

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner,

v.

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

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

**DECLARATION OF LEAH APPEL, PH.D.
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW**

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I, Leah E. Appel, Ph.D., hereby declare as follows:

I. INTRODUCTION

1. I am a pharmaceutical scientist with over 30 years of experience in the pharmaceutical industry. I am currently the managing partner at Green Ridge Consulting, where I help clients with formulation and process development for oral solid dosage forms.

2. I have been retained as an expert by counsel for Novartis Pharmaceuticals Corporation (“Petitioner” or “Novartis”) in connection with its petitions for *inter partes* review of U.S. Patent No. 10,633,344 (Ex. 1501, “the ’344 patent”). I understand that Petitioner is challenging claims 10, 11 and 18 of the ’344 patent in one IPR petition (Petition 1) and claim 16 of the ’344 patent in a second IPR petition (Petition 2). I will refer to claims 10, 11, 16, and 18 collectively as “the challenged claims.”

3. I have been asked by Petitioner’s counsel to provide a technical background on the state of the art with respect to pharmaceutical formulations and to opine on questions posed to me by counsel that are set forth in Section VI. I

have been asked to perform my analysis as of February 13, 2014¹ (which I will abbreviate as “2014”) from the perspective of an ordinary formulator, with whom a person of ordinary skill in the art (“POSA”) would consult (*i.e.*, a formulator consultant). In other words, my opinions herein are from the perspective of a person having ordinary experience in formulation of pharmaceutical compositions. For simplicity, I will refer to the knowledge of the formulator consultant as a POSA’s knowledge, because a POSA would have obtained this knowledge from the formulator consultant (if a POSA did not already have such knowledge). My opinions are based on my professional experience in pharmaceutical formulation and development including as of 2014.

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

5. The basis for my opinions is set forth in this declaration.

¹ I understand from Petitioner’s counsel that February 13, 2014 is the filing date of U.S. Application No. 14/179,862 (“the ’862 application”), which issued as the ’344 patent.

II. BACKGROUND AND QUALIFICATIONS

6. I earned a B.S. degree in Chemical Engineering from the University of California, Los Angeles in 1982, and a Ph.D. in Pharmaceutics from the University of Utah, Salt Lake City in 1988.

7. I have over 30 years of experience in the pharmaceutical industry, with extensive experience in solid oral dosage forms and developing drug delivery technology and products. I joined INTERx Research Corporation (owned by Merck & Co.) in 1988 as a Senior Research Chemist. I held that position until 1993 when I became a Research Fellow. From 1995 – 1996, I was a Project Leader at Sarcos Research Corporation. From 1996 – 2006, I worked as the Director of Controlled Research at Bend Research, where I was responsible for the development of a wide range of immediate and controlled release drug delivery technologies. I left that position in 2007 when I founded Green Ridge Consulting. At Green Ridge Consulting we help our clients formulate and develop oral solid dosage forms for their specific drug/drugs. In this role, I have formulated hundreds of compounds for oral delivery.

8. My areas of expertise include development and application of drug delivery technology, including formulation and process development for oral solid dosage forms, including controlled and sustained release formulations, poorly soluble compounds, fixed dose combinations, and pediatric formulations for oral

delivery. I also have extensive experience with tablets, capsules, osmotic systems, multiparticulates, and amorphous solid dispersions. I am familiar with formulating multiple-component crystals (as defined in paragraph 20 below) into pharmaceutical compositions.

9. Since 1989, I have published in various academic journals regarding formulation of oral dosage forms. I am also a named inventor on 44 issued patents and pending patent applications, including patents directed to a variety of dosage forms.

10. I have presented my work at various national and international meetings for those in the field of pharmaceutical formulation, including the American Pharmaceutical Association Academy of Pharmaceutical Sciences, the American Association of Pharmaceutical Scientists, the Controlled Release Society and the American Institute of Chemical Engineers. I also served as an Advisor to the *Journal of Pharmaceutical Sciences* from 2013 – 2016.

11. I have served as a consultant in the area of drug formulation and delivery for U.S. and international companies and have testified as an expert witness in the area of drug formulation and delivery in several patent trials. My publications, including publications authored within the past ten years, are listed in my CV (Ex. 1554).

III. LEGAL STANDARDS USED IN MY ANALYSIS

12. I am not a patent attorney and have not independently researched patent law. Counsel for Petitioner have explained certain legal standards to me that I have relied upon in forming my opinions set forth in this Declaration.

13. I understand from Petitioner's counsel that Petitioner has the burden of proving that the challenged claims are unpatentable by a preponderance of the evidence, *i.e.*, Petitioner must show that the claims are more likely than not unpatentable.

14. I understand that obviousness is analyzed from the perspective of a POSA as of the date of the invention (here, 2014). I also understand that a POSA is a hypothetical person who is presumed to have been aware of all relevant art at the time of the invention. I understand that a POSA may also consult with others having ordinary experience in other pertinent disciplines.

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

16. I understand that obviousness requires assessing (1) the level of ordinary skill in the pertinent art, (2) the scope and content of the prior art, (3) the differences between the prior art and the claims at issue, and (4) if applicable,

secondary considerations of non-obviousness such as commercial success, long-felt but unsolved needs, failure of others, etc.

17. I understand that in assessing whether a patent claim is obvious, the Board will consider whether the prior art would have provided a POSA with a motivation to select and combine the teachings of the prior art to arrive at the claimed invention with a reasonable expectation of success as of the priority date. In determining whether there would have been a reasonable expectation of success, I understand that absolute predictability of the results is not required.

18. I understand that claims reciting “a pharmaceutical composition” do not require a commercially viable pharmaceutical composition. Accordingly, I understand that a POSA’s reasonable expectation of success with respect to the challenged claims pertains to the formulation of a pharmaceutically useful composition meeting the claim limitations but does not require a reasonable expectation of success in satisfying any additional hurdles associated with formulating a commercially viable pharmaceutical product.

IV. MATERIALS REVIEWED

19. For purposes of this declaration, I reviewed the ’344 patent and its prosecution history, the prosecution history of U.S. Application No. 10/378,956 (“the ’956 parent application”), which I understand is the parent application to which the ’344 patent claims priority, and the references cited in this declaration.

