

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 IPR2023-01346
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. 1001, “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. 1054).

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. 1001, 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. 1001, 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. 1001, col. 10, ll. 15-21 (citing Ex. 1041, 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. 1041, 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. 1010, “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. 1001, col. 10, ll. 14-15; Ex. 1041, Remington's 1995 at 1617, 1643-44; see also Ex. 1010, 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. 1043, 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. 1001, col. 10, ll. 14-15; Ex. 1042, Webster's Medical Dictionary at 98 (defining “carrier” as “a vehicle serving esp[ecially] as a diluent (as for a drug)”); Ex. 1041, 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. 1010, 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. 1041, 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. 1010, 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. 1043, 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. 1001, 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. 1001, 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 1 (claims 10, 11, and 18) and the IPR Grounds indicated below.

32. **Ground 1:** I have been asked to consider whether Hickey (Ex. 1004) disclosed “[a] pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of” a carbamazepine/saccharin co-crystal. For the reasons explained in Section VIII, I concluded that Hickey disclosed “[a] pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a” carbamazepine/saccharin co-crystal. In fact, Hickey made such a pharmaceutical

composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a carbamazepine/saccharin co-crystal.

33. **Ground 2:** I have been asked to consider whether Almarsson (Ex. 1005) disclosed “[a] pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of” a carbamazepine/saccharin co-crystal. Separately, I was also asked to consider whether a POSA would have been motivated to prepare a therapeutically effective amount of the carbamazepine/saccharin co-crystal of Almarsson, 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 that Almarsson disclosed “[a] pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of” a carbamazepine/saccharin co-crystal. For the reasons explained in Section X, 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. 1043, Handbook of Pharmaceutical Excipients 2009 at x.

35. Carriers (diluents) play an important role in oral solid dosage forms. Ex. 1010, 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. 1010, 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. 1035, Physicians' Desk Reference 2004 at 1048-52; Ex. 1044, 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 be tableted, or capsuled for oral use . . . "); Ex. 1043, 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. 1035, Physicians' Desk Reference 2004 at 2665-

² Ex. 1037, Coumadin[®] Label revised 10/2011 (showing initial U.S. approval in 1954).

³ Ex. 1038, Vibramycin[®] Label revised 1/2023 (showing initial U.S. approval in 1967).

68; Ex. 1043, 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. 1035, Physicians' Desk Reference 2004 at 1427-31; Ex. 1036, Hilton 1993 at Abstract ("A controlled-release tablet of amoxicillin trihydrate was developed . . ."); Ex. 1045, U.S. Patent No. 7,807,196 at col 1, ll. 3-5, col 2, ll. 3-26; Ex. 1043, 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. 1004, 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,

⁴ Ex. 1039, Amoxil[®] Label revised 9/2015 (showing initial U.S. approval in 1974).

0.087 mol, particle size <53µm) 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. 1043, 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. 1004, 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. 1046, 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. 1043, 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. 1046, 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. 1010, 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. 1010, 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. 1010, 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. 1010, 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. 1010, 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. 1001, col. 10, ll. 6-39; Ex. 1010, 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. 1010, Remington's 2012 at 581. Remington's taught that tablets were typically prepared with suitable diluents (*i.e.*, pharmaceutically acceptable carriers). Ex. 1010, 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. 1010, 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. 1010, 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. 1010, 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. 1010, 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. 1010, 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. 1043, 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. 1043, 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. 1010, Remington’s 2012 at 583.

VIII. HICKEY DISCLOSED AND ACTUALLY MADE “[A] PHARMACEUTICAL COMPOSITION COMPRISING A PHARMACEUTICALLY ACCEPTABLE CARRIER AND A THERAPEUTICALLY EFFECTIVE AMOUNT OF” A CARBAMAZEPINE/SACCHARIN CO-CRYSTAL (PETITION 1, GROUND 1)

57. Hickey disclosed “mixing α -lactose monohydrate (2.52 g, 0.0069 mol . . .) with [a carbamazepine/saccharin co-crystal] (3.654 g, 0.087 mol . . .), and

blending the two solids [*i.e.*, the lactose and the co-crystal] in a mortar and pestle,” and adding 600 mg of the co-crystal and lactose mixture (corresponding to 200 mg of carbamazepine) to each capsule. Ex. 1004, Hickey at 115, 118. These capsules were administered orally to dogs to assess bioavailability. Ex. 1004, Hickey at 115, 118. A POSA would have understood that this dosage form (formulated co-crystal in a capsule) was a pharmaceutical composition comprising a pharmaceutically acceptable carrier since α -lactose monohydrate was a pharmaceutically acceptable carrier or diluent. Ex. 1043, Handbook of Pharmaceutical Excipients 2009 at 364-66; see paragraph 24 (discussing carriers).

