IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXOSMITHKLINE LLC (f/k/a SMITHKLINE BEECHAM CORPORATION),	)	
Plaintiff,	)	
v.	)	C.A. No. 11-046 (RGA)(MPT) CONSOLIDATED
ANCHEN PHARMACEUTICALS, INC.; ANCHEN, INC; BANNER PHARMACAPS, INC.; ROXANE LABORATORIES, INC.; WATSON LABORATORIES, INC. – FLORIDA; MYLAN, INC.; MYLAN PHARMACEUTICAL, INC.; and IMPAX LABORATORIES, INC.,	)	REDACTED - PUBLIC VERSION
Defendants.	)	

JOINT CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

Plaintiff GlaxoSmithKline LLC ("GSK") and defendants Anchen Pharmaceuticals, Inc., Anchen, Inc., Banner Pharmacaps Inc., Roxane Laboratories, Inc., Watson Laboratories, Inc. – Florida, Mylan Inc., Mylan Pharmaceuticals Inc., and Impax Laboratories, Inc. (collectively "Defendants") submit this Joint Claim Construction Brief pursuant to the Court's May 30, 2012 Order.[1]

This case relates to three GSK patents claiming compounds, formulations of those compounds, and methods of using those compounds for the treatment of androgen responsive or mediated conditions, such as benign prostatic hyperplasia ("BPH"), more commonly known as enlarged prostate. One of these claimed compounds is dutasteride. GSK markets dutasteride under the brand name AVODART®. GSK also markets dutasteride in combination with a muscle relaxant used for immediate relief of BPH symptoms under the brand name JALYN™.

Each of the Defendants has filed at least one Abbreviated New Drug Application ("ANDA") seeking to market generic versions of GSK's AVODART® and/or JALYN™ products prior to expiration of GSK's patents. GSK has asserted that one or more of the Defendants infringe one or more of U.S. Patent Nos. 5,565,467[2], 5,846,976[3], and 5,998,427[4] (collectively, the "Patents"). Specifically, GSK has asserted Claims 1–5 of the '467 Patent against Anchen and Watson; Claims 1–3 of the '467 Patent, Claims 1–3 of the '976 Patent, and

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[1] Copies of the Patents-in-Suit, as well as other portions of the intrinsic record relied upon by the parties, were attached as Exhibits B through I to the parties' Joint Claim Construction Statement ("JCCS") (D.I. 193). Additional exhibits are included as a Joint Appendix to this submission.

[2] JCCS Exhibit B, U.S. Patent No. 5,565,467.

[3] JCCS Exhibit C, U.S. Patent No. 5,846,976.

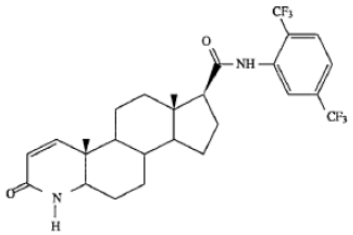
[4] JCCS Exhibit D, U.S. Patent No. 5,998,427.

Claim 10 of the '427 Patent against Mylan and Banner; Claims 1–3 of the '467 Patent, Claims 1–3 of the '976 Patent, and Claim 10 of the '427 Patent against Roxane; and Claims 1–5 of the '467 Patent, Claims 1–4 of the '976 Patent, and Claim 10 of the '427 Patent against Impax (collectively, the "Asserted Claims"). As set forth more fully below, the parties agree upon the construction of one claim term and dispute the construction of two claim terms.

II. AGREED-UPON CONSTRUCTIONS

A. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst-1-en-3-one[5]

The parties agree that the term "17β-N-(2,5-bis(Trifluoromethyl)) phenylcarbamoyl-4-aza-5α-androst-1-en-3-one" should be construed to mean "A compound having the following chemical structure:



(*i.e.*, dutasteride)."

III. DISPUTED CONSTRUCTIONS

A. Term 1 - "solvate thereof"[6]

Claim Term	GSK's Proposed Construction	Defendants' Proposed Construction
"solvate thereof" (claims 1-5, '467 Patent; claims 1-4,	A complex formed by dutasteride with a solvent in which dutasteride is reacted or from which it is precipitated or crystallized.	A complex of dutasteride molecules and solvent molecules, wherein the complex is in crystalline form such that the dutasteride molecules and

[5] The term "17β-N-(2,5-bis(Trifluoromethyl)) phenylcarbamoyl-4-aza-5α-androst-1-en-3-one" appears in asserted claims 1-5 of the '467 Patent and asserted claims 1-4 of the '976 Patent.

[6] The term "solvate thereof" is a limitation of all asserted claims.

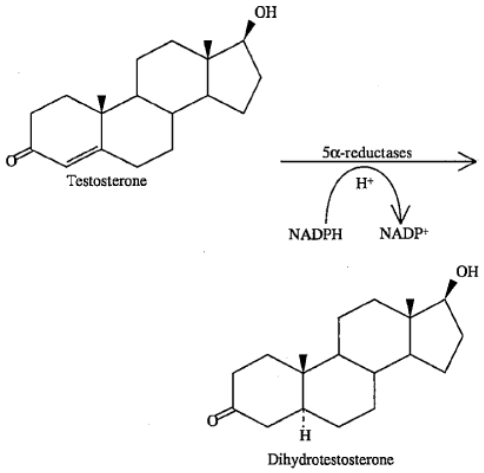
’976 Patent)		solvent molecules are part of the same crystal structure.
“solvate thereof” (claim 10, ’427 Patent)	A complex formed by a compound of formula (I) (as defined in claim 1) with a solvent in which that compound is reacted or from which it is precipitated or crystallized.	A complex of molecules of a compound of formula (IB) and solvent molecules, wherein the complex is in crystalline form such that the molecules of a compound of formula (IB) and solvent molecules are part of the same crystal structure.

1. GSK’s Opening Position

a. <u>The Patents</u>

(i) <u>The Background of the Invention</u>

Androgens, such as testosterone and dihydrotestosterone (“DHT”), are responsible for many physiological functions in humans. *See, e.g.,* Joint Claim Construction Statement (“JCCS”) Exhibit B, ’467 Patent at col. 1:15-16. As shown in the Patents, DHT is created when 5-α reductase enzymes catalyze the conversion of testosterone into DHT:



See, e.g., id., ’467 Patent at col. 1:27-49. Chemical compounds that inhibit 5-α reductase (“5AR”) prevent this conversion and the formation of DHT. These compounds are known as 5-α reductase inhibitors or 5AR inhibitors.

DHT plays an essential role in the development of the prostate. *See, e.g., id.,* '467 Patent at col. 1:50-55. However, DHT can also cause undesired androgen action resulting in androgen responsive or mediated conditions, including enlarged prostate. *See, e.g., id.*, at '467 Patent at col. 1:55-60. Inhibition of 5-α reductase (and thus the conversion of testosterone to DHT) can therefore be useful in the treatment of these androgen responsive or mediated conditions. *See, e.g., id.,* '467 Patent at col. 1:61-66 (referring to androgen responsive diseases such as benign prostatic hyperplasia, prostate cancer, acne, male pattern baldness and hirsutism).

In the early 1990s, researchers discovered that two isozymes[7] of 5-α reductase play a role in the conversion of testosterone to DHT. *See, e.g., id.,* '467 Patent at col. 1:66-2:3. These isozymes are known as "Type 1" and "Type 2" 5-α reductase. *See, e.g., id.,* '467 Patent at col. 1:61-2:5. At the time of the invention, it was anticipated that inhibitors of Type 1 and Type 2 5-α reductase could be useful in the treatment of androgen responsive or mediated conditions, including benign and malignant diseases of the prostate. *See, e.g., id.,* '467 Patent at col. 1:61-2:12; col. 10:18-21.

Given their therapeutic potential, 5-α reductase inhibitors were the focus of active research worldwide. *See, e.g.*, JCCS Exhibit C, '976 Patent at col. 2:22-25. Scientists specifically sought to develop inhibitors of Type 1 and Type 2 5-α reductase. *See, e.g.*, JCCS Exhibit B, '467 Patent at col. 2:46-3:3. In addition, scientists recognized that "optimal inhibitors of type 1 and type 2" 5AR also had to be "selective versus human adrenal 3βHSD," which plays a critical role in the body's production of steroids. *See, e.g., id.,* '467 Patent at col. 3:1-2. This was because unwanted inhibition of 3βHSD by a non-selective 5-α reductase inhibitor known as "4-MA" had been shown to cause liver toxicity. *See, e.g., id.,* '467 Patent at col. 2:46-3:7.

[7] Isozymes are enzymes that are related to each other and catalyze the same reaction (here, the conversion of testosterone to DHT), but have different chemical structures.

(ii) Summary of the Invention

The Patents describe "surprisingly potent and selective" ***dual*** inhibitors of Type 1 and Type 2 human 5-α reductase. *See, e.g.*, JCCS Exhibit B, '467 Patent, col. 1:8-11; JCCS Exhibit D, '427 Patent, col. 1:9-12. More specifically, data included in Table 1 of the '467 and '976 Patents shows that very small amounts of dutasteride (*i.e.*, less than 1 nanomolar) inhibited both Type 1 and Type 2 5-α reductase:

TABLE 1

5α-Reductase (5αR) and Human Adrenal 3β-Hydroxy-Δ^5-Steroid Dehydrogenase/3-Keto-Δ^5-Steroid Isomerase (3βHSD) In Vitro Inhibitory Activity		
IC_{50} Human Type 1 5AR	IC_{50} Human Type 2 5AR	K_i Human Adrenal 3BHSD
<1 nM	<1 nM	>1000 nM

See, e.g., *id.*, '467 Patent at col. 9, Table 1. Data in Table 1 also show that even very large amounts of dutasteride (*i.e.*, greater than 1000 nanomolar) did not inhibit 3βHSD.[8] *See, e.g.*, *id.*, '467 Patent at col. 9, Table 1.

(iii) The Asserted Claims

Claims 1-5 of the '467 Patent, which issued on October 15, 1996, relate to various forms of dutasteride, including pharmaceutically acceptable solvates and pharmaceutical formulations. Claims 1-4 of the '976 Patent, which issued on December 8, 1998, relate to methods of treating androgen responsive or mediated conditions (such as BPH) with dutasteride or its pharmaceutically acceptable solvates. Claim 10 of the '427 Patent, which issued on December 7,

[8] The parameter "K_i" referenced in Table 1 is a measurement of how tightly a compound binds to an isozyme. The tighter a compound binds to an isozyme, the stronger it inhibits that isozyme. High K_i concentrations indicate that a compound does not bind tightly to an isozyme, and thus is not a strong inhibitor of that isozyme.

1999, claims a group of sixteen compounds, including dutasteride, and their pharmaceutically acceptable solvates.[9] All of the asserted claims include dutasteride and "solvates" of dutasteride.

b. The Term "Solvate Thereof"

The parties agree that "solvates" are complexes of dutasteride molecules and solvent molecules. JCCS Exhibit A. GSK's construction, taken directly from the specification, includes any "complex formed by dutasteride with a solvent in which dutasteride is reacted or from which it is precipitated or crystallized." JCCS Exhibit A; JCCS Exhibit B, '467 Patent at col. 3:58-4:4; JCCS Exhibit C, '976 Patent at col. 4:11-18[10]; JCCS Exhibit D, '427 Patent at col. 5:4-10. In contrast, Defendants seek to limit the claimed solvates to a "crystalline form such that the dutasteride molecules and solvent molecules are part of the same crystal structure." JCCS Exhibit A. Thus, the dispute focuses on whether the claimed solvates can take any form (GSK's proposed construction) or must be crystalline (Defendants' construction).

There is no basis to import a "crystalline" limitation into the claims—the word crystalline does not appear in the claims and is inconsistent with the definition of the term "solvate" in the specification. The Court should thus adopt GSK's proposed construction.

(i) The Claims Are Not Limited to Any Specific Form of Solvate

The starting point for claim construction is the claims and their language. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc) ("[T]he claims themselves provide

[9] The '467 and '976 Patents claim dutasteride and solvates thereof. The '427 Patent claims a genus of compounds and solvates thereof, including dutasteride. Accordingly, the term "solvate thereof" in the '427 Patent modifies a different claim term (*i.e.*, a genus of compounds including dutasteride) than it does in the '467 and '976 Patents. Therefore, "solvate thereof" as used in the '427 Patent requires a slightly different construction. However, the analysis set forth herein applies equally to all of the Patents.

[10] The '467 Patent and '976 Patent have a common specification. Therefore, all cited portions of the specification of the '467 Patent also appear in the '976 Patent.

substantial guidance as to the meaning of particular claim terms."). Indeed, the language of the claims is of "paramount importance to claim construction." *E-Pass Techs., Inc. v. 3Com Corp.*, 473 F.3d 1213, 1220 (Fed. Cir. 2007); *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 2009 WL 4928029, at *5 (D. Del. Dec. 18, 2009). Here, the claims support GSK's proposed construction.

The asserted claims merely refer to "solvate[s]"; they do not contain the word "crystalline," or any other language that could be construed as limiting or restricting the claimed solvates to a particular form. Accordingly, the term "solvate thereof," as used in the Patents, includes all forms of solvates (as defined by the Patents). *See, e.g.*, *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1381 (Fed. Cir. 2009) (reversing the lower court's construction of "animal" that excluded humans where the patentee "used no words or expressions that manifestly excluded the coverage of human"); *Agfa Corp. v. Creo Prods. Inc.*, 451 F.3d 1366, 1376 (Fed. Cir. 2006) (construing the term "stack" "as 'encompassing a number of plates arranged together in an orderly fashion, regardless of the orientation (horizontal or vertical) of the collection as a whole'" instead of as "only a horizontal arrangement of plates" where claims did not recite "horizontal"). *See also Arlington Indus., Inc. v. Bridgeport Fittings, Inc.*, 632 F.3d 1246, 1253-56 (Fed. Cir. 2011) (holding that the district court "erred by importing a 'split' limitation into its constructions of 'spring metal adaptor' and 'spring steel adapter.'").

(ii) The Specifications Expressly Define The Term "Solvate"

The specifications of the Patents—which are the best guide to the meaning of a disputed term—also support GSK's proposed construction. *See Phillips*, 415 F.3d at 1314 ("[T]he specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.") (internal quotations

omitted). The inventors expressly defined the term "solvate" as a complex of an organic compound and a solvent.[11] For example, the '467 Patent states:

> Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. ***These complexes are known as "solvates".***

JCCS Exhibit B, '467 Patent at col. 3:58-4:2 (emphasis added). The '976 and '427 Patents contain a nearly identical definition. *See* JCCS Exhibit C, '976 Patent at col. 4:11-25; JCCS Exhibit D, '427 Patent at col. 5:4-17. The Federal Circuit has "frequently found that a definition set forth in the specification governs the meaning of the claims." *Sinorgchem Co. v. ITC*, 511 F.3d 1132, 1138 (Fed. Cir. 2008). Where, as here, "the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term." *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998).