V. SUMMARY OF THE '344 PATENT AND POSA

20. The '344 patent purports to describe “the design of new multiple-component solid phases, such as multiple-component crystals, having at least one active pharmaceutical component” and a co-crystal former. Ex. 1501, Figure 24, col. 3, ll. 8-59, col. 7, ll. 13-15, 19-23, col. 9, ll. 10-15. I understand that “[m]ultiple-component crystals” are crystalline compositions that contain at least two components.

21. The '344 patent also states that multiple-component solids “can be formulated according to known methods for preparing pharmaceutically useful compositions,” and these compositions “[o]ptionally, . . . can include a pharmaceutically acceptable carrier or diluent.” Ex. 1501, col. 10, ll. 6-39. The '344 patent cites Remington's as an example of a source describing formulations that were “well known and readily available to those in the art.” Ex. 1501, col. 10, ll. 15-21 (citing Ex. 1541, 19th Edition of Remington's, which is dated in 1995 (“Remington's 1995”)). Remington's was (and still is) an authoritative and well-known reference on the science and practice of pharmacy, including pharmaceutical formulation and manufacturing. Ex. 1541, Remington's 1995 at preface xiii-xiv. In this declaration, I also reference the 22nd Edition of Remington's, which is dated in 2012 (Ex. 1510, “Remington's 2012”). Where both

Remington's 1995 and Remington's 2012 are cited herein, Remington's 2012 includes essentially the same disclosure as Remington's 1995.

22. A POSA would have understood that “a pharmaceutically acceptable carrier or diluent” in the context of the '344 patent was an excipient (*i.e.*, an inactive substance) present in a pharmaceutical composition. Ex. 1501, col. 10, ll. 14-15; Ex. 1541, Remington's 1995 at 1617, 1643-44; see also Ex. 1510, Remington's 2012 at 581, 592-93.

23. A POSA would also have understood that for oral administration for example, drugs are almost always administered as a formulation rather than as a pure drug substance without any excipients. Ex. 1543, Handbook of Pharmaceutical Excipients 2009 at x.

24. For oral administration, the primary dosage forms used are tablets and capsules. A POSA would have understood that in the context of the '344 patent, the terms “carrier” and “diluent” were used synonymously when applied to oral solid dosage forms. Ex. 1501, col. 10, ll. 14-15; Ex. 1542, Webster's Medical Dictionary at 98 (defining “carrier” as “a vehicle serving esp[ecially] as a diluent (as for a drug)”); Ex. 1541, Remington's 1995 at 1626 (stating direct compression tablets can be made by “formulating with a suitable diluent which acts as a carrier or vehicle for the drug”); see also Ex. 1510, Remington's 2012 at 592-93. A POSA would have understood that in these dosage forms, carriers or diluents were

commonly used to add bulk to a tablet or capsule and for handling and processibility when making the dosage form. Ex. 1541, Remington's 1995 at 1617, 1626-27 (stating "vehicles or carriers must have good flow and compressible characteristics" for direct compression for tablets), 1643-44 ("the active ingredient is mixed with sufficient volume of a diluent" and filled into a capsule); see also Ex. 1510, Remington's 2012 at 581, 593, 606. There are many excipients that can be used as a carrier or diluent in tablets and capsules. One example is lactose, a pharmaceutically acceptable carrier that has different forms including α -lactose monohydrate and anhydrous lactose, which as of 2014 were commercially available forms of lactose. Ex. 1543, Handbook of Pharmaceutical Excipients 2009 at 359 (listing the "Functional Category" of anhydrous lactose as "tablet and capsule diluent"), 364-66 (listing the "Functional Category" of lactose monohydrate as "tablet and capsule diluent"; reporting "[l]actose is widely used as a filler and diluent in tablets and capsules," and " α -lactose monohydrate" was an available form of lactose).

25. I have also reviewed the file history of the '344 patent, including the file history of the '956 parent application, which I understand is a record of all communications between the patent applicant and the United States Patent and Trademark Office regarding the patent application that led to the '344 patent, and I did not see any correspondence discussing how to prepare multiple-component

crystals of the '344 patent into pharmaceutical compositions with pharmaceutically acceptable carriers.

26. I understand that claim 10 of the '344 patent is an independent claim. I have been asked by counsel for Petitioner to focus my analysis on the highlighted portion of claim 10, set forth below:

10. 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-former, wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form, wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding, wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form, wherein the supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

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

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

27. Claims 11, 16, and 18 each depend from, and therefore include all the limitations of, claim 10 as highlighted below. Claims 11, 16, and 18 are therefore also directed to “[a] pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal.”

11. The pharmaceutical composition of claim 10, wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

16. The pharmaceutical composition of claim 10, wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.

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

Ex. 1501, col. 25, ll. 40-43, col. 26, ll. 12-14, 22-23.

28. I understand that the remaining non-highlighted limitations of the challenged claims specifically concern the “co-crystal” and its components, so I will refer to these as the “co-crystal limitations.” I have been asked to assume that

“co-crystal” means “[a] multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.” My understanding of this terminology as it pertains to this proceeding is that “co-crystal” would include, among other things, co-crystals that fulfill the single crystalline phase criteria and that are hydrates and solvates.

29. I further understand from Petitioner’s counsel that the challenged claims, which recite a pharmaceutical composition comprising “a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal,” may contain one or more pharmaceutically acceptable carriers.

30. I have been asked to assume that the POSA as of 2014 would have had a Ph.D. in chemistry or a related field with at least two years of experience in solid-state chemistry, including experience preparing multiple-component crystalline solids and evaluating their single crystal structures, and the POSA would consult with others having ordinary experience in other disciplines, such as formulation of pharmaceutical compositions comprising such multiple-component crystalline solids. Alternatively, a POSA as of 2014 would have had a Ph.D. in chemistry, pharmacy, or a related field with at least two years of experience in formulation of pharmaceutical compositions, and the POSA would consult with others having ordinary experience in other disciplines, such as solid-state chemistry, including experience preparing multiple-component crystalline solids

and evaluating their single crystal structures. Alternatively, a POSA under either of these definitions could have a Master's degree in one of the above disciplines plus relatively more experience. These two alternate POSAs can also work together as part of a team, and consult with others having ordinary experience in other disciplines. As of 2014, I had at least ordinary experience in formulation of oral solid dosage form pharmaceutical compositions (*i.e.*, at least the experience of someone with whom the POSA would consult and the formulator POSA).