58. Hickey reported that each 600 mg formulated co-crystal capsule contained an amount of the carbamazepine/saccharin co-crystal that was equivalent to 200 mg carbamazepine. Ex. 1004, Hickey at 115, 118. I have independently confirmed that 600 mg of formulated 1:1 carbamazepine/saccharin co-crystal (which also included lactose) as prepared above contains 200 mg of carbamazepine:

Molecular Weight of Co-Crystal:

Molecular Weight of Carbamazepine: 236.27 g/mol⁵

⁵ <https://pubchem.ncbi.nlm.nih.gov/compound/Carbamazepine> (Ex. 1069).

Molecular Weight of Saccharin: 183.19 g/mol⁶

Total Molecular Weight of 1:1 Carbamazepine/Saccharin Co-Crystal:

$$236.27 + 183.19 = 419.46 \text{ g/mol}$$

Weight of Co-Crystal Containing 200 mg Carbamazepine:

Weight of Carbamazepine: **200 mg**

Total Weight of Co-Crystal: **355 mg** ($236.27/419.46 = 200/X$)

Ratio of Co-Crystal to Total Formulated Weight:

Bulk Substance: 0.59 ($3.65/(3.65 + 2.52)$)

Per Capsule: 0.59 ($355/600$)

59. Carbamazepine, marketed as Tegretol[®], was FDA approved and marketed to treat epilepsy in tablets containing the same 200 mg amount of carbamazepine as in the formulated co-crystal capsules in Hickey. Ex. 1004, Hickey at 112 (Carbamazepine is “an important anti-epileptic agent that has been in use for over 30 years.”), 115 (“Tegretol[®] 200 mg tablets (immediate release formulation) were obtained from a pharmacy and used as the reference dose.”),

⁶ <https://pubchem.ncbi.nlm.nih.gov/compound/5143> (Ex. 1070).

118 (“Tegretol® immediate release tablets, 200 mg strength.”). Hickey reported that based on “a performance comparison of the [carbamazepine/ saccharin] co-crystal [formulated with lactose] to the marketed form of carbamazepine (Tegretol®[]),” including comparing their oral bioavailabilities, the co-crystal is a “viable alternative” to Tegretol® with a “comparable oral absorption profile.” Ex. 1004, Hickey at 112-13, 118. Therefore, the formulated co-crystal in the capsules of Hickey contained a therapeutically effective amount of the carbamazepine/saccharin co-crystal.

60. Hickey disclosed a pharmaceutical composition comprising a carbamazepine and saccharin co-crystal in an amount therapeutically effective to treat epilepsy, and a pharmaceutically acceptable carrier.

IX. ALMARSSON DISCLOSED “[A] PHARMACEUTICAL COMPOSITION COMPRISING A PHARMACEUTICALLY ACCEPTABLE CARRIER AND A THERAPEUTICALLY EFFECTIVE AMOUNT OF” A CARBAMAZEPINE/ SACCHARIN CO-CRYSTAL (PETITION 1, GROUND 2)

61. Almarsson described pharmaceutical compositions comprising co-crystals, which may optionally include a pharmaceutically acceptable carrier. Ex. 1005, Almarsson, Abstract (“A pharmaceutical composition comprising a co-crystal of an API and a co-crystal former”), col. 8, ll. 59-61 (“[I]n a first aspect, the present invention provides a pharmaceutical composition comprising a co-crystal of an API and a co-crystal former”), col. 10, ll. 61-64, col. 21, ll.

63-65. Almarsson also described processes for preparing pharmaceutical compositions containing a pharmaceutically acceptable carrier, stating that the “co-crystals . . . may be readily incorporated into a pharmaceutical composition by conventional means. Pharmaceutical compositions . . . may further comprise a pharmaceutically[]acceptable . . . carrier.” Ex. 1005, Almarsson, col. 10, l. 59 – col. 11, l. 36, col. 21, l. 60 – col. 29, l. 2.

62. Almarsson listed suitable pharmaceutically acceptable carriers for use in these pharmaceutical compositions, including lactose. Ex. 1005, Almarsson, col. 21, l. 65- col. 22, l. 35 (disclosing a list of “[s]uitable [pharmaceutically acceptable] carriers or diluents,” which “illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; [and a list of other carriers or diluents].”). As of 2014, lactose was a known pharmaceutically acceptable carrier. Ex. 1043, Handbook of Pharmaceutical Excipients 2009 at 364-66; see paragraph 24 (discussing carriers).

63. Example 32 of Almarsson described a 1:1 carbamazepine/saccharin co-crystal. Ex. 1005, Almarsson at col. 42, ll. 20-23. Almarsson claims 19 and 20, reproduced below, disclosed a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a carbamazepine and saccharin co-crystal:

19. A pharmaceutical composition comprising a pharmaceutically acceptable diluent, excipient, or carrier and a co-crystal comprising an API and a co-crystal former selected from: (a) carbamazepine and saccharin; . . .

