

Date Filed: August 28, 2023

Filed on Behalf Of:

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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

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

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I. INTRODUCTION

Novartis Pharmaceuticals Corporation (“Petitioner”) petitions for *inter partes* review of claims 10, 11 and 18 (“challenged claims”) of U.S. Patent No. 10,633,344 (“the ’344 patent”) (Ex. 1001), assigned to the Regents of the University of Michigan and the University of South Florida (“Patent Owners”).

The challenged claims are directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal where the co-crystal is made up of an active pharmaceutical ingredient (“API”) and a co-former, each having certain properties.

The challenged claims are extremely broad genus claims. The claimed co-crystals contain an API that can be selected from a large genus of possible APIs having one of the first chemical functionalities recited in claim 10, and a complementary co-former selected from a large genus of possible solid co-formers. In a related patent application with application claims of similar broad scope, the examiner described the “possible structural variations” of the claims as “limitless.”

The challenged claims, with their limitless possible structural variations, lack written description and enablement support in the ’344 patent’s March 1, 2002 and March 3, 2003 priority applications. Despite the breadth of these claims, and the known unpredictability of co-crystal formation, the priority applications

disclosed nothing more than (at most) ten co-crystal Examples covered by the challenged claims, and a research plan for further investigation.

The priority applications lack written description support for the claimed subject matter. The Examples do not reflect the broad structural variations of possible co-crystals within the challenged claims, and the priority applications do not disclose any correlation between the structures of APIs and co-formers disclosed in the Examples and their claimed function (co-crystal formation). Thus, the priority applications fail to show possession. The patent examiners reviewing related patent applications with similar broad claims (that also claimed priority to the same priority applications), agreed that written description was lacking.

The priority applications also fail to enable the challenged claims. Given the breadth of the claims, the applicants' own statements and work showing that the art was unpredictable, and the lack of guidance provided in the priority applications, co-crystals covered by the broad scope of the challenged claims could not have been prepared without undue experimentation.

In view of the lack of written description and enablement support in the 2002/2003 priority applications, the earliest possible priority date for the challenged claims is February 13, 2014, the filing date of U.S. Application No. 14/179,862 ("the '862 application), which issued as the '344 patent.

But more than a year before 2014, subject matter falling within the challenged claims was disclosed in at least two prior art references, Hickey (Ex. 1004) and Almarsson (Ex. 1005). Hickey and Almarsson both disclose a pharmaceutical composition comprising a carrier and a 1:1 carbamazepine/saccharin (API/co-former) co-crystal falling within the scope of the challenged claims—a co-crystal also disclosed as Example 9 of the '344 patent. As explained in Ground 1, Hickey anticipates the challenged claims. As explained in Ground 2, Almarsson anticipates the challenged claims, or alternatively, renders them obvious alone or in combination with Hickey and Martindale (Ex. 1006).

The above analysis is supported by Petitioner's solid state chemistry expert, Dr. Robin Rogers, and Petitioner's drug formulation expert, Dr. Leah Appel, each having extensive experience in their respective disciplines. Ex. 1002, Rogers ¶¶ 2-14; Ex. 1003, Appel ¶¶ 6-11; Ex. 1053; Ex. 1054.

In short, it is more likely than not that at least one challenged claim is unpatentable, and Petitioner respectfully requests that trial be instituted.

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

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

III. IDENTIFICATION OF CHALLENGE AND STATEMENT OF PRECISE RELIEF REQUESTED (37 C.F.R. § 42.14(B))

Petitioner requests review of claims 10, 11 and 18 of the '344 patent under 35 U.S.C. § 311 and AIA § 6, on the following Grounds.

Ground	Claims Challenged	Statutory Grounds	Patents and Printed Publications Relied On
1	10, 11, 18	35 U.S.C. § 102(b)	Hickey (Ex. 1004)
2	10, 11, 18	35 U.S.C. §§ 102(b)/ 103 (AIA)	Almarsson (Ex. 1005) Hickey (Ex. 1004) Martindale (Ex. 1006)

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

IV. SUMMARY OF THE '344 PATENT AND CHALLENGED CLAIMS

The '344 patent entitled "Multiple-Component Solid Phases Containing At Least One Active Pharmaceutical Ingredient" issued from the '862 application, filed February 13, 2014. The '344 patent claims priority to provisional applications U.S. Application No. 60/360,768 ("the '768 priority application"), filed March 1, 2002, and U.S. Application No. 10/378,956 ("the '956 priority application"), filed March 3, 2003 (collectively, the "Priority Applications"). The '344 patent has expired.

The '344 patent purports to “relate[] to the application of the concepts of crystal engineering towards the design of new multiple-component solid phases” including “method[s] for identifying complementary chemical functionalities.” Ex. 1001, 7:19-23, 7:42-44; *see also* abstract.¹

Unlike the '344 patent's specification, which purports to provide methods to identify complementary chemical functionalities, the challenged claims are directed to pharmaceutical compositions comprising a wide range of co-crystals having certain properties. These claims are reproduced below, divided into limitations to simplify the analysis.

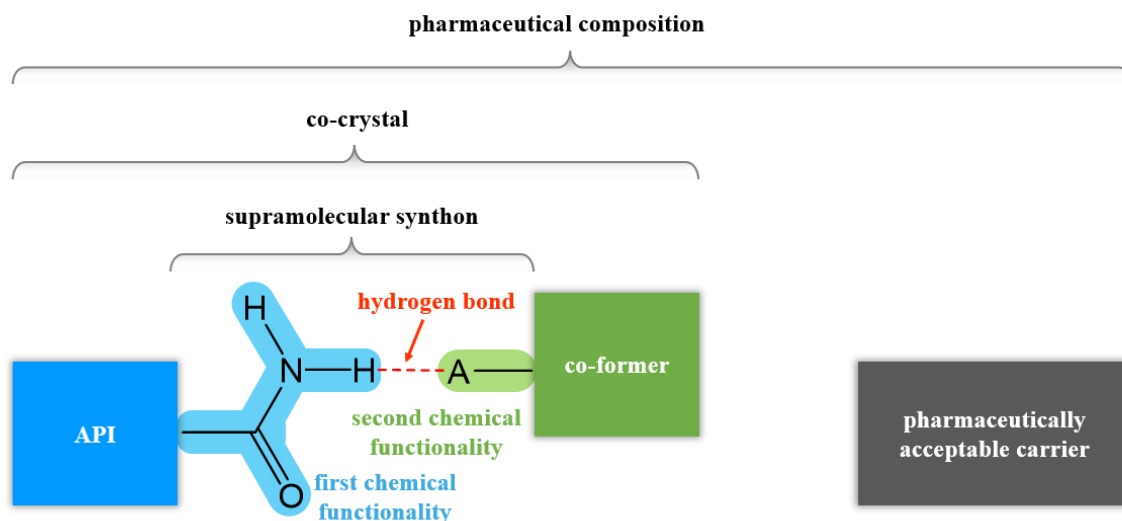
Claim	Limitations
10	[10a] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [10b] a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former, [10c] wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

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

Claim	Limitations
	[10d] wherein the co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding, [10e] wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form, [10f] wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and [10g] wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.
11	[11a] The pharmaceutical composition of claim 10, [11b] wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.
18	[18a] The pharmaceutical composition of claim 10, [18b] wherein the first chemical functionality is a carboxamide.

As depicted in the exemplary figure below, the challenged claims define a pharmaceutical composition comprising a therapeutically effective amount of a co-crystal and a pharmaceutically acceptable carrier. The claimed co-crystals comprise repeating units of an API (in blue) having a “first chemical functionality” (carboxamide is used in the figure below as an example) and a co-former (in green) having a complementary “second chemical functionality.” The second chemical

functionality can be a hydrogen bond donor or a hydrogen bond acceptor; the figure below generically depicts an acceptor (“A”). The API’s first chemical functionality, which is a carboxamide, carbonyl, or amine (claims 10 and 11) or carboxamide (claim 18), hydrogen bonds with the co-former’s second chemical functionality, forming a supramolecular synthon. Ex. 1002, Rogers ¶ 30.



In addition, the challenged claims require that the API’s first chemical functionality permits formation of API homosynthons when the API is in its pure form, and the co-former must be solid at room temperature and atmospheric pressure. Ex. 1002, Rogers ¶ 31.

V. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (“POSA”) of the ’344 patent as of 2002/2003 or 2014 would have had a Ph.D. in chemistry or a related field with at least two years of experience in solid state chemistry, including experience

preparing multiple-component crystalline solids and evaluating their single crystal structures. Alternatively, a POSA would have had a Ph.D. in chemistry, pharmacy, or a related field with at least two years of experience in formulation of pharmaceutical compositions, and the POSA would consult with others having ordinary experience in other disciplines, such as solid-state chemistry, including experience preparing multiple-component crystalline solids and evaluating their single crystal structures. These two alternate POSAs can also work together as part of a team, and consult with others having ordinary experience in other disciplines. Ex. 1002, Rogers ¶ 19; Ex. 1003, Appel ¶ 30.

VI. CLAIM CONSTRUCTION

In an IPR proceeding, claims should only be construed to the extent necessary to resolve a controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). Petitioner believes the constructions identified below will assist the Board in understanding and resolving disputed issues. The terms are grouped in two categories: (A) terms with agreed-upon constructions (or agreed-upon portions of constructions, where the disputed portions are not relevant to the issues raised in this Petition), and (B) terms currently disputed in parallel litigation; however, because the claims are unpatentable under Patent Owners' constructions, Petitioner adopts those constructions solely for the purpose of this Petition to minimize the issues the

Board must decide. For each of the terms below, it is Petitioner’s position that the terms would have been construed by the POSA the same way as of 2002/2003 and 2014.

A. Terms With Agreed-Upon Constructions

“active pharmaceutical ingredient (API)”/“API”: “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.” Ex. 1019, Plaintiffs’ Claim Construction Brief at 21.

“API homosynthons”: “synthons formed between identical and complementary chemical functionalities of the API.” Ex. 1018, Joint Claim Construction Statement, Ex. A at 6-7; Ex. 1002, Rogers ¶ 56.

“carbonyl”: “-C(=O)-; (for clarity, ‘carbonyl’ does not refer to the -C(=O)-portion of another functional group such as carboxylic acid or carboxamide).” Ex. 1018, Joint Claim Construction Statement at 1.

“carboxamide”: The parties dispute the meaning of “carboxamide” as used in the ’344 patent, but agree that it encompasses -C(=O)NH₂. Ex. 1019, Plaintiffs’ Claim Construction Brief at 22; Ex. 1002, Rogers ¶ 61.

“co-former”: The parties agree that co-former is used synonymously with co-crystal former and that a co-former is a component of a co-crystal. Ex. 1018, Joint Claim Construction Statement, Ex. A at 5-6; Ex. 1002, Rogers ¶ 62.

Petitioner describes the co-crystal as a “molecular *component*” whereas Patent Owner describes it as a “*component* compound”; however, that dispute is not pertinent to any issue in this Petition. Ex. 1018, Joint Claim Construction Statement, Ex. A at 5-6 (emphasis added); Ex. 1002, Rogers ¶ 62.

“heterosynthon dimer”: “synthon formed by two different, yet complementary chemical functionalities.” Ex. 1018, Joint Claim Construction Statement, Ex. A at 9-10.

“supramolecular synthon”: “[t]he sum of the components of a multiple-component non-covalent interaction, wherein the non-covalent interaction contributes to the formation of a discrete supramolecular entity or polymeric structure, wherein each component is a chemical functionality.” *Id.* at 1.

**B. Term Where Petitioner Adopts Patent Owners’
Constructions Solely for Purposes of this Petition**

“co-crystal”: Although Petitioner disagrees with Patent Owners’ construction of the term “co-crystal,” solely for purposes of this Petition, Petitioner adopts Patent Owner’s proposal: “A multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.” Ex. 1018, Joint Claim Construction Statement, Ex. A at 1-5; Ex. 1002, Rogers ¶ 65.

VII. RELEVANT PRIORITY DATE

Patent Owners must demonstrate entitlement to a priority date when they rely on that priority date to overcome an anticipation or obviousness argument. *See*

Dynamic Drinkware, LLC v. Nat'l Graphics, Inc., 800 F.3d 1375, 1378-81 (Fed. Cir. 2015).

Here, in Grounds 1 and 2, Petitioner relies on art dated after the 2002/2003 filing dates of the Priority Applications. Patent Owners will be unable to meet their burden of production of showing written description and enablement support for the challenged claims as of those 2002/2003 filing dates, as required by 35 U.S.C. §§ 112 and 120 (pre-AIA). As a result, the earliest possible priority date for the challenged claims is the February 13, 2014 filing date of the '862 application.