VI. SUMMARY OF OPINIONS

31. I have been asked to provide a technical background on the state of the art as of 2014 with respect to pharmaceutical formulation of multiple-component crystals (Section VII). I have also been asked to consider the following questions, which I understand from counsel relate to Petition 2 (claim 16) and the IPR Grounds indicated below.

32. **Ground 1:** I have been asked to consider whether a POSA would have been motivated to prepare a therapeutically effective amount of the furosemide/nicotinamide/water co-crystal of Ueto (Ex. 1507), and a pharmaceutically acceptable carrier, into a pharmaceutical composition with a reasonable expectation of success as of 2014. For the reasons explained in Section VIII, I concluded a POSA would have been motivated to make a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a

therapeutically effective amount of this co-crystal as of 2014 with a reasonable expectation of success.

33. **Ground 2:** I have been asked to consider whether a POSA would have been motivated to prepare a therapeutically effective amount of the genistein/nicotinamide/water co-crystal of the '408 Application (Ex. 1511) and Sowa (Ex. 1512), and a pharmaceutically acceptable carrier, into a pharmaceutical composition with a reasonable expectation of success as of 2014. For the reasons explained in Section IX, I concluded a POSA would have been motivated to make a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of this co-crystal as of 2014 with a reasonable expectation of success.

VII. TECHNICAL BACKGROUND AS OF 2014

A. Background On Pharmaceutical Compositions Comprising Multiple-Component Crystals

34. In 2014, pharmaceutical compositions administered in solid dosage forms for oral administration, such as tablets and capsules, almost always contained excipients (inactive ingredients) in addition to drug substance. Ex. 1543, Handbook of Pharmaceutical Excipients 2009 at x.

35. Carriers (diluent)s play an important role in oral solid dosage forms. Ex. 1510, Remington's 2012 at 583-84, 606. They are and were excipients that were used to add bulk to a tablet or capsule and to aid in handling and

processibility when making the dosage form. Ex. 1510, Remington's 2012 at 583, 606. In 2014, the use of excipients and specifically carriers or diluents in drug products was well-established and common in the formulation of oral solid dosage forms by pharmaceutical formulators.

36. A POSA as of 2014 would have understood that multiple-component crystals of a drug substance with a co-crystal former were known. The same formulation strategies, technologies and processes would have been considered and used for APIs not in a co-crystal as would be used for different types of multiple-component crystals. The formulator considers the specific physicochemical properties of the API and other factors to inform the selection of a dosage form type, the excipients to use and the processes used to make the dosage form. It would have been within the skill of the ordinary formulator to select an appropriate strategy depending on such properties.

37. Because co-crystals contain a fixed ratio of their components, the molecular weights of the individual components would have been used to ascertain the weight ratio of the individual components to the co-crystal. For a co-crystal of a drug substance and one or more other components, a POSA would have ascertained a therapeutically effective amount of co-crystal that corresponded to a desired amount of the drug substance for the intended therapeutic activity, and would have confirmed that the other component(s) of the co-crystal were present in

amount(s) suitable for pharmaceutical use, using basic arithmetic. This is also done for materials other than co-crystals so the formulator knows how much material to weigh out when making pharmaceutical dosage forms.

B. Pharmaceutically Acceptable Carriers And Therapeutically Effective Amounts Of Co-Crystals Had Been Formulated Into Pharmaceutical Compositions In 2014

38. As of 2014, pharmaceutical compositions had been formulated that included pharmaceutically acceptable carriers and therapeutically effective amounts of co-crystals as defined in paragraph 28.

39. Coumadin[®], which I have been asked to assume is a co-crystal of warfarin sodium, was FDA approved in 1954² as an anticoagulant in the form of tablets comprising a therapeutically effective amount of this co-crystal and a pharmaceutically acceptable carrier (*e.g.*, lactose and starch). Ex. 1535, Physicians' Desk Reference 2004 at 1048-52; Ex. 1544, U.S. Patent No. 2,777,859 at col. 5, ll. 58-67 ("The dry warfarin-alkali metal derivative obtained as described above in Example II [Preparation of stable warfarin-sodium derivative in the solid form] is a stable, free-flowing powder and . . . is of the type desired for clinical use . . . It may

² Ex. 1537, Coumadin[®] Label revised 10/2011 (showing initial U.S. approval in 1954).

be tableted, or capsuled for oral use . . . ”); Ex. 1543, Handbook of Pharmaceutical Excipients 2009 at 359, 364-66 (lactose), 685-86 (starch).

40. Vibramycin[®] Hyclate, which I have been asked to assume is a co-crystal of doxycycline hyclate, was FDA approved in 1967³ in the form of tablets comprising a therapeutically effective amount of this co-crystal and a pharmaceutically acceptable diluent (*e.g.*, microcrystalline cellulose) to treat various types of infections. Ex. 1535, Physicians’ Desk Reference 2004 at 2665-68; Ex. 1543, Handbook of Pharmaceutical Excipients 2009 at 129-30 (microcrystalline cellulose).

41. Amoxil[®], which I have been asked to assume is a co-crystal of amoxicillin trihydrate, was FDA approved in 1974⁴ in the form of tablets comprising a therapeutically effective amount of this co-crystal and a carrier (*e.g.*, microcrystalline cellulose) to treat various types of infections. Ex. 1535, Physicians’ Desk Reference 2004 at 1427-31; Ex. 1536, Hilton 1993 at Abstract (“A controlled-release tablet of amoxicillin trihydrate was developed . . .”); Ex. 1545, U.S. Patent No. 7,807,196 at col 1, ll. 3-5, col 2, ll. 3-26; Ex. 1543,

³ Ex. 1538, Vibramycin[®] Label revised 1/2023 (showing initial U.S. approval in 1967).