20. The pharmaceutical composition according to claim **19**, wherein said co-crystal comprises carbamazepine and saccharin.

64. Almarsson disclosed that “[a] pharmaceutical composition of the invention contains *a desired amount of API per dose unit* and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule. . . . Presently preferred are oral dosage forms that are discrete dose units each containing *a predetermined amount of the API*, such as tablets or capsules.” Ex. 1005, Almarsson, col. 21, ll. 39-52 (emphases added). Even though Almarsson did not explicitly use the words “therapeutically effective amount,” because Almarsson disclosed “pharmaceutical composition[s]” comprising co-crystals containing APIs like carbamazepine for pharmaceutical use (Ex. 1005, Almarsson, Abstract, col. 1, l. 65 – col. 2, l. 3, col. 21, ll. 34-52, col. 25, ll. 56-57, col. 26, l. 53 – col. 29, l. 2 (describing dosage forms for administration of the co-crystals), col. 179, Table IV), the language “a desired amount of API per dose unit” and “a predetermined amount of the API” for such a co-crystal disclosed a therapeutically effective amount of the co-crystal.

65. Accordingly, Almarsson disclosed a pharmaceutical composition comprising a carbamazepine and saccharin co-crystal in an amount therapeutically effective to treat epilepsy, and a pharmaceutically acceptable carrier.

66. Even if Almarsson did not specifically disclose a pharmaceutical composition comprising a carbamazepine and saccharin co-crystal in an amount therapeutically effective to treat epilepsy and a pharmaceutically acceptable carrier, a POSA would have been motivated to prepare such a pharmaceutical composition with a reasonable expectation of success as of 2014 in view of Almarsson alone for the same reasons as stated above, and further in view of Hickey and Martindale 2011 (addressed in Section X below).

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

67. As of 2014, a POSA would have been motivated to use a therapeutically effective amount of the carbamazepine/saccharin co-crystal of Almarsson's Example 32 (Ex. 1005) in the pharmaceutical composition taught by Almarsson, which also included a pharmaceutically acceptable carrier, in view of Almarsson's teachings alone (as described above in Section IX) or in combination with Hickey and Martindale 2011.

68. A POSA would have understood that carbamazepine, marketed as Tegretol[®], was an FDA-approved and important drug used to treat epilepsy. Ex. 1004, Hickey at 112 (Carbamazepine is “an important anti-epileptic agent that has been in use for over 30 years.”), 115; Ex. 1006, Martindale 2011⁷ at 520.

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. Ex. 1004, 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 physical stability, solubility, oral bioavailability, and dissolution, and reporting “favorable dissolution properties” and “comparable oral absorption” in dogs); *see also* Ex. 1007, Ueto at 485 (noting co-crystals of drugs have the “potential to improve physicochemical properties” of drugs); Ex. 1047, Aronhime at col. 1, ll. 12-49, col. 6, ll. 52-58 (describing a new multiple component crystal of

⁷ 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. 1006, Martindale 2011 at preface v-vi.

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). Indeed, Almarsson disclosed that the carbamazepine/saccharin co-crystal of Example 32 had improved solubility over previously known forms of carbamazepine, which a POSA would have understood could impact its dissolution or bioavailability and thus may warrant further investigation. Ex. 1005, Almarsson at col. 42, ll. 22-30; Ex. 1004, Hickey at 117-18. A POSA would have been motivated to evaluate whether the properties of a carbamazepine/saccharin co-crystal, such as oral bioavailability and dissolution, were improved compared to carbamazepine alone, as was done by Hickey *et al.* Ex. 1004, Hickey at 114-15, 117-118; *see also* Ex. 1007, 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 in a pharmaceutical composition so that the co-crystal would be suitable to administer to an animal or human. *See* Section VII.A; Ex. 1004, Hickey at 114-15, 117-118

(formulating carbamazepine/saccharin co-crystals with pharmaceutically acceptable carriers into pharmaceutical compositions to evaluate oral bioavailability and dissolution).

70. In such pharmaceutical compositions, a POSA would have (i) been motivated to use, and would have ascertained a therapeutically effective amount of, the carbamazepine/saccharin co-crystal of Almarsson for the treatment of epilepsy and (ii) confirmed that the other component of the co-crystal was present in an amount that was suitable for pharmaceutical use.

