IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXOSMITHKLINE LLC (f/k/a SMITHKLINE BEECHAM CORPORATION),	:	C.A. 11-046-RGA
Plaintiff,	:	
v.	:	
BANNER PHARMACAPS, INC., *et al.*,	:	
Defendants.	:	

OPINION AFTER TRIAL

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August 9, 2013
Wilmington, Delaware

ANDREWS, UNITED STATES DISTRICT JUDGE:

Plaintiff Glaxosmithkline LLC ("GSK") asserts one patent,[1] U.S. Patent No. 5,565,467 ("the `467 Patent") against Defendants Banner Pharmacaps, Inc., Roxane Laboratories, Inc., Watson Laboratories, Inc. – Florida, Mylan, Inc., Mylan Pharmaceuticals, Inc., and Impax Laboratories, Inc. (collectively "Defendants").[2] The `467 Patent is directed at the synthetic drug compound dutasteride as well as the pharmaceutically acceptable solvates of dutasteride. Each Defendant has filed at least one Abbreviated New Drug Application ("ANDA"), seeking to market generic drug products containing dutasteride. Dutasteride is marketed under the brand name Avodart, and is used to treat androgen responsive or mediated conditions, including benign prostatic hyperplasia ("BPH"), more commonly known as enlarged prostate. Dutasteride is a selective dual inhibitor of the enzyme known as 5-α reductase ("5AR"). The 5AR enzyme converts testosterone into dihydrotestosterone ("DHT"). DHT plays an essential role in the development of the male prostate, but also may cause undesired androgen action resulting in an enlarged prostate later in life. By inhibiting 5AR, dutasteride is able to halt the conversion of testosterone into DHT and is thus able to treat BPH and possibly other conditions.

Defendants stipulated to infringement, but contend that the `467 Patent is invalid due to the failure to meet the written description and enablement requirements, as well as due to the existence of intervening anticipatory prior art. Defendant Roxane also independently asserts that the utility requirement is not met. The Court held a bench trial from January 28 through January 30, 2013.[3] This Memorandum Opinion represents the Court's findings of facts and conclusions

[1] (D.I. 287).
[2] Defendants Anchen Pharmaceuticals, Inc. and Anchen, Inc., were dismissed before trial. (D.I. 262, 270).
[3] The trial transcripts are available at D.I. 305, 306, and 307. The page numbers of the transcripts used in the briefing was consecutive. The page numbers in the filed transcripts begin at "1" in each separate volume. This opinion uses the consecutive numbering.

of law. As explained below, the Defendants did not prove any of the invalidity defenses by clear and convincing evidence, and thus the Court finds in favor of GSK on all issues.

I. WRITTEN DESCRIPTION & ENABLEMENT

The Court first addresses the defenses of written description and enablement under § 112. Defendants argue that although the `467 Patent claims the entire universe of pharmaceutically acceptable solvates of dutasteride, it fails to disclose or enable a single solvate of dutasteride, much less solvates that satisfy the complete scope of the Court's claim construction. GSK disagrees, arguing that solvates are well-known in the art of drug development, the specification expressly describes solvates of dutasteride, and the creation and testing of dutasteride solvates would be routine for someone skilled in the art. Claim 1 of the `467 Patent claims: "[dutasteride] or a pharmaceutically acceptable solvate thereof." The Court construed two terms. (D.I. 243). The first is "solvate," construed as "a complex formed by dutasteride with a solvent in which dutasteride is reacted or from which it is precipitated or crystallized." The second term is "pharmaceutically acceptable," construed as "suitable for use when administered to the recipient thereof in a pharmaceutical."

The parties agree that one of ordinary skill in the art would have an advanced degree in organic or medicinal chemistry, with some experience in drug discovery and development. (Tr. at 130, Dr. Rogers; Tr. at 645-46, Dr. Byrn). The relevant time period is the early to mid-1990s. Defendants further propose that a person of ordinary skill would have access to a team of drug development scientists, including biologists, pharmacologists, and solid-state chemists and formulation scientists. (*Id.*). The Court accepts these proposals for its definition of a person skilled in the art.

(A). Written Description

(i). Findings of fact.

1. One of ordinary skill in the art would have an advanced degree in organic or medicinal chemistry, with some experience in drug discovery and development, and access to a team of drug development scientists, including biologists, pharmacologists, and solid-state chemists and formulation scientists. (Tr. at 130, Dr. Rogers; Tr. at 645-46, Dr. Byrn).

2. The relevant time period is the early to mid-1990s. *See* `467 Patent.

3. Claim 1 of the `467 Patent recites: "[dutasteride] or a pharmaceutically acceptable solvate thereof."

4. "Solvate" is construed as "a complex formed by dutasteride with a solvent in which dutasteride is reacted or from which it is precipitated or crystallized."

5. "Pharmaceutically acceptable" is construed as "suitable for use when administered to the recipient thereof in a pharmaceutical."

6. The solvate concept is introduced in the specification as follows:

> 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 [dutasteride] 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 [dutasteride] or the pharmaceutically acceptable solvates thereof are within the scope of the present invention.
>
> `467 Patent at 3:59-4:12.

7. Technologies such as high throughput screening, which allows the rapid identification of solvates, did not exist in 1993. (Tr. at 128-29).

8. The drug compound dutasteride is the key structural component distinguishing the `467 Patent from the prior art. *See* `467 Patent.

9. A solvate is detected when a person skilled in the art sees a complex of a solvent and a chemical compound, regardless of whether it is said to be reacted, precipitated, or crystallized. (Tr. at 201-03, Dr. Rogers; PTX 222).

10. The concept of solvation has been known in the art for over 100 years. (Tr. at 201-03, Dr. Rogers).

11. Steroids in particular have been known to be prone to solvate formation since 1983. (Tr. at 670, Dr. Byrn; PTX 135).

12. Dutasteride is a steroid. `467 Patent at 10:18.

13. The universe of solvents thought to be pharmaceutically acceptable was well-known and relatively small. (Tr. at 222-29, Dr. Rogers; Tr. at 661, 666-68, Dr. Byrn).

14. All solvates of dutasteride retain the molecular structure and chemical function of dutasteride, and if those solvates were to arrive at the active sites, they would have the therapeutic effect. (Tr. at 653-54, Dr. Bryn; Tr. at 233-34, Dr. Rogers).

15. A "pharmaceutically acceptable solvate" that is "suitable for use" does not need to meet all the requirements of a finished drug product. (*See* D.I. 226, p. 42-43).

16. The "suitable for use when administered to the recipient thereof as a pharmaceutical" construction of "pharmaceutically acceptable solvate" requires the solvate to be safe and to offer some therapeutic effect. (*Id.*).

17. It would be routine for a person skilled in the art to select a solvent to make a safe solvate, meeting the first "suitable for use" requirement. *See* Factual Finding # 13.

18. For the solvate to offer some therapeutic effect, it must be bioavailable. (Tr. at 234-36, Dr. Rogers; Tr. at 703, Dr. Byrn).

19. To achieve bioavailability, the solvate must be dissolved and have the requisite solubility in the body. (Tr. at 234-35, Dr. Rogers).