⁴ Ex. 1539, Amoxil[®] Label revised 9/2015 (showing initial U.S. approval in 1974).

Handbook of Pharmaceutical Excipients 2009 at 129-30 (microcrystalline cellulose).

42. In 2007, Hickey, *et al.* reported on *in vitro* and *in vivo* studies that used a pharmaceutical composition comprising a “carbamazepine:saccharin co-crystal” and a pharmaceutically acceptable carrier. Ex. 1504, Hickey at 115 (“A prototype oral dosage form in an HPMC capsule (Shionogi Qualicaps) containing [the carbamazepine:saccharin co-crystal and a pharmaceutically acceptable carrier] was prepared by mixing [the carrier] α -lactose monohydrate (2.52g, 0.0069 mol, Sigma, Lot 43254338) with [the carbamazepine:saccharin co-crystal] (3.654g, 0.087 mol, particle size <53 μ m) and blending the two solids in a mortar and pestle. Capsules containing 600 mg of formulated co-crystal [containing the co-crystal and lactose] (corresponding to 200 mg of carbamazepine) were prepared. Both dosage forms [the formulated co-crystal and Tegretol®] were administered orally to four animals in a 2-way cross-over design.”); 118 (describing the “[i]n-vitro dissolution experiments carried out on formulated co-crystal containing lactose”); Ex. 1543, Handbook of Pharmaceutical Excipients 2009 at 364-66 (lactose monohydrate). The Hickey investigators concluded that “[i]t seems reasonable to assert that co-crystal approaches should be considered routinely as part of a broader set of form and formulation explorations to strive for the best possible drug products.” Ex. 1504, Hickey at 118.

43. And in 2010, Jung, *et al.* reported an *in vivo* pharmacokinetic study in beagle dogs using a pharmaceutical composition comprising a co-crystal of indomethacin with saccharin and a pharmaceutically acceptable carrier. Ex. 1546, Jung at 1562 (“Hard gelatin capsules (No. 4) were filled with lactose-based formulations: ... (4) ground [indomethacin-saccharin] co[-]crystals, as detailed in Table 1. Lactose was used as filler. Prior to filling the capsules, the formulation ingredients were geometrically mixed with a mortar and spatula and passed twice through a 450-µm sieve to ensure proper mixing.”); 1562, Table 1 (describing the formulation of [indomethacin-saccharin] co-crystals containing 25 mg of indomethacin, 12.8 mg of saccharin, and 120 mg of lactose, with a total weight of 157.8 mg. . . .); 1562, Table 1 & 1563 (“The pharmacokinetic data of the [indomethacin-saccharin] co[-]crystals were compared with those of [a physical mixture (containing 25 mg indomethacin and 12.8 mg saccharin)] and the commercial product, Indomee® [(containing 25 mg indomethacin)], in beagle dogs.”); 1565 (“The objectives of the formulation work were to identify a simple, relevant formulation that would facilitate filling the hard gelatin capsules and would not influence the performance characteristics of [the drug indomethacin] in either stable or co[-]crystalline form A simple formulation of unground and ground [indomethacin-saccharin] co[-]crystals with lactose (as filler) that allowed easy filling of the hard capsules was chosen for further study.”); Ex. 1543,

Handbook of Pharmaceutical Excipients 2009 at 359, 364-66 (lactose). The Jung investigators concluded that “the study demonstrates that co[-]crystals provide an alternative platform for formulation exploration in the search for the best possible drug products.” Ex. 1546, Jung at 1566.

44. In sum, Hickey and Jung each described simple capsule formulations in which the co-crystal was mixed with a carrier (lactose), blended with a mortar and pestle, and filled into capsules. The experiments discussed above by Hickey, *et al.* and Jung, *et al.* are examples where co-crystals (the “carbamazepine:saccharin co-crystal” and “[indomethacin-saccharin] cocrystals,” respectively) were formulated with a carrier (lactose) to prepare pharmaceutical compositions which were then filled into capsule dosage forms.

C. A POSA Would Have Known How To Formulate A Pharmaceutical Composition Comprising A Multiple-Component Crystal and a Pharmaceutically Acceptable Carrier Using Well-Known Formulations And Methods In 2014

45. As of 2014, a POSA also would have known how to formulate a pharmaceutically acceptable carrier and a therapeutically effective amount of a multiple-component crystal into a pharmaceutical composition using formulations and methods that were readily available and well known to those in the art.

1. Remington's Described Solid Oral Dosage Forms Suitable For Formulating A Pharmaceutical Composition Comprising A Multiple-Component Crystal and a Pharmaceutically Acceptable Carrier

46. As was discussed in paragraph 34, as of 2014, a POSA would have known and the Handbook of Pharmaceutical Excipients taught that drug substances are almost always administered as formulations with excipients (*i.e.*, pharmaceutical compositions). For the oral route, the most common dosage forms were tablets and capsules. Ex. 1510, Remington's 2012 at 581.

47. When developing a formulation, a POSA would have known that the specific formulation for a specific API is dependent on its physicochemical properties and the desired properties of the dosage form.

48. Because a commercial product is not required by the claims here (paragraph 18), I will focus on early pharmaceutical development work. Often in early development (for animal studies or even early clinical trials), simple formulations designed to simply administer the drug to the subject were used. These simple formulations did not necessarily have all the desirable features of a dosage form intended for commercial manufacture (long term stability, ability to make at scale, *etc.*) but instead were fit-for-purpose to determine the result of administering a pharmaceutical composition to an animal or human subject.

49. Tablets can be made with different types of ingredients (Ex. 1510, Remington's 2012 at 583), that may be classified according to the part they play in

the finished tablet. One type of ingredient or excipient (inactive material) is known as a diluent. A diluent may help impart satisfactory processing and compression characteristics to the formulation. Ex. 1510, Remington's 2012 at 583. In tablets made via direct compression, a suitable diluent can act as a carrier or vehicle for the drug. Ex. 1510, Remington's 2012 at 593.