71. With respect to (i), Almarsson disclosed a pharmaceutical composition comprising a therapeutically effective amount of a carbamazepine/saccharin co-crystal and a pharmaceutically acceptable carrier. See Section IX (citing Ex. 1005, Almarsson, Abstract, col. 8, ll. 59-61, col. 10, ll. 61-64, col. 21, ll. 39-52, 63-65, col. 42, ll. 20-23, claims 19, 20). Almarsson also described processes for preparing pharmaceutical compositions containing a pharmaceutically acceptable carrier, and listed suitable pharmaceutically acceptable carriers including lactose. See Section IX (citing Ex. 1005, Almarsson, col. 10, l. 59 – col. 11, l. 36, col. 21, l. 60 – col. 29, l. 2). As explained in Section VIII, Hickey disclosed how to make and use a pharmaceutical composition comprising a therapeutically effective amount of carbamazepine/saccharin co-

crystal and a pharmaceutically acceptable carrier (lactose). Hickey reported on such a pharmaceutical composition that was made and evaluated in dogs.

72. A POSA would have known that carbamazepine, marketed as Tegretol[®], was FDA approved to treat epilepsy in tablets containing 200 mg of carbamazepine. Ex. 1004, Hickey at 115 (“Tegretol[®] 200 mg tablets (immediate release formulation) were obtained from a pharmacy and used as the reference dose.”), 118 (“Tegretol[®] immediate release tablets, 200 mg strength.”). The other co-crystal component, saccharin, was not known to treat epilepsy. Ex. 1006, Martindale 2011 at 2242 (omitting epilepsy as a therapeutic indication for saccharin). The POSA would have therefore incorporated into the pharmaceutical composition an amount of the Almarsson co-crystal sufficient to provide exposure equivalent to a 200 mg amount of carbamazepine.

73. Because the carbamazepine-saccharin co-crystal has a 1:1 molar ratio of its components, a POSA would have calculated a therapeutically effective amount of co-crystal having a 200 mg amount of the anti-epileptic drug substance (carbamazepine):

Molecular Weight of Co-Crystal:

Molecular Weight Carbamazepine: 236.27 g/mol⁸

Molecular Weight of Saccharin: 183.19 g/mol⁹

Total Molecular Weight of 1:1 Co-Crystal: 236.27 + 183.19 = 419.46 g/mol

Total Weight of Co-Crystal: 355 mg (236.27/419.46 = 200/X)

74. With respect to (ii), a POSA would have understood that 355 mg of this co-crystal contained 155 mg saccharin. Saccharin was used as a sweetener in foods and beverages. Ex. 1006, Martindale 2011 at 2242; *see also* Ex. 1001, col. 11, ll. 2-5, col. 17, ll. 46-48 (reporting for a carbamazepine/saccharin co-crystal that saccharin was “GRA[S],” meaning “Generally Regarded as Safe by the FDA”); Ex. 1010, Remington’s 2012 at 198 (stating that saccharin is “used [as a co-crystal component] in the pharmaceutical field”). Hickey *et al.* reported that “[t]he amount of saccharin delivered by [the carbamazepine-saccharin co-crystal], assuming the highest approved dose of the drug, would be close to current limits based on acceptable use levels.” Ex. 1004, Hickey 2007 at 118 n.18 (disclosing

⁸ <https://pubchem.ncbi.nlm.nih.gov/compound/Carbamazepine> (Ex. 1069).

⁹ <https://pubchem.ncbi.nlm.nih.gov/compound/5143> (Ex. 1070).

saccharin maximum tolerable limit of 10 mg/kg/day (*e.g.*, 700 mg/day for a 70 kg human)).

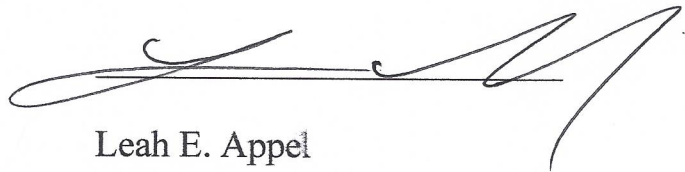
75. Because a POSA would have known that pharmaceutically acceptable carriers and therapeutically effective amounts of multiple-component crystals had been formulated into pharmaceutical compositions (Section VII.B), and a POSA also would have known how to formulate a pharmaceutically acceptable carrier 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 (Section VII.C), 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 as taught in Almarsson.

76. A POSA would have been motivated to combine Almarsson with Hickey and Martindale 2011 as Almarsson and Hickey both concern the same carbamazepine/saccharin co-crystal, and Martindale concerns the carbamazepine and saccharin components. With respect to the pharmaceutical composition comprising the carbamazepine/saccharin co-crystal of Almarsson, a POSA would have looked to Hickey and Martindale 2011 for guidance on determining a therapeutically effective amount of the co-crystal because these references each disclosed using the drug substance carbamazepine to treat epilepsy. 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 carbamazepine/saccharin co-crystal of Almarsson 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