistein/nicotinamide/water co-crystal for use in the pharmaceutical and cosmetic industries. Ex. 1511 at 1-9; Ex. 1502, Rogers ¶¶ 246-47.

The '408 Application discloses that genistein has various therapeutic activities including "estrogenic activity," "anti-inflammatory and antioxidant properties," and "potential multidirectional application[s] in the treatment and prevention of cancer." Ex. 1511 at 1. The '408 Application further discloses that nicotinamide is a water-soluble form of vitamin B3 that has been used in the treatment of inflammatory skin conditions, is approved for safe use as a food additive, and "is widely used in co-crystallization of ... pharmaceutical preparations and dietary supplements." Ex. 1511 at 1-2; Ex. 1502, Rogers ¶¶ 248-50.

## B. Sowa

Sowa, “Cocrystals of Fisetin, Luteolin and Genistein with Pyridinecarboxamide Coformers: Crystal Structures, Analysis of Intermolecular Interactions, Spectral and Thermal Characterization” is authored by the named inventors of the ’408 Application and first published in *CrystEngComm* on July 19, 2013. Ex. 1512, Sowa at 7696-707; Ex. 1502, Rogers ¶¶ 252-53. Sowa is prior art under 35 U.S.C. § 102(a)(1) (AIA) as of its July 19, 2013 publication date. Like the ’408 Application, Sowa discloses a 1:1:1 genistein/nicotinamide/water co-crystal referred to as “genistein-nicotinamide (1:1) monohydrate” or “GenNam.” Ex. 1512, Sowa at 7696-707; Ex. 1502, Rogers ¶ 252.

Sowa discloses that genistein is a flavonoid, a class of compounds that “are of scientific interest due to health-prolonging effects attributed mainly to their antioxidant, antitumor, and anti-inflammatory properties.” Ex. 1512, Sowa at 7696. Sowa further discloses that flavonoids’ efficiency *in vivo* “is hindered by low solubility in water and low bioavailability, therefore reducing the potential of possible applications in pharmaceutical formulations or nutritional supplements”; however, co-crystallization is a potential solution to this problem that was successfully applied to the flavonoid quercetin. Ex. 1512, Sowa at 7696-97; Ex. 1502, Rogers ¶¶ 254-55.

Sowa also discloses that nicotinamide is a suitable co-former for pharmaceutical applications that has been “successfully applied” to other APIs. *See* Ex. 1512, Sowa at 7697; Ex. 1502, Rogers ¶ 256.

**C. Marini**

Marini, “Effects of the Phytoestrogen Genistein on Bone Metabolism in Osteopenic Postmenopausal Women” was published in the *Annals of Internal Medicine* in 2007. It discloses the results of a clinical trial studying the effects of genistein on bone metabolism in osteopenic postmenopausal women and concludes that genistein has positive effects on bone mineral density (BMD). Ex. 1513, Marini at 839-46; Ex. 1502, Rogers ¶¶ 258-61.

**D. Li, ’006 Publication, and Remington**

These references are discussed in Ground 1, *supra*. Ex. 1502, Rogers ¶¶ 176-77, 181-83, 262-64.

**E. Claim 16 Is Obvious Over the ’408 Application and/or Sowa in View of Li, Marini, the ’006 Publication, and Remington**

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**

The ’408 Application and Sowa each disclose the same “genistein-nicotinamide monohydrate,” which is a co-crystal of genistein, nicotinamide and water in **stoichiometric amounts** of 1:1:1. Ex. 1511, ’408 Application at 1-9; Ex. 1512, Sowa at 7696-707, 7703 (“genistein-nicotinamide (1:1) monohydrate

cocrystal (GenNam)”; “The asymmetric unit [of the co-crystal] contains one genistein, one nicotinamide, and one water molecule.”); Ex. 1502, Rogers ¶¶ 267-69. This qualifies as a **co-crystal** under the ’344 patent as it is “[a] multiple component, single crystalline phase, having a fixed stoichiometry of its component compounds,” wherein the components are genistein, nicotinamide, and water in a fixed 1:1:1 stoichiometry, and they are present as a single crystalline phase as evidenced by the fact that the ’408 Application and Sowa authors prepared and evaluated a single crystal. *See supra* § VI.B (construction of co-crystal); Ex. 1511, ’408 Application at 4, 6; Ex. 1512, Sowa at 7696-97, 7702, Fig. 9, 7703; Ex. 1502, Rogers ¶¶ 268-69.