20. Solvate formation within a series of related compounds tends to lack a discernible pattern, with each compound having a unique response to solvate formation. (PTX 144 at 234; *see also* DTX 88 at 1148).

21. It can be difficult or even impossible to predict whether a particular solvate form will offer bioavailability prior to the solvate's actual formation. (Tr. at 654, 800-01, Dr. Byrn; *see* DTX 309 at 4).

22. Routine testing techniques allow the bioavailability of a solvate to be determined after the fact. (Tr. at 111-14, 209, Dr. Rogers).

23. To ascertain solubility of a particular form in 1993, one would perform a solubility test. (Tr. at 235, Dr. Rogers).

24. A solubility test could be done within a week. (Tr. at 235-36, Dr. Rogers).

25. Example 3D of the `467 Patent's specification shows dutasteride dissolved in a solution. `467 Patent at 15:21-25.

26. A chemical reaction as it is typically referred to involves the transformation of a compound's chemical identity via the creation or destruction of covalent bonds. (Tr. at 114-18, Dr. Rogers).

27. The specification at times uses the word "reaction" in conjunction with examples of such covalent bond formation. (Tr. at 751-53, Dr. Byrn; `467 Patent at 5:37-44, 7:63-68; 12:29-45).

28. Example 3D does not style itself as a reaction, but rather a dissolution, and does not depict the creation of covalent bonds. (467 Patent at 15:21-25).

29. The term "reacted" is used in the context of solvation. `467 Patent at 3:61.

30. Solvation does not involve the transformation of chemical identity, *i.e.*, the creation of covalent bonds. (Tr. at 653-54, Dr. Bryn; Tr. at 233-34, Dr. Rogers).

31. A "reacted" solvate would not require the creation of covalent bonds. (*See id.*).

32. Solvation has been closely associated with dissolution for over 100 years. (PTX 222 at 160).

33. Solvates can form when an organic compound is dissolved in water. (Tr. at 202-03, Dr. Rogers).

34. Solvent molecules interact with dissolved molecules of a compound to create a solvate. (Tr. at 201-03, Dr. Rogers; PTX 222; PTX 340).

35. The Avodart label is identified as a dissolved compound but is not labeled as a solvate. (Tr. at 758-762, Dr. Byrn; DTX 438 at 11-12).

36. Example 3D depicts the dissolution of the steroid dutasteride in the safe solvent known as propylene glycol. (Tr. at 255, Dr. Rogers).

37. Example 3D describes a solvate of dutasteride. (Tr. at 688, Dr. Byrn).

(ii). Legal discussion and conclusions of law.

The written description "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The test is whether the disclosure "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* This requires an "objective inquiry into the four corners of the

specification from the perspective of a person of ordinary skill in the art." *Id.* This is a question of fact. *Id.*

"[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* "[The] sufficient description of a genus requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 1350. "'A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials.'" *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1363 (Fed. Cir. 2011) (citations omitted). Factors to be examined include "'the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.'" *Ariad*, 598 F.3d at 1351. "A patent is presumed to be valid, and this presumption can only be overcome by clear and convincing evidence to the contrary." *Id.* at 1354.

As discussed above, the `467 Patent claims both dutasteride and pharmaceutically acceptable solvates thereof. The dispute as to written description is focused on the pharmaceutically acceptable solvate limitation of the claim, as Defendants argue that those solvates are not adequately described. The solvate concept is introduced in the specification as follows:

> 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 [dutasteride] 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 [dutasteride] or the pharmaceutically acceptable solvates thereof are within the scope of the present invention.

`467 Patent at 3:59-4:12. Defendants argue that these conclusory statements are not sufficient to adequately describe solvates, as the specification must adequately describe all three solvate subgroups included in the Court's construction, *i.e.*, crystalline, precipitated, and reacted solvates. Defendants rely on *Eli Lilly Co. v. Teva Pharmaceuticals USA, Inc.*, 619 F.3d 1329 (Fed. Cir. 2010). In that case, the claim term "in particulate form" was construed broadly to include drug particles of a particular measurement in both the bulk form and within the tablet form after formulation. *Id.* at 1344. The specification, however, only described the measurement of the drug particles in the bulk form. *Id.* at 1345. It did not describe the measurement within the formulated tablet. *Id.* For this reason, the specification did not adequately describe the "in particulate form" claim term. *Id.*

Defendants also rely on *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353 (Fed. Cir. 2011). In that case, the patent claimed both rapamycin and its structurally similar macrocyclic analogs. *Id.* at 1362. The patent was invalid for failing to adequately describe and enable those macrocyclic analogs, even though rapamycin itself was fully disclosed. *Id.* at 1366-67. "There [was] insufficient correlation between the function and structure of rapamycin and its analogs to provide adequate written description support for the entire genus of macrocyclic lactone analogs of rapamycin." *Id.* at 1366. The reasons provided also included "the absence of information regarding structural characteristics of macrocyclic lactone analogs or examples of

macrocyclic lactone analogs in the specification, the unpredictability of the art and the nascent state of using drug-eluting stents to inhibit restenosis[.]" *Id.* at 1366-67.

GSK disagrees with the relevance of this authority, arguing that as a matter of law the specification need not disclose solvates of a drug compound where the underlying drug compound is adequately disclosed. In support of this argument, GSK cites two opinions from the Board of Patent Appeals and Interferences ("BPAI"). They are *Ex Parte Sabine Germeyer*, 2010 WL 4961695 (B.P.A.I. Dec. 1, 2010) and *Ex parte Yijuan Chern*, 2011 WL 5080233, *1-2 (B.P.A.I. Oct. 24, 2011). In *Germeyer*, the Examiner rejected the application for failing to describe and enable "hydrates" of the claimed compounds, focusing on the difficulty of predicting hydrate structures.[4] 2010 WL 4961695 at *2. The BPAI reversed the Examiner, finding that the claims included using any available hydrate, and did not require a hydrate having a specific or identified structure. *Id.* at *3. The BPAI also found that hydrates form naturally, whether or not their structures can be predicted in advance. *Id.* Finally, it was noted that no evidence was provided that a hydrate cannot be used until its structure is identified. *Id.*

GSK also cites *Ex parte Yijuan Chern*, where the BPAI held that solvates of a drug compound were described and enabled even though the specification did not disclose specific solvate chemical structures or methods of making those solvates, and that the formation of a particular solvate was unpredictable. The BPAI held that solvates need not be described or enabled, as the claimed drug compound itself was a sufficient common structural feature to meet the requirements of the law. *Id.* at *3. Finally, it was noted that the applicants did not claim that

[4] Hydrates are solvates made from a water solvent.

their inventive contribution was to provide solvates of the drug compound, but to use the drug compound to treat Huntington's disease. *Id.*