A. The Priority Applications Lack Adequate Written Description For the Full Scope of Claimed Co-Crystals

Adequate written description requires that the patent specification “clearly allow persons of ordinary skill in the art to recognize that [the inventors] invented what is claimed,” *i.e.*, it must “reasonably convey[] to those skilled in the art that the inventor[s] had possession of the claimed subject matter as of the filing date.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Written description of a genus claim requires disclosure of either (1) structural features common to all members of the genus allowing a POSA to “visualize or recognize” the members of the genus, or (2) a representative number of species within the genus, neither of which is present here. *Ariad*, 598 F.3d at 1350; Ex. 1002, Rogers ¶¶ 67-68, 84.

The challenged claims are extremely broad. They are not limited to a specific co-crystal, or even a small group of co-crystals where the API and co-former are each selected from a limited set of options. Instead, the API may be selected from a large genus of potential APIs and the co-former from a large genus of potential co-formers. Ex. 1002, Rogers ¶¶ 69-74. But beyond specifying that the API must have a carboxamide, carbonyl, or amine first chemical functionality, and the supramolecular synthons must comprise certain hydrogen bonds, the challenged claims do not limit the structure of the co-crystal or its API and co-former components. *Id.* ¶¶ 69-74. Essentially, limitless structural variations are permitted.

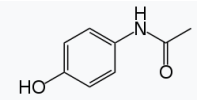
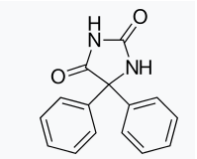
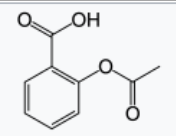
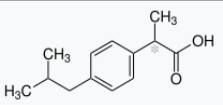
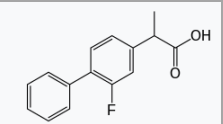
Indeed, as of 2002/2003, just considering those APIs with a -C(=O)NH_2 carboxamide group, there were over 50 known compounds reported in the 2001 Merck Index having therapeutic activity (and many more that were known but not included in this one reference, and countless others that had not yet been tested for therapeutic activity). *Id.* ¶¶ 70-71; Ex. 1049, 2001 Merck Index. These APIs could be combined with thousands of potential co-formers, in any stoichiometric amount, and with additional molecules like solvent added to the co-crystal, making the number of possible co-crystals captured by the challenged claims essentially infinite. Ex. 1002, Rogers ¶¶ 72-74.

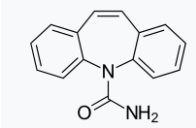
No common structural features: Because the challenged claims do not limit the structure of the API (beyond specifying the first chemical functionality) or the co-former of the claimed co-crystals, let alone their structures when combined into a co-crystal, the common structural features test for establishing written description does not apply; there are no structural features common to all embodiments of the challenged claims. *Id.* ¶¶ 69, 75.

No representative species: The Priority Applications fail to provide a representative number of species to support the breadth of the challenged claims. *Id.* ¶¶ 76-82.

As shown in the table below, no Example in the Priority Applications involves a co-crystal where the API has a first chemical functionality that is a carbonyl (defined *supra* § VI.A) as recited in claims 10 and 11. Ex. 1002, Rogers ¶ 76. And, at most, there are only ten Examples where the API has a carboxamide or amine² and the co-former is solid, as required by the challenged claims: Examples 1, 2, 7-11, 13, 14, 19 (those not shaded in the table below). *Id.* ¶¶ 76-77.

² While Petitioner disputes that “carboxamide” as used in the ’344 patent would be construed to encompass acetaminophen (Example 1) and phenytoin (Example 2), and it is not clear whether either (or carbamazepine) has an “amine” as that term is used in the ’344 patent, the Board need not decide those issues here.

Ex.	API (first chemical functionality carboxamide, carbonyl, or amine)	Co-former
1	acetaminophen (may have carboxamide or amine depending on claim construction) 	4,4'-bipyridine (solid)
2	phenytoin (may have carboxamide or amine depending on claim construction) 	pyridone (solid)
3	aspirin 	4,4'-bipyridine (solid)
4	ibuprofen 	4,4'-bipyridine (solid)
5	flurbiprofen 	4,4'-bipyridine (solid)
6	flurbiprofen (<i>see</i> Ex. 5)	trans-1,2-bis(4-pyridyl)ethylene (solid)

Ex.	API (first chemical functionality carboxamide, carbonyl, or amine)	Co-former
7	carbamazepine (carboxamide and may also have amine depending on claim construction) 	p-phthalaldehyde (solid)
8	carbamazepine (<i>see</i> Ex. 7)	nicotinamide (solid)
9	carbamazepine (<i>see</i> Ex. 7)	saccharin (solid)
10	carbamazepine (<i>see</i> Ex. 7)	2,6-pyridinedicarboxylic acid (solid)
11	carbamazepine (<i>see</i> Ex. 7)	5-nitroisophthalic acid (solid)
12	carbamazepine (<i>see</i> Ex. 7)	acetic acid (liquid)
13	carbamazepine (<i>see</i> Ex. 7)	1,3,5,7-adamantanetetracarboxylic acid (solid)
14	carbamazepine (<i>see</i> Ex. 7)	benzoquinone (solid)
15	carbamazepine (<i>see</i> Ex. 7)	butyric acid (liquid)
16	carbamazepine (<i>see</i> Ex. 7)	DMSO (liquid)
17	carbamazepine (<i>see</i> Ex. 7)	formamide (liquid)
18	carbamazepine (<i>see</i> Ex. 7)	formic acid (liquid)
19	carbamazepine (<i>see</i> Ex. 7)	trimesic acid (solid)

These ten Examples (involving only three different APIs with a carboxamide or amine and no examples of an API with a carbonyl first chemical functionality) are not representative of all APIs and co-formers that provide co-crystals

encompassed by the challenged claims. Ex. 1002, Rogers ¶¶ 76-78. Even all 19 Examples would not be representative of the extremely broad genus. *Id.* ¶¶ 79, 82.

Further, the Priority Applications' identification of some functional groups that "can form" (not that they *will* form) synthons with an amide (*i.e.*, amide, acid, and pyridine) or amine (*i.e.*, alcohol), does not overcome the lack of representative species. *See* Ex. 1015, '956 application, ¶ [0009]. In addition, focusing on just the interactions between functional groups ignores that the challenged claims are directed to co-crystals that comprise APIs and co-formers in their *entirety*, and as such, the entire structure of the API and co-former must be considered. Ex. 1002, Rogers ¶¶ 77-78, 80-82.

Therefore, beyond the limited disclosures in the Examples, which provide the structures of ten API/co-former combinations, the Priority Applications do not identify which chemical functionalities, or co-formers with such chemical functionalities, will in fact form supramolecular synthons with any API's "carboxamide," "carbonyl," or "amine." Said another way, apart from the ten Examples discussed above, the Priority Applications do not provide any correlation between the structure of any given co-former or its "second chemical functionality" and the function required by the claims, *i.e.*, forming co-crystals that contain supramolecular synthons between an API and co-former via hydrogen bonding. *Id.* ¶¶ 77-78, 80-82. Accordingly, the Priority Applications do not

disclose a representative number of species sufficient to demonstrate that the inventors had possession of the claimed pharmaceutical compositions comprising a broad genus of co-crystals. *Id.* ¶ 83.

1. Other Examiners Have Found Claims Similar to the Challenged Claims in Related Applications Lacking in Written Description

That the challenged claims lack written description support in the Priority Applications is further confirmed by the prosecution histories of related patent applications, U.S. Patent Application No. 15/639,223 (“the ’223 application”) and U.S. Patent Application No. 10/660,202, which issued as U.S. Patent No. 7,927,613 (“Almarsson”). The examiners in these applications, unlike the ’344 patent examiner, expressly considered written description and/or enablement, and rejected overbroad application claims similar to the challenged claims here on those bases. Unfortunately, the ’344 patent examiner did not have the benefit of reviewing these rejections, including those dated before the ’344 patent issued.

(a) The ’223 Application

The ’223 application shares a common specification with the 2003 ’956 priority application and names the same three ’344 patent inventors. Ex. 1002, Rogers ¶¶ 86-87. There are significant similarities between ’223 application claim 37 (the sole independent claim when the application was rejected and then

abandoned) and claim 10 of the '344 patent as shown below (differences are underlined and comments added in italics). *Id.* ¶ 98.

'223 Application Claim 37	'344 Patent Claim 10
37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of	[10a] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of
a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-crystal former ³	[10b] a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,
<u>and each supramolecular synthon comprising a heterosynthon formed via non-covalent hydrogen bonding,</u>	[<i>The supramolecular synthons of claim 10 of the '344 patent can be heterosynthons or homosynthons formed via non-covalent hydrogen bonding (Ex. 1002, Rogers ¶ 98)</i>]
wherein the API has a first chemical functionality that permits	[10c] wherein the API has a first chemical functionality that permits

³ As the parties agree that “co-former” and “co-crystal former” are used synonymously in the '344 patent (*supra* § VI.A), these differences are not underlined.

'223 Application Claim 37	'344 Patent Claim 10
formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form, <u>and</u>	formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,
wherein the first chemical functionality is <u>selected from carboxylic acid, amide, N-heterocycle, and alcohol</u> ;	[10g] ⁴ wherein the first chemical functionality is <u>“(i) a carboxamide, (ii) a carbonyl, or (iii) an amine.</u> [“carboxamide” is a type of “amide” (Ex. 1002, Rogers ¶ 98)]
wherein the co-crystal former has a second chemical functionality complimentary [<i>sic</i>] to the first chemical functionality via non-covalent hydrogen bonding,	[10d] wherein the co-former has a second chemical functionality compl[e]mentary to the first chemical functionality via non-covalent hydrogen bonding,
[<i>The '223 application provides that the co-former can be an API, GRAS compound, a food additive, a low toxicity organic, or a metal-organic complex, nearly all of which will be solids at room temperature and atmospheric pressure (Ex. 1002,</i>	[10e] <u>wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,</u>

⁴ Limitation [10g] of claim 10 of the '344 patent is listed out of order to facilitate comparison.

'223 Application Claim 37	'344 Patent Claim 10
Rogers ¶ 98; Ex. 1021, '223 application ¶ [0042])]	
wherein supramolecular synthons <u>comprise</u> non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former, and	[10f] wherein supramolecular synthons <u>are formed via</u> non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former,
<u>wherein the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol.</u>	<i>[As a result of limitation [10g], above, the supramolecular synthons of claim 10 of the '344 patent must comprise a carboxamide (a type of amide), carbonyl, or amine (Ex. 1002, Rogers ¶ 98)]</i>

Ex. 1022, p. 368, '223 application file history, November 12, 2021 Amendment in Response to Office Action at 2; Ex. 1001, claim 10.

During prosecution of the '223 application, application claim 37 was rejected for lack of written description because its specification (which is the same as the '956 priority application, Ex. 1002, Rogers ¶¶ 87, 89, 99) failed to reasonably convey possession of the full scope of the claimed subject matter.

Specifically, the '223 application examiner made the following comments, which are relevant here:

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

Ex. 1022, pp. 394-95, '223 application file history, March 22, 2022 Office Action at 3-4 (emphasis added). *See also id.*, pp. 316-18, February 5, 2021 Office Action at 2-4. The examiner specifically considered, and rejected, the applicants' arguments that there was a correlation between structure and function in the context of hydrogen bonding because the '223 application claims were not limited to the hydrogen bonding interactions described in the Examples. Ex. 1022, p. 398, '223 application file history, March 22, 2022 Office Action at 7 ("Although [the

19] examples [in the specification] show the relationship of different groups for H-bonding . . . they do not limit the scope of the claims.”). The examiner further stated that because the claims are not limited to interactions between functional groups and also require interactions between APIs and co-formers, “[t]he whole structure of each component of the co-crystal has to be taken into consideration.”

Id. The ’223 applicants did not respond to this office action, and ultimately abandoned the application. Ex. 1002, Rogers ¶¶ 88-97.

The examiner’s comments discussed above about application claim 37 of the ’223 application, apply to the challenged claims of the ’344 patent, which also are “broad and generic,” with “limitless” possible structural variations. *Id.* ¶ 99. In the ’956 priority application (which is the same as the ’223 application and has the same 19 Examples), as the ’223 application examiner noted, “there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the [E]xamples in the specification.” And, the Priority Applications “lack[] sufficient variety of species to reflect th[e] variance in the [claimed] genus” and “do[] not provide sufficient descriptive support for the myriad of compounds embraced by the claims.” Ex. 1022, pp. 394-95, ’223 application file history, March 22, 2022 Office Action at 3-4. Finally, like the ’223 application examiner noted about application claim 37 there, the ’344 patent’s challenged claims are not limited to the functional groups involved in hydrogen

bonding but instead encompass co-crystals comprising APIs and co-formers in their entirety. Ex. 1002, Rogers ¶¶ 95, 99. Therefore, any structure-function relationship would have to address the entirety of the API and co-former that hydrogen bond to one another to form the claimed co-crystals. No such relationships are taught in the Priority Applications, let alone those sufficient to support the broad genus of co-crystals encompassed by the challenged claims. *Id.* ¶ 100.