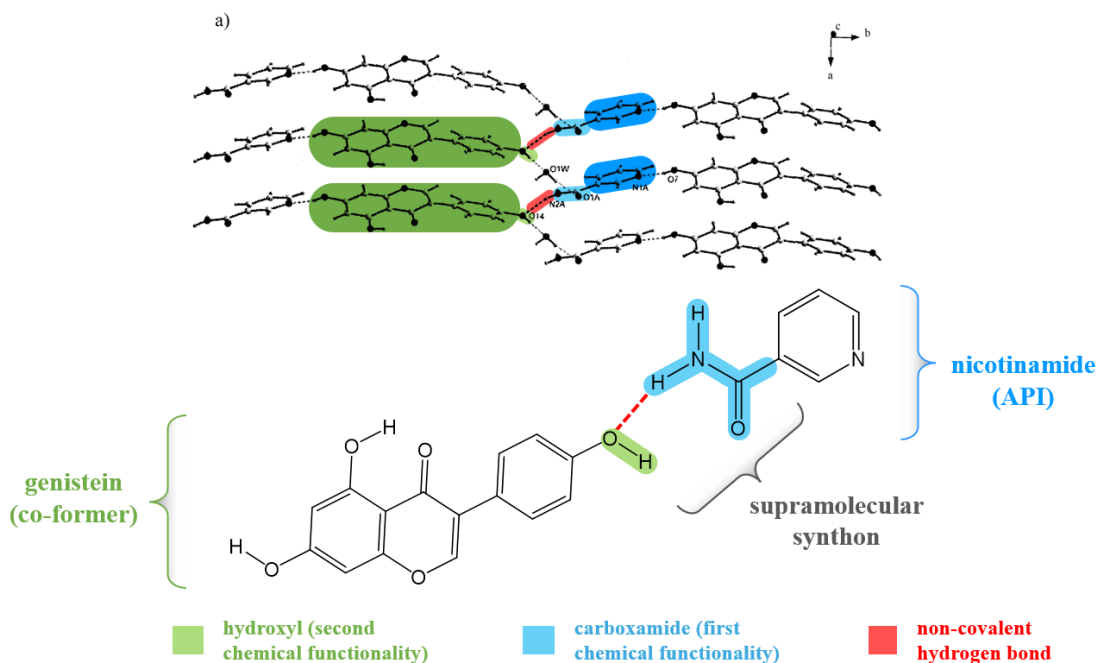
A POSA would have understood that nicotinamide qualifies as an “**API**” under the agreed-upon construction, because it was indicated to treat vitamin B3 deficiency, and is therefore a “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition.” Ex. 1511, ’408 Application at 1-2; *supra* § VI.A; Ex. 1502, Rogers ¶ 270.

Genistein qualifies as a “**co-former**” under the ’344 patent, which provides that “co-formers can be . . . drug molecules.” Ex. 1501, 3:35-37; Ex. 1502, Rogers ¶ 271. The ’408 Application and Sowa disclose that genistein has therapeutic properties, including “estrogenic activity” and “anti-inflammatory and antioxidant properties,” with potential “application in the treatment and prevention of cancer”

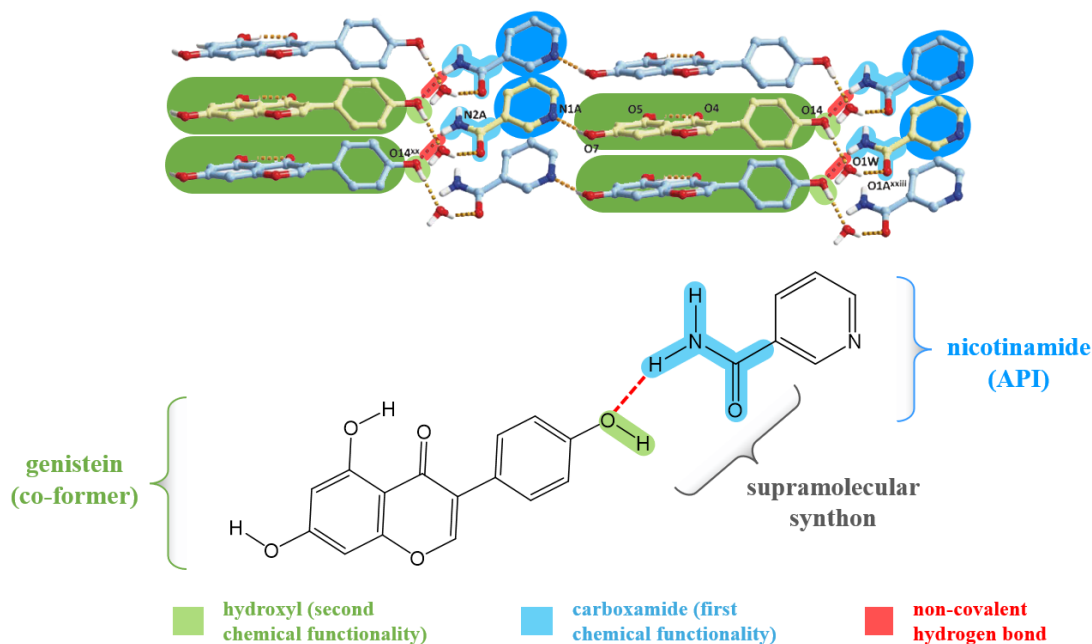
(Ex. 1511, '408 Application at 1) and “antioxidant, antitumor and anti-inflammatory properties” (Ex. 1512, Sowa at 7696); Ex. 1502, Rogers ¶¶ 271-72, 279-80; Ex. 1503, Appel ¶ 68.

As shown in the annotated figures below, the '408 Application/Sowa co-crystal contains **supramolecular synthons**. Specifically, the first chemical functionality (carboxamide, shaded light blue) of the “API” (nicotinamide) interacts with the second chemical functionality (hydroxyl, shaded light green) of the “co-former” (genistein) via non-covalent hydrogen bonds (shaded red) to form a supramolecular synthon. Ex. 1511, '408 Application at 4, 9; Ex. 1512, Sowa at 7702-03 (discussing “interactions between the amide [carboxamide] moieties of Nam and the O14 hydroxyl substituent in Gen.”); Ex. 1502, Rogers ¶¶ 273-76.

'408 Application Figure 3(a):



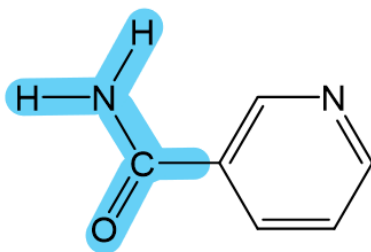
Sowa Figure 9(b):



Therefore, the '408 Application and Sowa each teach limitation [10b]. Ex. 1502, Rogers ¶ 277.