The inventors' definition does not limit the claimed solvates to a particular form. To the contrary, the definition explicitly contemplates non-crystalline solvates. JCCS Exhibit B, '467 Patent at col. 3:58-4:4. In particular, the inventors describe solvates forming when organic compounds are "reacted" in a solvent, "precipitated" from a solvent, "***or*** crystallized" from a solvent. *Id.*, '467 Patent at col. 3:58-4:4 (emphasis added). The definition thus makes clear that while crystallization is *one* way to form a solvate, it is not the *only* way to form a solvate. *Id.*, '467 Patent at col. 3:59-4:1. Solvates resulting from a reaction between a compound and a solvate, or from precipitation from a solvate, are not necessarily crystalline. Limiting the

[11] In organic chemistry, a complex is "a chemical association of two or more species (as ions or molecules) joined usu[ally] by weak electrostatic bonds rather than covalent bonds." Joint Appendix Ex. 502, MERRIAM-WEBSTER'S COLLEGIATE DICTIONARY (10th ed. 1993) at 235.

claimed solvates to crystalline forms would thus run afoul of the inventors' express definition. *See, e.g.*, *Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 493 F.3d 1358, 1364 (Fed. Cir. 2007) (affirming district court's construction because "[t]o hold otherwise … would ignore the patentees' definition of the term ….").

(iii) The Specification Contemplates Solvates of Various Forms

The specification discloses examples of various forms of solvates, both crystalline and non-crystalline.

For example, the specification explicitly states that "[A] complex [of an organic compound] with water is known as a 'hydrate.'" JCCS Exhibit B, '467 Patent at col. 4:2-3. "Hydrate" is defined as a "complex" without referring to any form of hydrate (*e.g.*, liquid or solid). *See, e.g.*, *id.*, '467 Patent at col. 4:2-3. The Patents thus define a "hydrate" without suggesting that hydrates must be crystalline. This is consistent with an unrestricted definition of "solvate." *See, e.g.*, *id.*, '467 Patent at col. 4:3-4.

Similarly, the specification discloses that solvates "can exist in more than one crystalline form." *See id.*, '467 Patent at col. 4:5-9. The specification thus recognizes that various crystal solvate forms are "within the scope of the present invention." *Id.*, '467 Patent at col. 4:5-11. This language (consistent with the definition of solvate) is broadly inclusive and does not restrict the claimed solvates to any particular crystal forms. *See, e.g., Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002) (refusing to limit construction of "clip" to "a single pair of legs" because "[n]either the specification nor prosecution history includes an expression of manifest exclusion or restriction demonstrating an intent to limit 'clip'" as such).

Moreover, the preferred embodiments described in the specification include liquid formulations, further demonstrating that the claimed solvates should not be limited to solid,

crystalline forms. Preferred orally administered formulations "may be presented as … a suspension or solution in an ***aqueous*** liquid or non-aqueous liquid, e.g., a syrup, an elixir, an emulsion or a draught." *Id.*, '467 Patent at col. 11:23-29 (emphasis added); JCCS Exhibit C, '976 Patent at col. 11:34-40; JCCS Exhibit D, '427 Patent at col. 19:52-58. *See also* JCCS Exhibit B, '467 Patent at col. 11:39-45; JCCS Exhibit C, '976 Patent at col. 11:51-57; JCCS Exhibit D, '427 Patent at col. 20:1-7. Preferred formulations for parenteral administration "conveniently comprise a sterile ***aqueous*** preparation[.]" *Id.* (emphasis added), '467 Patent at col. 11:51-54; JCCS Exhibit C, '976 Patent at col. 11:62-65; JCCS Exhibit D, '427 Patent at col. 20:12-15. *See also* '467 Patent at col. 15:11-25; JCCS Exhibit C, '976 Patent at col. 15:27-41; JCCS Exhibit D, '427 Patent at col. 32:54-67.

GSK's proposed construction of "solvate thereof" properly includes all of these preferred embodiments. *See Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1290 (Fed. Cir. 2010) ("A claim construction that excludes the preferred embodiment 'is rarely, if ever, correct and would require highly persuasive evidentiary support.'") (citation omitted); *see also Burke Inc. v. Bruno Independent Living Aids, Inc.*, 183 F.3d 1334, 1341 (Fed. Cir. 1999) ("The district court's claim interpretation … would exclude the preferred embodiment described in the specification and, thus, cannot be sustained.").

c. <u>The Prosecution History Supports GSK's Construction</u>

The prosecution history supports GSK's proposed construction of "solvate thereof." *Phillips*, 415 F.3d at 1317 ("In addition to consulting the specification, we have held that a court 'should also consider the patent's prosecution history, if it is in evidence.'") (citations omitted). During prosecution of the '467 Patent, the Examiner asked, "[w]hat solvents are intended in 'solvates'? Acetone? Water? Isopropanol? DMSO? DMF? (par 2) specification provides no guidance (par 1)." JCCS Exhibit E, November 24, 1995 Office Action at 6 (AN0005156). In

response, the Applicants stated that "[t]his term [solvates] is well understood by those in the art and is explained in the specification." JCCS Exhibit E, Amendment and Response dated February 22, 1996 at 7 (AN0005148). The Applicants also referred the Examiner to the definition of "solvate" in the application that led to the '467 Patent:

> Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of compound (I) are within the scope of the invention.

JCCS Exhibit E, U.S. Patent Application No. 08/405,120 ("the '120 Application") at page 4, lines 32-36 (AN0005780). At no point did the Applicants argue that the claimed solvates are limited to a particular form, such as solid or crystalline. Ultimately, the Examiner allowed the claims without requiring further clarification of the claim term "solvate thereof." JCCS Exhibit E, May 23, 1996 Notice of Allowability (AN0005137).

In sum, GSK's proposed construction of "solvate thereof" is firmly grounded in the intrinsic evidence—the claims, specification, and file history. Most notably, GSK's construction accords with the inventors' definition of "solvate" in the specification and the preferred embodiments.

2. Defendants' Opening Position

a. <u>Introduction</u>

Defendants' proposed construction of "solvate thereof" comports with the most basic principle of claim construction – terms in a claim are given their plain and ordinary meaning to one skilled in the art absent a clear definition in the patent demonstrating that the inventor intended a different meaning. Far from defining the term "solvate," the specifications, claims, and prosecution histories of the Patents all support the application of the plain and ordinary

meaning to one of skill in the art. The ordinary meaning of "solvate" is "a complex of dutasteride molecules and solvent molecules wherein the complex is in crystalline form such that the dutasteride molecules and solvent molecules are part of the same crystal structure."[12]

Consistent with this well-accepted meaning, every court confronted with this claim term has recognized that a solvate must be in crystalline form, and every learned treatise of record reflects that common understanding. Indeed, GSK's own expert, Dr. Byrn, in his extensive literature on solvates, has consistently used the term "solvate" to refer to crystalline forms containing solvent molecules within the crystal structure. That the inventors intended this well-accepted meaning of "solvate" to control is clear from the specifications and prosecution histories, which expressly state that the meaning of the term "solvate" was "appreciated by" and "well understood by those skilled in the art." The inventors confirmed this understanding when they recently testified that they never intended to impart any special meaning to the claim term solvate.

Despite this well-accepted meaning and the intrinsic evidence, GSK argues for a broader construction in an attempt to expand the definition of solvate beyond a crystalline form and encompass any liquid suspension or solution containing dutasteride. GSK's construction, however, would not have comported with the understanding of one of ordinary skill in the art at the times the Patents were filed. To one of skill in the relevant art at that time, solvates, suspensions, and solutions were (and still are) three distinct things. Dutasteride in suspension or

[12] Claims 1–5 of the '467 patent and Claims 1–4 of the '976 patent are specifically directed to the compound dutasteride and solvates thereof. Claim 10 of the '427 patent is directed more broadly to a genus of compounds of the formula (IB), which includes dutasteride. Defendants' proposed construction of "solvate thereof" in Claim 10 of the '427 Patent is "a complex of molecules of a compound of formula (IB) and solvent molecules, wherein the complex is in crystalline form such that the molecules of a compound of formula (IB) and solvent molecules are part of the same crystal structure." The issues concerning these two definitions for purposes of claim construction are the same.

solution is not a solvate of dutasteride, and one of ordinary skill would not have referred to it as such.

Recognizing that its construction is not the ordinary meaning of solvate, GSK cites no scientific support, but instead argues that the specifications provide an "express definition" of solvate that somehow encompasses liquid suspensions and solutions. GSK adopts this position because the Patents fail to provide adequate written description support for or enable the claims under the ordinary meaning of solvate. Irrespective of GSK's motivation, there is no basis to deviate from the ordinary meaning.

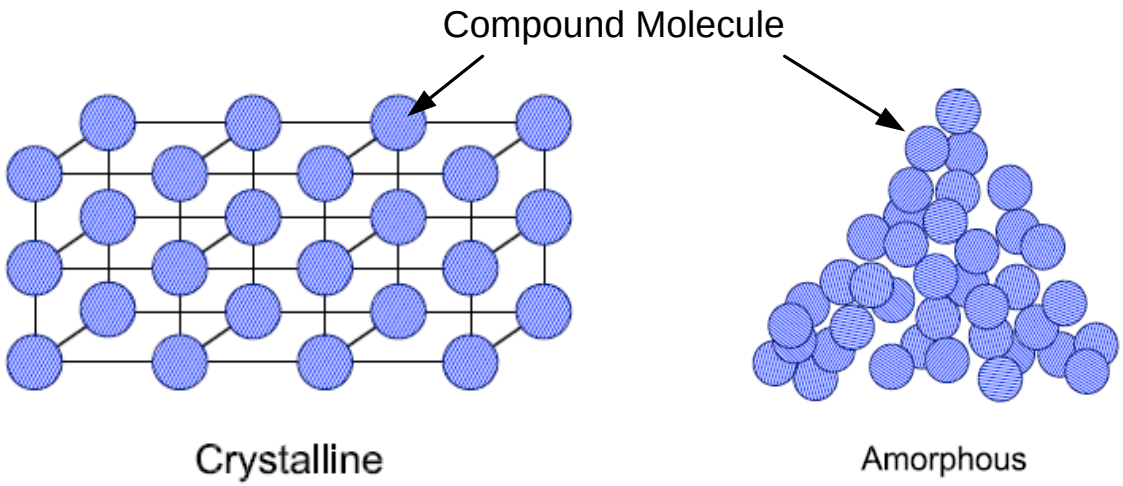
b. Technical Background

The asserted claims are directed to a class of compounds known as 5α-reductase inhibitors, including dutasteride "or a pharmaceutically acceptable solvate thereof," formulations containing such compounds, and methods of treating androgen-responsive conditions including benign prostatic hyperplasia ("BPH," *i.e.* enlarged prostate) with such compounds. JCCS Ex. B ('467 Patent, Claims 1-5); JCCS Ex. D ('427 Patent, Claim 10); JCCS Ex. C ('976 Patent, Claims 1-4). Some background on the relevant technology related to active drug compounds, solvates, and their development may prove useful to the Court in construing the disputed claim terms.[13]

A compound can generally exist in one of three different states: solid, liquid, or gas. When a compound is in the solid state, the molecules of the compound can be arranged in a repeating, three-dimensional ordered manner (called a crystalline form) or they can be arranged

[13] This background is set forth in more detail in the expert reports of Robin D. Rogers, Ph.D. *See* Ex. 500, *e.g.*, ¶¶20–46 (Opening Expert Report of Robin D. Rogers, Ph.D.); Ex. 501 (Supplemental Expert Report of Robin D. Rogers, Ph.D.). Dr. Rogers cites to numerous literature references in explaining the background of the technology.

randomly (called an amorphous form). The figures below schematically illustrate the arrangement of molecules in crystalline and amorphous forms:



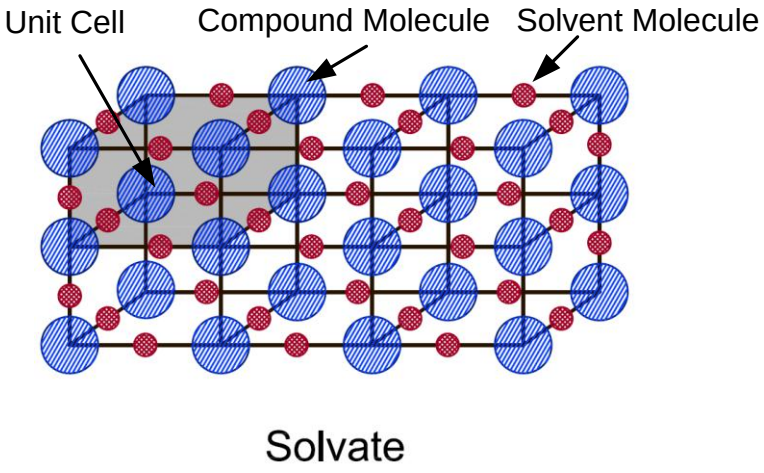
Ex. 500, ¶21.

How the molecules are arranged (either in crystalline or amorphous form) often depends on the conditions under which the compound is isolated (*e.g.*, removed from solution). Conditions that may affect the arrangement of molecules in their solid state include, among others, (1) drying time and temperature, (2) the solvent(s) from which the compound is isolated, (3) the ambient pressure during isolation, and (4) the rate of temperature and pressure change. Ex. 500, ¶22 (citing Ex. 300, Haleblian, *Characterization of Habits & Crystalline Modification of Solids & Their Pharmaceutical Applications*, 64 (8) J. Pharm. Sci. 1269, 1270–1 (1975)).

In one arrangement, solvent molecules can become associated with compound molecules and comprise part of a three-dimensional crystal structure. This complex, *i.e.*, the crystalline material, is called a solvate. Ex. 500, ¶27. When the solvent is water, the resulting solvate is called a "hydrate." Ex. 500, ¶33 (citing Ex. 300, Haleblian at 1276).

The figure below graphically depicts an example of a solvate, showing the solvent molecules as part of the crystalline structure. The smallest representative unit of a crystal is

referred to as a "unit cell," which is repeated within the crystalline network or "crystal lattice." The unit cell is the simplest three dimensional repeating unit making up the crystal lattice.



Ex. 500, ¶27.

Solvates may be formed, for example, when a compound is isolated from a solution, which is a liquid mixture of a solid compound (called the solute) dissolved in a liquid (called a solvent).[14] Ex. 501, ¶28. As explained in the literature:

> During crystallization from a solution, crystals separating may consist of a pure component or be a molecular compound. Molecular compounds may contain two or more constituents that have completely satisfied classical "valence forces" and are crystallized together as a new single crystalline entity. **Solvates are molecular complexes that have incorporated the crystallizing solvent molecule in their lattice**.