(b) Almarsson

Almarsson was filed as a continuation-in-part of the 2003 '956 priority application. Ex. 1005, Almarsson, cover. Almarsson includes many of the '956 priority application's 19 Examples as well as additional disclosures, and includes as inventors the '344 patent inventors. Ex. 1002, Rogers ¶¶ 101-02.

During prosecution of Almarsson, the applicants attempted to pursue (1) broad claims to a pharmaceutical co-crystal composition comprising one of eight APIs (including carbamazepine) and a co-crystal former (*e.g.*, independent application claim 1, set forth below), where each API was an API used in one of the co-crystal Examples and (2) claims directed to the specific co-crystals in the Examples (*e.g.*, independent application claim 11), where both the API and co-former used in the Examples were recited in the claim. Ex. 1023, pp. 779-83, Almarsson file history, May 29, 2008 Amendment at 2-6.

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

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

Ex. 1023, pp. 779-82, Almarsson file history, May 29, 2008 Amendment at 2-5 (cleaned up); Ex. 1002, Rogers ¶¶ 103-07.

After numerous rounds of written description and enablement rejections, the examiner issued an Advisory Action indicating that “Applicants have only shown the formation of the particular co-crystals listed in [application] claim 11 [*i.e.*, those co-crystals in the patent’s Examples] but do not exemplify the formation of all co-crystals with the API’s listed in amended [application] claim 1. It is not described or shown how the numerous and diverse different co-crystals

[encompassed within application claim 1] could be obtained.”⁵ In response, the applicants cancelled all pending application claims and re-filed new claims limited to the specific co-crystals in the Almarsson Examples. Ex. 1023, pp. 807-11, Almarsson file history, October 10, 2008 Amendment at 2-6. The § 112 rejections were subsequently withdrawn. Ex. 1023, p. 823, Almarsson file history, March 24, 2009 Office Action at 2. Thus, the Almarsson applicants obtained claims to the specific API/co-former combinations set forth in the patent’s Examples, but were unable to obtain analogous claims where the API used in the Examples was specified, but the co-former was left open. Ex. 1002, Rogers ¶¶ 108-10.

Like Almarsson, the Priority Applications do not “describe[] or show[] how the numerous and diverse different co-crystals [encompassed within the scope of the challenged claims] could be obtained” and accordingly fail to provide written description support for those claims. *See* Ex. 1023, p. 747, Almarsson file history, December 10, 2007 Office Action at 5; Ex. 1002, Rogers ¶ 111. Notably, the challenged claims of the ’344 patent do not limit either the API or co-former by

⁵ Ex. 1023, p. 803, Almarsson file history, July 17, 2008, Advisory Action at 2; *see also id.*, p. 777, March 25, 2008 Advisory Action at 2; *see also id.*, pp. 744-47, December 10, 2007 Office Action at 2-5.

name, requiring only that the API have one of the recited first chemical functionalities and the co-former is a solid.

B. The Priority Applications Fail to Enable the Claimed Co-Crystals

A POSA in 2002/2003, with the Priority Applications in hand, could not have practiced the full scope of claims 10, 11 and 18 without undue experimentation, as reflected in the *Wands* analysis below. Accordingly, Patent Owners cannot claim priority to the Priority Applications' filing dates. Ex. 1002, Rogers ¶ 113.

(1) Breadth of the Claims: Claims 10, 11 and 18 are broad. They cover a vast genus of co-crystals made up of (a) any API⁶ having the claimed first chemical functionality, and (b) any solid co-former having a functionality complementary to the API's first chemical functionality, in any stoichiometric ratio, where the API and co-former have the claimed hydrogen bonding. Ex. 1002,

⁶ It is Petitioner's position that the '344 patent applicants disclaimed salts during prosecution and therefore the API (which is a component of the co-crystal) cannot itself be a salt; however, for purposes of this Petition, the Board need not address this issue as there is no priority support for the challenged claims irrespective of whether or not APIs can be salts.

Rogers ¶¶ 115-18. Claim 11 further requires that the API and co-former form a heterosynthon dimer.

(2) Nature of the Invention, (3) State of the Art, and (4) Predictability of the Art: The nature of the “invention” of claims 10, 11, and 18 is a pharmaceutical composition comprising a genus of co-crystals having certain properties. Ex. 1002, Rogers ¶ 119.

As of 2002/2003, it was not possible to predict with reasonable certainty either whether a co-crystal would form from two or more components, or, if a co-crystal did form, what specific hydrogen bonds would link the components, particularly if either component had multiple functional groups capable of forming hydrogen bonds. *See, e.g.*, Ex. 1020, Childs Dep. Tr. at 18:2-17 and 27:5-9; Ex. 1002, Rogers ¶ 120. As Desiraju explained, “[i]n any supramolecular assembly, a large number of intermolecular interactions is possible — but only a few are actually observed. The weakness of these interactions makes it difficult to predict supramolecular structures . . . [T]he synthon concept tries to simplify what is essentially a very difficult problem. But even with apparently straightforward synthons, things can go wrong.” Ex. 1024, Desiraju at 398-400; *see also* Ex. 1025, Aakeröy at 164 (“Cocrystals are not necessarily easy to prepare . . .”); Ex. 1026, Dunitz at 546 (“One can *describe* almost any observed crystal structure in terms of [hydrogen bond] interactions. The trouble with this approach is that its physical

basis is shaky and its predictive capacity is poor. Of course, inspired guessing may occasionally lead to a correct prediction with any approach.” (emphasis in original)); Ex. 1002, Rogers ¶ 120; Ex. 1034 Gavezzotti at 309-14 (explaining that the formation and structure of crystals are unpredictable). Further, the art includes many examples of failures to predict whether co-crystals will form at all, or what interactions they will have if they form. *See, e.g.*, Ex. 1027, Reddy at 90; Ex. 1025, Aakeröy at 160; Ex. 1007, Ueto at 487; Ex. 1024, Desiraju at 399; Ex. 1002, Rogers ¶ 121.

Even the '344 patent applicants acknowledged the complexity and unpredictability of co-crystal formation during prosecution of the '956 application, stating: “prior to this invention, . . . random trial-and-error was used to isolate [co-crystals]” and “making numerous such co-crystals without trial and error . . . heretofore *was not remotely possible*.” Ex. 1017, pp. 4071-72, '956 application file history, January 14, 2014 Response at 8-9 (emphasis added). While the applicants purported to set themselves apart from the unpredictable state of the prior art on the basis that they “discovered the critical aspects which control the formation of drug co-crystals, and demonstrated the power of this discovery by making numerous such co-crystals without trial and error,” that statement is misleading at best, and ignores the limited nature of the Examples and the breadth of the challenged claims. *Id.* There are no Examples in the Priority Applications where

the first chemical functionality is a “carbonyl” and therefore no evidence that co-crystals with this functionality can be made at all, let alone “without trial and error.” Ex. 1002, Rogers ¶¶ 122-23. And the inventors’ own work confirms the unpredictability of preparing co-crystals with APIs having a carboxamide first chemical functionality. Specifically, Fleischman (Ex. 1028), co-authored by the ’344 patent inventors, reports on attempts to prepare co-crystals of carbamazepine which has a carboxamide first chemical functionality (and discloses the co-crystals of Examples 7-9 and 11-19 of the Priority Applications). Ex. 1002, Rogers ¶ 124. The authors tested approximately 50 different co-formers, and even with this relatively simple API having few potential hydrogen-bonding sites, the “success ratio” was only 20%. Ex. 1028, Fleischman at 911. These data (available in 2003) confirm the unpredictability of co-crystal formation and contradict the applicants’ statements during prosecution (in 2014) that they were able to make “numerous” co-crystals “without trial and error.” Ex. 1017, pp. 4071-72, ’956 application file history, January 14, 2014 Response at 8-9; Ex. 1002, Rogers ¶¶ 122, 124-25.

Factors 2, 3, and 4 all support non-enablement.

(5) Relative Skill of Those in the Art: The relative skill of a POSA here is high, including experienced scientists having an advanced degree in chemistry with experience in solid state chemistry. *Supra* § V. This factor is neutral with respect to

enablement because although the level of skill is high, the art is unpredictable. Ex. 1002, Rogers ¶¶ 19, 126.

(6) Presence or Absence of Working Examples, (7) Amount of Direction or Guidance, and (8) Quantity of Experimentation: The Priority Applications do not teach a POSA how to prepare co-crystals with the required hydrogen bonding commensurate in scope with the challenged claims, or even how to reasonably predict that such co-crystals would form. Ex. 1002, Rogers ¶¶ 127-33.

As discussed above, no Example involves a co-crystal where the API has a first chemical functionality that is a carbonyl and at most there are ten examples with an API having a carboxamide or amine first chemical functionality and a solid co-former (Examples 1, 2, 7-11, 13, 14, 19). Ex. 1002, Rogers ¶¶ 76-77, 127-28. These examples (and even all 19 Examples in the '956 Priority Application) are insufficient to guide a POSA in practicing the full scope of broad claims 10, 11 and 18. Ex. 1002, Rogers ¶¶ 79, 128-30. In view of the unpredictability of co-crystal formation (factor 4), the breadth of the claims (factor 1), and the limited number of examples provided, to practice the full scope of the challenged claims, a POSA would have had to engage in the very iterative trial and error process referenced by the applicants during prosecution (Ex. 1017, pp. 4071-72, '956 application file history, January 14, 2014 Response at 8-9), involving the manipulation of numerous variables (*e.g.*, API, co-former, solvent, reaction time, temperature,

concentration), in which many failures would result. *See, e.g.*, Ex. 1029, Aitapamula at 2232; Ex. 1030, Guillory at 192; Ex. 1068, Vishweshwar at 788; Ex. 1002, Rogers ¶¶ 122, 131-33.

Conclusion: Seven of the eight *Wands* factors suggest undue experimentation is required to practice the full scope of the challenged claims and one factor is neutral. Thus, the *Wands* factors overwhelmingly support non-enablement as of the 2002/2003 filing dates of the Priority Applications. *Amgen Inc. v. Sanofi*, 143 S. Ct. 1243, 1254 (2023) (“If a patent claims an entire class of . . . compositions of matter, the patent’s specification must enable a [POSA] to make and use the entire class. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.”). Ex. 1002, Rogers ¶¶ 134.

This conclusion is further confirmed by the prosecution history of the related Almarsson patent discussed above (*supra* § VII.A.1(b)) where the examiner held that application claims covering co-crystals beyond “the particular co-crystals” in the Almarsson Examples lacked enablement.⁷ Ex. 1002, Rogers ¶¶ 136-42. The

⁷ Ex. 1023, p. 803, Almarsson file history, July 17, 2008, Advisory Action at 2; *see also id.*, p. 777, March 25, 2008 Advisory Action at 2; *id.*, pp. 747-53, December 10, 2007 Office Action at 5-11.

Almarsson patent examiner rejected the arguments that any experimentation was routine and that “the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” Instead, the examiner reiterated that “the formation and structure of crystals are unpredictable” and maintained the enablement rejection, leading the applicants to limit the claims to the co-crystals exemplified in the Examples.⁸ Ex. 1002, Rogers ¶¶ 140-43.

Like the Almarsson specification, the Priority Applications fail to enable a POSA to make without undue experimentation the co-crystals of the challenged claims, whose scope far exceeds the co-crystals in the Examples. Ex. 1002, Rogers ¶ 144.

⁸ Almarsson, like the '344 patent, claims priority to the '768 and '956 priority applications, and therefore the enablement analysis in the Almarsson prosecution history is relevant to enablement in the 2002/2003 Priority Applications here. *See, e.g.*, Ex. 1023, p. 745, Almarsson file history, December 10, 2007 Office Action at 3; *id.*, pp. 727-29, October 1, 2007 Amendment at 11-13.

C. Any Argument By Patent Owners that the Prior Art Fails to Provide a Reasonable Expectation That the Claimed Co-Crystals Can Be Formulated Into the Claimed Pharmaceutical Compositions Would Be an Admission That the Priority Applications Lack Enablement Support for Such Compositions

If Patent Owners argue the prior art does not provide a reasonable expectation of formulating a co-crystal into a pharmaceutical composition in a therapeutically effective amount with a pharmaceutically acceptable carrier, the challenged claims lack enablement support in the Priority Applications for this additional reason. The Priority Applications provide no examples, direction or guidance in this regard beyond pointing to the POSA's general knowledge and well-known references such as Remington (1995). Ex. 1002, Rogers ¶ 135.

VIII. GROUND 1: HICKEY ANTICIPATES CLAIMS 10, 11, AND 18

Hickey discloses a pharmaceutical composition comprising a therapeutically effective amount of a co-crystal (1:1 carbamazepine/saccharin) and a pharmaceutically acceptable carrier (lactose). Hickey was not cited in any IDS during the '344 patent prosecution. Ex. 1002, Rogers ¶¶ 305, 362. Because the challenged claims are not entitled to a 2002/2003 priority date, Hickey anticipates the challenged claims. *Id.* ¶ 149.