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

Nicotinamide (the “API”) has a  $-C(=O)NH_2$  chemical functionality (shaded light blue in the figure below), *i.e.*, a carboxamide (*see supra* § VI.A, claim construction), therefore meeting limitation [10g]. Ex. 1511, '408 Application at 4, 9; Ex. 1512, Sowa at 7702-03; Ex. 1502, Rogers ¶¶ 197, 199, 278, 288-89.



As discussed above in Ground 1, incorporated by reference here (*supra* § VIII.F.2, discussing Li), the '408 Application and Sowa each inherently discloses, and Li expressly discloses, limitation [10c]. Ex. 1502, Rogers ¶¶ 197-201, 278.

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

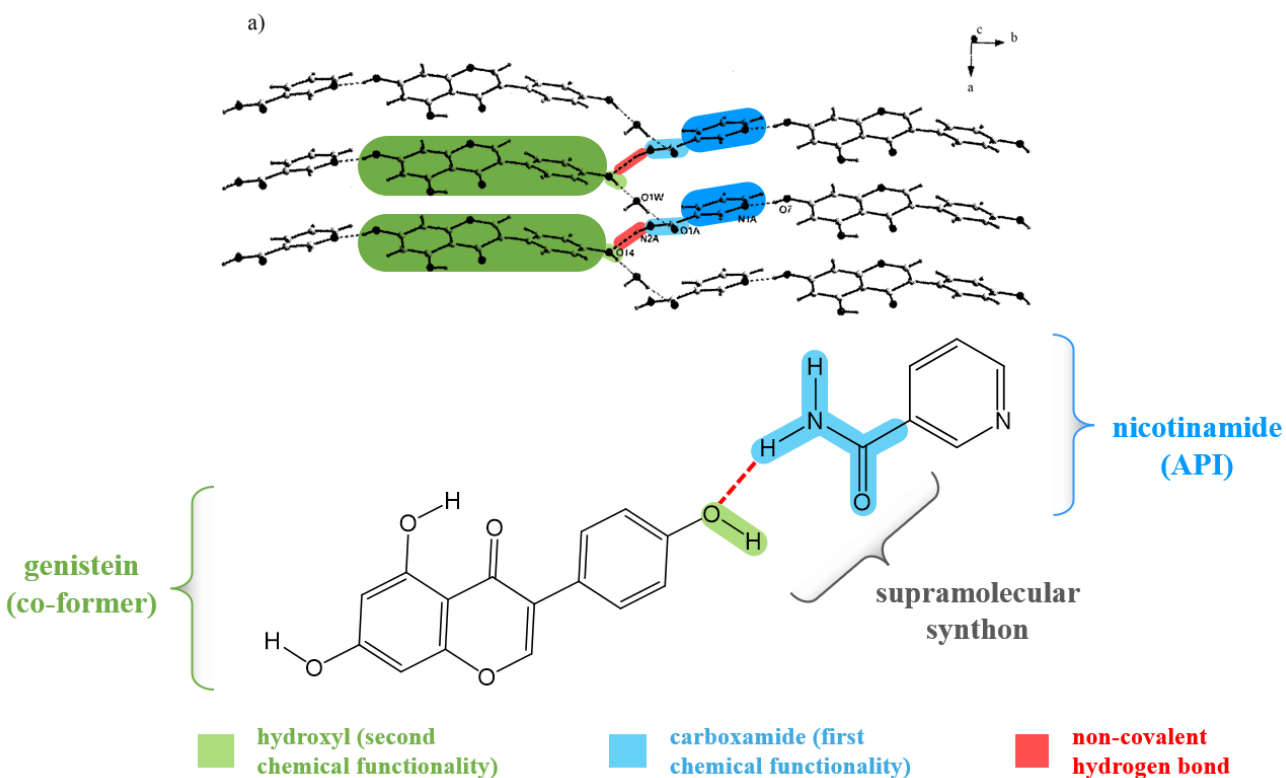
**[10f]: wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former**

In the '408 Application/Sowa co-crystal, genistein (the “co-former”) has a second chemical functionality (hydroxyl) that interacts with the first chemical functionality (carboxamide) of nicotinamide (the “API”) via non-covalent hydrogen bonding thereby forming supramolecular synthons, meeting limitation [10f]. Ex. 1502, ¶¶ 273-75, 279-80, 284-87.