Ex. 300 (Haleblian at 1276) (emphasis added).

Solvate formation is inherently unpredictable. Ex. 500, ¶¶35-40 (citing, *e.g.*, Ex. 309, Byrn *et al., Solid-State Chemistry of Drugs* at 234 (2nd ed. 1999)). Determining whether a

[14] A solute is the material dissolved in the solution, while a solvent is the material that does the dissolving. An example is a solution of table salt in water, the salt (*i.e.*, the solute) dissolves in the water (*i.e.*, the solvent). A suspension is similar, but in that instance the solid material does not dissolve in the liquid, but rather is suspended (or floating) in the liquid.

solvate of a particular compound exists is an arduous trial-and-error process, the results of which can only be confirmed through analytical testing, including, for example, X-ray diffraction ("XRD"), thermogravimetric analysis ("TGA"), and differential scanning calorimetry ("DSC"). Ex. 500, ¶¶44-46.

c. The Term "Solvate Thereof"

Defendants ask the Court to adopt the ordinary meaning of "solvate thereof," which is "a complex of dutasteride molecules and solvent molecules wherein the complex is in crystalline form such that the dutasteride molecules and solvent molecules are part of the same crystal structure." This definition, which is consistent with countless learned treatises and the understanding of experts in the field (including GSK's experts), requires a crystalline form in order to be a solvate. On the other hand, GSK argues for a purported "express definition" that includes not only additional solid-state forms, but also chemical entities that no person of ordinary skill at the relevant time would have referred to as a solvate.

GSK has characterized the claim construction dispute among the parties as "whether the claimed solvates can take any form (GSK's proposed construction) or must be crystalline (Defendants' construction)." GSK Section III.A.1.b. Defendants disagree. The fundamental question here is whether the term "solvate" should be given its ordinary meaning, or whether something in the Patents requires a special meaning that broadens the term "solvate" to include additional solid-state forms as well as chemical entities that no person of ordinary skill at the relevant time would have referred to as a solvate.

Nothing in the Patents or their prosecution histories supports such a broad definition of the term solvate. In seeking to broadly redefine solvate, GSK has improperly ignored the ordinary meaning of the term. Absent a clear intent within the Patents to the contrary, claim terms should be given their ordinary and customary meaning, which is "the meaning that the

term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*).

Here, the plain language of the patent claims and specifications not only fails to assign a unique meaning to the term "solvate thereof," it adopts the ordinary meaning. It is this ordinary meaning that the Court should adopt, *i.e.*, "a complex of dutasteride molecules and solvent molecules wherein the complex is in crystalline form such that the dutasteride molecules and solvent molecules are part of the same crystal structure."

(i) The Specifications Provide That the Ordinary Meaning of Solvate Applies

In this case, the specifications support application of this ordinary meaning. None of the specifications expressly define or ascribe any special meaning to the term "solvate thereof." *See Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012) ("To act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term other than its plain and ordinary meaning."). Rather, the specifications introduce solvates as something that "[t]hose skilled in the art of organic chemistry will appreciate." JCCS Ex. B ('467, 3:58–4:12). Specifically, the specifications mention solvates only in the following two paragraphs:

> **Those skilled in the art of organic chemistry will appreciate** that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates." For example, a complex with water is known as a "hydrate." Solvates of compound (I) are within the scope of the invention.
>
> **It will also be appreciated by those skilled in organic chemistry** that many organic compounds can exist in more than one crystalline form. For example, **crystalline form may vary from solvate to solvate**. Thus, **all crystalline forms** of the compounds of formula (I) **or the pharmaceutically acceptable solvates thereof are within the scope of the present invention**.

JCCS Ex. B ('467, 3:58–4:12); JCCS Ex. D ('427, 5:4–17); JCCS Ex. C ('976, 4:11–26) (emphases added).[15] Notably, the specifications use the phrase "known as" prior to using the terms "solvate" and "hydrate," indicating that the named inventors were referring to the ordinary meaning to those of skill in the art at the time (*i.e.*, what was already "known")—not attempting to re-define those terms in a manner that would depart from the ordinary meaning. Indeed, these two paragraphs indicate that a person of ordinary skill in the art would appreciate the meaning of solvate. In other words, the patents refer to the meaning of solvate as ordinarily understood in the art at the relevant time, *i.e.*, complexes in crystalline form. Ex. 500, ¶95. Thus, the Patents do not "expressly define" the term solvate, but instead adopt the term's ordinary meaning.

The first paragraph describes a general chemical process that would be known to someone of ordinary skill in organic chemistry. The process of making and isolating an organic compound often involves many reaction, precipitation, and/or crystallization steps with various solvents used in each step. The paragraph explains that organic compounds can form complexes with solvents, and the solvents that are captured in the solvate can come from any of the solvents used for reaction, precipitation, or crystallization. Specifically, it describes three types of solvents that can complex with the organic compounds: a reaction solvent, a precipitation solvent, or a crystallization solvent, or any combination thereof. Ex. 500, ¶102; Ex. 501, ¶20. Any one of these solvents could become an integral part of the resulting crystalline structure along with the organic compound (*i.e.*, dutasteride).

[15] The inventors did not include these two paragraphs in the earliest filed application in September 1993 and instead added them later in their continuation-in-part application filed in September 1994.

The second paragraph goes on to explain that those skilled in organic chemistry will also appreciate that the "crystalline form may vary from solvate to solvate." Not surprisingly, the second paragraph recognizes that solvates are in crystalline form. It recognizes no other form.

These two paragraphs of the specifications, when read together, show that the inventors intended to apply the ordinary meaning of solvate, which they understood to be a complex in crystalline form where the solvent molecules (whether they come from a reaction, precipitation, and/or crystallization step) and compound molecules (*e.g.* dutasteride) are part of the crystalline structure. Nothing in the specifications suggests that the inventors intended any meaning of solvate other than this well-understood, generally-accepted meaning. In fact, these two paragraphs affirmatively state that the inventors intended to use the plain and ordinary meaning of solvate.

(ii) The Prosecution History Confirms the Ordinary Meaning of Solvate Applies

The prosecution history further supports application of the ordinary meaning of solvate. During prosecution, the Examiner rejected all of the claims under 35 U.S.C. § 112, because of the term "solvates." JCCS Ex. E (Nov. 24, 1995 Office Action at 6, ¶16) (AN0005156). The inventors responded by telling the Patent Office that the term solvate is "well understood by those skilled in the art." JCCS Ex. E (Feb. 22, 1996 Response at 7) (AN0005148). GSK should be held to that representation. *See Am. Piledriving Equip., Inc. v. Geoquip, Inc.*, 637 F.3d 1324, 1336 (Fed. Cir. 2011) (holding that patentee's representations to the Patent Office inform the proper construction of a claim term and rejecting patentee's asserted claim construction where patentee's representations conflicted with its construction).

(iii) Precedent [redacted] Support Applying the Ordinary Meaning of Solvate

District courts have applied the ordinary meaning in cases where the intrinsic record included language similar to that used here. For example, one district court applied the ordinary meaning where the specification referred to the disputed term as being "well known to those skilled in the art." *Accolade Sys. v. Citrix Sys.*, 634 F. Supp. 2d 738, 754 (E.D. Tex. 2009). Another district court applied the ordinary meaning where the specification stated that the term was "understood by those skilled in the art." *Brocade Commc'ns Sys., Inc. v. A10 Networks, Inc.*, No. 10-CV-03428, 2012 WL 33251 at *9, 2012 U.S. Dist. LEXIS 2024 (N.D. Cal. Jan. 6, 2012).

[redacted] In prior litigation involving the same Patents and the same drug,[16] GSK's expert testified that the Patents did not provide an express definition of the term solvate, but rather, merely used the term as it would have been understood by a person of ordinary skill.

[16] *See SmithKline Beecham Corp. v. Barr Labs., Inc.*, C.A. No. 08-112(SLR) (D. Del.).

Ex. 314p (Davies Tr. at 76:8–77:19). Even GSK's new expert in this litigation had to admit that the Patents are applying the ordinary meaning of the term solvate. Ex. 387p (Byrn Tr. at 188:3-189:11).

Sinorgchem Co. v. International Trade Commission, 511 F.3d 1132, 1134 (Fed. Cir. 2007), cited by GSK, does not support application of an express definition over the ordinary meaning of the term solvate in this case. In *Sinorgchem*, the parties had agreed that the disputed term, "controlled amount," did not have any well-accepted meaning in the field of chemistry. 511 F.3d at 1136. That is not the case here. Moreover, in *Sinorgchem*, the specification expressly defined the term with clear definitional language, including the use of the definitional term "is." *Id.* ("A 'controlled amount' of protic material ***is*** an amount up to that which inhibits the reaction of aniline with nitrobenzene . . . .") (emphasis added). In the present case, the specifications contain no such definitional terminology. Rather, the specifications use the phrase "known as" to refer to the ordinary meaning of the term and otherwise indicate that "solvate" is a term that will be appreciated by those of skill in the art. Additionally, the prosecution histories state that the term solvate was well understood in the art. As such, the Patents have not expressly defined the term "solvate thereof" and the ordinary meaning should control.

(iv) The Ordinary Meaning of Solvate Refers to a Crystalline Form

A person of ordinary skill in 1993,[17] upon reading the Patents, would have understood "solvate thereof" to mean "a complex of dutasteride molecules and solvent molecules, wherein

[17] Claim terms should be construed at the time the inventors filed their earliest patent application to which they are entitled to claim priority. Here, the inventors filed their first application in September 1993, so that is the earliest possible priority date. However, Defendants contend that GSK is not entitled to that priority date, because the inventors never even mentioned solvates in the September 1993 application, let alone described or enabled them. Whether the priority is ultimately determined to be 1993 or a

the complex is in crystalline form such that the dutasteride molecules and solvent molecules are part of the same crystal structure." Ex. 500, ¶17.

At the time of the invention, the literature defined solvates as crystalline forms that contain solvent molecules in the crystal structure. For instance, in 1994, outside of the litigation context, GSK's own expert, Dr. Byrn, defined "solvates" as "forms containing solvent molecules within the crystal structure." Ex. 88 at 1148. Such a definition was nothing new to Dr. Byrn, who defined "solvate" in the glossary of his 1982 book as: "A crystal form that contains . . . solvent." Ex. 364p (Byrn, Solid-State Chemistry of Drugs at 339 (1982)); *see also* Ex. 364p at 7 ("Crystals that contain solvent of crystallization are termed *solvates*."). Many other literature references similarly defined solvates. *See, e.g.,* Ex. 300 at 1276 ("Solvates are molecular complexes that have incorporated the crystallizing solvent molecule in their lattice."); Ex. 306 (Khankari et al., *Pharmaceutical Hydrates*, Thermochimica Acta 248 (1995) 61, 62) ("With some crystalline solids, solvent in the surrounding medium may become incorporated into the crystal lattice. . . . These molecular adducts are termed solvates. Hydrates are formed when water is the solvent of crystallization.").

Since the time of the invention, the literature, including a paper authored by a former GSK chemist who performed solid-state testing on dutasteride, has continued to define solvates as crystalline forms that contain solvent molecules in the crystal structure. *See, e.g.,* Ex. 89 (Jozwiakowski *et al., Water-Insoluble Drug Formulation* at 534 (Rong Liu ed., 2008) ("If the crystals contain solvent molecules within the lattice structure in defined locations . . ., these are referred to as *solvates* (*hydrates* if the solvent is water).")) (emphasis added). Consistent with

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later date (*i.e.*, 1994) would not change the ordinary meaning of the term solvate. Indeed, GSK's expert, Dr. Byrn, testified that the term "solvate" is not used any differently today than it was in 1993. Ex. 387p (Byrn Tr. 27:4-6).

this definition, in 2002, GSK's expert, Dr. Byrn, filed a patent application that states that a solvate or hydrate "is defined by its crystal structure and properties." Ex. 358 (U.S. Patent No. 6,605,729 at 23:35–36).

Courts have likewise understood solvates to be in crystalline form. For example, in discussing the background of the technology in a case involving a GSK patent to a particular hydrate, a Federal Circuit judge explained:

> A common type of pseudopolymorph is a *solvate,* which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure. When the trapped and bonded solvent is water, the solvate is called a *hydrate.*

SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1348 (Fed. Cir. 2005) (Gajarsa, J., concurring) (emphasis added). In that case, GSK provided the following definition of hydrate to the appellate court:

> A crystal formed during the crystallization process may contain bound molecules of water arranged in a regular way, in which case the crystal formed is termed a "hydrate."

Ex. 388 (SmithKline Beecham Opening Appeal Brief at 12). GSK also presented Dr. Byrn as its expert in that case; however, Dr. Byrn never used the term solvate to refer to anything other than a crystalline form. Ex. 387p (Byrn Tr. 150:15-22). Additionally, this Court recently explained that "[h]ydrates occur when water molecules are arranged among drug molecules in a crystal structure." *Cephalon Inc. v. Watson Pharm., Inc*., 769 F. Supp. 2d 761, 766 (D. Del. 2011).

Accordingly, the ordinary meaning of "solvate," based on the literature in the art (including that authored by both GSK's expert and own scientist) and the court opinions that have addressed the term, is a complex in crystalline form. Specifically, the ordinary meaning of "solvate" here is "a complex of dutasteride molecules and solvent molecules wherein the

complex is in crystalline form such that the dutasteride molecules and solvent molecules are part of the same crystal structure."

(v) GSK's Construction Is Overly Broad and Inconsistent with the Patent Specifications

GSK argues for a definition of solvate that would extend well beyond the claim terms, as they were understood by one of ordinary skill in the art in the 1990s. GSK's definition would extend to controversial and new ideas about solvates that were advanced more than ten years after patent filing and are not even well accepted today.[18] At the time of patenting, solvates were well-understood to be exclusively in crystalline form. Now, reaching beyond the well-known use of the term solvate, GSK seeks to capture within its definition any mixture of a compound and a solvent, including any suspension or solution where no crystalline structure is formed between the compound and the solvent. *See* GSK Section III.A.1.b(iii) (arguing that the definition of solvate be broad enough to include liquid formulations, such as suspensions and solutions).