A. Hickey

Hickey, "Performance comparison of a co-crystal of carbamazepine with marketed product," was published in 2007 in the *European Journal of*

Pharmaceutics and Biopharmaceutics. One of the authors is a '344 patent inventor (Zaworotko), and four authors are Almarsson inventors (Zaworotko, Hickey, Peterson, Almarsson). Ex. 1005, Almarsson, cover; Ex. 1004, Hickey at 112; Ex. 1002, Rogers ¶¶ 150, 155, 205.

Hickey reports that carbamazepine is an anti-epileptic marketed as Tegretol®. Ex. 1004, Hickey at 112. Hickey compared Tegretol® with a pharmaceutical composition containing a 1:1 carbamazepine saccharin co-crystal and lactose. The formulated carbamazepine/saccharin co-crystal was determined to be a “viable alternative” to Tegretol® with a “comparable oral absorption profile in dogs.” *Id.* at 112, 118; Ex. 1002, Rogers ¶¶ 151-54.

Hickey provides that the 1:1 carbamazepine/saccharin co-crystal was previously reported in Fleischman (reference “[6]”) (Ex. 1028), which also published the co-crystal structure. Ex. 1004, Hickey at 113, 115; Ex. 1002, Rogers ¶¶ 156-57. As discussed further below, Almarsson (Ex. 1005) also discloses, in Example 32, a 1:1 carbamazepine/saccharin co-crystal having the same structure as that reported in Fleischman. Ex. 1002, Rogers ¶¶ 156-57, 207, 214; Ex. 1005, Almarsson, 42:20-43:3.

Each limitation of the challenged claims is disclosed in Hickey or is an inherent feature of co-crystal components disclosed in Hickey. Ex. 1002, Rogers ¶ 159.

B. Anticipation of Claims 10 and 18

Claim 18 incorporates all the limitations of claim 10 and further requires that “the first chemical functionality is a carboxamide,” whereas claim 10 recites that the first chemical functionality is one of: “(i) a carboxamide, (ii) a carbonyl, or (iii) an amine.” Any prior art that anticipates claim 18 will also anticipate claim 10. Therefore, these two claims are considered together below.

For purposes of the analysis below (both Grounds), the claims are divided into the claim limitations reproduced above (*supra* § IV). To simplify the discussion, certain claim limitations are addressed together or out of order.

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

Hickey discloses a 1:1 co-crystal of carbamazepine and saccharin identified as “1” and depicted in “Chart 1”, shown below. Ex. 1004, Hickey at 113-15. Chart 1 shows there is one carbamazepine for each saccharin in the co-crystal, and thus the co-crystal is formed from **stoichiometric amounts** of these components. Ex. 1002, Rogers ¶¶ 161-63, 166.

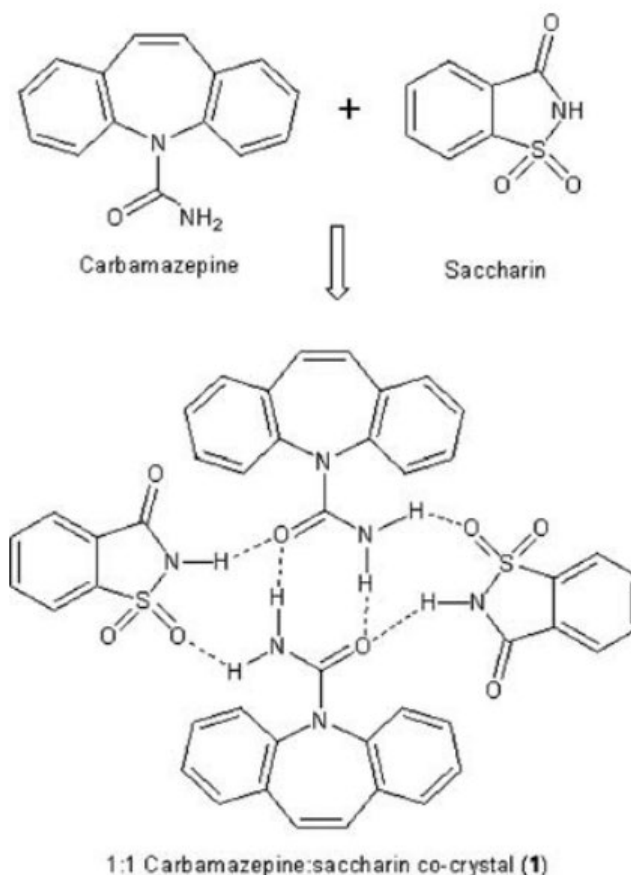


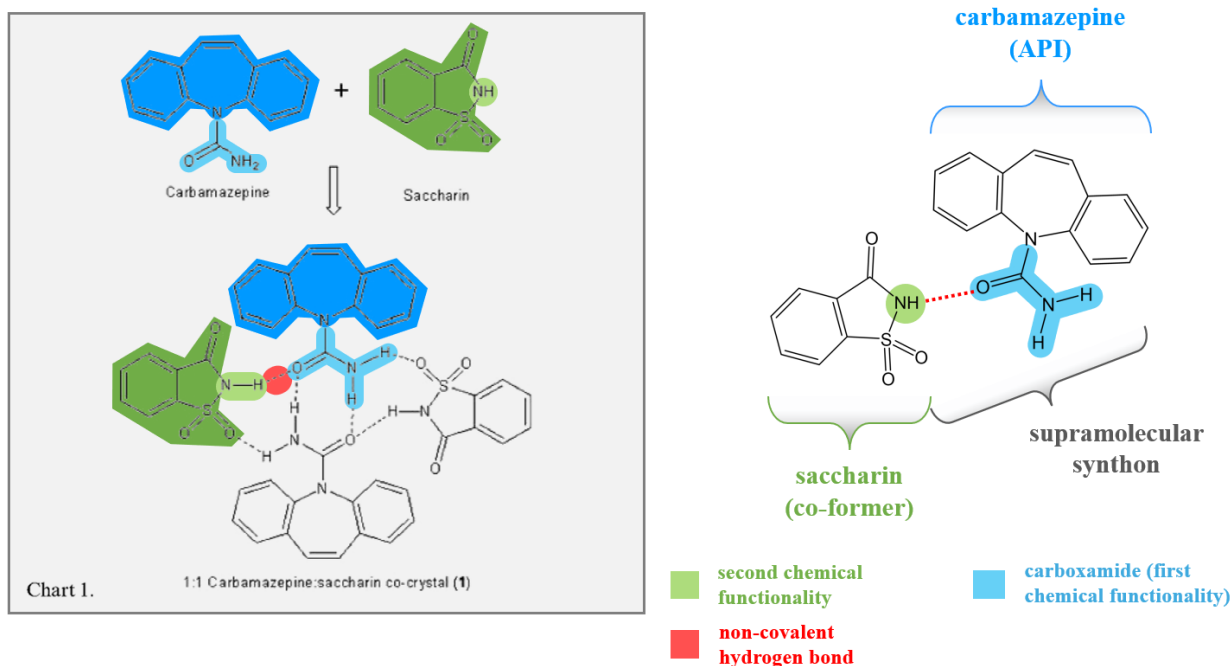
Chart 1. Components and schematic packing motif present in co-crystal **1**.

Hickey describes carbamazepine as “an important anti-epileptic agent that has been in use for over 30 years” (Ex. 1004, Hickey at 112), thus meeting the agreed-upon **API** definition, *i.e.*, “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition.” *Supra* § VI.A. A POSA would understand that saccharin is a **co-former** in the co-crystal because it is complementary to, and forms a co-crystal with, carbamazepine (Ex. 1004, Hickey at 113-15). Ex. 1002, Rogers ¶¶ 164-67, 174-75.

The carbamazepine/saccharin co-crystal qualifies as a **co-crystal** under the '344 patent as it is “[a] multiple component, single crystalline phase, having a fixed stoichiometry of its component compounds,” wherein the components are carbamazepine and saccharin in a fixed 1:1 stoichiometry, and they are present as a single crystalline phase, as evidenced by the statement that “only a single crystalline form of **1** was obtained” and the reference to single crystal data, which requires a single crystalline phase. *See supra* § VI.B (construction of co-crystal); Ex. 1004, Hickey at 115 and n.3; Ex. 1002, Rogers ¶¶ 161-63.

In the co-crystal, shown below, the carboxamide group of carbamazepine (the API), shown in light blue, and the second chemical functionality of saccharin (the co-former), shown in light green, interact via non-covalent interactions (hydrogen bonds) to form a **supramolecular synthon**.⁹ Ex. 1002, Rogers ¶¶ 166-67.

⁹ The supramolecular synthon is the sum of the first and second chemical functionalities involved in the non-covalent (hydrogen bond) interaction. Ex. 1002, Rogers ¶¶ 30, 44-46, 167; Ex. 1001, 1:48-50, 9:66-10:4; *supra* § VI.A.

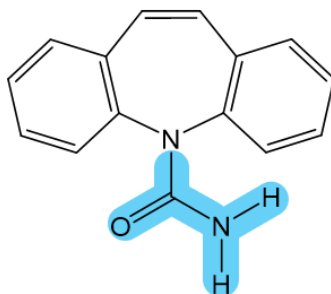


Thus, Hickey discloses a co-crystal comprising supramolecular synthons formed from 1:1 stoichiometric amounts of the API carbamazepine and the co-former saccharin, meeting limitation [10b]. Ex. 1002, Rogers ¶¶ 160, 168.

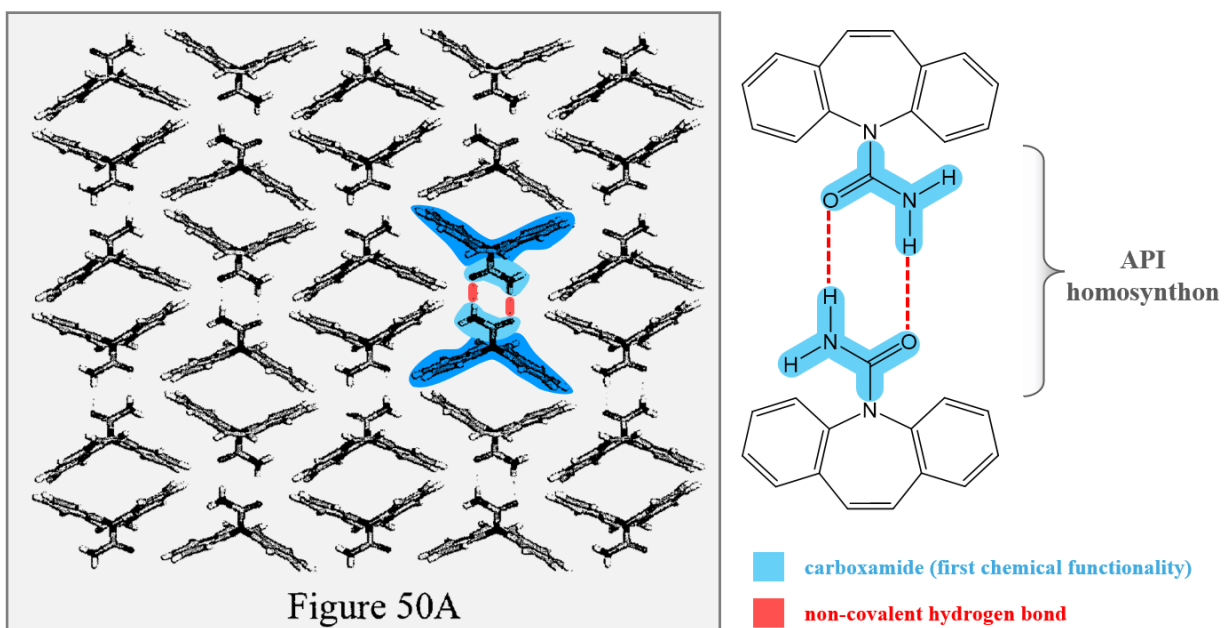
2. **[10c]: wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form**

[10g/18b]: wherein the first chemical functionality is a carboxamide

Hickey discloses the API carbamazepine. As shown below, carbamazepine has a -C(=O)NH_2 chemical functionality (shaded light blue), *i.e.*, a carboxamide, as that term is used in the '344 patent (*see supra* § VI.A), thus meeting limitations [10g/18b]. *See, e.g.*, Ex. 1004, Hickey at 113, Chart 1 (disclosing structure of carbamazepine); Ex. 1002, Rogers ¶¶ 169, 171, 173, 183-84, 201-02.