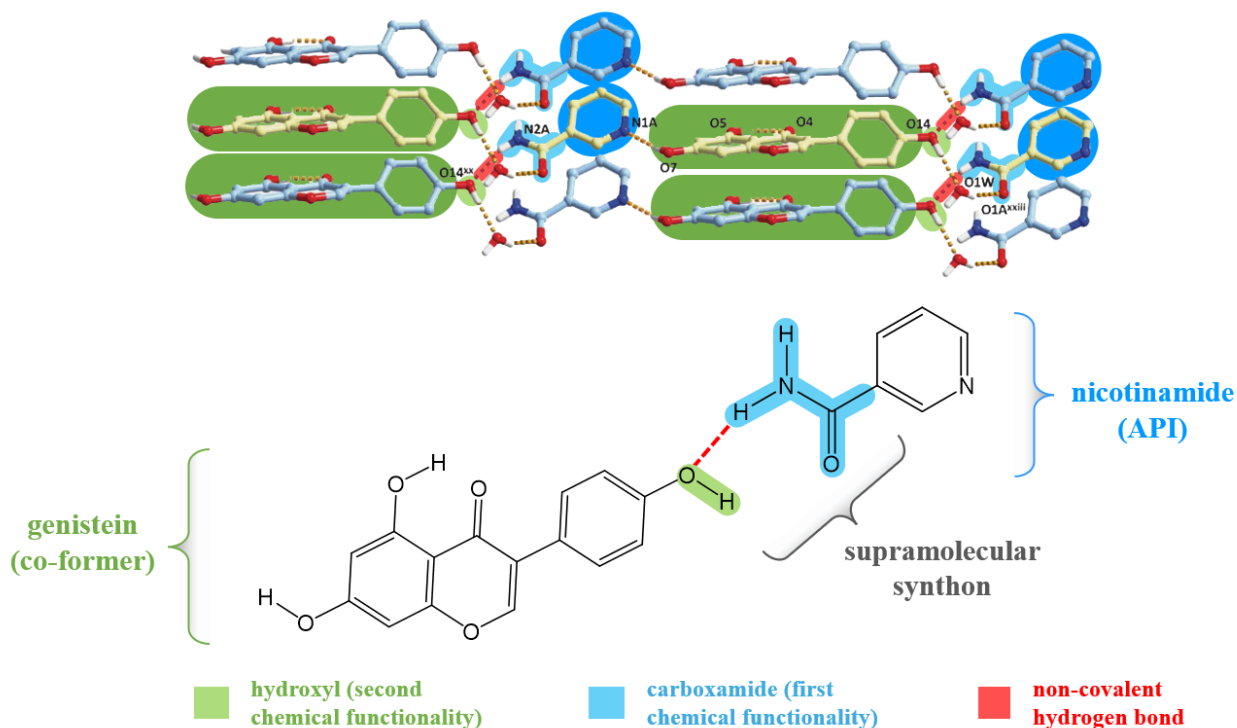
Specifically, Figure 3(a) of the '408 Application and Figure 9(b) of Sowa (depicted in annotated figures below) show that the 1:1:1 genistein, nicotinamide, and water co-crystal has (i) an API (nicotinamide) that has a first chemical functionality (a carboxamide, shaded light blue) and (ii) a co-former (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 at 7702 (Figures 9(a)-(c)). The carboxamide of nicotinamide hydrogen bonds with the hydroxyl of genistein (shaded red), Ex. 1511, '408 Application at 9; Ex. 1512, Sowa 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* § VI.A; *see also* Ex. 1501, 3:37-59, 9:43–10:5; Ex. 1502, Rogers ¶¶ 273-76, 285-86.

'408 Application (Figure 3(a)):



Sowa 2013 (Figure 9(b)):



Ex. 1511, '408 Application at 8-9 (Figures 2, 3(a)-(c)); Ex. 1512, Sowa at 7702 (Figures 9(a)-(c)); Ex. 1502, Rogers ¶¶ 273-75, 285-86.

As for limitation [10d], since the first chemical functionality of the API and the second chemical functionality of the co-former form a non-covalent hydrogen bond, a POSA would understand that the chemical functionalities are *complementary* to each other. Ex. 1502, Rogers ¶¶ 271-76, 279-80.

Therefore, the '408 Application and Sowa each discloses or teaches that the co-former genistein has a second chemical functionality complementary to the first chemical functionality (carboxamide) via non-covalent hydrogen bonding thereby meeting limitation [10d]. Ex. 1502, Rogers ¶¶ 279-80.

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

Each of the '408 Application and Sowa describes dissolving genistein in a solvent, which a POSA would understand means that genistein is a solid at room temperature and atmospheric pressure. Ex. 1511, '408 Application at 3, Ex. 1512, Sowa at 7697; Ex. 1502, Rogers ¶ 282; *see also* Ex. 1579 at 756-57 (disclosing the melting point of genistein in pure form is 297-298 °C, which is above room temperature); Ex. 1502, Rogers ¶¶ 251, 257, 281-83.

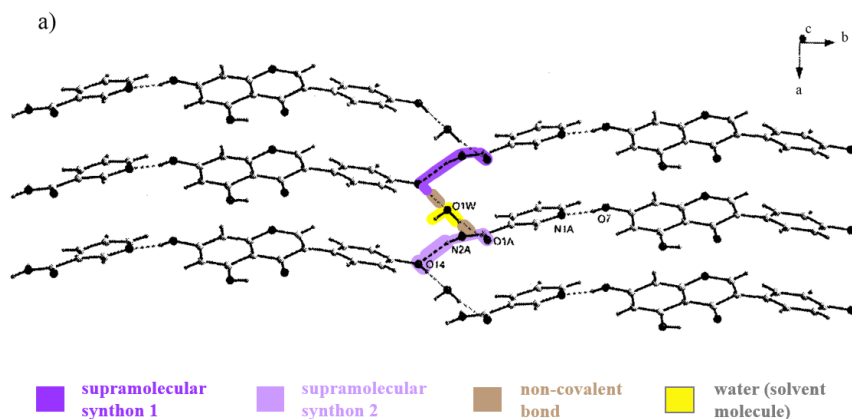
**5. [16b]: wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule**

In the '408 Application/Sowa genistein/nicotinamide/water co-crystal, supramolecular synthons are formed between the carboxamide (first chemical functionality) of nicotinamide (the “API”) and the hydroxyl (second chemical functionality) of genistein (the “co-former”). *Supra* § VIII.F.3; Ex. 1502, Rogers ¶¶ 284-87, 292.