[18] The idea that pharmaceutical solvates could exist as an amorphous solid or as a liquid is somewhat new and controversial. For example, in 2004, chemists at the pharmaceutical company Abbott referred to an "amorphous hydrate." The literature criticized this label as "meaningless." Ex. 375 (Cabri et al., *Polymorphisms and Patent, Market, and Legal Battles: Cefdinir Case Study*, 11 Organic Process Research & Development 64, 68 (2007)). Other chemists, including Defendants' expert, have recently labeled certain ionic liquid compositions as solvates. Ex. 301 (U.S. Patent App. Pub. No. 2007/0093462 to Rogers et al. at [0083]). But, in doing so, the chemists specifically explained that the ionic liquid compositions that could be called a solvate were different than a liquid solution, which is not a solvate. *Id.* Regardless, this is a recent development that could not have informed the understanding of one of ordinary skill in the art in 1993. Indeed, the Patents make no mention of these rare and controversial amorphous solids or ionic liquid compositions. Rather, consistent with the early-1990s literature, the Patents state that those of skill will appreciate that "crystalline form may vary from solvate to solvate," meaning that all solvates are in crystalline form. JCCS Ex. B ('467, 4:7–8); JCCS Ex. D ('427, 5:13–14); JCCS Ex. C ('976, 4:21–22).

In other words, it is GSK's position that any time dutasteride is dissolved in, or in contact with, a liquid, such as a drop of water, a solvate exists. That is an extreme position that eviscerates the ordinary meaning of solvate. To be clear, one of ordinary skill would not have called dutasteride in suspension or in solution a solvate. Ex. 501 ¶70. In fact, solvates are formed by crystallizing a compound out of a solution containing the compound and the solvent. Ex. 300 at 1276. It would be nonsensical to refer to both the compound in solution and the resulting crystalline compound as solvates.

In an attempt to support its argument, GSK argues that its proposed construction of solvate is correct because it would include certain "preferred embodiments" that are liquid formulations, whereas Defendants' proposed constructions would allegedly exclude them. *See* GSK Section III.A.1.b(iii). That argument is misleading, because those embodiments do not even relate to embodiments of solvates as understood by a person of skill in the art. Rather, they relate to ***pharmaceutical formulations*** that contain the compound dutasteride as the active ingredient "together with a pharmaceutically acceptable carrier." JCCS Ex. B ('467, 10:63–12:7). The Patents explain that the formulations are prepared by combining the active compound with various inactive ingredients, such as a liquid carrier or a solid carrier, to create something that can be administered to a patient, *e.g.*, tablet, capsule, injection, patch, etc. *Id.* at 11:18–22.

The original patent application to which the Patents claim priority included the ***exact*** liquid formulation embodiments now relied upon by GSK. JCCS Ex. H ('280 Original Appl. at 12:30–34; 13:5–10; 13:15–19). Tellingly, neither the specification nor the claims of that application even contained the word solvate. *See* JCCS Ex. H. Indeed, the inventors first added the two paragraphs mentioning solvates and claims directed to solvates in a later-filed application. JCCS Ex. I ('530 PCT App. at 4:24–34).

Moreover, the pharmaceutical formulations containing the claimed compounds or solvates thereof ***are*** covered by the asserted claims, regardless of the construction of solvate. The claims cover dutasteride ***or*** a pharmaceutically acceptable solvate thereof. Thus, to the extent the specifications describe embodiments that are liquid formulations of dutasteride, they are covered by the asserted claims independent from the solvate. *See, e.g.*, JCCS Ex. B ('467 Patent at Claim 2). The claim construction canon that a patent claim should be construed to encompass at least one embodiment, if possible, does not mean or even imply that every claim term must be construed to encompass every disclosed embodiment. *See Sinorgchem*, 511 F.3d at 1138.

In sum, the ordinary meaning of solvate controls the claim construction of "solvate thereof." As the Patents explain and the inventors acknowledged both during prosecution and in recent testimony, the inventors did not expressly define solvate in the specifications. Thus, this Court should reject GSK's attempt to expand the definition of solvate beyond its ordinary meaning to include suspensions and solutions.

d. <u>The Only Issue Before The Court Is Claim Construction</u>

GSK's Opening Position on "solvate thereof" contains an extensive discussion of its view on the "background of the invention" and its version of the "summary of the invention." *See* Section III.A.1.a(i) & (ii). GSK's discussion includes numerous statements that are relevant, if at all, only to some of the obviousness and utility issues that may arise later in this case. Defendants disagree with GSK's characterization of the facts and claims. However, because this "background" is not relevant to the issue of claim construction, Defendants reserve the right to respond at the appropriate time.

The issues that may be affected by this Court's claim construction, but which are not presently before the Court on this briefing, are Defendants' assertions that the patents are invalid

due to lack of sufficient written description and enablement. Under the patent law, the patent specification must contain a written description of the invention and it must enable one of ordinary skill to make the invention. 35 U.S.C. § 112. Defendants contend that the Patents lack any, let alone sufficient, written description of "pharmaceutically acceptable solvates" of dutasteride or any other compound. Defendants also contend that the Patents fail to enable any "pharmaceutically acceptable solvates" of dutasteride or any other compound. The Patents do not contain a single example of a solvate of dutasteride or of any other compound. Nor do they explain how to make any solvate of such compounds. Rather, they contain only two paragraphs that refer to solvates in the abstract without disclosing any specific solvate of dutasteride, much less test results sufficient to show that the inventors actually invented a solvate of dutasteride or of any other compound, or any direction on how to obtain any specific solvate of dutasteride or of any other compound. Thus, at the appropriate time, Defendants intend to prove that the Patents are invalid under Section 112.

3. GSK's Reply Position on "Solvate Thereof"

Defendants' proposed construction of "solvate thereof" is not only inconsistent with the express definition in the patent specification, but also rests almost exclusively on an unreliable assortment of extrinsic evidence. In particular, Defendants' purported "plain and ordinary meaning" derives not from any single, authoritative source, but from their own expert reports, cherry-picked quotes from the inventors' depositions, references to the writings of GSK's expert, and cases involving unrelated patents. As will be demonstrated more fully below, Defendants' selective and misleading presentation aptly illustrates why courts give little weight to extrinsic evidence. *Phillips*, 415 F.3d at 1318 (discussing flaws of extrinsic evidence and noting that "[i]n the course of litigation, each party will naturally choose the pieces of extrinsic evidence most

favorable to its cause, leaving the court with the considerable task of filtering the useful extrinsic evidence from the fluff.").

Here, the explicit definition of "solvates" in the patent specification eliminates any need to resort to extrinsic evidence in this case. *See Sinorgchem Co. v. ITC*, 511 F.3d 1132, 1138 (Fed. Cir. 2007) (recognizing that "a definition set forth in the specification [frequently] governs the meaning of the claims"); *Phillips*, 415 F.3d at 1312-17 (recognizing that the specification usually is dispositive in claim construction); *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998) (where, as here, "the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term.").

a. The Intrinsic Evidence Is Clear: Solvates are "Complexes"

(i) The Specification Expressly Defines the Term "Solvates"

The specifications of the Patents expressly define "solvates" as "complexes [of organic compounds] with solvents in which they are reacted or from which they are precipitated or crystallized." *See, e.g.*, JCCS Exhibit B, '467 Patent at col. 3:58-4:2. This definition (unlike Defendants' proposed construction) does not specify that the solvates must be crystalline. Thus, the definition includes any complex of dutasteride and a solvent, regardless of the form. There is no reason to import an additional limitation requiring that the solvate be a "crystalline" solvate. *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004); *see also E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988) ("Where a specification does not *require* a limitation, that limitation should not be read from the specification into the claims." (internal quotations and citations omitted) (emphasis in original)).

Defendants' contention that there is no express definition of the term "solvates" in the Patents is difficult to reconcile with the plain language of the specification. For example, Defendants appear to contend that the phrase "known as" is not consistent with an express definition. (*See supra* Defendants' Opening Position at III.A.2.c(i).) However, the phrase "*[t]hese complexes are known as 'solvates'*", placed directly after a description of such complexes, would be recognized by a person of ordinary skill in the art (and, indeed, any English speaker) as an express definition. This is particularly clear from the quotation marks around the word "solvates," and the use of the demonstrative adjective "*these*" to refer back to the immediately preceding description of complexes between compounds and solvents.

Moreover, even were this phrase not an "express definition" of the term "solvates" (a proposition GSK strongly disputes), the meaning of the term is no less clear; patents need not use an "explicit definitional format" to define claim terms. *Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1300 (Fed. Cir. 2004) ("Even when guidance is not provided in explicit definitional format, the specification may define claim terms by implication such that the meaning may be found in or ascertained by a reading of the patent documents.") (internal quotations and citations omitted); *Phillips*, 415 F.3d at 1320-21 (holding definition of claim language may be implicit in specification); *Novartis Pharms. Corp. v. Abbott Labs.*, 375 F.3d 1328, 1334-35 (Fed. Cir. 2004) (same). A patent can define a claim term implicitly or in a manner that can be readily ascertained from reading the intrinsic evidence. *See Irdeto*, 383 F.3d at 1300.[19]

[19] Defendants' reliance on *Accolade Sys. LLC v. Citrix Sys., Inc.*, 634 F. Supp. 2d 738, 754 (E.D. Tex. 2009) is misplaced. In *Accolade*, the specification said that the disputed term was "well known to those skilled in the art" but did not provide any further details about the term. *Id.* In the instant case, the specification provides a definition.

Defendants also incorrectly assert that the following paragraph in the Patents implicitly limits the definition of "solvates" to crystalline structures:

> It will ***also be appreciated*** by those skilled in organic chemistry that many organic compounds can exist in more than one crystalline form. For example, crystalline form may vary from solvate to solvate. Thus, all crystalline forms of the compounds of formula (I) or the pharmaceutically acceptable solvates thereof are within the scope of the present invention.

See e.g., JCCS Exhibit B, '467 Patent, col. 4:5-4:12 (emphasis added). Far from supporting Defendants' proposed construction, this paragraph is wholly consistent with GSK's proposal. In particular, the use of the word "***also***" indicates that the paragraph is intended to provide ***additional*** information regarding solvates, but not to limit the definition in the preceding paragraph, as Defendants suggest. *See, e.g., id.* at col. 3:58-4:4. The paragraph does not say, as Defendants suggest, that solvates must exist in crystalline form.

Further, the last sentence of the paragraph, read plainly, provides that "all crystalline forms of the compounds of formula (I)" and "all crystalline forms of…the pharmaceutically acceptable solvates [of the compounds of formula (I)] are within the scope of the invention." *See, e.g., id.* at col. 3:58-4:12. This supports GSK's position that the patentees considered both crystalline and non-crystalline forms of solvates to be within the scope of their invention.

Brocade Commc'ns Sys., Inc. v. A10 Networks, Inc., No. 10-CV-03428, 2012 WL 33251, 2012 U.S. Dist. LEXIS 2024 (N.D. Cal. Jan. 6, 2012), cited by Defendants, is also inapposite. In *Brocade*, the specification said that a particular event was "generally performed" under certain conditions. *Id.* at *9. The court found that the specification was "hardly of 'sufficient clarity to put one reasonably skilled in the art on notice that the inventor intended to redefine the claim term.'" *Id.* (citation omitted). Here, the specification is not vague—it provides a clear definition.

(ii) The Disclosed Embodiments Support GSK's Construction of "Solvate Thereof"

Defendants also argue that the examples of dutasteride formulations described in the Patents "do not even relate to embodiments of solvates as understood by a person of skill in the art." (*See supra* Defendants' Opening Position at III.A.2.c(v).) Again, Defendants' statement is not consistent with the language of the specification.

The Patents state that "[f]ormulations of the present invention for medical use ***comprise an active compound, i.e., the compound of formula (I)***, together with an acceptable carrier thereof and optionally other therapeutically active ingredients." *See* JCCS Exhibit B, '467 Patent, col. 10:65- 11:1 (emphasis added); *see also id.*, col. 3:29-38 ("Other aspects of the invention are … [p]harmaceutical formulations containing the compound of formula (I) as an active ingredient."). Nothing in this phrase excludes the use of ***solvates of dutasteride*** within a formulation. Indeed, the Patents define the "compound of formula (I)" as "[dutasteride] ***and*** pharmaceutically acceptable salts and solvates thereof." *See, e.g., id.* at col. 3:10-28 (emphasis added).

Moreover, the Patents do not limit the active ingredient of the claimed pharmaceutical formulations to solid or crystalline forms of dutasteride, as Defendants argue. For example, parenteral (injectable) liquid formulations are included as preferred embodiments. *See, e.g., id.* at col. 11:11-12. The Patents state that "[f]ormulations suitable for parenteral administration conveniently ***comprise a sterile aqueous preparation of the active compound*** …." *Id.* at col. 11:51-54 (emphasis added). Nothing in the specification would preclude use of an aqueous preparation of a dutasteride solvate (which is an active compound) in liquid form.

(iii) The File History Supports GSK's Proposed Construction

Defendants' contention that GSK is taking a different position in these claim construction proceedings than it did during prosecution is also incorrect.

During prosecution of the '467 Patent, the Examiner asked, "[w]hat ***solvents*** are intended in '***solvates'***? Acetone? Water? Isopropanol? DMSO? DMF? (par 2) specification provides no guidance (par 1)." JCCS Exhibit E, November 24, 1995 Office Action at 6 (emphasis added). In responding to this question about ***solvents***, the patentees referred to the definition of ***solvate*** as a complex of an organic compound and a solvent. *See* JCCS Exhibit E, Amendment and Response dated February 22, 1996 at 7 (AN0005148). In other words, the patentees answered the Examiner's question about ***solvents*** by emphasizing that the claimed ***solvates*** may be formed by using solvents that complex with dutasteride. The patentees never argued—as Defendants suggest—that the claimed solvates must be crystalline. *See id*. Moreover, GSK has consistently relied upon the definition in the Patents.[20]

In sum, the claim term "solvate" is defined in the Patents. As such, there is no need to resort to evaluation of extrinsic evidence. *Phillips*, 415 F.3d at 1312-17.

b. Defendants' Presentation of Extrinsic Evidence is Highly Selective and Unrepresentative

The Court should disregard Defendants' extrinsic evidence not only on the grounds that it is unnecessary, but also because but also because it does is not representative of the evidence of record or the art as a whole. Some of Defendants' alleged "evidence" is little more than unsupported assertion, such as Defendants' lengthy footnote that the mere idea that

[20] Defendants' citation to *Am. Piledriving Equip., Inc. v. Geoquip, Inc.*, 637 F.3d 1324, 1336 (Fed. Cir. 2011) is thus misplaced. In that case, the inventors defined a claim term as "one-piece" to overcome a prior art rejection during prosecution, then asserted during litigation that the term could ***not*** mean "formed or cast of one piece." *Id.* at 1335-36. By contrast, GSK has consistently relied on the definition of solvate in the specification.

pharmaceutical solvates exist as amorphous solids or liquids is "rare and controversial." (Defendants' Opening Position at III.A.2.c(v), n.18.) As set forth below, Defendants' contentions rely on selections from documents or testimony taken out of context or misconstrued.