GSK argues that this authority is persuasive for the conclusion that claimed solvates of a drug compound need not be individually described or enabled. The BPAI decisions, however, concern patents filed more than 15 years after the `467 Patent. They thus have reduced persuasive value as to the relevant state of the art here. Technologies such as high throughput screening, which allows the rapid identification of solvates, did not exist in 1993.[5] The concept, however, that the drug compound is the key structural feature of the solvate was applicable at the time of the `467 Patent's filing, and has some value here. As to Defendants' case law, the Court does not agree that the specification must independently describe crystalline, precipitated, and reacted solvates as subgroups of the genus of pharmaceutically acceptable solvates. The claim recites "pharmaceutically acceptable solvates." There is no reason why a person skilled in the art would not credit a patentee with possession of a solvate merely because the patentee did not disclose solvates formed by each solvation process. Regardless of the characterization of the chemical process forming a solvate, i.e., whether it is said to be reacted, precipitated, or crystallized, a solvate is a solvate, and a solvate is detected when a person skilled in the art sees a complex of a solvent and a chemical compound.[6] The language of the specification itself suggests that any one of the solvate forms will suffice equally.[7] There is no suggestion that the

[5] Dr. Rogers, Defendants' expert, testified that the state of the art has improved greatly since 1993 with the use of "high throughput screening." (Tr. at 128-29).
[6] (Tr. at 201-03, Rogers; PTX 222).
[7] "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." `467 Patent at 3:60-4:02. The specification's use of "or" suggests that not all organic compounds are expected to form solvates from all three chemical interactions. Contrast this with the holding in *Eli Lilly*, which held that the patent necessarily claimed the particular size of drug particles both in bulk form and in tablet form, and thus the requirements of § 112 needed to be met for both forms.

scope of the invention may only be satisfied where solvates formed by each possible process are present. According to Defendants' logic, even if the specification indisputably disclosed a pharmaceutically acceptable crystalline solvate of dutasteride, a person skilled in the art would not credit the patentee with possession of the claimed material, "dutasteride and pharmaceutically acceptable solvates thereof," for failing to disclose the precipitated and reacted permutations.

The cases cited by Defendants do not persuade otherwise. In *Eli Lilly Co.*, "in particulate form" was construed to require measurements of the drug particle in tablet form. 619 F.3d at 1344-45. Those measurements were not disclosed, and the court credited testimony that a person skilled in the art would not know whether the inventor possessed the measurements of the drug particle in tablet form, which was key to the scope of the invention. *See id.* at 1345. Here, in contrast, there is no requirement that all three solvate forms be disclosed for the full scope of the claims to be adequately described. What is important is the end result, which is a pharmaceutically acceptable solvate, and the scope of the claims is not dependent on how that solvate is formed. It is important to keep in mind that it is the molecule dutasteride which sets the `467 Patent apart from the prior art. Dutasteride is where the novelty lies, and that is where a person skilled in the art would need the most information. As conceded by Defendants' own expert, Dr. Rogers, the concept of solvation, in contrast, has been known in the art for over 100 years. (Tr. at 201-03). Steroids in particular have been known to be prone to solvate formation since 1983. (Tr. at 670, Dr. Byrn; PTX 135). Dutasteride is a steroid. `467 Patent at 10:18. Further, the universe of solvents thought to be pharmaceutically acceptable was well-known and

relatively small.[8] It is undisputed that all solvates of dutasteride retain the molecular structure and chemical function of dutasteride, and if those solvates were to arrive at the active sites, they would have the therapeutic effect. (Tr. at 653-54, Dr. Bryn; Tr. at 233-34, Dr. Rogers). There is thus less uncertainty facing a person skilled in the art attempting to envision a pharmaceutically acceptable solvate of dutasteride, where dutasteride is readily described, than was faced in *Eli Lilly Co.*, where the person skilled in the art faced envisioning the novel drug particle size concept.

For similar reasons, *Boston Scientific* is not applicable. 647 F.3d at 1353. In that case, the Federal Circuit found it key that there was insufficient correlation between the structural characteristics of rapamycin and the entire genus of macrocyclic lactone analogs of rapamycin. *Id.* at 1366-67. Here, there is no dispute that a solvate of dutasteride has the same effective chemical function of dutasteride, and thus no correlation need be shown. Moreover, unlike the relevant field of *Boston Scientific*, which was described as "nascent" in the decision, the art of steroid solvates had been studied and developed prior to the filing of the `467 Patent. There is a difference between claiming an identified compound in isolation with its solvates, and claiming an identified compound and a vast number of similar but unidentified compounds. For these reasons, the cases relied on by Defendants are not dispositive, and indeed, not persuasive.

Defendants also argue that the specification must make clear that the claimed solvates are sufficiently soluble, have sufficient dissolution rates, are physically and chemically stable, and can be produced consistently. (Tr. at 159-61, Dr. Rogers). This is argued to be necessary to meet the Court's construction of "pharmaceutically acceptable," which is "suitable for use when

[8] Dr. Byrn testified that nine safe solvents were universally known. (Tr. at 661, 666-68). Dr. Rogers testified that less than 20 safe solvents were available. (Tr. at 222-29).

administered to the recipient thereof as a pharmaceutical." Defendants argue that there is high unpredictability as to how a particular solvate form will behave in a body, and because of this unpredictability, the specification must provide specific information as to acceptable solvate forms to ensure the inventors actually possessed the invention. This interpretation of the Court's claim construction is too strict. A "pharmaceutically acceptable solvate" that is "suitable for use" does not need to meet all the requirements of a finished drug product. (*See* D.I. 226, p. 42-43). Dr. Rogers' opinion was thus wrongly derived at least in part from the disowned finished drug product standard. (Tr. at 238). The "suitable for use when administered to the recipient thereof as a pharmaceutical" construction of "pharmaceutically acceptable solvate" requires the solvate to be safe and to offer some therapeutic effect. The uncontradicted evidence is that there were solvents known to be safe for a person skilled in the art to choose from in 1993. (Tr. at 661, 668-68, Dr. Byrn; Tr. at 222-29, Dr. Rogers). This suggests that it would be routine for a person skilled in the art to select a solvent to make a safe solvate, meeting the first "suitable for use" requirement.

The second requirement, *i.e.*, offer therapeutic effect, is more complicated. For the solvate to offer some therapeutic effect, it must be bioavailable. (Tr. at 234-36, Dr. Rogers; Tr. at 703, Dr. Byrn). To achieve bioavailability, the solvate must be dissolved and have the requisite solubility in the body. (Tr. at 234-35, Dr. Rogers). Defendants did prove that it can be difficult or even impossible to predict whether a particular solvate form will offer bioavailability, at least prior to the solvate's actual formation. (Tr. at 654, 800-01, Dr. Byrn; *See* DTX 309 at 4). Solvate formation within a series of related compounds tends to lack a discernible pattern, with each compound having a unique response to solvate formation. (PTX 144 at 234; *see also* DTX 88 at 1148). "Perhaps the chief challenge in managing the phenomenon of multiple solid forms

of drugs is our inability to predict how many forms can be expected in a given case[.]" (DTX 88 at 1148). If a drug's behavior cannot be predicted in a dosage form, it would be a problem. (Tr. at 801, Dr. Byrn). There thus would be a high degree of uncertainty as to whether a yet-to-be-formed solvate of dutasteride would meet the bioavailability requirement.