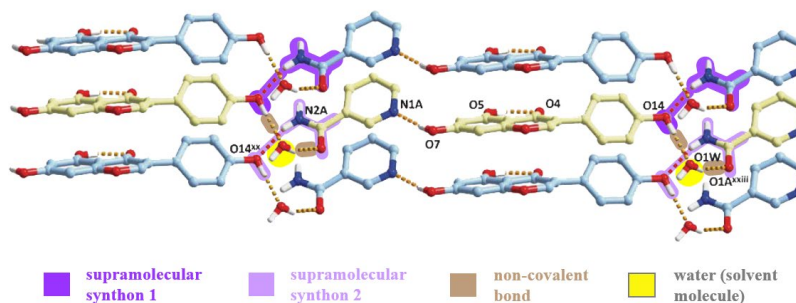
These genistein/nicotinamide supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to water, which a POSA would understand is a solvent molecule. *See* Ex. 1502, Rogers ¶¶ 290-98; Ex. 1573, UM00005308. Specifically, as shown in the annotated Figure 3(a) of the '408 Application and Figure 9(b) of Sowa below, water molecules (shaded yellow) link

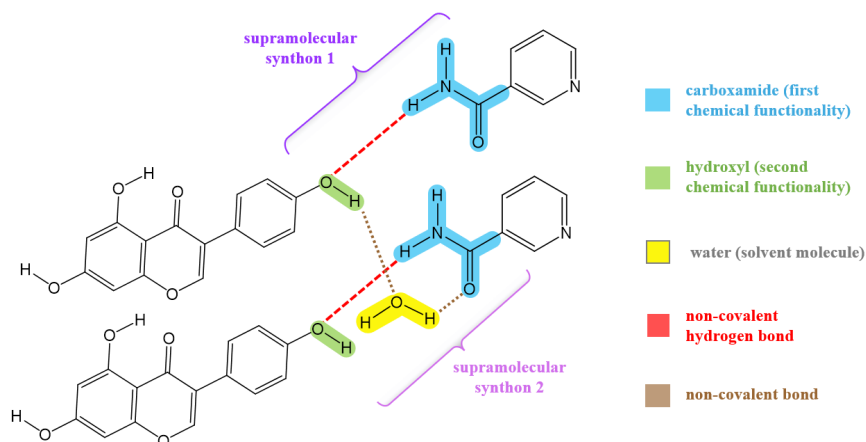
via non-covalent bonding (shaded brown), one supramolecular synthon (shaded dark purple) to an adjacent supramolecular synthon (shaded light purple). Ex. 1511, '408 Application at 9; Ex. 1512, Sowa at 7702; Ex. 1502, Rogers ¶¶ 293-97. Sowa also explains this interaction, referring to: “the presence of Gen-Nam-H<sub>2</sub>O chains . . . hydrogen bon[d]ed via . . . O14-H14 [hydroxyl of genistein]⋯O1W [of water] . . . and O1W-H2W [of water]⋯O1A<sup>xxiii</sup> [carboxamide of nicotinamide].” Sowa at 7703; Ex. 1502, Rogers ¶ 298.

'408 Application (Figure 3(a)):



Sowa 2013 (Figure 9(b)):





Ex. 1502, Rogers ¶¶ 293-97.

Therefore, the '408 Application and Sowa disclose limitation [16b]. *Id.*

¶ 299.

**6. [10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount [of a co-crystal comprising supramolecular synthons]**

As of 2014, a POSA would have been capable of formulating a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the '408 Application/Sowa genistein/nicotinamide/water co-crystal in view of the teachings of well-known references such as Remington. Ex. 1503, Appel ¶¶ 67, 77; Ex. 1502, Rogers ¶¶ 305-07.

As discussed in Ground 1, *supra*, the '006 Publication admits that formulating multiple-component phase compositions of the invention (*e.g.*, co-crystals) with a pharmaceutically acceptable carrier can be done using known

methods, citing Remington 1995 as support, and these formulation methods were well known to a POSA by 2014. *Supra* § VIII.F.6; Ex. 1502, Rogers ¶ 307.

Therefore, it would be well within the POSA's knowledge to formulate the '408 Application/Sowa co-crystal into a pharmaceutical composition. Ex. 1503, Appel ¶ 76.

To determine a therapeutically effective amount of the co-crystal to include in that composition, a POSA would look at the co-crystal's components and consult references such as Marini. Ex. 1503, Appel ¶¶ 68, 71-74, 77; Ex. 1502, Rogers ¶¶ 304, 306.

Marini teaches that genistein has therapeutic activity to reduce bone loss in osteopenic postmenopausal women in amounts of 54 mg/day. Ex. 1513, Marini at 839-40, 844-45; Ex. 1502, Rogers ¶¶ 304, 306.

The '408 Application further taught that nicotinamide was "approved for safe use" as a food additive and "widely used in co-crystallization of . . . pharmaceutical preparations and dietary supplements." Ex. 1511, '408 Application at 2; Ex. 1502, Rogers ¶ 303. Likewise, Sowa disclosed that nicotinamide is a "[s]uitable cocrystal former" that has been "successfully applied to cocrystallize carboxyl- and hydroxyl-derived APIs including some flavonoids." Ex. 1512, Sowa at 7697. *See also* Ex. 1506, Martindale at 2118-19 (teaching that nicotinamide is present in various foods, commonly added to other foods, and can be used safely at

daily doses of up to 500 mg to treat vitamin B deficiency); Ex. 1509, '006 Publication ¶ [0040], Ex. 8 (teaching use of nicotinamide as a co-former, describing it as a GRAS compound); Ex. 1502, Rogers ¶¶ 302-03.