(i) [redacted]

[redacted]

(ii) Defendants' Presentation Also Mischaracterizes Dr. Byrn's Prior Opinions and Publications

Defendants also selectively quote statements by GSK's expert, Dr. Stephen Byrn, taken out of context, to support their position.

Dr. Byrn, a leading expert on solvates, has offered the expert opinion that solvates may exist in liquid, amorphous or crystalline form.[21] *See, e.g.*, Joint Appendix Ex. 158, Rebuttal Expert Report of Stephen R. Byrn, Ph.D., at ¶¶ 40-55. Dr. Byrn's opinion is supported by, among other things, the Patents' definition of "solvate," dictionaries,[22] and scientific literature published as early as 1913.[23] *See id.* at ¶¶ 40-55; ¶¶ 103-113.

Defendants seek to undermine Dr. Byrn by alleging that in a prior case where he served as an expert witness for GSK, he "never used the term solvate to refer to anything other than a crystalline form." (Defendants' Opening Position at III.A.2.c(iv).) What Defendants do not tell the Court, however, is that the claim at issue in that case was explicitly directed to a crystalline solvate: "[C]laim 1 of the '723 patent reads: '***Crystalline*** paroxetine hydrochloride hemihydrate." *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1339 (Fed. Cir.

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21 Indeed, Defendants do not appear to dispute that solvates can exist in liquid and amorphous form. Nor can they. Defendants' expert on solvates, Dr. Rogers, has admitted solvates can be liquid and amorphous. *See* Ex. 500, Opening Expert Report of Dr. Rogers at ¶ 26, n. 11; *see also* Joint Appendix Ex. 394p, Rogers July 18, 2012 Tr. at 40:23-41:10. Defendants merely contend that a person of ordinary skill in the art would not have construed the term "solvates" in the GSK Patents to include those known forms.

22 *See* Joint Appendix Ex. 503., *Grant & Hackh's Chemical Dictionary*, (5th ed., 1986) at 542 ("**solvate**[:] A molecular or ionic complex of molecules or ions of solvent with those of solute."); Joint Appendix Ex. 502, MERRIAM-WEBSTER'S COLLEGIATE DICTIONARY (10th ed. 1993) at 235 (complex is "a chemical association of two or more species (as ions or molecules) joined usu[ally] by weak electrostatic bonds rather than covalent bonds.").

23 In 1913, a scientific publication described the "Solvate Theory of Solution" as follows: "[i]n terms of this theory, when a salt is dissolved in water it combines with more or less of the water, forming hydrates. When dissolved in alcohol it combines with that solvent forming alcoholates." Joint Appendix Ex. 359, Harry Clary Jones, *The Solvate Theory of Solution and the Importance of Solutions for Science in General*, in A NEW ERA IN CHEMISTRY 145-171 (D. Van Norstrand Company 1913) at 160. *See also* Joint Appendix Ex. 506, Bernard Trémillon, CHEMISTRY IN NON-AQUEOUS SOLVENTS (D. Reidel Publishing Co. 1974) at 22, 24 ("After dissolving a substance, the solution contains molecules or ions which are 'solvated'."; "Overall, a solvated species can be defined as the entity formed by the foreign substance dissolved . . . and by the solvent molecules surrounding it and associated with it as a consequence of solvation interactions.").

2005) (emphasis added). Similarly, Defendants cite Dr. Byrn's U.S. Patent No. 6,605,729 to support the assertion that he has previously taken the position that a solvate must be crystalline. (Defendants' Opening Position at III.A.2.c(iv).) Again, what Defendants do not point out is that the claims of Dr. Byrn's patent are directed to a "***crystalline form*** . . . or a hydrate thereof." Ex. 358, U.S. Patent No. 6,605,729 at col. 29-30 (emphasis added). The fact that Dr. Byrn did not use the term solvate to refer to anything other than in crystalline form in the context of addressing patents with claims explicitly directed to crystalline structures is hardly surprising. If anything, this extrinsic evidence highlights the fact that if the claims in this case were intended to be limited to crystalline solvates, they would use the word "crystalline."

Defendants also rely on quotations from Dr. Byrn's book, SOLID-STATE CHEMISTRY OF DRUGS (2nd ed. 1999) (Ex. 309). But those are hardly relevant to the issue before the Court given that the book, by virtue of its focus on drugs in the "solid state," does not focus on solvates in liquid forms. Moreover, Defendants ignore the portion of Dr. Byrn's book that does address solvated species in solution:

> 1 The nature and concentration of differently ***solvated solute species*** that exist at different solvent ratios will change considerably as we move from one side of the diagram to the other.
>
> 2 Each alternative crystal form in the diagram will grow best when the ***solvated solution species*** it favors is at a maximum concentration.

Ex. 309 at 244 (emphasis added).

In sum, Dr. Byrn's opinions in this case are not inconsistent with his prior testimony and publications.

(iii) Defendants' Selective Presentation Ignores Other Extrinsic Evidence that Supports GSK

Defendants' cherry-picking is also evident from their failure to cite extrinsic evidence that does not support their proposed construction of "solvate." Although GSK does not believe there is any need to resort to extrinsic evidence in this case, it is worth noting that, as discussed above, there is abundant extrinsic evidence to support GSK's proposed construction. (*See supra* GSK's Reply Position at III.A.3.b(ii), nn. 4-5.) Indeed, even the scientific literature Defendants cite supports GSK's position. For example, Haleblian, *Characterization of Habits and Crystalline Modification of Solids and Their Pharmaceutical Applications*, *J. Pharm. Sci.* 64(8):1269-1288 (1975) (Ex. 300), which Defendants cite extensively in their brief, includes the following diagram to show how a salt hydrate (*i.e.*, a solvate) can form:

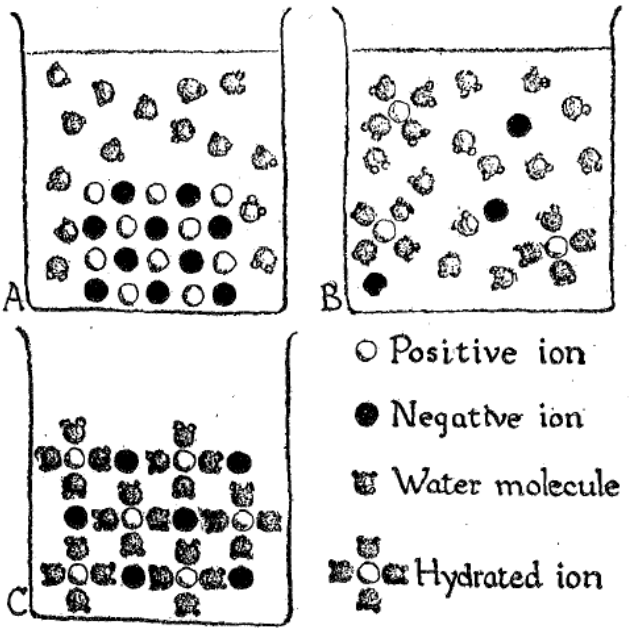


Figure 10—*Formation of a salt hydrate. When the anhydrous salt comes in the presence of water (A), it dissolves and the positive ions become hydrated (B). When crystallizing from solution again, the ions may remain hydrated and then the water molecules play an orderly role in the crystalline salt hydrate (C). (Reproduced, with permission, from Ref. 113.)*

Ex. 300 at 1276. In the above description of the figure, the author noted that when salt (a compound) contacts water it dissolves and becomes "hydrated."[24] The author also states that upon crystallization the compound "***may remain hydrated***," thus indicating that hydrates can exist in solution *before* they become crystals. *Id.*

c. Conclusion

GSK's proposed construction for "solvate thereof" is supported by the intrinsic record—the claims, specification and prosecution history. The inventors clearly defined a "solvate" as a complex of an organic compound (such as dutasteride) and a solvent. Neither the claims nor the specification include any language that would limit the claimed solvates to a crystalline form. In an attempt to improperly narrow the claims, Defendants ignore this intrinsic evidence and instead resort to extrinsic evidence under the guise of "plain and ordinary meaning." Not only do Defendants misapply the law of claim construction, their presentation mischaracterizes the extrinsic record. The Court should adopt GSK's proposed construction.

4. Defendants' Sur-Reply Position on "Solvate Thereof"

GSK has the burden to show that the term "solvates thereof" should have a meaning distinct from the ordinary meaning known to those in the field of art. *See Thorner*, 669 F.3d at 1365. When the only two paragraphs in the specifications that address solvates are read in their totality, it is clear that GSK has not met its burden. The inventors used "solvate" consistent with its ordinary meaning of a complex in crystalline form and never intended to redefine solvates to include solutions or compounds in solution.

[24] Notably, the Patents state that a "hydrate" is an example of a solvate. *See, e.g.*, JCCS Ex. B, '467 Patent at col. 4:1-3.

a. Solvates Are Complexes But Not All Complexes Are Solvates

GSK argues that "the intrinsic evidence is clear: solvates are 'complexes.'" *See* GSK Section III.A.3.a.(i). Defendants have never disputed that solvates are complexes. However, not all complexes are solvates, and the patents do not depart from the ordinary meaning that solvates are complexes in crystalline form.

(i) The Specifications Do Not Expressly Define Solvates

For a specification to expressly define a term, it must do so in a clear manner. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) ("Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision."). The specifications say nothing to alert the reader that the inventors intended a special meaning of solvate. They do not use explicit language such as "is," "means," or "as used herein." Rather, they expressly state that "[t]hose skilled in organic chemistry will appreciate . . ." and these complexes "are known," *i.e.*, already known to one of skill, "as solvates." JCCS Ex. B ('467 Patent, 3:59-4:12).

[redacted]

[redacted]

Further, the lack of intent to alter the plain meaning of the term "solvate" is reflected by the specifications and prosecution histories, both of which indicate that the well-understood meaning of solvates applies. Thus, the ordinary meaning controls.[25] *See Thorner*, 669 F.3d at 1368 ("But the 'implied' redefinition must be so clear that it equates to an explicit one.").

(ii) The Ordinary Meaning of Solvates in the Pharmaceutical Arts Is Well Settled

In the pharmaceutical arts, "solvates" has only one meaning: a complex in crystalline form. Defendants have cited to extensive evidence, including evidence from GSK's expert Dr. Byrn, supporting this commonly accepted meaning. *See* Defendants Section III.A.2.c.(iv).

GSK does not counter this overwhelming evidence but instead relies solely on Dr. Byrn's present day testimony — testimony that is flatly contradicted by his publications from the relevant time period. Those publications repeatedly stated:

[25] Recognizing that the quoted language is not an explicit definition, GSK offers authority on implied definitions. GSK Section III.A.3.a.(i). But that case involved construction of a term that admittedly had no ordinary meaning. *See Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1300-03 (Fed. Cir. 2004). Here, even the inventors represented to the Patent Office that the term solvate is "well understood by those skilled in the art." JCCS Ex. E, (February 22, 1996 Response at 7) (AN0005148).

- "solvates, forms containing solvent molecules ***within the crystal structure***"[26]
- "Solvate—***A crystal form*** that contains either stoichiometric or nonstoichiometric amounts of solvent."[27]

GSK tries to explain away Dr. Byrn's prior writings as irrelevant because his book[28] focuses on drugs in the "solid state." *See* GSK Section III.A.3.b.(ii). But Dr. Byrn admitted at his deposition that the term solvate has the same meaning to an organic chemist as to a solid-state chemist, Ex. 387p (Byrn Tr. 26:17-22), and GSK never explains how a focus on the solid state would make a difference.

Amorphous forms are solids too — indeed, Dr. Byrn's 1982 book contains an entire section on "amorphous solids." Ex. 364p at 10-11. Yet Dr. Byrn never stated in either his 1994 paper or his 1982 book that solvates could also exist in amorphous form. It is only now that Dr. Byrn relies upon a general chemical dictionary given to him by GSK's attorneys to opine that solvates may exist in non-crystalline forms. *See* GSK Section III.A.3.b(ii), n. 22; Ex. 387p (Byrn Tr. 141:21-142:2). But a "general-usage dictionary cannot overcome credible art-specific evidence of the meaning or lack of meaning of a claim term." *Irdeto*, 383 F.3d at 1300.

Further, in his 1999 book, Dr. Byrn addressed "solvated species in solution" and described various characteristics of what he refers to as "solvated solute species." Ex. 309 at 243-44. Not once did Dr. Byrn refer to those species as solvates, demonstrating that these are

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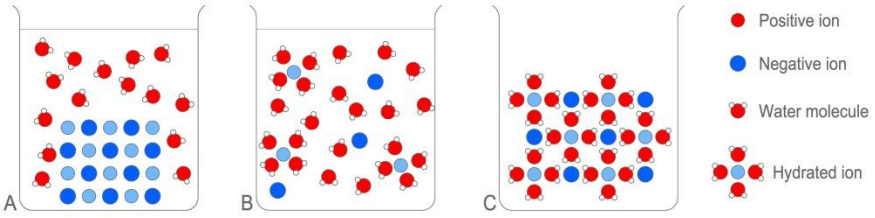
[26] Ex. 88 at 1148 (Byrn, 1994) (emphasis added).

[27] Ex. 364p at 339 (Byrn, Solid State Chemistry of Drugs 1982) (emphasis added).

[28] GSK cites to the 1999 edition of Dr. Byrn's book, overlooking that Defendants relied on the 1982 edition of Dr. Byrn's book, as well as Dr. Byrn's 1994 article. In any event, Dr. Byrn reported that solvate meant a crystalline form in all of those references.

distinct concepts. Rather, the 1999 book expressly defines "solvate" as a "crystal form," consistent with that term's well-recognized meaning. Ex. 155 at 516.

Figure 10 in the Haleblian article, reproduced below, further illustrates this point. Figure A shows a solution of salt and water (with a line across the top of the beaker indicating a solution). Figure B shows certain salt ions "hydrated" with water molecules surrounding them while still in solution. "When these ***hydrated ions*** arrive at the surface of a growing crystal, they ***crystallize*** into a salt ***hydrate***, carrying some or all of their attached water molecules into the solid composition." Ex. 300 at 1276 (emphasis added). Figure C shows this crystalline salt "hydrate;" notably there is no line across the top of the beaker, indicating this is not a solution.