That being said, although bioavailability could not be predicted in advance of solvate formation, it was determinable after the fact. Crystal x-ray refraction and other techniques allowed for the identification of a solvate form. (Tr. at 111-14, Dr. Rogers). Dr. Rogers himself admitted to testing and characterizing compounds as an undergraduate in 1978 using this technique. (Tr. at 209). To ascertain solubility of a particular form in 1993, one would perform a solubility test. (Tr. at 235, Dr. Rogers). This test could be done in less than a week. (Tr. at 235-36, Dr. Rogers). Thus, methods of identifying solvates and determining solvate solubility were well-known and routine in the art in 1993. This ameliorates the difficulty that would arise from being unable to predict whether a solvate would offer bioavailability before it is created, as it could be routinely identified, with solubility tested, after creation. This lessens the force of Defendants' argument that the '467 Patent must explicitly describe and identify particular forms of pharmaceutically acceptable solvates to meet the written description requirement, as the general knowledge of the art determines the degree of detail needed for a patent to meet the written description requirement.

This brings the Court to what is actually disclosed in the specification. Defendants argue that the specification completely fails to disclose crystallized, precipitated or reacted solvates of dutasteride. GSK disagrees, arguing that solvates are indeed disclosed, highlighting Example 3D from the specification in particular, which shows dutasteride dissolved in a solution as a

purported reacted solvate.[9] Example 3D describes an injection dosage formulation of dutasteride as follows:

> The active compound and buffering agents are dissolved in the propylene glycol at about 50° C. The water for injection is then added with stirring and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving.

`467 Patent at 15:21-25. GSK argues that the described dissolving of dutasteride in propylene glycol is the disclosure of a reacted solvate. Defendants disagree, arguing that a reacted solvate must result from a chemical reaction, *i.e.*, the creation of a new chemical compound via the breaking or forming of covalent bonds. According to Defendants, the specification's usage of "reacted" is consistent with this meaning, as the term is only used in conjunction with examples of covalent bond formation, and the specification makes clear that dissolution and reaction are different concepts. Defendants argue that Example 3D's dissolution does not style itself as a reaction, nor is it an example of the covalent bond formation, and it thus cannot serve as an example of a reacted solvate of dutasteride.

Defendants are correct on some points. A chemical reaction as it is typically referred to involves the transformation of a compound's chemical identity via the creation or destruction of covalent bonds. (Tr. at 114-18, Dr. Rogers). The specification at times uses the word "reaction" in conjunction with examples of such covalent bond formation; in contrast, Example 3D does not style itself as a reaction, but rather a dissolution. (Tr. at 751-53, Dr. Byrn); `467 Patent at 5:37-44, 7:63-68; 12:29-45. Example 3D further does not depict the creation of covalent bonds. Defendants are incorrect, however, in that the patentee does not uniformly use the term "reacted" in the context of covalent bond creation or destruction. "Reacted" is also used squarely in the

[9] GSK also argues that the specification discloses crystalline solvates, but Dr. Byrn admitted that he would have to "modify" the disclosure to get to this result. (Tr. at 766-67). This lessens the credibility of this aspect of his opinion.

context of solvation, and it is not disputed that the solvation of dutasteride would not involve the transformation of dutasteride's chemical identity.[10] (Tr. at 653-54, Dr. Bryn; Tr. at 233-34, Dr. Rogers). Covalent bonds would thus not be formed during the formation of a "reacted" solvate, or found in any example thereof. This may cut against the plain and ordinary meaning of "reacted," but "the patentee is free to define the invention how he pleases," even if that definition is not perfectly consistent with the extrinsic evidence.[11] *GlaxoSmithKline LLC v. Anchen Pharmaceuticals, Inc.*, CA 11-046-RGA, 2012 WL 5594540, *3 (D. Del. Nov. 15, 2012). This understanding of "reacted" is consistent with the scope of the invention, as it would make no sense to require the solvation of dutasteride to result in the creation of a new chemical compound, as doing so would alter the nature of the active ingredient and defeat the entire purpose of creating a pharmaceutically acceptable solvate thereof.

The evidence is also that solvation has been closely associated with dissolution for over 100 years.[12] Dr. Rogers admitted that "hydrates can form when an organic compound is dissolved in water." (Tr. at 202-03). Solvent molecules interact with dissolved molecules of a compound to create a solvate.[13] (Tr. at 201-03, Dr. Rogers; PTX 222; PTX 340). It was further known since at least the 1980s that steroids are prone to solvate formation. (Tr. at 670, Dr. Byrn; PTX 144 at 233.) A person skilled in the art would correspondingly understand that dissolution is a concept essential to solvation and the steroid drug class forms solvates routinely. This

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[10] "Reacted" is used in a variety of contexts in the `467 Patent, and the specification's use of a term in various contexts speaks to that word's breadth.

[11] This undermines Defendants' reference to the Trémillon publication, as the fact that dissolution must occur prior to a covalent bond chemical reaction in a solvent is of no importance when that is not the type of chemical reaction that occurs during solvation. (*See* PTX 340 at 3).

[12] "The most important fact that was discovered by Anderson, as far as the solvate theory is concerned, is the following. In 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." (PTX 222 at 160).

[13] This is demonstrated by Dr. Rogers' testimony: "Q: In fact, the term solvation is often used to describe the process by which solvent molecules interact with dissolved molecules; correct? A. Yes. Solvation has been used in that way." (Tr. at 201).

removes the barrier to recognizing Example 3D as the formation of a solvate via dissolution. Although a person skilled in the art might have trouble predicting which precise form of a dutasteride solvate would be created through dissolution, he or she would have available routine testing methods for identification after the fact. (Tr. at 256-257, Dr. Rogers). Defendants counter, however, that GSK's own Avodart submissions to the FDA mention soft gel capsules, which would form a solvate according to GSK's argument, but Avodart is only identified as a dissolved compound and is not labeled as a solvate.[14] (Tr. at 758-762, Dr. Byrn; DTX 438 at 11-12). The accuracy of the Avodart label, however, is not on trial here, nor is its labeling determinative. It has been established that solvation and dissolution are closely intertwined, and a person skilled in the art would understand that dutasteride is the common structural component distinguishing the `467 Patent from the prior art. Further, Example 3D depicts the dissolution of the steroid dutasteride in the safe solvent known as propylene glycol. (Tr. at 255, Dr. Rogers). Once dissolved, dutasteride would inhibit 5AR, thus offering a therapeutic effect, as conceded by Dr. Rogers. (Tr. at 234). The combination of what was known in the art with Example 3D's description of dutasteride's dissolution in a known solvent is sufficient to meet the written description requirement of a "pharmaceutically acceptable solvate." Thus, Defendants have not shown by clear and convincing evidence that the patent does not satisfy the written description requirement.

(B). Enablement

(i). Findings of fact.

1. The claiming of pharmaceutically acceptable solvates does not render the claims of the `467 Patent unusually broad.

[14] This was contrasted to another GSK drug product, which was expressly identified as containing a solvated form of the active ingredient.

2. Internal GSK documents demonstrate that GSK had problems developing a hydrate formulation of dutasteride both before and after the filing date. (*See, e.g.*, JTX 5 at 11).

3. In July 1994, a GSK technical report stated, "The nonsolvated form [] was preferred because it was expected to have a higher dissolution rate than the less soluble hemihydrate [] in solid oral dosage forms (2) and the hydrated form showed the tendency to form incompletely." (JTX 5 at 11).