Although nicotinamide satisfies the '344 patent's broad definition of "API," which merely requires some therapeutic effect against some pathological condition in a human or animal (*see supra* § VI.A), the '344 patent nowhere indicates that claim 16 requires that the co-crystal's therapeutically effective amount be derived in whole or in part from the activity of the "API" (nicotinamide) when the "co-former" itself has therapeutic activity for a sought after indication (here, reducing bone loss in osteopenic postmenopausal women) and the "API" does not for that particular indication. A POSA looking to prepare a pharmaceutical composition for reducing bone loss in osteopenic postmenopausal women would not have been concerned with whether the co-crystal's therapeutic activity for a particular indication comes from a component that technically qualifies as the "API" or "co-former" under the '344 patent's use of those terms. Ex. 1502, Rogers ¶¶ 302-05.

Rather, considering the known uses and therapeutically effective amounts of genistein and nicotinamide, a POSA would prepare a pharmaceutical composition comprising a therapeutically effective amount of the '408 Application/Sowa co-crystal for, for example, reduction of bone loss in osteopenic postmenopausal women. In doing so, the POSA would rely on information about the therapeutically

effective amount of genistein as taught in Marini to determine the therapeutically effective amount of the co-crystal. The POSA would incorporate amounts of the '408 Application/Sowa co-crystal sufficient to provide genistein at 54 mg/day, a therapeutically effective amount for the reduction of bone loss in osteopenic postmenopausal women.<sup>11</sup> Ex. 1503, Appel ¶¶ 68, 71-73; Ex. 1502, Rogers ¶¶ 301-07.

Therefore, the '408 Application or Sowa in combination with Marini, the '006 Publication, and Remington teach limitation [10a]. Ex. 1502, Rogers ¶¶ 300, 308.

#### **7. Motivation to Combine the Ground 2 References With a Reasonable Expectation of Success**

A POSA would have been motivated to combine the '408 Application and/or Sowa with Li, Marini, the '006 Publication and Remington. Ex. 1502, Rogers ¶ 309.

The '408 Application, Sowa, and Marini taught that genistein had a number of pharmaceutical applications, including estrogenic activity for the reduction of bone loss in osteopenic women. E.g., Ex. 1511, '408 Application at 1; Ex. 1512, Sowa at 7696-97; Ex. 1513, Marini at 839-46; Ex. 1502, Rogers ¶¶ 310, 316.

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<sup>11</sup> See *supra* n.10.

The '408 Application and Sowa also taught that genistein has low aqueous solubility and bioavailability, hindering its use as an effective drug. Ex. 1511 at 2-3 (“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 at 7696 (similar); *see also* Ex. 1502, Rogers ¶ 311; Ex. 1503, Appel ¶ 68.

A POSA would have understood, including from the '408 Application and Sowa, that co-crystals had the potential to improve therapeutic activity for drugs with low solubility and bioavailability. *E.g.*, Ex. 1511, '408 Application at 2-3 (describing co-crystallization as a “promising method[] for modifying unfavorable physicochemical parameters of pharmaceutically active substances”); Ex. 1512, Sowa at 7696 (describing co-crystallization as “a method of obtaining novel forms of [APIs] with improved physicochemical properties” that “has been successfully employed to modify the solubility of some APIs”); Ex. 1503, Appel ¶ 69; Ex. 1502, Rogers ¶ 312. As such, a POSA would have been motivated to pursue studies with the genistein/nicotinamide/water co-crystal. Ex. 1502, Rogers ¶¶ 310-15.

Because drugs are not typically administered to animals and humans on their own, a POSA would have been motivated to formulate the '408 Application/Sowa co-crystal into a pharmaceutical composition to evaluate whether it had improved

pharmaceutical properties as compared to genistein alone; a POSA would have looked to Marini for guidance on determining a therapeutically effective amount of the co-crystal as it specifically discusses therapeutically effective amounts of genistein for use in reducing bone loss. Ex. 1503, Appel ¶¶ 34, 68-73, 77; Ex. 1502, Rogers ¶¶ 315-16, 319. A POSA also would have looked to Remington (and the '006 Publication) for guidance on how to formulate the co-crystal into a pharmaceutical composition with a pharmaceutically acceptable carrier in view of Remington's teachings about formulating pharmaceutical compositions of multiple-component solids, such as those disclosed in the '408 Application/Sowa. Ex. 1510, Remington at 581-610; Ex. 1503, Appel ¶¶ 75-77; Ex. 1502, Rogers ¶¶ 315, 318-20.

Further, a POSA would have been motivated to combine the '408 Application and/or Sowa with Li, as they all concern nicotinamide, and would have been motivated to combine the '408 Application and/or Sowa with Marini as they all concern genistein. Ex. 1502, Rogers ¶¶ 316-17.

In view of the teachings discussed above, a POSA would have had a reasonable expectation of successfully formulating a pharmaceutical composition comprising a pharmaceutically acceptable carrier and therapeutically effective amount of a 1:1:1 genistein/nicotinamide/water co-crystal that meets all the limitations of claim 16. *Id.* ¶¶ 309, 321; Ex. 1503, Appel ¶¶ 76-77. Indeed, if

Patent Owners were to argue that there was no reasonable expectation of success, the Priority Applications would lack enablement as they fail to provide any specific guidance on how to formulate any of the disclosed or claimed co-crystals into a pharmaceutical composition in a therapeutically effective amount. Ex. 1502, Rogers ¶ 150. As a result, claim 16 is obvious over the '408 Application and/or Sowa in view of Li, Marini, the '006 Publication, and Remington. *Id.* ¶¶ 266, 322.