GSK misreads the description of Figure 10 to argue that a hydrate exists in solution. *See* GSK Section III.A.3.b.(iii). Haleblian states that the ion may remain hydrated *when* recrystallizing (and not *upon* crystallization as GSK argues), and *when* it does, it then becomes part of the hydrate. A hydrated salt ion in solution is not a hydrate, and Haleblian does not state that it is. Haleblian is consistent with the different ways in which the pharmaceutical literature treats the terms "hydrate" and "hydrated." This difference is even recognized in general dictionaries. For example, "hydrate" is defined as "[a] solid compound containing water molecules combined in a definite ratio as an integral part of the crystal." Ex. 392 (The American Heritage Dictionary of the English Language, 3d ed. 1996, 1992 at 885). In contrast, "hydrated" simply means "chemically combined with water, especially existing in the form of a hydrate." *Id.* Thus, a salt

ion surrounded by water molecules in solution is "hydrated," but it is not a "hydrate." GSK points to no objective evidence that indicates otherwise.

Finally, Defendants' expert, Dr. Robin Rogers, has always maintained that solutions are not solvates and certainly would not have been understood to be solvates at the time the patents were filed. Indeed, his patent application, which he filed years before this litigation commenced, explains that solutions are not solvates. Ex. 301 at [0083]. The Background section also explains that solvates are generally understood to be "crystalline solids." *Id.* at [0004]. There is only one expert in this litigation whose pre-litigation statements contradict his opinion in this litigation as to the meaning of solvate and that is GSK's expert, Dr. Byrn.

b. Conclusion

GSK has not overcome the heavy presumption that the ordinary meaning should apply to the claim term "solvates thereof." Accordingly, this Court should adopt Defendants' proposed construction.

B. Term 2 - "pharmaceutically acceptable"[29]

Claim Term	GSK's Proposed Construction	Defendants' Proposed Construction
"pharmaceutically acceptable"	Not deleterious to the recipient thereof when administered as a pharmaceutical.	Suitable for use in a finished drug product to be administered to a patient.

1. GSK's Opening Position

a. The Parties Dispute the Meaning of "Pharmaceutically Acceptable"

The parties dispute the meaning of the term "pharmaceutically acceptable." JCCS Exhibit B, '467 Patent claims 1-5, col. 11:1-4; JCCS Exhibit C, '976 Patent claims 1-4, col.

[29] All of the asserted claims include the limitation "pharmaceutically acceptable." JCCS Exhibit A.

11:12-15; JCCS Exhibit D, '427 Patent claim 10, col. 19:30-33. GSK's proposed construction, taken from the specification, is "not deleterious to the recipient thereof when administered as a pharmaceutical." In contrast, the Defendants' proposed construction imports an ambiguous limitation ("finished drug product") into the claims and is unsupported by the specification. For all the reasons set forth below, the Court should adopt GSK's proposed construction.

b. GSK's Proposed Construction is Consistent With the Intrinsic Evidence

(i) The Claims

The asserted claims use the term "pharmaceutically acceptable" to describe the claimed solvates as well as the carriers used in the claimed pharmaceutical formulations. *See, e.g.*, JCCS Exhibit B, '467 Patent claims 1-5. For example, Claim 1 of the '467 Patent is directed to dutasteride "or a pharmaceutically acceptable solvate thereof." *Id.*, '467 Patent claim 1. Claims 2-5 of the '467 Patent are directed to "[a] pharmaceutical formulation comprising the compound of claim 1 and a pharmaceutically acceptable carrier thereof." *See id.*, '467 Patent claims 2-5. As used in the asserted claims, "pharmaceutically acceptable" thus modifies two different terms: "solvate thereof" and "carrier." JCCS Exhibit B, '467 Patent claims 1-5; JCCS Exhibit C, '976 Patent claims 1-4; JCCS Exhibit D, '427 Patent claim 10 (citations omitted). None of the claims refer to a "finished drug product."

(ii) The Specification Defines "Pharmaceutically Acceptable"

The specifications of the Patents expressly define the term "pharmaceutically acceptable." In discussing the types of carriers that can be combined with dutasteride to prepare the claimed formulations, the specification states that "[t]he carrier must be ***pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.***" JCCS Exhibit B, '467 Patent at col. 11:1-4; JCCS

Exhibit C, '976 Patent at col. 11:12-15; JCCS Exhibit D, '427 Patent at col. 19:30-33 (emphasis added). GSK's proposed construction relies upon this express definition of "pharmaceutically acceptable."[30] The Federal Circuit has "frequently found that a definition set forth in the specification governs the meaning of the claims." *Sinorgchem*, 511 F.3d at 1138. "When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term." *Multiform Desiccants*, 133 F.3d at 1478.

(iii) GSK's Construction Includes the Preferred Embodiments, Which are Not Finished Drug Products

The words "finished drug product" do not appear *anywhere* in the specification nor is it even clear what that phrase means. Construing the claims to include this limitation, as Defendants propose, would thus import an ambiguous limitation that is nowhere referenced in the Patents into the claims. This is improper, and GSK's proposed construction appropriately avoids doing so. *See, e.g.*, *Arlington Indus.*, 632 F.3d 1256 ("'Where a specification does not require a limitation, that limitation should not be read from the specification into the claims.'") (citation omitted).

GSK's proposed construction of "pharmaceutically acceptable" also properly includes the preferred embodiments disclosed in the Patents. In particular, the Patents disclose formulations made on a small, non-commercial scale. For example, Example 3(B) of the '467 Patent discloses a process for making a small batch of 1000 oral tablets with a total weight of 41 grams (*i.e.*, 1.4 ounces), only 20 grams of which is "active compound." JCCS Exhibit C, '467 Patent at col.

[30] The definition in the specification applies to a "carrier" in a formulation and refers to the carrier "being compatible with the other ingredients of the formulation." JCCS Exhibit B, '467 Patent at col. 11:1-4. Given that not all of the asserted claims involve formulations, GSK's proposed construction focuses on the portion of the definition of pharmaceutically acceptable that is equally applicable to the formulation and non-formulation claims, *i.e.*, "not deleterious to the recipient thereof."

14:49-60. *See also* JCCS Exhibit C, '976 Patent at col. 15:1-13; JCCS Exhibit D, '427 Patent at col. 32:29-41. Other examples similarly disclose small batch formulations of dutasteride and other compounds. *See* JCCS Exhibits B and C, '467 and '976 Patents at Examples 3(D), 3(E); JCCS Exhibit D, '427 Patent at Examples 58(D), 58(E).[31] GSK's construction of "pharmaceutically acceptable" properly includes these preferred, small batch formulation embodiments and does not create uncertainty about whether they would be considered suitable for use in a "finished drug product." *See Adams Respiratory*, 616 F.3d at 1290; *Burke*, 183 F.3d at 1341.

GSK's proposed construction of "pharmaceutically acceptable" is properly grounded in the intrinsic evidence—the claims, specification, and file history. It reflects the inventors' chosen definition of "pharmaceutically acceptable" and is consistent with the language of the claims.

2. Defendants' Opening Position

a. <u>Introduction</u>

"Pharmaceutically acceptable" is a common phrase used in innumerable patents to modify, in the same way, any number of drug-product terms, such as, solvates, hydrates, salts, acids, polymers, and carriers. In the claims of the Patents at issue here, "pharmaceutically acceptable" modifies two different terms, "solvate" and "carrier"—one is an active ingredient for therapeutic effect and the other is an inactive ingredient in a pharmaceutical formulation that

[31] Examples 3(D) of the '467 and '976 Patents and 58(D) of the '427 Patent disclose a process for making a liquid injectable formulation with a total weight of 1005 grams (*i.e.*, 35.5 ounces), which is filled into 1000 ampules containing 1 mL each. *See* JCCS Exhibit B, '467 Patent at col. 15:11-25; JCCS Exhibit C, '976 Patent at col. 15:26-40; JCCS Exhibit D, '427 Patent at col. 32:54-67. Examples 3(E) of the '467 and '976 Patents and 58(E) of the '427 Patent disclose a process for making 1000 capsules with a total weight of 475 grams (*i.e.*, 16.8 ounces). *See* JCCS Exhibit B, '467 Patent at col. 15:26-16:2; JCCS Exhibit C, '976 Patent at col. 16:1-8; JCCS Exhibit D, '427 Patent at col. 33:1-10.

serves to aid in formulation and delivery of the active ingredient to the patient. Logically, "pharmaceutically acceptable" must mean the same thing whether it modifies the active "solvate" ingredient or the inactive "carrier" ingredient, and the evidence confirms that it does. The ordinary meaning of "pharmaceutically acceptable," no matter what it modifies, is what the pharmaceutical industry would find (for the active or inactive ingredient) **acceptable** (*i.e.*, *suitable*) *for use in* a **pharmaceutical,** *the finished drug product to be administered to a patient* (in a tablet, capsule, or other formulation). Absent an express contrary definition in the Patents, not present here, that ordinary meaning applies.

Nevertheless, GSK proposes a construction—not deleterious to the recipient when administered as a pharmaceutical—based on a truncated part of a specification sentence that describes an acceptable ***inactive carrier*** ingredient. On its face, that sentence has nothing to do with the ***active solvate*** ingredient or the definition of "pharmaceutically acceptable." Indeed, GSK's proposed construction confuses the definition of a pharmaceutically acceptable ingredient with the function of the ingredient.

By way of explanation, an inactive ingredient, such as the carrier, may be suitable for use in the finished drug product for administration to the patient if it is both compatible with the other ingredients *and* not deleterious (*i.e.*, not harmful) to the patient. For the active ingredient, however, the standard for being suitable for use in the finished drug product for administration to the patient is different because that ingredient is actually intended to provide the therapy to the patient. Accordingly, a "pharmaceutically acceptable" active ingredient (here, a "solvate") must be capable of being safely and effectively dosed, reproducibly manufactured and stable over time. To be merely "not deleterious" to the patient does not make it "pharmaceutically acceptable" as an active ingredient. To the contrary, "pharmaceutically acceptable" has one

consistent meaning—suitable for use in a finished drug product for administration to a patient. Absent express definitions to the contrary, the meaning of that term does not change depending on what ingredient the term is modifying.

Accordingly, the Court should reject GSK's proposed construction that is inconsistent with the common meaning and terms of the Patents and instead adopt the construction of "pharmaceutically acceptable" proposed by Defendants—suitable for use in the finished drug product to be administered to a patient.

b. The Patents Support Applying the Ordinary Meaning of "Pharmaceutically Acceptable"

Absent a clear definition to the contrary within a patent, claim terms are given their ordinary and customary meaning, which is "the meaning that the term would have to a person of ordinary skill in the art in question . . . as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1312-13; *see Thorner*, 669 F.3d at 1365 ("To act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term other than its plain and ordinary meaning.") (internal citations omitted). Here, there is no express definition of "pharmaceutically acceptable" in the claims, specifications, or preferred embodiments. As a result, the common and well-known meaning of the term applies.

(i) The Claims Use "Pharmaceutically Acceptable" Without Replacement or Modification of Its Ordinary Meaning

The term "pharmaceutically acceptable" appears in various Patent claims asserted by GSK in this suit. *See, e.g.*, JCCS Ex. B ('467, claims 1, 2, 3); JCCS Ex. D ('427, claim 1); JCCS Ex. C ('976, claims 1, 2). In each of the Asserted Claims, the term modifies "solvate thereof" so that the claim limitation reads "a pharmaceutically acceptable solvate thereof." *See, e.g., JCCS* Ex. B ('467, claim 1); JCCS Ex. D ('427, claim 1); JCCS Ex. C ('976, claim 1). In other claims,

the term is used to modify "carrier" so that in those claims, the limitation reads "pharmaceutically acceptable carrier thereof." *See, e.g.,* JCCS Ex. B ('467, claim 2); JCCS Ex. D ('427, claim 11). The ordinary meaning of the phrase "pharmaceutically acceptable" is straightforward; to be pharmaceutically acceptable, the ingredient modified by the term must be acceptable for use in a pharmaceutical. Stated differently, it must be suitable for use in a finished drug product for administration to the patient.

None of the claims modify the ordinary meaning of the phrase "pharmaceutically acceptable" or otherwise define it. Nor do any of the claims refer to "not deleterious," the unique meaning that GSK would like to ascribe to the common term. However, by modifying two separate types of ingredients, the active solvate ingredient and inactive carrier ingredient, what is clear is that the term "pharmaceutically acceptable" has the same definition regardless of what it modifies. Defendants' construction is consistent regardless of the ingredient modified by the term. GSK's construction is not.

(ii) The Specifications Do Not Define, Replace or Otherwise Modify the Ordinary Meaning of "Pharmaceutically Acceptable"

The Patent specifications also do not define, replace or modify the ordinary meaning of "pharmaceutically acceptable." Indeed, the specifications make no mention at all of what a "pharmaceutically acceptable solvate thereof" might be. And the specifications only mention "pharmaceutically acceptable" in the context of describing when a ***carrier***, not a solvate or active ingredient, would qualify as pharmaceutically acceptable, *i.e.*, when a carrier would be suitable for use in a finished drug product for administration to a patient. JCCS Ex. B ('467, 11:1–4); JCCS Ex. D ('427, 19:30–33); JCCS Ex. C ('976, 11:11–14). The description of the inactive

carrier, not surprisingly given the different functions of the ingredients, is unrelated to the active solvate ingredient. Specifically, in a section entitled "Formulations," the Patents state as follows:

> The ***carrier*** must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Id. (emphasis added). This passage, however, is not an "express definition" or replacement of the ordinary meaning of the term "pharmaceutically acceptable" as to a carrier *or* an active (solvate) ingredient; it merely describes what characteristics a specific inactive ingredient, the carrier, may need to be suitable for use in a finished drug product for administration to a patient.

To replace the ordinary meaning of a claim term, the assigned meaning must be expressly defined in the claims or the specification. *Sinorgchem*, 511 F.3d at 1136. To constitute an express definition that overcomes the ordinary meaning of a term, the Federal Circuit has indicated that the specification must unambiguously signify that the description provided is indeed intended to be definitional. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1358-1360 (Fed. Cir. 2008). To satisfy this definitional requirement, the specifications must reflect the claim drafter's clear intent to define the term, such as by use of the word "is" as an indicator of a defined term. *Sinorgchem*, 511 F.3d at 1136 (finding "controlled amount" expressly defined in specifications where "is" was used to delineate a definition and the parties agreed there was no well-accepted meaning of term in the relevant field).

Here, there is no express definition or markers in the formulation description to indicate a definition intended to replace or modify the ordinary meaning of "pharmaceutically acceptable" as applied to a carrier or otherwise. GSK's expert, Dr. Byrn, agreed:

> Q. Does the '467 patent define pharmaceutically acceptable to have a different meaning than its ordinary meaning?
>
> A. No.

Ex. 387p (Byrn Tr. 231:14-17). Moreover, the carrier description could in no way modify the meaning of "pharmaceutically acceptable" for purposes of the term "solvate." As GSK acknowledges in its brief, the description is expressly limited to the carrier in a formulation. *See* GSK Section III.B.1.b.(ii), n.30.