4. That report also stated, "The presence of multiple types of hydrates of [dutasteride], for which the factors governing which one will appear are currently unknown, is another reason to develop the nonsolvated form." (*Id.* at 12).

5. In October 1994, an internal memo from GSK researcher Dr. Dhingra discussed data concerning certain generated batches, stating, "It would be a process nightmare to control the amount of water and also unpredictable behavior in solid formulation [of the hydrate form]." (DTX 28, October 1994).

6. Dr. Dhingra testified that he did not know "whether a hydrated form of dutasteride could be used for a formulation" as of January 1995. (Tr. at 511).

7. A later July 1995 GSK research report stated, "The results of the study showed that the hydrate could not be produced in a consistent manner and was therefore eliminated from further consideration as another potential form of the bulk drug substance." (JTX 37 at 4).

8. The report continued, "These results indicate that it will be very difficult to consistently produce a hydrated form of [dutasteride] that contains a stoichiometric amount of water.... From these results, the decision was made to proceed the anhydrous form as the selected form of dutasteride bulk drug substance through full development." (*Id.* at 10).

9. In 2006, a GSK scientist stated that results indicating the presence of multiple types of hydrates supported the decision not to select that form for development. (DTX 70 at 1).

10. In 2006, a GSK scientists reclassified the studied hydrate form as somewhere between a hemi-hydrate and a monohydrate. (*Id.* at 1-2).

11. These problems occurred in the earlier days of development. (Tr. at 800).

12. U.S. Patent No. 4,391,755, filed in 1983, taught that steroid solvates could be formed in a matter of hours by merely grinding up the steroid and suspending it in water. (Tr. at 216-17, Dr. Rogers).

13. A person skilled in the art who desired a solid solvate would merely need to dissolve a compound in a warm solvent to achieve a solution, and then let the solution cool to yield a precipitate or crystals. (Tr. at 654-55, 693, 695, Dr. Byrn).

14. Characterization testing would take anywhere from a day to several days, and dissolution and solubility testing would be just a matter of hours to a day. (Tr. at 195-96, 212-14, Dr. Rogers).

15. The difficulties encountered by GSK in relation to the hydrate of dutasteride were associated with commercialization of a finished drug product, *i.e.*, bulk form development, rather than demonstrating how to make a safe solvate with therapeutic effect.

16. Example 3D describes a dissolved solvate in solution. `467 Patent at 15:21-25.

17. The level of skill in the art is high, and would allow for a team of drug development scientists. (Tr. at 130, Dr. Rogers; Tr. at 645-46, Dr. Byrn).

18. Trial and error would be necessary to form a solvate of dutasteride involving the following variables: the solvent used, amount of solvent, amount of pharmaceutical compound, relative humidity, temperature, and incubation time. (Tr. at 128-129, Dr. Rogers; DTX 339 at 10).

(ii). Legal discussion and conclusions of law.

Defendants argue that the `467 Patent fails to meet the enablement requirement of § 112. To satisfy this requirement, the specification must enable a person of ordinary skill in the art to make and use the invention. Section 112 provides in pertinent part that the specification must describe "the manner and process of making and using [the invention], in such clear and concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use [the invention]." 35 U.S.C. § 112, ¶ 1.[15] This requirement is met when, at the time of filing the application, one skilled in the art, having read the specification, could practice the invention without "undue experimentation." *Cephalon, Inc. v. Watson Pharmaceuticals, Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013). Whether undue experimentation is required is not a single, simple factual determination, but rather a conclusion reached by weighing many factual considerations. *Id.* The following factors may be considered when determining if a disclosure requires undue experimentation:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

[15] Now known as § 112(a).

> invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. (citing *In re Jack R. Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

GSK relies heavily on three BPAI cases that rejected arguments similar to those of Defendants regarding the necessity of specific directions to enable a drug solvate claim limitation. One of these cases is *Germeyer*, which was discussed in the written description analysis. *Germeyer* found that an inability to predict a hydrate structure in advance of its formation does not require the specification to identify a specific hydrate structure. 2010 WL 4961695 at *3. There was further no evidence that a hydrate cannot be used until its structure is determined. *Id.* The rejections for a lack of enablement were thus overruled. *Id.*

A second case is *Ex Parte Xiong Cai*, 2011 WL 6127936 (B.P.A.I. Dec. 7, 2011). In that case, the examiner was reversed after concluding that undue experimentation would be required to make and use solvates, hydrates, and polymorphs of the claimed genus compounds, even though the compounds themselves were enabled, because of the unpredictability of the art of solvation and the extensive study that would be necessary for the characterization. *Id.* at 2. The BPAI held that solvates, hydrates, and polymorphs of a compound are the same compound in different physical forms, with the compound and solvent molecules retaining their chemical identities. *Id.* at 6. The BPAI also relied on the existence of "high-throughput methods of crystal growth and analysis" that are capable of rapidly testing thousands of compounds. *Id.* at 7. The BPAI also questioned why differences in a form's solubility or even therapeutic activity would necessarily result in the need for more than routine experimentation. *Id.* at 9.

GSK also cites *Ex parte Liu*, 2010 WL 3615693 (B.P.A.I. Sept. 15, 2010). In that case, the claims involved a genus of compounds and their solvates. *Id.* at *3. The examiner found that

the claims were not enabled because solvate formation is unpredictable, and because "[t]here is no evidence that solvates of these compounds actually exist." *Id.* The BPAI disagreed, finding that references showed that solvates and hydrates are routinely produced and characterized empirically, despite the difficulty in prediction and the possibility that the experimentation would be tedious and time-consuming. *Id.* at 4.

Defendants argue that these authorities are irrelevant, for they come approximately 15 years after the filing date of the `467 Patent, in the era of high-throughput testing, which did not yet exist in 1994. Defendants further point out that there was no evidence of the patentee's actual failed attempts to make the compound, as exists here. The Court agrees with Defendants that the later date of these opinions reduces their persuasiveness on the subject of high-throughput testing, but certain underlying principles were active in the early to mid-90's, *i.e.*, the solvate of a compound is merely the compound in a different physical form, an unidentified solvate is not always unusable, and even tedious and time-consuming experimentation does not make that experimentation undue. These principles assist in the Court's enablement analysis.

The Court will now address the *Wands* factors argued by the parties.

(a). Breadth of claims

Defendants argue that the claims of the `467 Patent are broad, as the Court's claim construction requires the enablement of all three categories of pharmaceutically acceptable solvates: reacted, precipitated, and crystalline. Further, Defendants argue that the patent must enable the full scope of "pharmaceutically acceptable" solvates, which requires more extensive and difficult enablement than solvates alone. GSK argues that, for the same reasons a solvate formed by any individual chemical process need not necessarily be disclosed to meet the written

description requirement, the specification need not enable any particular individual process of solvation. A solvate is a complex of dutasteride with a solvent, no matter how the solvate is formed.[16] Further, the fact that solvates are recited does not render the claims unusually broad. As discussed, solvates of organic compounds have long been known in the art, and the chemical compound of dutasteride is precisely claimed. For this reason, the Court finds that the claims of the `467 Patent are not unusually broad, and this factor is neutral in the analysis of whether the `467 Patent is enabled.