#### **X. THERE ARE NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS**

Although Petitioner does not presently know which objective indicia Patent Owners may rely on, Petitioner addresses below statements in the intrinsic record potentially directed to objective indicia. Petitioner reserves its right to revisit claim construction should Patent Owners attempt to argue that Petitioner's Entresto® product falls within the scope of claim 16.

To rely on objective indicia, Patent Owners must establish a nexus between the evidence and the merits of the claimed invention. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). Here, Patent Owners cannot establish a nexus between claim 16 and the unsupported statements in the '344 patent and prosecution history alleging that: multiple component phase compositions (which include co-crystals) “can” improve drug properties; it was unexpected that APIs could “be used in co-crystals” and “exhibit improved characteristics as compared to the API alone”; and the invention satisfied an unmet need by “allow[ing]

predictable crystal engineering.”<sup>12</sup> Nexus is lacking because these statements focus on features that were not novel features of claim 16 as of 2014 and they lack a direct relationship to the features of claim 16.<sup>13</sup> Ex. 1502, Rogers ¶¶ 326, 330-31, 334, 336-37, 339, 341-42.

Co-crystals falling within claim 16’s co-crystal limitation were known as of 2014. *See, e.g.*, Grounds 1 and 2, *supra*.<sup>14</sup> Because the co-crystal claim limitation was not a novel feature of claim 16, evidence relating to this limitation cannot establish nexus. Ex. 1502, Rogers ¶¶ 330-31, 336-37, 339; *Lectrosonics, Inc. v. Zaxcom, Inc.* (designated precedential), IPR2018-01129, Paper 33 (Final Written Decision) at 33 (PTAB Jan. 24, 2020) (“[T]here must be a nexus to some aspect of

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<sup>12</sup> *See* Ex. 1501, 2:18-20, 3:26-28, 17:50-58; Ex. 1517, p. 4416; Ex. 1516, p. 359; Ex. 1516, pp. 445-46; Ex. 1502, Rogers ¶¶ 329-32, 336-39.

<sup>13</sup> To the extent Patent Owners rely on any properties of the carbamazepine/saccharin co-crystal to support objective indicia (*e.g.*, Ex. 1501, 3:26-28, 17:50-58), such evidence is irrelevant because it is specific to a co-crystal that does not include solvent and thus does not fall within claim 16. Ex. 1502, Rogers ¶ 332.

<sup>14</sup> Further, if Patent Owners argue that the Priority Applications disclose any co-crystal within the scope of claim 16, that co-crystal would have been publicly disclosed prior to 2014 in the ’006 Publication. Ex. 1502, Rogers ¶¶ 333, 340.

the claim not already in the prior art.”); *see also Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1330-31 (Fed. Cir. 2017); *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356 (Fed. Cir. 2023). Further, the intrinsic record does not establish that any purported objective indicia referenced in the ’344 patent or prosecution history is attributable to the subject matter of claim 16, let alone any novel feature. Thus, Patent Owners cannot establish nexus. *Id.* Moreover, the applicants’ statements lack supporting evidence and thus are not entitled to weight. *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1377 (Fed. Cir. 2011); *Ex. 1502, Rogers ¶¶ 330-32, 336-39.*

#### **XI. TRIAL SHOULD BE INSTITUTED (35 U.S.C. § 314(a))**

Petitioner stipulates that if this IPR is instituted, it will not pursue in a parallel district court proceeding the same grounds as in this petition or any other ground that could have reasonably been raised (*i.e.*, grounds under §§ 102 and/or 103 on the basis of prior art patents or printed publications) concerning the challenged claim. This stipulation is dispositive of § 314(a) under the Interim Procedure For Discretionary Denials In AIA Post Grant Proceedings With Parallel District Court Litigation (June 21, 2022) (“Interim Procedure”). *See, e.g., Ericsson Inc. v. Dali Wireless Inc.*, IPR2022-01212, Paper 17 at 55-56 (PTAB Feb. 1, 2023) (declining to exercise discretion to deny institution “[g]iven [a] Sotera stipulation

and the guidance under the Interim Procedure” without addressing the *Fintiv* factors).

For completeness, Petitioner will address the *Fintiv* factors, which together weigh in favor of institution.

**Factor 1:** Petitioner will immediately move to stay the parallel litigation pending denial of institution or a final written decision.

**Factor 2:** No trial date has been set in the parallel litigation. Ex. 1550, N.D. Cal. Case No. 3:22-cv-04913-AMO, D.I. 55, 57. Further, Petitioner will immediately move to stay the litigation.

**Factor 3:** Substantial work remains to be completed in the parallel litigation. No Markman Hearing has been scheduled, fact discovery remains open and no fact depositions have been noticed, expert discovery has not yet begun, and deadlines for dispositive motions have not yet been set. Ex. 1550, N.D. Cal. Case No. 3:22-cv-04913-AMO, D.I. 55, 57. *See Extractiontek Sales LLC v. Gene Pool Techs., Inc.*, IPR2022-00832, Paper 15 at 10-11 (PTAB Oct. 31, 2022).

**Factor 4:** Petitioner has provided a stipulation with respect to the challenged claim identical to the one provided in *Sotera Wireless, Inc. v. Masimo Corp.*,

IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020) (precedential as to § II.A).<sup>15</sup>

**Factor 5:** Petitioner is the defendant in the parallel litigation.

**Factor 6:** As evidenced by the above showing for Grounds 1 and 2, the merits of this Petition are strong.

In view of the above *Fintiv* factors, IPR should be instituted. In addition, the instant petition presents “compelling evidence of unpatentability” for the same reasons as in *Fintiv* Factor 6, and thus trial should be instituted on this basis as well. *See* Interim Procedure at 9.