50. Carriers were used to add bulk to a tablet or capsule and ensure that the desired dose of the drug substance was contained in the dosage form. Ex. 1510, Remington's 2012 at 583, 606.

51. A POSA would know the types and identities of well-known formulation methods for making pharmaceutical compositions which would have been used to prepare a pharmaceutical composition comprising a multiple-component crystal (that included a drug substance) and a pharmaceutically acceptable carrier. Ex. 1501, col. 10, ll. 6-39; Ex. 1510, Remington's 2012 at 586-87, 592-93, 604-10. These compositions can be very simplistic early phase dosage forms.

52. Remington's explained that tablets were a common solid oral dosage form, in part, because of the many advantages they afforded the manufacturer, including their simplicity of preparation. Ex. 1510, Remington's 2012 at 581. Remington's taught that tablets were typically prepared with suitable diluents (*i.e.*, pharmaceutically acceptable carriers). Ex. 1510, Remington's 2012 at 581-83.

Remington's taught that tablets could be prepared either by compression or molding methods, which had "been in widespread use since the latter part of the 19th century." Ex. 1510, Remington's 2012 at 581. Remington's further explained that compressed tablets could be prepared by various known methods, including dry granulation which was useful for ingredients that were "sensitive to moisture or are unable to withstand elevated temperatures during drying." Ex. 1510, Remington's 2012 at 592.

53. Remington's taught that capsules were another solid dosage form, in which the drug substance was enclosed in either a hard or soft, soluble container or shell. Ex. 1510, Remington's 2012 at 604. Remington's taught that capsules were typically filled with the drug mixed with suitable diluents (*i.e.*, pharmaceutically acceptable carriers). Ex. 1510, Remington's 2012 at 605-606.

54. As of 2014, a POSA would have been aware that certain conditions or factors, including exposure to moisture, elevated temperature, and mechanical stress (such as the forces applied to a co-crystal during grinding or milling) could cause a multiple-component crystal such as a co-crystal to dissociate during formulation. Accordingly, a POSA looking to formulate a therapeutically effective amount of a co-crystal into a pharmaceutical composition would have used a formulation strategy that would avoid these conditions.

2. Remington's Described The Use of Pharmaceutically Acceptable Carriers In Solid Oral Dosage Forms

55. Remington's taught that carriers would be included in the pharmaceutical compositions for oral administration as discussed above (Section VII.C.1). Ex. 1510, Remington's 2012 at 583 (discussing tablets containing diluents (*i.e.*, pharmaceutically acceptable carriers)), 592-93 ("Direct compression for tablets containing 25% or less of drug substances can frequently be used by formulating with a suitable diluent that acts as a carrier or vehicle for the drug"), 605-06 (discussing capsules filled with mixtures of drugs plus diluents (*i.e.*, pharmaceutically acceptable carriers)). Carriers were routinely used in formulation of oral solid dosage forms in 2014.

56. When looking to select a carrier for use in a pharmaceutical composition, a POSA would have been aware of the Handbook of Pharmaceutical Excipients, which originally published in 1986 and was "conceived as a systematic, comprehensive resource of information" on excipients, including carriers. Ex. 1543, Handbook of Pharmaceutical Excipients 2009 at x. As of 2014, a POSA would have known that the Handbook "is a comprehensive, uniform guide to the uses, properties, and safety of pharmaceutical excipients and is an essential reference source for those involved in the development . . . of pharmaceutical preparations." Ex. 1543, Handbook of Pharmaceutical Excipients 2009 at x. Remington's recognized the importance of the Handbook, noting that "[t]he need

for acquiring more information and use standards for excipients ha[d] been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain” and that “[t]he result [was] called the Handbook of Pharmaceutical Excipients” which is “distributed widely throughout the world.” Ex. 1510, Remington’s 2012 at 583.

VIII. A POSA WOULD HAVE BEEN MOTIVATED TO FORMULATE A THERAPEUTICALLY EFFECTIVE AMOUNT OF A FUROSEMIDE/NICOTINAMIDE/WATER CO-CRYSTAL AND A PHARMACEUTICALLY ACCEPTABLE CARRIER INTO A PHARMACEUTICAL COMPOSITION WITH A REASONABLE EXPECTATION OF SUCCESS AS OF 2014 (PETITION 2, GROUND 1)

57. As of 2014, a POSA would have been motivated to formulate a therapeutically effective amount of the furosemide/nicotinamide/water co-crystal of Ueto (Ex. 1507) with a pharmaceutically acceptable carrier into a pharmaceutical composition in view of Martindale 2011, the ’006 Publication, and Remington’s 2012.

58. Furosemide was a known diuretic used in treating hypertension, among other conditions. Ex. 1506, Martindale 2011⁵ at 1421-25; Ex. 1507, Ueto at 486 (“Furosemide . . . is a loop diuretic drug”). However, furosemide was known to be “[p]ractically insoluble in water.” Ex. 1506, Martindale 2011 at 1421.

59. A POSA would have understood that co-crystals could have potentially improved on the properties of a drug substance compared to existing forms of the drug substance alone, such as its solubility, bioavailability and dissolution rate. Ex. 1507, Ueto at 485 (noting co-crystals of drugs have the “potential to improve physicochemical properties” of the drugs); *see also* Ex. 1504, Hickey at 113 (“Co-crystals may also play a role in modulating the physical properties of an API, including . . . solubility and dissolution”), 112-118 (evaluating properties of a carbamazepine co-crystal compared to carbamazepine alone, including solubility, oral bioavailability, and dissolution, and reporting “favorable dissolution properties” and “comparable oral absorption” in dogs); Ex. 1547, Aronhime at col. 1, ll. 12-49, col. 6, ll. 52-58 (describing a new multiple

⁵ A POSA would have understood that Martindale 2011 was a drug reference that provided up-to-date information on drugs used throughout the world, such as therapeutic indications and dose information. Ex. 1506, Martindale 2011 at preface v-vi.