(b). The quantity of experimentation necessary and the state of the art

Defendants argue that an inordinate amount of trial and error would be required to make a pharmaceutically acceptable crystalline solvate, citing the difficulties a person skilled in the art would have predicting whether a particular solvate would form and the characteristics that the solvate might display. Defendants put forth GSK's real-world failure to make a crystalline solvate of dutasteride to be used as an active pharmaceutical ingredient to show that even if GSK formed solvates of dutasteride, they were by no means pharmaceutically acceptable, citing *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (holding that patentee's failure to make and use the claimed invention at the time of the application weighed against finding enablement). Defendants also argue that this evidence shows that the field of solvation is unpredictable. Internal GSK documents do demonstrate that the drug company had problems developing a hydrate formulation of dutasteride both before and after the filing date. In July 1994, a GSK technical report stated, "The nonsolvated form [] was preferred because it was

[16] Defendants cite *Alza Corp. v. Andrx Pharmaceuticals, LLC*, 603 F.3d 935 (Fed. Cir. 2010) in support of their position, but *Alza Corp.* involved a field that "was not mature" at the time of filing, and the claimed dosage form was described as a "breakaway from the prior art." *Id.* at 941. The concept of solvation does not share those characteristics.

expected to have a higher dissolution rate than the less soluble hemihydrate [] in solid oral dosage forms (2) and the hydrated form showed the tendency to form incompletely." (JTX 5 at 11). Further, "[t]he presence of multiple types of hydrates of [dutasteride], for which the factors governing which one will appear are currently unknown, is another reason to develop the nonsolvated form." (*Id.* at 12). In October 1994, an internal memo from GSK researcher Dr. Dhingra discussed data concerning certain generated batches, stating, "It would be a process nightmare to control the amount of water and also unpredictable behavior in solid formulation [of the hydrate form]." (DTX 28, October 1994). Dr. Dhingra testified that he did not know "whether a hydrated form of dutasteride could be used for a formulation" as of January 1995.[17] (Tr. at 511).

A later July 1995 GSK research report stated, "The results of the study showed that the hydrate could not be produced in a consistent manner and was therefore eliminated from further consideration as another potential form of the bulk drug substance." (JTX 37 at 4). The report continued, "These results indicate that it will be very difficult to consistently produce a hydrated form of [dutasteride] that contains a stoichiometric amount of water…From these results, the decision was made to proceed the anhydrous form as the selected form of dutasteride bulk drug substance through full development." (*Id.* at 10). Finally, years later, in 2006, a GSK scientist revisited the issue of the development of dutasteride solvate batches. He stated that results indicating the presence of multiple types of hydrates supported the decision not to select that form for development. (DTX 70 at 1). He also reclassified the form as somewhere between a hemi-hydrate and a monohydrate. (*Id.* at 1-2). Defendants argue that this shows GSK did not

[17] This questioning was elicited based on Dr. Dhingra's memo asking, "Can a hydrate form be used for formulation development? Once a decision is made on the clinical dose, it would be easy to speculate if a soft gel capsule or a tablet formulation will be progressed." (DTX 30)

even know exactly what form it had. Dr. Byrn admitted that these problems occurred during the early stages of drug development. (Tr. at 800). Defendants argue it is thus difficult to chalk these problems up to issues involving manufacturing and commercialization that would be less relevant to the enablement analysis.

In response, GSK argues that solvates could be formed and screened according to routine processes that do not preclude enablement. *In re Wands*, 858 F.2d at 736. The question is whether such screening is undue. *See id.* According to GSK, a person skilled in the art who desired a solid solvate would merely need to dissolve a compound in a warm solvent to achieve a solution, and then let the solution cool to yield a precipitate or crystals. (Tr. at 654-55, 693, 695, Dr. Byrn). This would take a half an hour to overnight. (Tr. at 696, Dr. Byrn). The solvates would then need to be characterized, and GSK points to Dr. Rogers' own testimony that he made and characterized solvates as an undergraduate, prior to becoming a person skilled in the art. (Tr. at 208-10). Dr. Rogers further testified that characterization testing would take anywhere from a day to several days, and that dissolution and solubility testing would be just a matter of hours to a day. (Tr. at 195-96, 212-14). GSK argues that this is all supported by U.S. Patent No. 4,391,755 ("the Wang patent"), filed more than ten years prior to the `467 Patent in 1983, which taught steroid solvate formation in simple terms. (Tr. at 216-17, Dr. Rogers). Specifically, the Wang patent taught that steroid solvates could be formed in a matter of hours by merely grinding up the steroid and suspending it in water. (Tr. at 216-17, Dr. Rogers). A routine technique known as a "screen" allows the testing of several solvates at once. (Tr. at 656-57, Dr. Byrn; PTX 135). GSK argues that Defendants wrongfully attempt to import requirements that pharmaceutically acceptable solvates must "be physically and chemically stable, and be able to be produced consistently," which are characteristics of a finished drug product. GSK also notes

that Dr. Rogers' person skilled in the art would have access to a team of drug development scientists, meaning that the person would have considerable resources at his disposal during this process. (Tr. at 130). Finally, GSK notes that in the case of solvated dutasteride in solution, dissolution testing would be unnecessary because the dutasteride could be administered in solution and would have therapeutic effect, as shown in Example 3D. (Tr. at 701-02, Dr. Byrn; Tr. at 236-37, Dr. Rogers).

The evidence shows that GSK's difficulties with the hydrated solvate of dutasteride pertained to its attempt to shepherd the form into the development stage. For example, the July 1995 memo specifically rejected the idea of moving the hydrate form of dutasteride along for development of the bulk drug form. The fact that the difficulties applied to a step associated with commercialization of a finished drug product, *i.e.*, bulk form development, rather than demonstrating how to make a safe solvate with therapeutic effect, is key, as the `467 Patent only requires GSK to enable a solvate meeting the latter standard. As to the difficulties testified to by Dr. Dhingra, they pertained to the development of soft gel capsule and tablet formulations, which are finished drug products that need not be enabled by the patent. There is further no requirement for GSK to show an ability to precisely control the amount of water that would be present in the hydrated form; although such a characteristic would certainly amount to a requirement for a finished drug product, it is not a requirement of enablement. GSK's rejection of the hydrate as a candidate for large-scale production, even early in the development process, does not dictate finding a lack of enablement. Steroids were routinely ground up and dissolved in solutions to make solvates, as shown by the Wang patent, and Dr. Rogers himself testified that the Court's finding regarding Example 3D would enable a pharmaceutically acceptable solvate

of dutasteride if the Court were to find it a dissolved solvate. Thus, this factor weighs in favor of finding enablement.

(c). Amount of direction and guidance in the `467 Patent

Defendants argue that the patent does not provide working examples or guidance, citing Dr. Byrn's testimony that he would need to modify the specification to find a working example of any crystalline solvate. (Tr. at 766-67, 784, 78). Defendants also argue that Dr. Byrn ignored the evidence that GSK was never able to make a crystalline solvate of dutasteride that was pharmaceutically acceptable. In response, GSK argues that the solution formulations described in the `467 Patent, including Example 3D for an injectable formulation, teach a person skilled in the art how to make and use the invention. Dr. Rogers admitted that, were the description in Example 3D to be considered a solvate, then those solution formulations would be enabled by the `467 Patent. (Tr. at 181). As the Court found that Example 3D does describe a dissolved solvate in solution, this factor favors a finding that the `467 Patent is enabled.