The very language on which GSK relies demonstrates that its proposed construction is erroneous. *See, e.g.* JCCS Ex. B ('467, 11:1-4). At least with regard to defining "pharmaceutically acceptable" as it modifies solvates, GSK ignores the "compatibility" language, purportedly doing so because compatibility applies to formulations and not all Asserted Claims involve formulations. *See* GSK Section III.B.1.b.(ii), n.30. Not only does the ordinary meaning of "pharmaceutically acceptable" not vary by claim, the same sentence cannot generate two different definitions for "pharmaceutically acceptable." GSK offers no explanation of why the alleged definition of the same term, "pharmaceutically acceptable," would vary by the term it modifies or the claim in which it is found.

Additionally, the language on which GSK relies relates to ***carriers***, which are ***inactive*** ingredients in a pharmaceutical formulation that do not impact the efficacy of the product. Ex. 501, ¶52; Ex. 387p (Byrn Tr. at 69:13-17). ***Solvates*** are ***active*** ingredients that control the efficacy of the product. Thus, what is "pharmaceutically acceptable" for a carrier, an inactive ingredient, may mean only what the carrier description in the specifications says—something compatible with the other ingredients and not harmful to the recipient. That, however, does not define or alter what is "pharmaceutically acceptable" for a solvate, an active ingredient, which must be capable of being safely and effectively dosed, reproducibly manufactured and stable over the product's shelf life. Ex. 500, ¶53. Merely being "not deleterious" would not make a solvate pharmaceutically acceptable. Thus, the description of an acceptable carrier in the

specifications does not define pharmaceutically acceptable at all or describe what is pharmaceutically acceptable for a solvate.

Moreover, GSK's only argument against using the ordinary meaning of "pharmaceutically acceptable" is the erroneous suggestion that the term must be defined only using the words found in the specifications. That misses the point—there is no definition in the specifications, and it is thus unremarkable that the words of the ordinary meaning would not appear in the specifications. *Sandoz, Inc*., 544 F.3d at 1360 (holding district court did not err in using the word "matrix" in its definition of "pharmaceutically acceptable polymer" even though it does not appear in the claims or specification).

In short, "pharmaceutically acceptable" means the same for both the inactive and active ingredients—suitable for use in the final drug product for administration to a patient—but the properties of what is suitable differs between the two ingredients. Nothing in the specification replaces the ordinary meaning of "pharmaceutically acceptable" as a modifier of "carrier" *or* "solvate." The Court should therefore adopt the common, ordinary meaning of the term as proposed by Defendants.

(iii) The Preferred Embodiments Are Consistent With the Ordinary Meaning of the Term "Pharmaceutically Acceptable"

The preferred embodiments do nothing to detract from the ordinary meaning of the term "pharmaceutically acceptable." Contrary to GSK's argument, *see* GSK Section III.B.1.b.(iii), whether a batch is small in size or intended for millions of patients, the claims require that the product be "pharmaceutically acceptable." JCCS Ex. B ('467, claim 1). Applying the ordinary meaning of that term to require that the product be suitable for use in a finished product capable of being administered to a patient—no matter the batch size—is not ambiguous or inconsistent

with the embodiments. It is the ordinary meaning of the term. Indeed, even GSK's proposed construction includes "when administered as a pharmaceutical." [32]

c. The Ordinary Meaning of "Pharmaceutically Acceptable" Is "Suitable for Use in a Finished Drug Product to Be Administered to a Patient

As explained above, the ordinary meaning of a "pharmaceutically acceptable" ingredient is one that is acceptable (*i.e.*, suitable) for use in a pharmaceutical (*i.e.*, finished drug product to be administered to a patient). That is the definition one of ordinary skill in the art would have understood "pharmaceutically acceptable" to mean at the time of the Patents. Ex. 500, ¶88.

Even GSK's experts agreed. Dr. Byrn testified:

> Q. Would a medicinal chemist in 1993 have understood pharmaceutically acceptable to mean acceptable for use in a pharmaceutical formulation?
>
> A. I mean I think that's, it sounds circular but I think I can agree to that. I mean my—what I said is it's ***pharmaceutically acceptable for its intended purpose***. I think that's basically the same thing. Maybe there's a difference. But I think it sounds, I think what you're asking me is the same as what I'm saying.

Ex. 387p (Byrn Tr. at 80:24–81:9) (emphasis added).

Similarly, GSK's expert, Dr. Davies declared under oath in a different federal court action that the plain and ordinary meaning of "pharmaceutically acceptable," when used in the context of describing a salt (like a solvate, a form of the active ingredient) is "one that is suitable for pharmaceutical administration." Ex. 152 (Davies Decl. ¶62). Moreover, Dr. Davies admitted in his deposition in this case that, at least in some contexts, the ordinary meaning of "pharmaceutically acceptable" means "suitable for pharmaceutical administration." Ex. 389p (Davies Tr. at 246:3–7).

[32] For an active ingredient, such as a solvate, to be administered as a pharmaceutical, as required by GSK's proposed definition, it would still need to be safe and effective, capable of reproducibly being manufactured, and stable.

The dictionary definitions of the words "pharmaceutically" and "acceptable" also support Defendants' construction.[33] Specifically, Merriam-Webster Medical Dictionary defines the term "pharmaceutical" to mean *n.* "a medicinal drug." Ex. 390. "Medicinal" means "tending or used to cure disease or pain." *Id.* Merriam-Webster Dictionary defines "acceptable" as "capable or worthy of being accepted." *Id.* Combining these definitions, the ordinary meaning of the term "pharmaceutically acceptable" is: capable of being accepted (*i.e.*, suitable for use) in a pharmaceutical (*i.e.*, a finished drug product) for curing disease or pain (*i.e.*, administration to a patient).

In sum, the Patents do not modify or replace the ordinary meaning of "pharmaceutically acceptable" at all and particularly not as it relates to "solvates thereof." This Court should apply the ordinary meaning of "pharmaceutically acceptable" proposed by Defendants.

3. GSK's Reply Position on "Pharmaceutically Acceptable"

Defendants' proposed construction of "pharmaceutically acceptable" not only contradicts the explicit definition of the term in the Patents, but also imports a vague and ambiguous "finished drug product" limitation into the claims. The phrase "finished drug product" appears nowhere in the claims, specifications or prosecution histories, and Defendants cite *no* evidence—intrinsic or otherwise—explaining its meaning. Indeed, Defendants appear to concede the ambiguity of their proposed limitation when they argue that a "pharmaceutically acceptable solvate" can only be a "finished drug product" if it is "capable of being safely and effectively dosed, reproducibly manufactured and stable over time." (Defendants' Opening Position at

[33] Where, as here, the intrinsic evidence does not shed any light on the ordinary meaning of a claim term, courts may turn to dictionary definitions for guidance. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1306 (Fed. Cir. 2006) (in claim construction, holding it is appropriate to "look to dictionary definitions" where specification failed to define term); *see also Phillips*, 415 F.3d at 1317-18.

III.B.2.a.) These four additional limitations, which Defendants seek to import into the claims through the vague phrase "finished drug product," are themselves unsupported, vague, and ambiguous.

The correct construction of "pharmaceutically acceptable" as used in the Patents is the definition the Patents provide. *See Affymetrix, Inc. v. Illumina, Inc.*, 446 F. Supp. 2d 277, 283 (D. Del. 2006) ("A patentee 'is free to act as his own lexicographer, and may set forth any special definitions of the claim terms in the patent specification or file history, either expressly or impliedly.'" (internal citation omitted)).

a. The Intrinsic Evidence Supports GSK's Proposed Construction

(i) The Patents Clearly Define "Pharmaceutically Acceptable"

As the Court recognized, the Patents define the claim term "pharmaceutically acceptable." (D.I. 209, n. 1.) The Patents state that "[t]he carrier must ***be pharmaceutically acceptable in the sense of being*** compatible with the other ingredients of the formulation and not deleterious to the recipient thereof." JCCS Exhibit B, '467 Patent at col. 11:1-4 (emphasis added).

Defendants' contention that this definition applies only when used to modify the noun "carrier" and not with reference to "solvates," (Defendants' Opening Position at III.B.2.a(ii)), cannot be reconciled with the plain language of the Patents. In particular, the phrase "***in the sense of being*** compatible with the other ingredients of the formulation and not deleterious to the recipient thereof" follows and defines the term "pharmaceutically acceptable." *See* JCCS Exhibit B, '467 Patent at col. 11:1-4 (emphasis added). Defendants' suggestion that this is not an express definition of "pharmaceutically acceptable" (Defendants' Br. at 20) ignores this

sentence structure.[34] Moreover, Defendants cite nothing to support their apparent contention that the term "pharmaceutically acceptable" should be different when applied to "solvate" than when applied to a carrier. Indeed, Defendants appear to argue elsewhere in their brief that the same definition should apply in both cases. (*See* Defendants' Opening Position at III.B.2.b(i).)

(ii) GSK's Proposed Construction is Consistent with the Claims

GSK's proposed construction is consistent with the definition in the Patents and also properly takes into account the different scope of the Patent claims. *See E-Pass Techs., Inc. v. 3Com Corp.*, 473 F.3d 1213, 1220 (Fed. Cir. 2007) (language of the claims is of "paramount importance to claim construction"). In particular, claim 1 of the '467 Patent only requires dutasteride or a "pharmaceutically acceptable solvate thereof." JCCS Exhibit B, '467 Patent, col. 16, claim 1. Unlike asserted claims 2-5, claim 1 does not require a formulation consisting of multiple ingredients. *See id.*, '467 Patent, col. 16. Thus, the "pharmaceutically acceptable" solvate of dutasteride covered by claim 1 need not be "compatible with the other ingredients of the formulation" because those ingredients are not required by the claims. For this reason, GSK's proposed construction focuses on the portion of the definition of pharmaceutically acceptable that is equally applicable to the formulation and non-formulation claims, *i.e.*, "not deleterious to the recipient thereof."[35]

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[34] To the extent Defendants argue that the inventors needed to use express definitional language, they are wrong. Express definitional language is not required for a specification to define a claim term. *See Phillips*, 415 F.3d at 1320-21; *Irdeto*, 383 F.3d at 1300; *Novartis*, 375 F.3d at 1334-35.

[35] Further to the issue raised by the Court, GSK has explained its rationale for truncating the definition in the Patents above. (*See also* GSK's Opening Position at III.B.1.b(ii), n.30.) However, GSK has no objection to the use of the entire definition. In any event, there is no basis to import the "finished drug product" limitation into the claims.

(iii) Defendants' Proposed Construction Imports a Non-Existent "Finished Drug Product" Limitation into the Claims

Defendants' proposed construction seeks to import the limitation "suitable for use in a finished drug product" into the claim term "pharmaceutically acceptable." However, the claims, specifications and prosecution histories say nothing about "finished drug products." Indeed, even if the phrase "finished drug product" were mentioned in the specification (which it is not), importing such a limitation into the claims would be improper. *Falana v. Kent State Univ.*, 669 F.3d 1349, 1355 (Fed. Cir. 2012) ("'[A] court may not import limitations from the written description into the claims.'" (quoting *Laitram Corp. v. NEC Corp.*, 163 F.3d 1342, 1347 (Fed. Cir. 1998))).

Moreover, the Patent specifications make clear that the preparation of a pharmaceutical product is not required, but rather permissible, stating as follows: "formulations ***may*** conveniently be presented in unit dosage form and ***may*** be prepared by any of the methods well known in the art of pharmacy." JCCS Exhibit B, '467 Patent at col. 11:13-15 (emphasis added); *see also id*., at col. 14-15, Example 3 (describing small scale formulations).

(iv) The Vague and Ambiguous Term "Finished Drug Product" Does Not Reflect Plain and Ordinary Meaning

Defendants' proposed construction introduces the concept of a "finished drug product," which they assert is consistent with "plain and ordinary meaning" and is "straightforward." (Defendants' Opening Position at III.B.2.b(i).) Tellingly, however, Defendants do not cite a single piece of intrinsic or extrinsic evidence to support the proposition that "finished drug product" is associated with the plain and ordinary meaning of "pharmaceutically acceptable." Indeed, the only reference to "finished drug product" in the documents Defendants intend to

submit to the Court appears in Dr. Rogers's expert report. (Defendants' Opening Position at III.B.2.b(ii).) Otherwise, Defendants rely *entirely* on unsupported attorney argument.[36]

In addition to lacking evidentiary support, Defendants' proposal is fundamentally flawed because the phrase "finished drug product" is vague and ambiguous. Given the lack of intrinsic or even extrinsic support for the phrase, one can only guess as to what a "finished drug product" actually is. A vague and ambiguous construction that requires further construction is not favored. *See, e.g., Paragon Solutions, LLC v. Timex Corp.*, 566 F.3d 1075, 1092 (Fed. Cir. 2009) (rejecting claim construction as "too vague to be of significant help in resolving the dispute in this case").

(v) Defendants Seek to Import Additional, Non-Existent Limitations Into the Claims

Implicitly conceding the ambiguity of their construction, Defendants now contend that a pharmaceutically acceptable active ingredient must "be capable of being safely and effectively dosed, reproducibly manufactured and stable over time." (Defendants' Opening Position at III.B.2.a; *see also id.* at III.B.2.b(ii).) But Defendants' apparent attempt to import these additional, non-existent limitations into the claims through the phrase "finished drug product" lacks support in the intrinsic evidence. The Patents and their file histories say *nothing* about reproducible manufacturing or stability over time.

Instead, Defendants cite to a single extrinsic source—one paragraph in the report of their expert witness that does not even discuss the term "pharmaceutically acceptable"—to support their argument. (*See* Defendants' Opening Position at III.B.2.b(ii).) However, this extrinsic evidence must be discounted. It "is clearly at odds with the claim construction mandated by the

[36] Indeed, the phrase "finished drug product" appears to be something Defendants have concocted in an admitted attempt to manufacture a defense under Section 112 of the Patent Act. (*See* Defendants' Opening Position at III.A.2.d.)

claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent."[37] *Phillips*, 415 F.3d at 1318 (quotation omitted).