component crystal of a known drug, oxcarbazepine chloroform solvate), col. 1, l. 53 – col. 2, l. 22 (reporting that “[s]olid state physical properties” including rate of dissolution and oral bioavailability are influenced by a drug’s crystalline form), col. 3, ll. 7-14 (reporting new crystalline forms “provide[] a new opportunity to improve the performance characteristics of a pharmaceutical product” and “enlarge[] the repertoire of materials that a formulation scientist has available for designing” dosage forms). A POSA would have been motivated to evaluate whether the properties of a furosemide/nicotinamide/water co-crystal, such as oral bioavailability and dissolution, were improved compared to furosemide alone, analogous to what was done by Hickey *et al.* in dogs. Ex. 1504, Hickey at 117-18; Ex. 1507, Ueto at 485 (“evaluating [the] physicochemical properties” of various forms of drugs is “of particular importance for pharmaceutical research and development”). To enable this testing, a POSA would have combined the co-crystal with a pharmaceutically acceptable carrier into a pharmaceutical composition so that the co-crystal would be suitable to administer to an animal or human. See Section VII.A; Ex. 1504, Hickey at 114-15, 117-118 (formulating carbamazepine/saccharin co-crystals with lactose into pharmaceutical compositions to evaluate oral bioavailability and dissolution).

60. In such pharmaceutical compositions, a POSA would have (i) been motivated to use, and would have ascertained a therapeutically effective amount of,

the furosemide/nicotinamide/water co-crystal of Ueto for use in hypertension and (ii) confirmed that the other components of the co-crystal were present in amounts that were suitable for pharmaceutical use.

61. With respect to (i), in the treatment of hypertension, furosemide is given orally at doses of 40 to 80 mg daily. Ex. 1506, Martindale 2011 at 1423. The other co-crystal components, nicotinamide and water, were not known to treat hypertension. Ex. 1506, Martindale 2011 at 2117-19 (omitting hypertension as a therapeutic indication for nicotinamide). The POSA would have incorporated an amount of the Ueto co-crystal sufficient to provide exposure equivalent to furosemide at 40-80 mg/day, which a POSA would have understood was an active amount for hypertension. Because the furosemide/nicotinamide/water co-crystal has a 1:1:2 ratio of its components, a POSA would have calculated a therapeutically effective amount of co-crystal having a 40-80 mg amount of the drug substance (furosemide):

Molecular Weight of Co-Crystal:

Molecular Weight Furosemide: 330.74 g/mol⁶

Molecular Weight of Nicotinamide: 122.12 g/mol⁷

⁶ <https://pubchem.ncbi.nlm.nih.gov/compound/Furosemide> (Ex. 1581).

⁷ <https://pubchem.ncbi.nlm.nih.gov/compound/Nicotinamide> (Ex. 1582).

Molecular Weight of Water: 18.02 g/mol⁸

Total Molecular Weight of 1:1:2 Co-Crystal: $330.74 + 122.12 + 2(18.02) = 488.89$ g/mol

Total Weight of Co-Crystal: 59-118 mg ($330.74/488.89 = (40-80)/X$)

62. With respect to (ii), a POSA would have understood that 59-118 mg of this co-crystal contained 15-30 mg nicotinamide. Nicotinamide was commonly used as an inactive ingredient and was in food like yeast, meat, fish, potatoes, legumes, and cereals. Ex. 1506, Martindale 2011 at 2117-19. A POSA would also have known that the amount of nicotinamide in the furosemide-nicotinamide co-crystal was within the maximum tolerable limit. Ex. 1506, Martindale 2011 at 2117-19 (nicotinamide may be administered orally at doses of up to 500 mg daily in divided doses); Ex. 1510, Remington's 2012 at 198 (stating that nicotinamide is "used [as a co-crystal component] in the pharmaceutical field"); *see also* Ex. 1501, col. 11, ll. 2-5, col. 16, ll. 57-59 (reporting for a carbamazepine/nicotinamide co-crystal that nicotinamide was "GRA[S]," meaning "Generally Regarded as Safe by the FDA"); Ex. 1585, European Commission Opinion on Tolerable Upper Intake

⁸ <https://pubchem.ncbi.nlm.nih.gov/compound/Water> (Ex. 1584).

Levels of Nicotinamide at 14 (disclosing upper-level intake of nicotinamide of 900 mg/day for adults). The water in the furosemide/nicotinamide/water co-crystal of Ueto was likewise suitable for pharmaceutical use.

63. I understand from Petitioner's counsel that the claimed "co-crystal" contains an "API" and a "co-former," which each have certain claimed properties relating to activity and chemical structure for example. I understand that the "API" must have a therapeutic effect, and the "co-former" may also have a therapeutic effect. I understand from counsel that there is no requirement that the claimed "therapeutically effective amount" of the co-crystal for a particular indication must be derived in whole or in part from the activity of the component that meets the claimed requirements of the "API" (here, nicotinamide) when the other co-crystal component (here, the "co-former" furosemide) itself has therapeutic activity for that indication. Here, I understand from Petitioner's counsel that nicotinamide has the claimed "API" properties and furosemide has the claimed "co-former" properties. However, there is no requirement in the '344 patent that the claimed "therapeutically effective amount" of the co-crystal for use in hypertension is to be derived in whole or in part from the activity of nicotinamide (the "API") because furosemide (the "co-former") has therapeutic activity for that indication.

64. Like the '344 patent, the '006 Publication⁹ stated that formulating multiple-component phase compositions (including co-crystals) with a pharmaceutically acceptable carrier can be done using known methods, and cited Remington's 1995 (an earlier version of Remington's 2012) as support. Ex. 1509, '006 Publication at paragraph [0051].

65. Because a POSA would have known that pharmaceutically acceptable carriers and therapeutically effective amounts of multiple-component crystals had been formulated into pharmaceutical compositions (Section VII.B), and a POSA also would have known how to formulate a pharmaceutically acceptable carrier and a therapeutically effective amount of a multiple-component crystal into a pharmaceutical composition using formulations and methods that were readily available and well known to those in the art, as described in Remington's 2012 (Section VII.C) and the '006 Publication, a POSA would have had a reasonable expectation that a pharmaceutically acceptable carrier and therapeutically effective amount of a multiple-component crystal could be formulated into a pharmaceutically useful composition.