(d). Level of skill in the art

GSK argues that the level of skill in the art of the `467 Patent is very high, thus reducing the amount of disclosure required, and noting that Dr. Rogers' own hypothetical person of ordinary skill would have access to a team of drug development scientists. GSK also notes that Dr. Rogers made and characterized solvates when he was in college, long before he was a person of ordinary skill in the art.[18] Dr. Rogers testified that this factor was "neutral." (Tr. at 178). This factor is not briefed by Defendants, but Defendants' own admission that a person of ordinary skill in the art would have access to a team of drug development scientists provides the

[18] To be fair, Dr. Rogers testified that the solvates were formed by accident.

inference that the level of skill in the art is very high. This means the person would have significant resources at his disposal and this factor favors finding the `467 Patent to be enabled.

(e). Nature of the invention and predictability of the art

Defendants argue that GSK failed to make a pharmaceutically acceptable crystalline solvate of dutasteride, indicating the unpredictable nature of the art. This was also supported by the evidence showing that a person of ordinary skill would be unable to predict the characteristics that a crystalline solvate of a newly discovered drug compound might display. (*See* pp. 13-14, *supra*). This would accordingly require substantial trial and error with many variables, including solvent mixtures, amount of solvent, amount of pharmaceutical compound, relative humidity, temperature, and incubation time. (Tr. at 128-129, Dr. Rogers; DTX 339 at 10). GSK argues that steroids had been known to form solvates as of 1993, as earlier discussed and as described in the Wang patent, that GSK scientists even made solvates by accident, and that it was actually easier to make a crystalline hydrate of dutasteride than the non-solvated form. (JTX 5 at 1, 8-9; JTX 37 at 4). Thus, while there is a considerable degree of unpredictability of which particular form a solvate would take prior to its creation, the evidence also shows that solvation has long been known in the art, steroids are prone to solvation, and methods of creating and testing solvates have also long been known. These latter facts makes this factor weigh slightly in favor of finding the claims enabled.

Viewing the totality of these factors, Defendants have not shown by clear and convincing evidence that the claims of the `467 Patent are not enabled.

II. ANTICIPATION

Defendants assert that Merck's synthesis of dutasteride in May 1994 is intervening prior art that anticipates the claims of the `467 Patent under 35 U.S.C. § 102(g)(2). Defendants argue that the `467 Patent is not entitled to claim priority from the September 1993 filing date of its familial `280 Application, as the `280 Application does not contain any information about the solvates of dutasteride that are claimed in the `467 Patent. Accordingly, GSK's priority date would be the actual filing date of the `467 Patent in March 1995, rendering the Merck synthesis of dutasteride anticipatory art. GSK, of course, disagrees. GSK first argues that Defendants put forth no evidence that Merck's synthesis meets the requirements of conception, due diligence in reduction to practice, or independent inventorship. GSK next argues that the prior reduction to practice of a species within a genus is sufficient to establish the priority of invention, meaning that GSK's 1993 reduction to practice of the compound dutasteride is sufficient to establish priority to the claimed genus of "dutasteride and pharmaceutically acceptable solvates thereof."

(A). Findings of fact

1. Merck chemists synthesized dutasteride in May 1994. (Tr. at 442, Dr. Pirrung).

2. The laboratory notebook of Dr. Raman Bakshi, a Merck chemist, depicts the synthesis of dutasteride on May 4, 1994. (DTX 814).

3. A Merck compound data sheet showed that scientists by the names of Harris and Epstein-Toney requested 2.7 milligram and 2.2 milligram samples of dutasteride, respectively, on May 10, 1994. (DTX 816; Tr. at 447-48, Dr. Pirrung).

4. The samples were intended for 5AR and androgen receptor assays. (Tr. at 448, Dr. Pirrung).

5. Dr. Bakshi of Merck authored a *Journal of Medicinal Chemistry* article that discussed dutasteride and detailed its 5AR inhibitor properties, along with four other compounds. (DTX 674; Tr. at 451-52).

6. No inventor testimony was offered indicating whether Merck independently invented dutasteride.

7. There was no explanation given for the lack of inventor testimony.

8. There was no evidence indicating how Merck first became aware of dutasteride.

9. Two Merck "Monthly Highlights" documents refer to dutasteride as "[t]he purported Glaxo 5α-reductase product candidate in Phase 2 trials" and "the Glaxo lead candidate [] compound," in December 1994 and March 1995, respectively. (PTX 404, 405).

10. The Merck "Monthly Highlights" documents suggest that Merck personnel did not independently conceive of dutasteride.

(B). Legal discussion and conclusions of law.

To prove Merck's prior invention of dutasteride, Defendants must prove Merck's prior conception as well as Merck's diligence in reduction to practice. *Creative Compounds, LLC v. Starmark Laboratories*, 651 F.3d 1303, 1312-13 (Fed. Cir. 2011). "Conception is the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is therefore to be applied in practice." *Id.* An idea is sufficiently definite for conception "when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue." *Burroughs Wellcome Co. v. Barr Labs.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). In the chemical arts, "[c]onception requires (1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it." *Oka v. Youssefyeh*, 849 F.2d 581, 583 (Fed. Cir. 1988). Further, "originality is…inherent to the notion of conception." *Solvay S.A. v. Honeywell Intern, Inc.*, 622 F.3d 1367, 1377 (Fed. Cir. 2010). Where a purported inventor does not independently conceive of an invention, but appropriated it from another source, there is no prior inventorship under §102(g). *Id.* Finally, Defendants must establish that Merck exercised reasonable diligence in reducing the invention to practice. *See Fox Grp., Inc. v. Cree, Inc.*, 700 F.3d 1300, 1304 (Fed. Cir. 2012).

Dr. Pirrung, Defendants' expert for the anticipation defense, testified that Merck chemists synthesized dutasteride in May 1994. (Tr. at 442). In forming this opinion, Dr. Pirrung relied on three pieces of evidence: (1) a laboratory notebook of Dr. Raman Bakshi, a Merck chemist; (2) a compound data sheet, and (3) a *Journal of Medicinal Chemistry* article co-authored by Dr. Bakshi. (DTX 814, 816, 674; Tr. at 449). Dr. Pirrung first described the lab notebook. (Tr. at 442-44). He testified that a compound on page 245 of the notebook depicts the synthesis of dutasteride on May 4, 1994, providing enough information to allow someone to make the compound. (Tr. at 443-44). He further compared the dutasteride structure as depicted in the claim construction opinion with the hand-drawn structure from the notebook, and stated they are the same compound. (Tr. at 455). Dr. Pirrung then turned to the compound data sheet. He testified that the sheet referenced page 245 of the Bakshi lab notebook, and showed that scientists by the names of Harris and Epstein-Toney requested 2.7 milligram and 2.2 milligram samples of dutasteride, respectively, on May 10, 1994. (Tr. at 447-48). Dr. Pirrung further testified that abbreviations on the compound data sheet's table showed that the samples were intended for 5AR and androgen receptor assays. (Tr. at 448). In Dr. Pirrung's opinion, the lab notebook and the compound data sheet prove that Merck actually formed dutasteride in May 1994. (Tr. at 449). Dr. Pirrung lastly relied on Dr. Bakshi's article from the *Journal of Medicinal Chemistry*, which appeared August 18, 1995. (Tr. at 449; DTX 674). Dr. Pirrung testified that the article discussed dutasteride and detailed its 5AR inhibitory properties in the context of four other compounds. (Tr. at 451-52). Dr. Pirrung characterized the publication as the "public coming out" of Merck's work on dutasteride. (Tr. at 452-53). Finally, Dr. Pirrung testified that Merck's work on dutasteride anticipated all of the `467 Patent's claims. (Tr. at 454-464).