As for limitation [10c], carbamazepine “has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form.” This inherent property of carbamazepine is exemplified in Figure 50A of Almarsson, which depicts the crystal structure of carbamazepine in pure form and is reproduced below with annotations added. *Id.* ¶¶ 169-72. The carboxamide on one carbamazepine hydrogen bonds with the carboxamide of an adjacent carbamazepine to form an API homosynthon, *i.e.*, a synthon between identical and complementary chemical functionalities (the carboxamide groups) of the API (carbamazepine). Ex. 1005, Almarsson, Figure 50A; 6:38-40, 6:47-61; Ex. 1002, Rogers ¶¶ 171-73.



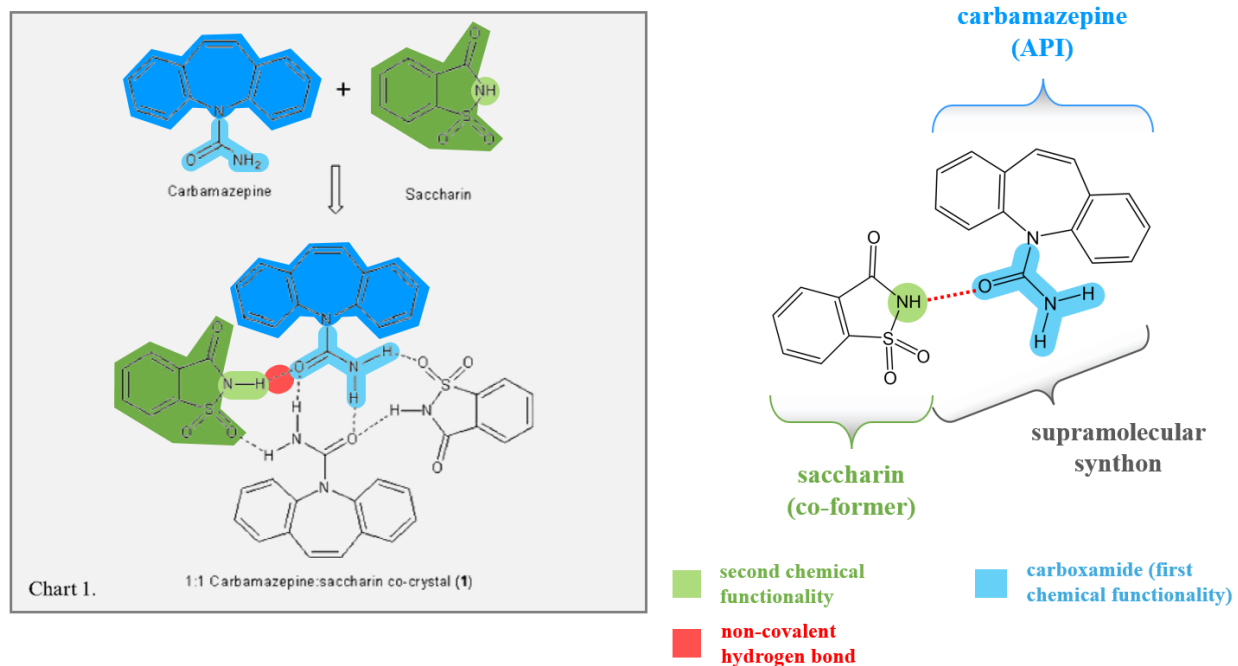
Therefore, by disclosing carbamazepine, Hickey discloses an API having a first chemical functionality (carboxamide) “that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,” meeting limitation [10c]. Ex. 1002, Rogers ¶ 173.

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

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

As shown in Hickey’s Chart 1 (reproduced again below, with the same annotations), saccharin has a second chemical functionality (highlighted in light green) that forms non-covalent hydrogen bonds with the first chemical

functionality (carboxamide) of the API (carbamazepine). Ex. 1004, Hickey at 113; Ex. 1002, Rogers ¶¶ 166-67, 174-175, 180-81. The second chemical functionality of saccharin is therefore complementary to the first chemical functionality (carboxamide) of carbamazepine, meeting limitation [10d]. Ex. 1002, Rogers ¶¶ 165, 174-75. That same non-covalent hydrogen bonding between the first chemical functionality of the API and second chemical functionality of the co-former gives rise to supramolecular synthons, identified in Chart 1, meeting limitation [10f]. *Id.* ¶¶ 166-67, 180-82.



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

The co-former saccharin, disclosed in Hickey, has a melting point of 228.8 °C. Ex. 1005, Almarsson, 42:53-57. A POSA would understand that because

saccharin's melting point, which is an inherent property of saccharin, is above room temperature (about 20-25 °C), saccharin is solid at room temperature and atmospheric pressure when in its pure form, meeting limitation [10e]. Ex. 1002, Rogers ¶¶ 176-79; *see also* Ex. 1017, pp. 3352-53, '956 application file history, March 5, 2010 Amendment at 6-7 (applicants admitting saccharin is solid at room temperature and under atmospheric pressure).

5. [10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [a co-crystal]

Hickey discloses a pharmaceutical composition “prepared by mixing α -lactose monohydrate (2.52 g, 0.0069 mol . . .) with [co-crystal] **1** (3.654 g, 0.087 mol . . .) and blending the two solids in a mortar and pestle” and then adding 600 mg of the formulated co-crystal to capsules. Ex. 1004, Hickey at 115, 118; Ex. 1002, Rogers ¶¶ 186-88; Ex. 1003, Appel ¶ 57. A POSA would have understood that this was a pharmaceutical composition, and α -lactose monohydrate (lactose) was a known pharmaceutically acceptable carrier. Ex. 1001, 10:14-15; Ex. 1042 at 98; Ex. 1043 at 364-66; Ex. 1003, Appel ¶¶ 21-24, 34, 57; Rogers ¶¶ 187, 189. Further, a POSA would have understood that the composition comprised a therapeutically effective amount of the co-crystal. According to Hickey, each capsule contained 600 mg of formulated co-crystal, “corresponding to 200 mg of carbamazepine,” *i.e.*, the same amount of carbamazepine included in the

commercial Tegretol[®] product. Ex. 1004, Hickey at 112, 115, 118; Ex. 1002, Rogers ¶¶ 187-88; Ex. 1003, Appel ¶¶ 58-59. Further, the capsules were administered to dogs to evaluate bioavailability and the authors reported that the formulated co-crystal was a “viable alternative” to Tegretol[®] with a “comparable oral absorption profile,” thus indicating to a POSA that the Hickey capsules included an amount of co-crystal that was therapeutically effective as an anti-epileptic. Ex. 1004, Hickey at 112-13, 115, 118; Ex. 1002, Rogers ¶¶ 186-89; Ex. 1003, Appel ¶¶ 57, 59-60. Therefore, Hickey discloses limitation [10a]. Ex. 1002, Rogers ¶¶ 185, 190; Ex. 1003, Appel ¶ 32.

* * *

Because Hickey discloses each limitation of claims 10 and 18, it anticipates those claims. Ex. 1002, Rogers ¶¶ 191, 201-02.

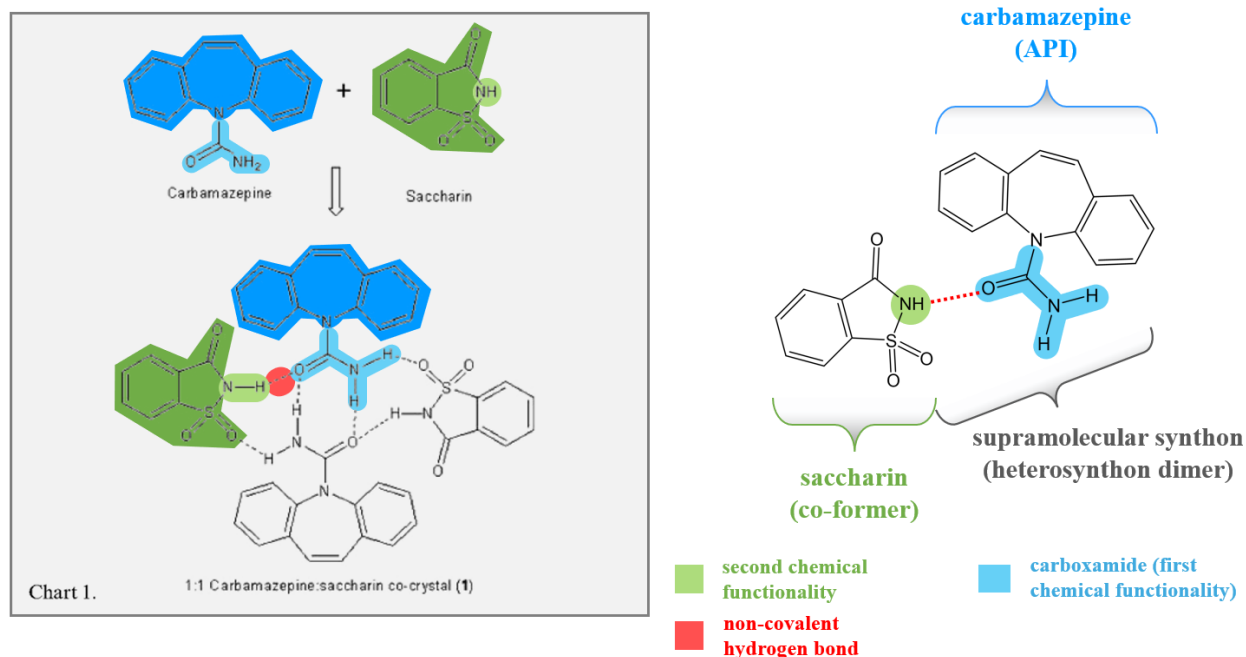
C. Anticipation of Claim 11

Claim 11 incorporates all limitations of claim 10 and additionally requires that the supramolecular synthon comprises a heterosynthon dimer.

Hickey anticipates claim 11 for the reasons described above for claim 10 (*supra* § VIII.B) and the additional reasons below. Ex. 1002, Rogers ¶ 193.

1. [11b]: wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former

Hickey discloses a co-crystal comprising an API (carbamazepine) and a co-former (saccharin). Ex. 1004, Hickey at 113-15. As shown below, there is non-covalent hydrogen bonding between the API's first chemical functionality (carboxamide) and the second chemical functionality of the co-former (which second chemical functionality is different from the first chemical functionality), thereby forming a heterosynthon dimer. *Id.* at 113-15; Ex. 1002, Rogers ¶¶ 194-97.



The first chemical functionality (carboxamide) of the API and the second chemical functionality of the co-former are *different* chemical functionalities therefore producing a **heterosynthon** when they hydrogen bond with one another. Ex. 1002, Rogers ¶¶ 196-98. This heterosynthon is made up of two different

chemical functionalities and is therefore a “**heterosynthon dimer**” formed by non-covalent hydrogen bonding of the API to the co-former,” meeting limitation [11b]. *See supra* § VI.A (construction of heterosynthon dimer); Ex. 1002, Rogers ¶¶ 194-99.

Because Hickey discloses each limitation of claim 11, it anticipates claim 11. Ex. 1002, Rogers ¶ 199.

IX. GROUND 2: ALMARSSON ANTICIPATES OR RENDERS OBVIOUS CLAIMS 10, 11, AND 18, ALONE, OR ALTERNATIVELY IN COMBINATION WITH HICKEY AND MARTINDALE

Because the challenged claims are not entitled to a 2002/2003 priority date, Almarsson anticipates and/or renders obvious each of the challenged claims alone or alternatively renders them obvious in combination with Hickey and Martindale. Ex. 1002, Rogers ¶¶ 203-04. Almarsson, like Hickey, discloses a pharmaceutical composition comprising a co-crystal (1:1 carbamazepine/saccharin) and a pharmaceutically acceptable carrier. While Almarsson teaches or renders obvious the use of a “therapeutically effective amount” of the co-crystal, the therapeutically effective amount claim limitation is further supported by Hickey and Martindale.

A. Almarsson

Almarsson, entitled “Pharmaceutical Co-Crystal Compositions,” issued April 19, 2011. Ex. 1005, Almarsson, cover. As discussed above, Almarsson is

related to the '344 patent and includes as inventors the '344 patent's inventors. *Id.*; Ex. 1002, Rogers ¶¶ 205, 155-57, 214.

Example 32 of Almarsson (which is the same as Example 9 of the '344 patent) discloses a 1:1 carbamazepine/saccharin co-crystal. Ex. 1005, Almarsson, 42:20-43:3, Figure 52; Ex. 1002, Rogers ¶¶ 156-57, 207, 214; Ex. 1001, 17:43-18:31. During prosecution of Almarsson, claims to a 1:1 carbamazepine/saccharin co-crystal, *i.e.*, a co-crystal of Example 32, were stated to be enabled. *See, e.g.*, Ex. 1023, pp. 747-48, December 10, 2007 Office Action at 5-6 (citing application claim 11). Ex. 1002, Rogers ¶¶ 140, 207.

Almarsson discloses that carbamazepine is indicated to treat epilepsy and thus an API. Ex. 1005, Almarsson, col. 179 (Table IV); Ex. 1002, Rogers ¶ 208. Saccharin is disclosed as a co-crystal former (*i.e.*, co-former) that can be used in the pharmaceutical compositions of Almarsson. *See* Ex. 1005, Almarsson, col. 63-64 (Table I), 9:25-45; Ex. 1002, Rogers ¶ 208.