⁹ I understand that the '006 Publication is a publication of the '956 parent application.

66. A POSA would have been motivated to combine Ueto with Martindale 2011, the '006 Publication and Remington's 2012, as Ueto concerns a furosemide/nicotinamide/water co-crystal, Martindale 2011 concerns the furosemide and nicotinamide components, and the '006 Publication and Remington's 2012 concern the preparation of pharmaceutical compositions comprising multiple-component crystals. With respect to the furosemide/nicotinamide/water co-crystal of Ueto, a POSA would have looked to Martindale 2011 for guidance on determining a therapeutically effective amount of the co-crystal, because this reference disclosed the use of furosemide to treat hypertension, and for guidance on whether nicotinamide was present in an amount suitable for pharmaceutical use, because this reference disclosed the use of nicotinamide. A POSA would have looked to Remington's 2012 (and the '006 Publication) for guidance on how to formulate the co-crystal, because this reference disclosed formulations and methods that were known to those in the art. For these reasons, as of 2014, a POSA would have been motivated to make a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the furosemide/nicotinamide/water co-crystal of Ueto, using methods and formulations that were readily available and well known to those in the art, with a reasonable expectation of success.

IX. A POSA WOULD HAVE BEEN MOTIVATED TO FORMULATE A THERAPEUTICALLY EFFECTIVE AMOUNT OF A GENISTEIN/NICOTINAMIDE/WATER CO-CRYSTAL AND A PHARMACEUTICALLY ACCEPTABLE CARRIER INTO A PHARMACEUTICAL COMPOSITION WITH A REASONABLE EXPECTATION OF SUCCESS AS OF 2014 (PETITION 2, GROUND 2)

67. As of 2014, a POSA would have been motivated to formulate a therapeutically effective amount of the genistein/nicotinamide/water co-crystal of the '408 Application (Ex. 1511) and the Sowa paper (Ex. 1512), with a pharmaceutically acceptable carrier into a pharmaceutical composition in view of Marini 2007, the '006 Publication, and Remington's 2012.

68. As of 2014, genistein was known to have various types of therapeutic activity, including estrogenic activity. Ex. 1513, Marini 2007 at 839-46; Ex. 1512, Sowa at 7696-97, Ex. 1511, '408 Application at 1-2. Genistein was also known to have poor water solubility, as explained by the '408 Application: "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." Ex. 1511, '408 Application at 2; *see also* Ex. 1512, Sowa at 7696 (Stating that, although "[s]ome beneficial results of flavonoid administration [a class that includes genistein] were shown *in vivo*" these compounds' "efficiency is hindered by low solubility in water and low

bioavailability, therefore reducing the potential of possible applications in pharmaceutical formations or nutritional supplements.”)

69. A POSA would have understood that co-crystals could have potentially improved on the properties of a drug substance compared to the drug substance alone, such as its solubility, bioavailability and dissolution rate. *See above* para. 59, citing Ex. 1507, Ueto at 485; Ex. 1504, Hickey at 112-118; Ex. 1547, Aronhime at col. 1, ll. 12-49, col. 1, l. 53 – col. 2, l. 22, col. 3, ll. 7-14, col. 6, ll. 52-58. Sowa also recognized that “[c]ocrystallization . . . is a method of obtaining novel forms of active pharmaceutical ingredients (APIs) with improved physicochemical properties (e.g., solubility, stability, melting point) and has gained much attention in recent years.” Ex. 1512, Sowa at 7696; *see also* Ex. 1511, ’408 Application at 2 (“Co-crystallization has been one of the promising methods for modifying unfavorable physicochemical parameters of pharmaceutically active substances for several years. In 2011, the first publication on the co-crystallization of flavonoids in the pharmaceutical aspect was published.”). Indeed, the Sowa authors recognized the low solubility of genistein, the potential to improve its water solubility by preparing a co-crystal with nicotinamide (which is water soluble), and prepared co-crystals of genistein, including a genistein-nicotinamide monohydrate co-crystal. Ex. 1512, Sowa at 7696-97; Ex. 1511, ’408 Application at 2-3. The ’408 Application provides that “[t]he subject of the invention is a co-

crystal of genistein monohydrate - nicotinamide,” for pharmaceutical use. Ex. 1511, ’408 Application at 1.

70. A POSA would have been motivated to evaluate whether the properties of the Sowa genistein/nicotinamide/water co-crystal, such as oral bioavailability and dissolution, were improved compared to genistein alone, analogous to what was done by Hickey *et al.* in dogs. Ex. 1504, Hickey at 117-18; Ex. 1507, Ueto at 485 (“evaluating [the] physicochemical properties” of various forms of drugs is “of particular importance for pharmaceutical research and development”). To enable this testing, a POSA would have combined the Sowa co-crystal with a pharmaceutically acceptable carrier into a pharmaceutical composition so that the co-crystal would be suitable to administer to an animal or human. See Section VII.A; Ex. 1504, Hickey at 114-15, 117-118 (formulating carbamazepine/saccharin co-crystals with lactose into pharmaceutical compositions to evaluate oral bioavailability and dissolution).

71. In such pharmaceutical compositions, a POSA would have (i) been motivated to use, and would have ascertained a therapeutically effective amount of, the genistein/nicotinamide/water co-crystal of Sowa for its estrogenic activity, including reducing bone loss in osteopenic postmenopausal women and (ii) confirmed that the other components of the co-crystal were present in amounts that were suitable for pharmaceutical use.

72. With respect to (i), in the reduction of bone loss in osteopenic postmenopausal women, genistein is given orally at a dose of 54 mg per day. Ex. 1513, Marini 2007 at 839-40, 844-45. The other co-crystal components, nicotinamide and water, were not known to treat bone loss in osteopenic postmenopausal women. Ex. 1506, Martindale 2011 at 2117-19 (omitting bone loss in osteopenic postmenopausal women as a therapeutic indication for nicotinamide). The POSA would have incorporated an amount of the Sowa co-crystal sufficient to provide exposure equivalent to genistein at 54 mg/day, which a POSA would have understood was an active amount for reducing bone loss in osteopenic postmenopausal women. Because the genistein/nicotinamide/water co-crystal has a 1:1:1 ratio of its components, a POSA would have calculated a therapeutically effective amount of co-crystal having a 54 mg amount of the drug substance (genistein):

Molecular Weight of Co-Crystal:

Molecular Weight Genistein: 270.24 g/mol¹⁰

Molecular Weight of Nicotinamide: 122.12 g/mol¹¹

¹⁰ <https://pubchem.ncbi.nlm.nih.gov/compound/Genistein> (Ex. 1583).