Further, Defendants' proposal to define "finished drug product" with additional claim limitations violates the doctrine of claim differentiation. Under that doctrine, the explicit "formulation" and "safe and effective amount" requirements in the dependent claims 2-5 of the '467 Patent give rise to the presumption that the broader, independent claim 1 does not include those limitations.[38] *See Phillips*, 415 F.3d at 1315 ("[T]he presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim."); *Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1319 (Fed. Cir. 2006) (finding that an independent claim ordinarily does not include limitations of a dependent claim); *Liebel-Flarsheim*, 358 F.3d at 910 ("[T]he presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the

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[37] Defendants' expert on claim construction, Dr. Rogers, testified that a "finished drug product" must be FDA approvable. *See* Joint Appendix Ex. 394p, Rogers Deposition Tr. at 273:1-10. Courts have rejected this position as "untenable" in the context of claim construction. *See, e.g., Am. Bioscience, Inc. v. Baker Norton Pharms., Inc.*, No. CV 00-09589-MRP, 2001 WL 36170997 (C.D. Cal. Aug. 31, 2001) (finding that the proposed construction "produced for a pharmaceutical manufacturer under conditions that satisfy FDA's cGMP [current Good Manufacturing practice] regulations" for the term "pharmaceutically acceptable" is "untenable"). Further, outside of the claim construction context, both the Federal Circuit and Patent Office generally reject the proposition that claimed pharmaceutical compounds must be FDA-approvable. *See, e.g., In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) ("FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws" (citing *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994)); MPEP § 2107.03.V; MPEP § 2164.05 ("However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled.").

[38] Defendants' expert Dr. Rogers testified that claim 2 of the '467 Patent did not require a "finished drug product." Joint Appendix Ex. 394p, Rogers Deposition Tr. at 273:15-274:4; *see also id.* at 56:22-57:19 (testifying that claim 1 of the '467 Patent does not require that the compound is in a dosage form). This admission is further evidence that Defendants' proposed construction of "pharmaceutically acceptable" is wrong—if the claims do not require a finished drug product, then they do not require a solvate that is suitable for use in a finished drug product.

independent claim."). Defendants have not (and cannot) present any evidence to overcome this presumption.[39]

b. Extrinsic Evidence Does Not Support the Defendants' Construction

(i) Defendants Have Cited No Extrinsic Evidence Supporting Their Proposed Construction

As discussed above, Defendants cite no evidentiary support for their proposed construction, but rely on unsubstantiated attorney argument. Specifically, Defendants repeatedly argue that their proposed construction reflects the "plain and ordinary" meaning of "pharmaceutically acceptable," but fail to cite even a single piece of evidence, intrinsic or extrinsic, to support this assertion. (*See* Defendants' Opening Position at III.B.2.) Defendants do cite three dictionary definitions—one for "pharmaceutical," one for "medicinal," and one for "acceptable"—but none of these definitions contains the words "finished drug product." (*See* Defendants' Opening Position at III.B.2.c.) *See also* Ex. 390. And there certainly is no reason to adopt these definitions over the express definition in the Patents.

(ii) Defendants Ignore Extrinsic Evidence Supporting GSK's Proposed Construction

Like they do for their proposed construction of "solvate thereof," Defendants cherry-pick the extrinsic evidence that they contend supports their construction of "pharmaceutically acceptable," and affirmatively ignore extrinsic evidence that supports GSK's construction. In particular, Defendants selectively cite deposition testimony of GSK's expert, Dr. Byrn, to

[39] Defendants' proposal to define "finished drug product" with additional limitations also would render claim language superfluous and redundant, particularly the "safe and effective amount" language of claims 3-5. This is improper. *See Mangosoft, Inc. v. Oracle Corp.*, 525 F.3d 1327, 1329 (Fed. Cir. 2008) (rejecting a construction that would "render the term . . . superfluous or redundant"); *Versa Corp. v. Ag-Bag Int'l Ltd.*, 392 F.3d 1325, 1330 (Fed. Cir. 2004) (holding that construction of an independent claim should not render a dependent claim superfluous).

support their proposed construction. (Defendants' Opening Position at III.B.2.b(ii); III.B.2.c.)

[redacted]

Defendants also fail to acknowledge other extrinsic evidence contrary to their position.

[redacted]

Moreover, Defendants' own patents do not use the term "finished drug product" to define "pharmaceutically acceptable." For example, a patent assigned to defendant Watson defines "pharmaceutically acceptable" as follows:

> The term pharmaceutically acceptable means that the ingredient that is being qualified is compatible with other ingredients of the formulation and not injurious to the patient. Several pharmaceutically acceptable ingredients are known in the art and official publications. For example, THE UNITED STATES PHARMACOPEIA describe the analytical criteria for assessing the pharmaceutical acceptability of numerous ingredients of interest.

See Ex. 393, US 6,544,553 Col. 6:9-16. Even Defendants' own expert on claim construction, Dr. Rogers, has elsewhere defined the term "pharmaceutically acceptable" without reference to "finished drug product":

> By 'pharmaceutically acceptable' is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical formulation in which it is contained.

Ex. 301, U.S. Appl. Pub. No. US 2007/0093462 at 87 (Rogers et al.).

Given that Defendants cite almost no supporting evidence for its proposed construction, it is not surprising that this extrinsic evidence directly contradicts Defendants' proposal. As such, to the extent there is a "plain and ordinary" meaning of "pharmaceutically acceptable," GSK's proposed construction accurately reflects it.

c. Conclusion

GSK's proposed construction for "pharmaceutically acceptable" is supported by the intrinsic record and reflects the proper scope of the asserted claims. In contrast, Defendants'

proposed construction has no support in the intrinsic or extrinsic evidence, and belies an effort to manufacture a Section 112 defense where none exists.

4. Defendants' Sur-Reply Position on "Pharmaceutically Acceptable"

The language of the Patents does not support GSK's proposal to narrow "pharmaceutically acceptable" from its ordinary meaning. GSK's "definition" does no more than describe *one* ("not deleterious") of two ("compatible") characteristics of a pharmaceutically acceptable *carrier*. GSK thus responds with straw-men arguments against Defendants' proposal, focusing on "finished drug product" in the definition. But a comparison shows that the parties actually disagree on "suitable for use," not "a finished drug product":

Claim Term	GSK's Proposed Construction	Defendants' Proposed Construction
Acceptable	*"Not deleterious"*	*"Suitable for use"*
Pharmaceutically	to the recipient thereof	"to a patient"
	when administered	"to be administered"
	as a pharmaceutical."	"in a finished drug product."[40]

GSK deletes "compatibility" from the language on which it relies and replaces acceptable with "not deleterious." But an ingredient must be more than not deleterious to be acceptable for use in a pharmaceutical. Thus, GSK's altered definition is insupportable and should be rejected.

a. <u>The ordinary meaning is consistent with the Patents</u>

The Patents do not define "pharmaceutically acceptable" contrary to the ordinary and customary meaning of the term understood by persons of ordinary skill in the art. The ordinary meaning—"suitable for use in a finished drug product to be administered to a patient"—thus

[40] Although "a finished drug product" is within the ordinary accepted meaning, the Court could adopt interchangeable language, such as "a pharmaceutical" or "a formulation." *See* Defendants Sections III.B.2.a & b.(i). But interchanging such words does not narrow "suitable for use" to mean only "not deleterious."

applies. GSK's argument that Defendants cite no intrinsic evidence to support the ordinary meaning misapplies the law. GSK Sections III.B.3.a.(v) & b.(i). It is GSK that must show, but does not, intrinsic evidence that "pharmaceutically acceptable" has been narrowed from its ordinary meaning to mean only "not deleterious." *See Thorner*, 669 F.3d at 1365.

(i) The specifications do not modify the ordinary meaning

The grammar and context of the language on which GSK relies disproves that it is an "explicit" definition that narrows the meaning of "pharmaceutically acceptable":

> Formulations of the present invention for medical use comprise [1] an active compound, i.e., the compound of formula (I), together with [2] an *acceptable carrier* thereof and [3] optionally other therapeutically active ingredients. *The carrier* must be *pharmaceutically acceptable* in the sense of being [a] **compatible with the other ingredients of the formulation** and [b] **not deleterious to the recipient thereof**.
>
> The present invention, therefore, further provides a pharmaceutical formulation comprising a compound of formula (I), together with a *pharmaceutically acceptable carrier thereof*.

JCCS Ex. B ('467, 10:63-67; 11:1-8) (emphasis added). Relying only on the underlined words, GSK argues "pharmaceutically acceptable" means only "not deleterious." That is incorrect.

Grammatically and contextually, the above characteristics apply only to the *carrier*. The sentences discuss the formulation, not the active compound. The first sentence lists formulation components—an active compound, an acceptable carrier, and other therapeutic ingredients. The second sentence refers only to the second component—the *carrier*. GSK points to "be" and "in the sense of being" as definitional markers. GSK Section III.B.3.a.(i). Even if these words were markers, which they are not, it is the *carrier*—the subject noun—that must "be" pharmaceutically acceptable "in the sense of being" compatible *and* not deleterious. The third sentence confirms that it is the *carrier* that should hold those characteristics for purposes of the formulation.

(ii) The ordinary meaning is consistent with the claims

GSK justifies omission of the compatibility characteristic from its construction because that *formulation* characteristic would make its definition inconsistent with "pharmaceutically acceptable" in claim 1, a claim directed to *compounds*. GSK Section III.B.3.a.(ii). But, GSK cannot arbitrarily excise the compatibility requirement from its purported "explicit" definition to make it consistent between claims. Instead, as GSK acknowledges, "pharmaceutically acceptable" must mean the same thing in each claim. *See, e.g., Phillips*, 415 F.3d at 1318.[41] Unlike GSK's construction, Defendants' construction means the same thing in each claim no matter what term it modifies.

(iii) An ingredient must be *suitable for use* in a pharmaceutical

Faced with Patent language contrary to its proffered construction, GSK tries to avoid the ordinary meaning of "pharmaceutically acceptable" by mounting an attack on use of the phrase "finished drug product" in Defendants' definition. Contrary to GSK's arguments, however, "finished drug product" merely refers to a dosage form that can be administered to a patient. *See* Defendants Section III.B.2. And, GSK's own definition requires "when administered as a pharmaceutical." Nevertheless, GSK uses "finished drug product" to deflect the Court from the real dispute between the parties: does *acceptable* mean "*suitable for use*" or "*not deleterious*" when administered to a patient in a pharmaceutical?

[41] Even if GSK now does not object to the inclusion of "compatibility" into its proposed construction, GSK Section III.B.3.a.(ii) n.35, it does not alter that GSK's purported "explicit definition" applies only to the carrier. Moreover, as noted in Defendants' Opening Brief, GSK's definition recognizes that "pharmaceutically acceptable" involves administration of a pharmaceutical. Clearly, all individual components of a formulation, including the active ingredient, must be suitable for such administration even under GSK's definition.

GSK erroneously suggests that Defendants' construction requires that there be a finished product. GSK Section III.B.3.a.(iii). That is incorrect on the face of the proposal. The definition does not require a finished drug product; it requires a compound that is *suitable for use* in a pharmaceutical, or "when administered as a pharmaceutical," as GSK includes in its definition.

GSK also argues that Defendants seek to turn characteristics of what might be required for an active ingredient to be "pharmaceutically acceptable" into claim limitations. GSK Section III.B.3.a.(v). That mischaracterizes Defendants' position. The question is what "pharmaceutically acceptable" means, not what characteristics would be pharmaceutically acceptable for a particular component. *See Am. Bioscience, Inc. v. Baker Norton Pharms., Inc.*, No. CV-00-09589-MRP, 2001 WL 36170997, at *2 (C.D. Cal. Aug. 31, 2001) (debate over what is an ideal formulation for administration has no place in the interpretation of unambiguous term). What characteristics may be acceptable does not modify what "pharmaceutically acceptable" means or import limitations into the claims.

GSK also asserts that "finished drug product" violates the claim differentiation doctrine by importing the "formulation" limitation of claim 2 and the "safe and effective amount" of claims 3-5 into claim 1. GSK Section III.B.3.a.(v). But Defendants' definition does not require incorporation of those limitations; rather, it requires only that the compound itself is acceptable (*i.e.*, suitable) for use in a pharmaceutical. Claim 2 is directed to the inclusion of the compound in the formulation; claims 3-5 are directed to formulations with safe and effective amounts of ingredients. Because the definition does not require a formulation or any amount, the "suitable for use" definition does not violate the claim differentiation doctrine.

b. "Pharmaceutically acceptable" is consistently used with the same meaning

GSK does not dispute that the ordinary meaning of the terms "pharmaceutical," "medicinal," and "acceptable" are "a medicinal drug," "tending or used to cure disease or pain," and "capable or worthy of being accepted." Ex. 390. That is, a "pharmaceutically acceptable" ingredient is one that is capable of being accepted for use in a pharmaceutical for curing disease. Rather than define acceptable, GSK purports to reduce *what* is acceptable to "not deleterious." That contradicts the plain meaning of acceptable. GSK also notes that the dictionary definitions do not contain the words "finished drug product," GSK Section III.B.3.b.(i), but Defendants' construction only requires an ingredient to be ***suitable for use*** in a pharmaceutical, a finished drug product. Indeed, one court confirmed that the dictionary provides the ordinary meaning:

> According to Oxford English Dictionary (Second Edition), the plain meaning of 'pharmaceutically' is 'related to pharmacy'; the plain meaning of 'pharmacy is 'the use or administration of drugs or medicine.' Thus, a 'pharmaceutically acceptable' formulation is one "acceptable for administration.'

Am. Bioscience, No. CV-00-09589-MRP, 2001 WL 36170997, at *2.

That definition is consistent with the ordinary meaning as used in other patents and understood by the experts. Yet GSK attacks Dr. Rogers's testimony because he acknowledged that a "finished drug product" must be FDA approvable and claims 1-2 do not require a dosage form or finished drug product. That testimony, however, is consistent with the ordinary meaning. The ordinary meaning and claims 1-2 require only that the ingredient be *suitable for use* in a finished drug product, not that there is a finished drug product. Moreover, the testimony of Dr. Byrn on which GSK relies is in reference to the characteristics of a pharmaceutically acceptable hydrate. Ex. 391p (Byrn Tr. 409:22-410:12). But, as discussed above, *what is* acceptable does not change *the meaning* of acceptable. Dr. Byrn's use of only "not deleterious"

would contradict the Patents, and he agreed that "pharmaceutically acceptable" means "pharmaceutically acceptable for its intended purpose," *i.e.*, for use in a pharmaceutical formulation. Ex. 387p (Byrn Tr. 80:24-81:9). Dr. Davies also testified that "pharmaceutically acceptable" means "suitable for pharmaceutical administration." Ex. 152 (Davies Decl. ¶62); Ex. 389p (Davies Tr. 246:3-7). Likewise, the Watson patent defines the term as safe and compatible, using the United States Pharmacopeia "criteria for assessing the pharmaceutical acceptability" of ingredients. Ex. 393 at 6:9-16. Thus, pharmaceutical acceptability may require more than safe and compatible.

c. Conclusion

The Patents do not modify the ordinary meaning of "pharmaceutically acceptable." Thus, it is Defendants' proposed construction of "pharmaceutically acceptable" that is the proper one.

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