Almarsson further discloses processes for preparing pharmaceutical compositions, providing that “co-crystals obtained as a result of [the disclosed] process steps may be readily incorporated into a pharmaceutical composition by conventional means. Pharmaceutical compositions . . . may further comprise a pharmaceutically-acceptable . . . carrier.” Ex. 1005, Almarsson, 10:59-11:36; *see*

id., 21:60-29:2 (describing suitable carriers, including lactose); Ex. 1002, Rogers ¶¶ 209-10; Ex. 1003, Appel ¶¶ 61-62, 71.

Unlike the '344 patent's broad claims covering a vast number of co-crystals, Almarsson's claims are directed to a limited number of specific co-crystals for which the specification provides single crystal data (*i.e.*, data confirming that the co-crystals were made, and showing the positions of the co-crystal components in three dimensions), and pharmaceutical compositions containing those specific co-crystals. Exemplary Almarsson claims are reproduced below:

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

Ex. 1002, Rogers ¶¶ 211-12.

B. Martindale

Martindale, "The Complete Drug Reference," provides clinically useful information on drugs and other compounds, including their indications and dosage information. Ex. 1006, Martindale at preface v-vi; Ex. 1002, Rogers ¶ 215.

Martindale provides that carbamazepine is used, *inter alia*, in the treatment of epilepsy at initial doses of "100 to 200 mg once or twice daily gradually

increased by increments of up to 200 mg daily every week to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses; up to 2 g daily may occasionally be necessary.” Ex. 1006, Martindale at 514-20; Ex. 1002, Rogers ¶ 216.

Martindale also teaches that saccharin exists as crystalline powder or crystals, and is used in pharmaceuticals and food. Ex. 1006, Martindale at 2242; Ex. 1002, Rogers ¶ 217.

C. Anticipation and/or Obviousness of Claims 10 and 18

Each limitation of claims 10 and 18 of the ’344 patent is disclosed in or taught by Almarsson, which anticipates or renders obvious those claims either alone or renders them obvious in combination with Hickey and Martindale. Ex. 1002, Rogers ¶¶ 219, 277-78.

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

Almarsson specifically claims a pharmaceutical composition containing “a *co-crystal* comprising an *API* and a co-crystal former selected from: (a) carbamazepine and saccharin; . . .” Ex. 1005, Almarsson, claims 19, 20. Ex. 1002, Rogers ¶¶ 221-23. Example 32 provides a procedure for preparing such a co-crystal, and indicates that there is a *1:1 stoichiometric ratio* between the API and co-former, which is shown in Figure 52, reproduced below (*infra* p. 50) with annotations added. Ex. 1002, Rogers ¶ 223; Ex. 1005, Almarsson, Ex. 32

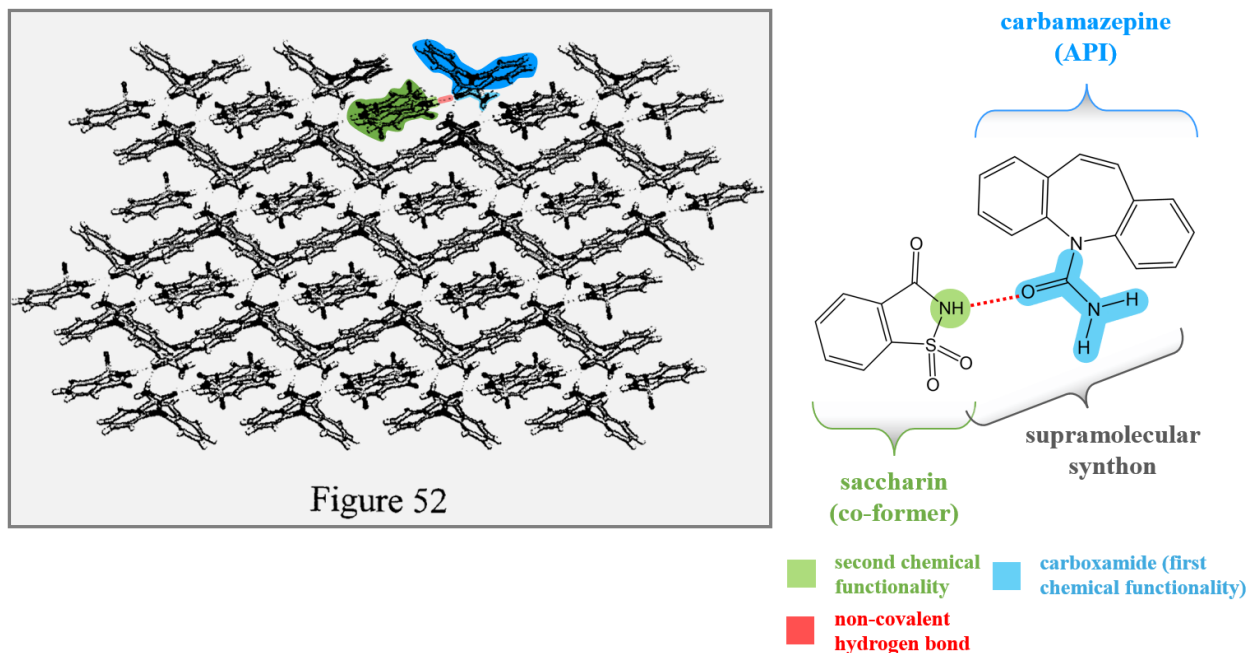
(“Carbamazepine:saccharin (Form II) (**1:1 stoichiometry**)”) (emphasis added); Fig. 52. Example 32 of Almarsson is the same as Example 9 in the Priority Applications.¹⁰ Compare Ex. 1005, Almarsson, 42:20-43:3 with Ex. 1015, ’956 priority application at 24 and Ex. 1014, ’768 priority application at 19. Ex. 1002, Rogers ¶¶ 223.

The carbamazepine/saccharin co-crystal of Almarsson Example 32 qualifies as a **co-crystal** under the ’344 patent as it is “[a] multiple component, single crystalline phase, having a fixed stoichiometry of its component compounds,” wherein the components are carbamazepine and saccharin in a fixed 1:1 stoichiometry, and they are present as a single crystalline phase, as evidenced by the fact that the Almarsson inventors were able to prepare and evaluate a single crystal. See *supra* § VI.B (construction of “co-crystal”); Ex. 1005, Almarsson, 6:43-44, 42:20-43:3, Fig. 52; Ex. 1002, Rogers ¶¶ 221-24.

The Almarsson carbamazepine/saccharin co-crystal likewise contains supramolecular synthons as shown in Figure 52 below. Specifically, the

¹⁰ It is well-established that an earlier publication of a patentee’s own work can serve as an anticipatory disclosure where the patentee is not entitled to claim priority. See, e.g., *Lacks Indus. v. McKechnie Vehicle Components USA, Inc.*, 322 F.3d 1335, 1346 (Fed. Cir. 2003).

carboxamide group of carbamazepine (the API), shown in light blue interacts with a second chemical functionality on the saccharin molecule (the co-former), shown in light green via non-covalent interactions (hydrogen bonds, shown with a red dashed line) to form a **supramolecular synthon**. Ex. 1002, Rogers ¶¶ 227-28.



Almarsson specifically identifies carbamazepine as an **API** and explains that it is indicated to treat epilepsy (*id.* ¶ 225); a POSA would therefore understand that carbamazepine qualifies as an API, which the parties agree means a “biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.” *See supra* § VI.A (claim construction); Ex. 1002, Rogers ¶ 225. Almarsson further identifies saccharin as a co-crystal former in the carbamazepine/saccharin co-crystal (Ex. 1002, Rogers ¶ 226), which the parties agree is used synonymously

with **co-former** (*see supra* § VI.A). Further, saccharin qualifies as a co-former because it is complementary to, and forms a co-crystal with, carbamazepine. Ex. 1002, Rogers ¶¶ 225-28, 234-35.

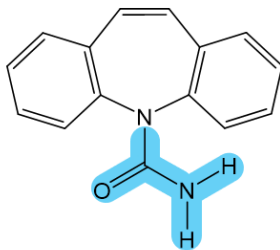
For these reasons, Almarsson discloses in Example 32 a co-crystal comprising supramolecular synthons formed from 1:1 stoichiometric amounts of the API carbamazepine and the co-former saccharin, meeting limitation [10b]. *Id.* ¶¶ 220, 229. During prosecution, the Almarsson patent examiner expressly stated that “[t]he [Almarsson] specification is enabling for the preparation and use of the particular pharmaceutical co-crystals as recited in [application] claim 11, such as co-crystals of carbamazepine and saccharin . . .” Ex. 1023, pp. 747-48, Almarsson prosecution history, December 10, 2007 Office Action at 5. Ex. 1002, Rogers ¶¶ 140, 207.

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

[10g/18b]: wherein the first chemical functionality is a carboxamide

The API carbamazepine has a -C(=O)NH₂ chemical functionality (shaded light blue in the figure below), *i.e.*, a carboxamide, as that term is used in the ’344 patent (*see supra* § VI.A), thus meeting limitations [10g/18b]. *See e.g.*, Ex. 1005, Almarsson, col. 179 (chemical name of carbamazepine is “5H-Dibenz[b,f]azepine-

5-*carboxamide*” (emphasis added); Fig. 50A (showing chemical structure of carbamazepine); Ex. 1002, Rogers ¶¶ 232-33, 243-44, 275-77.



As for limitation [10c], as discussed in Ground 1, Figure 50A of Almarsson depicts the crystal structure of carbamazepine in pure form and shows that carbamazepine has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding. *Supra* § VIII.B.2; Ex. 1005, Almarsson, Figure 50A; 6:38-40, 6:47-61; Ex. 1002, Rogers ¶¶ 230-34.

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

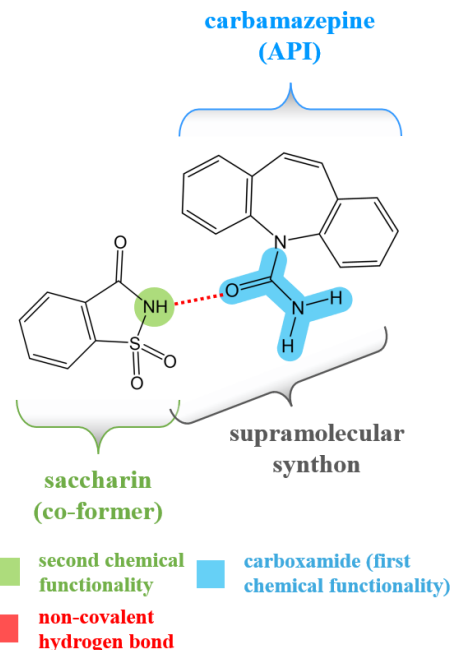
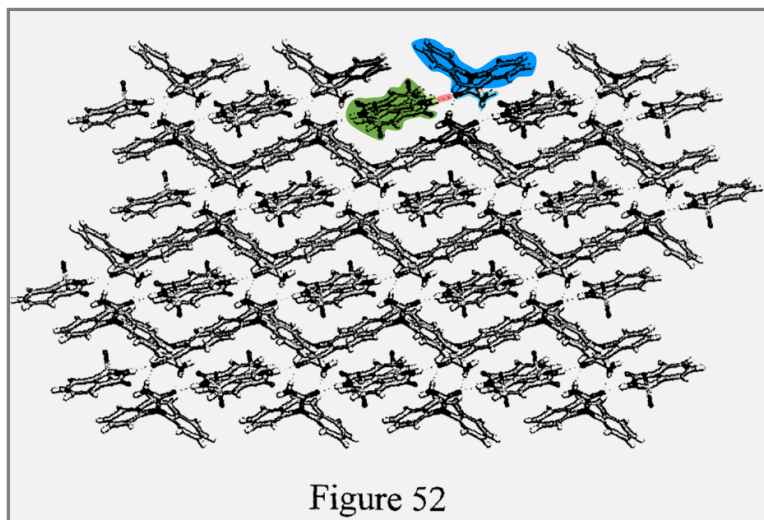
[10f]: wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former

Almarsson’s carbamazepine/saccharin co-crystal has saccharin as a co-former. Saccharin has a second chemical functionality that forms non-covalent hydrogen bonds with the first chemical functionality (carboxamide) of the API (carbamazepine), and the second chemical functionality of saccharin is therefore

complementary to the first chemical functionality of carbamazepine, meeting limitation [10d]. Ex. 1002, Rogers ¶¶ 226, 234-35.

That same non-covalent hydrogen bonding between the first chemical functionality of the API and second chemical functionality of the co-former gives rise to supramolecular synthons, meeting limitation [10f]. *Id.* ¶¶ 227-28, 234-35, 240-42.