## **XII. TRIAL SHOULD BE INSTITUTED (35 U.S.C. § 325(d))**

Institution should not be denied under 35 U.S.C. § 325(d) because the arguments and evidence presented here were not previously and/or substantively considered by the Office. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, (designated precedential) IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020); Ex. 1502, Rogers ¶¶ 345, 403.

Part One of *Advanced Bionics* is not satisfied for Grounds 1 or 2. Petitioner’s primary references, Ueto (Ground 1) and the ’408 Application and

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<sup>15</sup> The instant Petition (directed to claim 16) and another concurrently filed petition directed to claims 10, 11, and 18 of the ’344 patent together challenge all claims that Patent Owners have asserted that Petitioner infringes.

Sowa (Ground 2), were not cited at all during prosecution. Ex. 1502, Rogers ¶¶ 346-47, 398.

The art in Grounds 1 and 2 and Petitioner's associated arguments are not cumulative of those substantively considered during prosecution because, among other things, Petitioner's primary references disclose co-crystals that are different from the materials disclosed in the references substantively considered during prosecution. *Id.* ¶¶ 348-97. The examiner further did not have the opportunity to consider the combinations of references in Grounds 1 and 2 or Petitioner's experts' testimony explaining them. *Id.* ¶¶ 346-47, 398-99. The examiner also did not consider Petitioner's priority challenges or the prior art as of 2014 (including Ueto, the '408 Application, and Sowa). Notably, while written description and enablement rejections were made during prosecution of at least one related application (Almarsson) for similarly overbroad claims, Patent Owners failed to bring any rejections from the Almarsson prosecution to the '344 patent examiner's attention. *Supra* §§ VII.A.1, VII.B; Ex. 1502, Rogers ¶¶ 400-02; *cf. McKesson Info. Solutions, Inc. v. Bridge Med., Inc.*, 487 F.3d 897, 925 (Fed. Cir. 2007) (no clear error in district court's finding that rejections in a related application would have been important to disclose to the examiner).

Although the Board need not reach *Advanced Bionics* Part Two, it also favors institution because the Office erred in a manner material to the patentability of claim 16.

As explained above, the '344 patent examiner did not substantively address any of Petitioner's asserted art or arguments, or substantially similar art or arguments, and neither Ueto (Ground 1) nor the '408 Application or Sowa (Ground 2) was before the examiner during prosecution. Ex. 1502, Rogers ¶¶ 345-99. Nor did the examiner address written description or enablement, or the prior art as of 2014, and never specifically discussed claim 16 in particular. *Id.* ¶¶ 400-02.

Finally, Petitioner submits declarations from Drs. Rogers and Appel, which were not before the examiner and which further explain a POSA's understanding of the art. *See Celltrion, Inc. v. Genentech, Inc.*, No. IPR2017-01140, Paper 31 at 13-14 (PTAB Jan. 25, 2018).

### **XIII. CONCLUSION**

For the reasons above, the Board should cancel claim 16 as unpatentable.

### **XIV. MANDATORY NOTICES**

#### **A. Real Party in Interest (37 C.F.R. § 42.8(b)(1))**

Novartis Pharmaceuticals Corporation is the real party-in-interest.

**B. Related Matters (37 C.F.R. § 42.8(b)(2))**

The '344 patent is the subject of pending litigation: *Regents of the Univ. of Mich. v. Novartis Pharm. Corp.*, No. 3:22-cv-04913-AMO (N.D. Cal.); however, one of the Plaintiffs in the litigation, “University of South Florida Board of Trustees,” has a different name from that listed in the U.S. Patent and Trademark Office’s Patent Assignment Database, “University of South Florida,” as an assignee for the '344 patent. Ex. 1551, USPTO Patent Assignment Database Entry for U.S Patent No. 10,633,344.

**C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3))**

| Lead Counsel                                                                                                                                                                                                                                                  | Backup Counsel                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
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|--|--------------------------------------------------------------------------------------------------------------------------------------------------|

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney for Petitioner has been filed herewith.

**D. Service Information (37 C.F.R. § 42.8(b)(4))**

Service of any documents via hand-delivery or postal mailing may be made at the mailing address of lead and backup counsel designated above. Petitioner consents to electronic service at the e-mail addresses of lead and backup counsel designated above.

**XV. PAYMENT OF FEES**

Pursuant to 37 C.F.R. §§ 42.103 and 42.15(a), the required fee is being submitted herewith.

**XVI. WORD COUNT**

Under 37 C.F.R. § 42.24(d), Petitioner certifies that this Petition for *Inter Partes* Review has a word count of 13,977, excluding the portions exempted by 37 C.F.R. § 42.24(a), as calculated by the built-in word-count function in the Microsoft Word software used to prepare this document, and a manual count of the number of words appearing in the figures.

## **XVII. CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on August 28, 2023, a complete copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,633,344, Power of Attorney, Exhibit List, and all supporting exhibits were served via FedEx to the Patent Owner by serving the correspondence address of record indicated in the Patent Office's Patent Center for U.S. Patent No. 10,633,344:

23628 - WOLF GREENFIELD & SACKS, P.C.  
Edward R. Gates  
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A courtesy copy of the foregoing was also served by email upon the following counsel of record for the Patent Owner in litigation pending before the United States District Court for the Northern District of California Case No. 3:22-cv-04913-AMO:

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