¹¹ <https://pubchem.ncbi.nlm.nih.gov/compound/Nicotinamide> (Ex. 1582).

Molecular Weight of Water: 18.02 g/mol¹²

Total Molecular Weight of 1:1:1 Co-Crystal: 270.24 + 122.12 + 18.02 =
410.375 g/mol

Total Weight of Co-Crystal: 82 mg (270.24/410.375 = (54 mg)/X)

73. With respect to (ii), a POSA would have understood that 82 mg of this co-crystal contained 24 mg nicotinamide. Nicotinamide was commonly used as an inactive ingredient and was in food like yeast, meat, fish, potatoes, legumes, and cereals. Ex. 1506, Martindale 2011 at 2117-19. The '408 Application includes the following discussion about nicotinamide in co-crystallization: "Nicotinamide is on the list of compounds approved for safe use as additives to food products, thanks to which it is widely used in the co-crystallization of pharmaceutically active carboxylic acids and can be used as an ingredient in pharmaceutical preparations and dietary supplements." Ex. 1511, '408 Application at 2. A POSA would also have known that the amount of nicotinamide in the genistein-nicotinamide co-crystal was within the maximum tolerable limit. Ex. 1506, Martindale 2011 at 2117-19 (nicotinamide may be administered orally at doses of up to 500 mg daily

¹² <https://pubchem.ncbi.nlm.nih.gov/compound/Water> (Ex. 1584).

in divided doses); Ex. 1510, Remington's 2012 at 198 (stating that nicotinamide is "used [as a co-crystal component] in the pharmaceutical field"); *see also* Ex. 1501, col. 11, ll. 2-5, col. 16, ll. 57-59 (reporting for a carbamazepine/nicotinamide co-crystal that nicotinamide was "GRA[S]," meaning "Generally Regarded as Safe by the FDA"); Ex. 1585, European Commission Opinion on Tolerable Upper Intake Levels of Nicotinamide at 14 (disclosing upper-level intake of nicotinamide of 900 mg/day for adults). The water in the genistein/nicotinamide/water co-crystal of Sowa was likewise suitable for pharmaceutical use.

74. I understand from Petitioner's counsel that the claimed "co-crystal" contains an "API" and a "co-former," which each have certain claimed properties relating to activity and chemical structure for example. I understand that the "API" must have a therapeutic effect, and the "co-former" may also have a therapeutic effect. I understand from counsel that there is no requirement that the claimed "therapeutically effective amount" of the co-crystal for a particular indication must be derived in whole or in part from the activity of the component that meets the claimed requirements of the "API" (here, nicotinamide) when the other co-crystal component (here, the "co-former" genistein) itself has therapeutic activity for that indication. Here, I understand from Petitioner's counsel that nicotinamide has the claimed "API" properties and genistein has the claimed "co-former" properties. However, there is no requirement in the '344 patent that the claimed

“therapeutically effective amount” of the co-crystal for reducing bone loss in osteopenic postmenopausal women is to be derived in whole or in part from the activity of nicotinamide (the “API”) because genistein (the “co-former”) has therapeutic activity for that indication.

75. Like the ’344 patent, the ’006 Publication¹³ stated that formulating multiple-component phase compositions (including co-crystals) with a pharmaceutically acceptable carrier can be done using known methods, and cited Remington’s 1995 (an earlier version of Remington’s 2012) as support. Ex. 1509, ’006 Publication at paragraph [0051].

76. Because a POSA would have known that pharmaceutically acceptable carriers and therapeutically effective amounts of multiple-component crystals had been formulated into pharmaceutical compositions (Section VII.B), and a POSA also would have known how to formulate a pharmaceutically acceptable carrier and a therapeutically effective amount of a multiple-component crystal into a pharmaceutical composition using formulations and methods that were readily available and well known to those in the art, as described in Remington’s 2012 (Section VII.C) and the ’006 Publication, a POSA would have had a reasonable

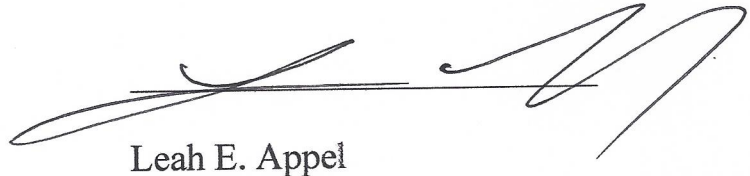
¹³ I understand that the ’006 Publication is a publication of the ’956 parent application.

expectation that a pharmaceutically acceptable carrier and therapeutically effective amount of a multiple-component crystal could be formulated into a pharmaceutically useful composition.

77. A POSA would have been motivated to combine Sowa and the '408 Application with Marini 2007, the '006 Publication and Remington's 2012, as Sowa concerns a genistein/nicotinamide/water co-crystal, Marini 2007 concerns genistein, and the '006 Publication and Remington's 2012 concern the preparation of pharmaceutical compositions comprising multiple-component crystals. With respect to the genistein/nicotinamide/water co-crystal of Sowa, a POSA would have looked to Marini 2007 for guidance on determining a therapeutically effective amount of the co-crystal, because this reference disclosed the use of genistein to treat bone loss in osteopenic postmenopausal women. A POSA would have looked to Remington's 2012 (and the '006 Publication) for guidance on how to formulate the co-crystal, because this reference disclosed formulations and methods that were known to those in the art. For these reasons, as of 2014, a POSA would have been motivated to make a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the genistein/nicotinamide/water co-crystal of Sowa, using methods and formulations that were readily available and well known to those in the art, with a reasonable expectation of success.

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

Dated: 8/24/23



Leah E. Appel