Specifically, Figure 52 of Almarsson, reproduced again below with the same annotations added, depicts the hydrogen bonding between the carbamazepine's carboxamide (first chemical functionality) and the complementary second chemical functionality of the saccharin co-former, resulting in supramolecular synthons. Ex. 1005, Almarsson, Figure 52; *see id.*, 6:41-42; 42:40-45 (Example 32, “The 2° amines of the saccharin are hydrogen bonded to the carbonyl of the [carbamazepine] on each side . . .”); Ex. 1002, Rogers ¶¶ 227-28, 234-35, 240-42.



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

As discussed in Ground 1, saccharin has a melting point of 228.8 °C, and is therefore a solid at room temperature and atmospheric pressure, meeting limitation [10e]. *Supra* § VIII.B.4; Ex. 1005, Almarsson, 42:53-57; Ex. 1002, Rogers ¶¶ 236-39; *see also* Ex. 1017, pp. 3352-53, '956 application file history, March 5, 2010 Amendment at 6-7 (applicants admitting saccharin is solid at room temperature and under atmospheric pressure).

5. **[10a]: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of [a co-crystal]**

Almarsson claims “[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; ...” Ex. 1005, Almarsson, claims 19, 20. A POSA would understand that the co-crystals of claims 19 and 20 include the 1:1 carbamazepine/saccharin co-crystal of Example 32. Ex. 1002, Rogers ¶¶ 213, 245-46. Therefore, Almarsson discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a 1:1 carbamazepine/saccharin co-crystal, meeting limitation [10a]. *Id.* ¶ 246.

Claims 19 and 20 of Almarsson do not expressly reference the use of a therapeutically effective amount of the carbamazepine/saccharin co-crystal in the claimed pharmaceutical composition; however, that claim limitation would be taught or at least obvious in view of Almarsson’s teachings alone. *Id.* ¶¶ 247-52; Ex. 1003, Appel ¶¶ 33, 63-66.

Almarsson, which is entitled “[p]harmaceutical co-crystal compositions” is specifically directed to compositions comprising co-crystals that include at least one pharmaceutically active ingredient, and carbamazepine is identified as an active ingredient in Table IV. Ex. 1005, Almarsson, col. 179; Ex. 1002, Rogers ¶ 246. The specification provides that “[a] pharmaceutical composition of the invention contains a *desired amount of API per dose unit*” and “[p]resently 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, 21:39-52 (emphasis added); Ex. 1002, Rogers ¶¶ 247-48. A POSA would understand these Almarsson references (bolded above) teach, or at least render obvious, a therapeutically effective amount of the disclosed carbamazepine/saccharin co-crystal in the claimed pharmaceutical composition, including for use as an anti-epileptic, meeting element [10a]. Ex. 1002, Rogers ¶¶ 246-52; Ex. 1003, Appel ¶¶ 33, 64.

If necessary, the POSA would also have looked to references like Hickey and Martindale to determine a therapeutically effective amount of this Almarsson co-crystal. Ex. 1002, Rogers ¶¶ 253-58; Ex. 1003, Appel ¶ 67.

A POSA would have been motivated to combine these two additional references in view of their overlapping subject matter. Ex. 1002, Rogers ¶¶ 259-61; Ex. 1003, Appel ¶ 76. Almarsson and Hickey both discuss 1:1 carbamazepine/saccharin co-crystals, and indicate that carbamazepine is indicated to treat epilepsy, and Martindale discusses the use of carbamazepine to treat epilepsy and dosage amounts for such use. Ex. 1005, Almarsson, claims 19-20, 42:20-43:3, col. 179; Ex. 1004, Hickey at 112-15, 118; Ex. 1006, Martindale at 518; Ex. 1003, Appel ¶¶ 63, 68, 71-72; Ex. 1002, Rogers ¶¶ 254-57, 260.

In view of Almarsson's disclosures of a pharmaceutical composition comprising a carbamazepine/saccharin co-crystal, with the co-crystal having improved solubility over other forms of carbamazepine, Ex. 1005, Almarsson,

42:22-30, a POSA would have been motivated to include a therapeutically effective amount of carbamazepine (*i.e.*, the “desired amount of API per dose unit” or “predetermined amount of the API” referenced in Almarsson) in such pharmaceutical compositions and would have looked to Hickey and Martindale. Ex. 1003, Appel ¶¶ 64, 69-71, 76; Ex. 1002, Rogers ¶¶ 253, 255, 257, 260-61.

Martindale provides suggested initial oral doses of carbamazepine for the treatment of epilepsy of “100 to 200 mg once or twice daily gradually increased by increments of up to 200 mg daily every week to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses.” Ex. 1006, Martindale at 514-20. Martindale further teaches that saccharin is a pharmaceutical and food sweetener. Ex. 1006, Martindale at 2242. Ex. 1002, Rogers ¶¶ 256-57, 260. A POSA would have understood that to determine a therapeutically effective amount of a 1:1 carbamazepine/saccharin co-crystal for use as an anti-epileptic, the POSA would focus on carbamazepine and the amounts disclosed in Martindale. Ex. 1006, Martindale at 518; Ex. 1003, Appel ¶¶ 70, 72-74; Ex. 1002, Rogers ¶¶ 256-57, 260.

This understanding is confirmed by Hickey, which describes the preparation of a pharmaceutical composition (added to capsules) comprising a carbamazepine/saccharin co-crystal with a pharmaceutically acceptable carrier (lactose), *i.e.*, the co-crystal disclosed in Example 32 and claims 19-20 of Almarsson. Ex. 1004, Hickey at 115; Ex. 1002, Rogers ¶¶ 251, 254, 260-61; Ex.

1003, Appel ¶¶ 21-24, 32, 57, 71; Ex. 1001, 10:14-15; Ex. 1042 at 98; Ex. 1043 at 364-66 (lactose is a carrier). These Hickey capsules contained 355 mg of the carbamazepine/saccharin co-crystal, which the authors reported corresponds to 200 mg of carbamazepine (*i.e.*, the same amount of carbamazepine as included in the commercial Tegretol® product). Ex. 1004, Hickey at 114-15, 118; Ex. 1002, Rogers ¶¶ 255, 260-61; Ex. 1003, Appel ¶¶ 58-59, 71-72. The authors' use of an amount of the carbamazepine/saccharin co-crystal providing 200 mg of carbamazepine is consistent with Martindale's teaching that carbamazepine is used initially at doses of "100 to 200 mg once or twice daily ...". Ex. 1006, Martindale at 518; Ex. 1002, Rogers ¶¶ 255, 257, 260; Ex. 1003, Appel ¶ 68. And, the formulated co-crystal had a comparable oral absorption profile in dogs compared with the marketed carbamazepine formulation (having the same amount of carbamazepine). Ex. 1004, Hickey at 118; Ex. 1002, Rogers ¶ 255; Ex. 1003, Appel ¶¶ 59, 71.

Accordingly, a POSA seeking to prepare a pharmaceutical composition comprising a therapeutically effective amount of the carbamazepine/saccharin co-crystal for use as an anti-epileptic would have been motivated to include an amount of co-crystal that provides a therapeutically effective amount of carbamazepine as taught in Hickey and Martindale. Ex. 1002, Rogers ¶¶ 260-61; Ex. 1003, Appel ¶¶ 23, 33-34, 76. The POSA would have had a reasonable expectation that they

could successfully prepare such a composition. Ex. 1002, Rogers ¶¶ 246-48, 261; Ex. 1003, Appel ¶¶ 33-56, 75-76. Indeed, the Hickey authors did just that.

* * *

For these reasons, because the challenged claims are not entitled to a 2002/2003 priority date, they are anticipated by or obvious in view of Almarsson alone or obvious in combination with Hickey and Martindale. Ex. 1002, Rogers ¶¶ 262-63, 276-78.

D. Anticipation and/or Obviousness of Claim 11

Claim 11 incorporates all limitations of claim 10 and additionally requires that the supramolecular synthon “comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.”

Claim 10 (*i.e.*, limitation [11a]) is anticipated by Almarsson, or obvious in view of Almarsson alone or in combination with Hickey and Martindale as set forth above. *Supra* § IX.C. Claim 11, which includes an additional heterosynthon dimer limitation is also anticipated or rendered obvious by Almarsson alone or rendered obvious in view of the Ground 2 references in combination. Ex. 1002, Rogers ¶ 265.

1. [11b]: wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former

A supramolecular synthon “comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former” when the API’s first chemical functionality hydrogen bonds with the second chemical functionality on the co-former and the first and second chemical functionalities are different. *See supra* § VI.A.

Almarsson discloses and claims a co-crystal comprising carbamazepine (API) and saccharin (co-former), and a pharmaceutical composition thereof. Ex. 1005, Almarsson, claims 1, 2, 19, 20. Example 32 describes the crystal structure of the carbamazepine/saccharin co-crystal:

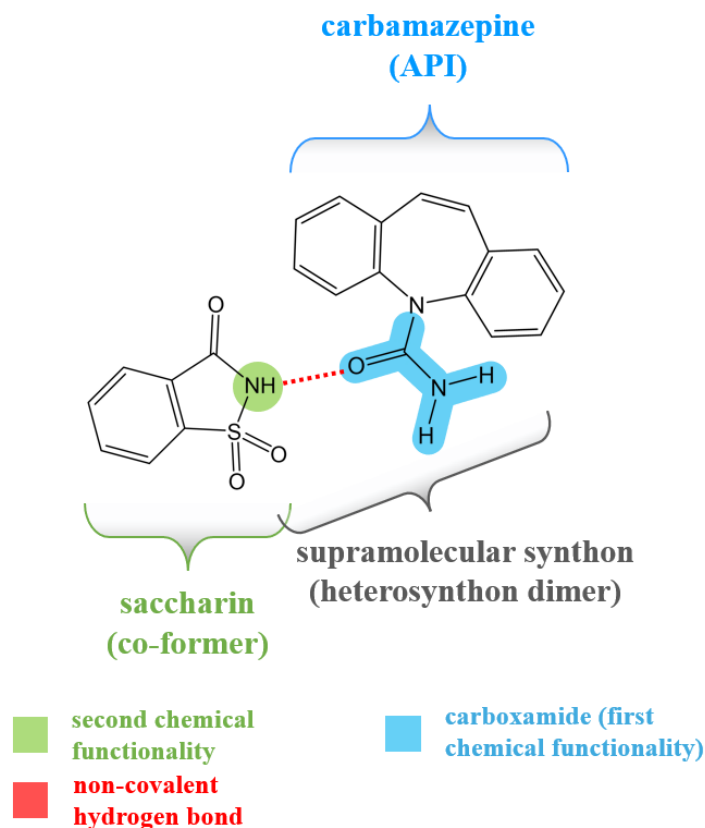
Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. **The 2° amines of the saccharin are hydrogen bonded to the carbonyl of the CBZ on each side** forming a tetramer.¹¹ The crystal has a

¹¹ While this passage refers to a tetramer, as Dr. Rogers explains, even though each molecule of carbamazepine and saccharin forms interactions with functional groups on other molecules, the interaction formed between the first chemical functionality of carbamazepine and the second chemical functionality of saccharin in Example 32 is between two different, yet complementary chemical

space group of P-1 with π - π interactions between the phenyl groups of the CBZ and the saccharin phenyl groups.

Ex. 1005, Almarsson, 42:20-43:3 (emphasis added). The crystal structure is shown in Figure 52 of Almarsson, with the key portions depicted in the figure below. As shown below, there is **non-covalent hydrogen bonding between the first chemical functionality (carboxamide) of the API (carbamazepine) and the second chemical functionality of the co-former (saccharin)**. Ex. 1005, Almarsson, Figure 52; 6:43-44; *see also id.*, 42:40-45; Ex. 1002, Rogers ¶¶ 267-69.

functionalities and therefore is a heterosynthron dimer. Ex. 1002, Rogers ¶¶ 196, 197, 268-70. Examples 12 and 15 of the '344 patent are additional examples where heterodimers are joined together to form a tetramer. Ex. 1001 (Example 12 (Fig 16B, carbamazepine/acetic acid) is “sustained by hydrogen bonded carboxamide-carboxylic *heterodimers*. The second 1° amine hydrogen from each [carbamazepine] joins 2 heterodimers side by side forming a *tetramer*.”); *see also* Example 15 (Fig 19B)). Ex. 1002, Rogers ¶¶ 198, 271.



The first chemical functionality (carboxamide) of the API and the second chemical functionality of the co-former are *different* chemical functionalities therefore producing a **heterosynthon**. Ex. 1002, Rogers ¶¶ 267-70. This heterosynthon is made up of two different functionalities and is therefore a “**heterosynthon dimer** formed by non-covalent hydrogen bonding of the API to the co-former,” meeting limitation [11b]. Ex. 1002, Rogers ¶ 266-72.

For these reasons, Almarsson anticipates or renders obvious claim 11 alone or renders it obvious in combination with Hickey and Martindale. Ex. 1002, Rogers ¶¶ 272-74.

X. THERE ARE NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

Petitioner addresses below statements in the intrinsic record potentially directed to objective indicia for Ground 2. Petitioner reserves its right to respond to any additional objective indicia raised, and to revisit claim construction should Patent Owners attempt to argue that Petitioner's Entresto[®] product falls within the scope of the claims.

Patent Owners must establish a nexus between the evidence and the merits of the claimed invention. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). There is no nexus unless the evidence is “commensurate in scope with the claims.” *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010). In addition, “there must be a nexus to some aspect of the claim not already in the prior art.” *Lectrosonics, Inc. v. Zaxcom, Inc.*, (designated precedential), IPR2018-01129 (Final Written Decision), Paper 33 at 33 (PTAB Jan. 24, 2020) (quoting *In re Kao*, 639 F.3d 1057, 1068-69 (Fed. Cir. 2011)).

Patent Owners will not be able to establish the requisite nexus between the challenged claims and any potential objective indicia in the intrinsic record, *i.e.*, (1) the '344 patent's statement that the carbamazepine/saccharin co-crystal of Example 9 “has improved solubility over previously known forms of carbamazepine” (Ex. 1001, 3:26-28, 17:50-58); or (2) the unsupported statements that the disclosed multiple component phase compositions (which include co-

crystals) “can” improve drug properties, it was unexpected that “APIs could not only be used in co-crystals, but that the co-crystals exhibit improved characteristics as compared to the API alone”; and the invention satisfied an unmet need by “provid[ing] a transformative technology which allowed predictable crystal engineering, which was previously lacking in the art.”¹²

As a preliminary matter, the alleged improved solubility of carbamazepine (category 1) and any allegations of unexpected results or meeting an unmet need in the ’344 patent specification (category 2) could not have been unexpected as of 2014, or met only as of 2014, because the ’006 Publication, which has the same specification as the ’344 patent and therefore includes the same statements as the ’344 patent, was published in 2003. Ex. 1009, ’006 Publication at cover; Ex. 1002, Rogers ¶¶ 290, 297.

Further, the improved solubility in category (1) is stated to be attributable to the carbamazepine/saccharin co-crystal, yet co-crystals falling within the scope of the challenged claims’ co-crystal limitation were known in the prior art as of 2014.

¹² Ex. 1001, 2:18-20, 3:26-28, 17:50-58; Ex. 1017, p. 4416, ’956 application file history, July 25, 2016 Response at 8-10; Ex. 1016, p. 359, ’344 patent file history, April 1, 2016 Amendment at 14; Ex. 1016, pp. 445-46, Aug. 10, 2017 Appeal Brief at 21-22; Ex. 1002, Rogers ¶¶ 286-89, 293-96.

See supra Grounds 1 and 2; *see also* Ex. 1009, '006 Publication at 6-7, 9-11, 13 (disclosing the same ten Examples discussed *supra* § VII.A); Ex. 1002, Rogers ¶¶ 287-88. Because the co-crystal claim limitation was not a novel feature of the challenged claims as of 2014, evidence relating to this limitation cannot establish nexus. Ex. 1002, Rogers ¶¶ 287-88; *Lectrosonics*, (designated precedential) IPR2018-01129 (Final Written Decision), Paper 33 at 33; *see also* *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1330-31 (Fed. Cir. 2017); *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356 (Fed. Cir. 2023). Further, any evidence of improved solubility for a single co-crystal is not co-extensive with the breadth of the challenged claims. *In re Tiffin*, 448 F.2d 791 (CCPA 1971); *Ex Parte Smith* (designated informative), Appeal 2011-003337 at 13 (BPAI Feb. 28, 2012). A POSA would not conclude that the improved solubility of one co-crystal would apply to all structurally diverse co-crystals encompassed by the challenged claims, and the '344 patent includes no evidence to support any such conclusion. Ex. 1002, Rogers ¶¶ 287, 289, 291; *In re Lindner*, 457 F.2d 506, 509 (CCPA 1972) (rejecting evidence relating to a single composition within a genus because there was “no ‘adequate basis for reasonably concluding that the great number and variety of compositions included in the claims would behave in the same manner as the tested composition.’”); *see also* *Praxair Tech., Inc. v. Entegris, Inc.*, IPR2016-01845, Paper 20 (Final Written Decision) at 36-37 (PTAB Mar. 29, 2018).

The allegations in category (2) are similarly deficient. The intrinsic record does not allege, let alone establish, that these purported objective indicia are attributable to any feature of the challenged claims in particular, let alone any novel feature. Ex. 1002, Rogers ¶¶ 293-96. Thus, Patent Owners cannot establish nexus. *Id.* Moreover, the applicants’ statements lack supporting evidence and thus are not entitled to any weight. *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1377 (Fed. Cir. 2011); Ex. 1002, Rogers ¶¶ 293-96, 298.

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

Petitioner stipulates that if this IPR is instituted, it will not pursue in the parallel district court proceeding the same grounds as in this Petition or any other ground that could have reasonably been raised in an IPR (*i.e.*, any ground that could be raised under §§ 102 and/or 103 on the basis of prior art patents or printed publications) concerning the challenged claims. This stipulation is dispositive of § 314(a) under the Interim Procedure For Discretionary Denials In AIA Post Grant Proceedings With Parallel District Court Litigation (June 21, 2022) (“Interim Procedure”). *See, e.g., Ericsson Inc. v. Dali Wireless Inc.*, IPR2022-01212, Paper 17 at 55-56 (PTAB Feb. 1, 2023) (declining to exercise discretion to deny institution “[g]iven [a] *Sotera* stipulation and the guidance under the Interim Procedure” without addressing the *Fintiv* factors).

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

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

Factor 2: No trial date has been set in the parallel litigation. Ex. 1050, N.D. Cal. Case No. 3:22-cv-04913-AMO, D.I. 55, 57. Further, Petitioner will immediately move to stay the parallel litigation.

Factor 3: Substantial work remains to be completed in the parallel litigation. No Markman Hearing has been scheduled, fact discovery remains open and no fact depositions have been noticed, expert discovery has not yet begun, and deadlines for dispositive motions have not been set. Ex. 1050, Case No. 3:22-cv-04913-AMO, D.I. 55, 57; *see Extractiontek Sales LLC v. Gene Pool Techs., Inc.*, IPR2022-00832, Paper 15 at 10-11 (PTAB Oct. 31, 2022).

Factor 4: Petitioner has provided a stipulation with respect to the challenged claims identical to the one provided in *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020) (precedential as to § II.A).¹³

¹³ The instant Petition (directed to claims 10, 11, and 18) and a second concurrently filed petition filed directed to claim 16 together challenge all claims that Patent Owners have asserted Petitioner infringes.

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

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

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

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

Institution should not be denied under 35 U.S.C. § 325(d) because the arguments and evidence presented here were not previously and/or substantively considered by the Office. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, (designated precedential) IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020). Ex. 1002, Rogers ¶¶ 302, 361.

Part One of *Advanced Bionics* is not satisfied for Grounds 1 and 2. Of Petitioner’s primary references, Hickey (Grounds 1 and 2) was not cited at all during prosecution, and Almarsson (Ground 2) was merely cited in an IDS among hundreds of references (not discussed by the applicants or examiner). Ex. 1002, Rogers ¶¶ 304, 305, 364. Burying Almarsson among hundreds of references, without highlighting its significance, was not sufficient to present this reference to the Office. *See Samsung Elecs. Co. v. XR Commc’ns LLC*, IPR2022-00613, Paper

12 at 47-48 (PTAB Oct. 20, 2022) (citing with approval Petitioner’s position that one of 155 references submitted in an IDS was “not previously presented to the Office within the spirit of *Advanced Bionics* and § 325(d)” and noting the examiner’s statement that “an applicant’s duty of disclosure . . . is not satisfied by presenting a patent examiner with ‘a mountain of largely irrelevant [material] from which the examiner is presumed to have been able, with his experience and with adequate time, to have found the critical [material]. It ignores the real world conditions under which examiners work.’” (citation omitted)); *cf.* Manual of Patent Examining Procedure § 2004 (2023) (identifying as a “best practice[]” that “[i]t is desirable to avoid the submission of long lists of documents. . . . If a long list is submitted, highlight those documents which . . . are known to be of most significance.”).

The art in Grounds 1 and 2 and Petitioner’s associated arguments are not cumulative of those substantively considered during prosecution because, among other things, Petitioner’s primary references disclose API-containing co-crystals that are different from the materials disclosed in the references substantively considered during prosecution. Ex. 1002, Rogers ¶¶ 306-55. The examiner further did not have the opportunity to consider the combinations of references asserted in Ground 2 or Petitioner’s experts’ testimony explaining how that art meets the limitations of the challenged claims under Grounds 1 or 2. *Id.* ¶¶ 303, 356-57, 362-

64, 366, 369; *see Cisco Sys., Inc. v. Ramot At Tel Aviv Univ.*, IPR2022-01283, Paper 12 at 12-13 (PTAB Feb. 22, 2023). The examiner also did not consider Petitioner’s priority challenges or the prior art as of 2014 (including Hickey and Almarsson). Notably, while written description and enablement rejections were made in related application Almarsson for similarly overbroad claims (*see supra* §§ VII.A.1, VII.B; Ex. 1002, Rogers ¶¶ 356-60, 364-66), Patent Owners failed to bring any rejections from the Almarsson prosecution to the ’344 patent examiner’s attention. *Cf. McKesson Info. Solutions, Inc. v. Bridge Med., Inc.*, 487 F.3d 897, 925 (Fed. Cir. 2007) (no clear error in district court’s finding that rejections in a related application would have been important to disclose to the examiner).

Although the Board need not reach Part Two of *Advanced Bionics*, Part Two also favors institution.

As discussed above, the Office erred in a manner material to the patentability of the challenged claims. The ’344 patent examiner did not substantively address any of Petitioner’s asserted art or arguments, or substantially similar art or arguments; Hickey, relied on in both Grounds, was not even cited during prosecution, Almarsson was never discussed. Ex. 1002, Rogers ¶¶ 303-370. *Trend Micro Inc. v. CUPP Computing AS*, IPR2021-00813, Paper 7 at 23-24 (PTAB Oct. 25, 2021) (Where the examiner did not address a reference cited in an IDS on the merits, *Becton* factor (c) “strongly favors not exercising . . . discretion

to deny the petition.”). The ’344 patent examiner did not raise any written description or enablement rejections and did not address Petitioner’s priority challenges or the prior art as of 2014. Ex. 1002, Rogers ¶¶ 358-60, 365.

The ’344 patent examiner’s failure to raise any rejection based on Hickey (which was not even cited) or Almarsson constitutes material error. Ex. 1002, Rogers ¶¶ 304-05, 362-64, 367-68, 370; *see Advanced Bionics*, (designated precedential) IPR2019-01469, Paper 6 at 10-11 (“[I]f the record of the Office’s previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive. . . .”); *Samsung Elecs. Co. v. Evolved Wireless LLC*, IPR2021-00943, Paper 9 at 12 (PTAB Dec. 1, 2021) (examiner materially erred by overlooking a particular combination of references “among the hundreds of references listed on the IDS”).

Finally, Petitioner submits declarations from Drs. Rogers and Appel, which were not before the ’344 patent examiner and which further explain a POSA’s understanding of the art as of 2014, including an analysis of the single crystal structures presented in the references in the Grounds. Ex. 1002, Rogers ¶ 369; *see Celltrion, Inc. v. Genentech, Inc.*, No. IPR2017-01140, Paper 31 at 13-14 (PTAB Jan. 25, 2018) (instituting when “Petitioner’s testimonial evidence presents the prior art in a new light”).

XIII. CONCLUSION

For the reasons above, the Board should institute IPR of challenged claims 10, 11, and 18, of the '344 patent and cancel them as unpatentable.

XIV. MANDATORY NOTICES (37 C.F.R. §42.8)

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

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

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

The '344 patent is the subject of pending litigation: *Regents of the Univ. of Mich. v. Novartis Pharm. Corp.*, No. 3:22-cv-04913-AMO (N.D. Cal.); however, one of the Plaintiffs in the litigation, “University of South Florida Board of Trustees,” has a different name from that listed in the U.S. Patent and Trademark Office’s Patent Assignment Database for the '344 patent, “University of South Florida.” Ex. 1051, USPTO Patent Assignment Database Entry for U.S Patent No. 10,633,344.

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

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

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

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

XV. PAYMENT OF FEES

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

XV. WORD COUNT

Under 37 C.F.R. § 42.24(d), Petitioner certifies that this Petition for *Inter Partes* Review has a word count of 13,807, excluding the portions exempted by 37 C.F.R. § 42.24(a), as calculated by the built-in word-count function in the Microsoft Word software used to prepare this document, and a manual count of the number of words appearing in the figures.

XVI. CERTIFICATE OF SERVICE

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

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

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