Defendants offered no inventor testimony in support of Merck's independent conception of dutasteride; only documentary evidence bolstered by the testimony of Dr. Pirrung. The Federal Circuit has stated that the clear and convincing standard precludes reliance on uncorroborated inventor testimony to prove a date of conception.[19] Here lies the reverse: documentary evidence of possession of the invention, but no inventor testimony offering the story of its discovery. The precedent does not preclude the recognition of a priority date based on documentary evidence alone, but it does highlight the difficulty a party faces meeting the clear and convincing standard absent a thorough showing of the circumstances surrounding the supposed inventive process. The lab notebook and compound data sheet are clear and convincing proof to show that Merck knew of dutasteride and ordered samples of the compound. (DTX 814, 816; Tr. at 442-48, Dr. Pirrung). The content of the Bakshi article suffices for the inference that Merck conducted testing on dutasteride for the purpose of 5AR inhibition, meaning the company appreciated the significance of the drug. (Tr. at 451-52, Dr. Pirrung; DTX 674). This appreciation alone, however, is not enough. It must also be established that Merck independently conceived of dutasteride: "The definition and test of conception...necessitates that the conception of an invention be an original idea of the inventor." *Solvay S.A.*, 622 F.3d at 1378-79.

Although inventor testimony is not required as a matter of law to lay the foundation for an alleged invention, "the unexplained absence of [the] inventor's testimony cannot and should not be ignored." *Borror v. Herz*, 666 F.2d 569, 573 (C.C.P.A. 1981). An inference is raised that the testimony would be unfavorable or at least not support the case, lest there is "ample

[19] "The case law is unequivocal that an inventor's testimony respecting the facts surrounding a claim of derivation or priority of invention cannot, standing alone, rise to the level of clear and convincing proof." *Price v. Symsek*, 988 F.2d 1187, 1194 (Fed. Cir. 1993).

documentary support properly authenticated by other witnesses[.]" *Id.* at 574. Defendants do not explain how Merck originally became aware of or interested in dutasteride and do not explain why no inventor testimony was offered. Further, the evidence indicates that Merck itself associated dutasteride, in one way or another, with GSK. Two Merck "Monthly Highlights" documents refer to dutasteride as "[t]he purported Glaxo 5α-reductase product candidate in Phase 2 trials" and "the Glaxo lead candidate [] compound," in December 1994 and March 1995, respectively. (PTX 404, 405). The statements tend to support the inference that Merck learned of dutasteride from GSK. At a minimum, they inject ambiguity into the independent conception inquiry.[20] "Where ambiguities exist in the record or there is conflicting testimony as to events which an inventor's testimony could clear up, a strong negative inference may be reasonable that his testimony would be unfavorable to his case." *Borror*, 666 F.2d at 574.

Such an inference is at play here. No witness with personal knowledge was offered to clarify or provide context for the meaning of the Merck "Monthly Highlights" statements. Dr. Bakshi's article, which Dr. Pirrung lauded as the "public coming out" (Tr. at 452) of Merck's work on dutasteride, described a group of compounds that were among the various potential 5AR inhibitors. (DTX 674). Dutasteride is one of those compounds. (Tr. at 472). The article cites only one reference for dutasteride – the GSK patent application for dutasteride. (DTX 674 at 4 n.12(c)). This suggests that Merck itself did not view dutasteride to be a Merck drug. There is substantial uncertainty of whether Merck independently conceived of dutasteride, and this uncertainty prevents Defendants from meeting the clear and convincing evidence standard.

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[20] The statements do not rule out the possibility that Merck's conception of dutasteride was independent. The fact that Merck personnel were aware that GSK also was conducting research on dutasteride and associated the drug with GSK does not necessarily mean that Merck learned of dutasteride from GSK. Defendants, however, face a clear and convincing standard, and the most plausible inference drawn, in the Court's view, is that Merck would not have referred to dutasteride as a GSK product unless they somehow learned of the drug or its potential from GSK, especially in the context of the drug industry where the sharing of compounds and research results can occur. Indeed, evidence relevant to other defenses in this trial shows that Merck and GSK shared drug development data.

Thus, Merck's synthesis of dutasteride cannot serve as anticipatory prior art under §102(g)(2), and the Court finds in favor of GSK on that defense.

III. UTILITY

Roxane argues that the `467 Patent should be invalidated for failing to meet the utility requirement of 35 U.S.C. §§ 101 and 112.[21]

(A). Findings of fact.

1. The `467 Patent begins with the statement that dutasteride is "a surprisingly potent and selective dual inhibitor of type 1 and 2 human 5α-reductase." `467 Patent at 1:7-10.

2. The "Utility" section of the `467 Patent begins with the following:

> The steroid 5α-reductase inhibitor of the present invention is useful in the treatment of androgen responsive diseases, e.g., benign and malignant diseases of the prostate, especially benign prostatic hyperplasia, in a manner similar to that for other 5α-reductase inhibitors such as finasteride and SKF105657.

Id. at 10:17-23.

3. The `467 Patent discloses dutasteride's effective dosage range of "about 0.001 to about 2mg/kg body weight per day, preferably in the range of about 0.005 to about 1 mg/kg per day." *Id.* at 10:45-47.

4. The `467 Patent includes *in vitro* data, showing that less than one nanomolar of dutasteride may effectively inhibit both isozymes of 5AR, and that dutasteride is selective against 3BHSD at dosages greater than 1000 nanomolars. *See id.* at 9:57-67 ("Table 1").

5. The `467 Patent also includes a section entitled, "In vivo Evaluation of Steroid 5α-Reductase Inhibitors." *Id.* at 10:01-02.

6. The "In vivo" section discusses the use of the "chronic rat model" to determine the *in vivo* activity of 5AR inhibitors, described as involving the use of castrated male rats, dosed daily with testosterone and the test compound. *Id.* at 10:03-08.

[21] Unlike the written description, enablement, and anticipation defenses, which are proffered by all defendants, the utility defense is only proffered by Roxane.

7. The rats were then sacrificed and their prostates weighed. *Id.* at 10:09-10. A reduction in prostate weight was found, and this is said to have signaled the 5AR reductase inhibition activity of the compound. *Id.* at 10:09-11.

8. There is no disclosure of any underlying experimental data to support the *in vivo* findings. *See id.* at 10:03-11.

9. To substantiate the "correlation of in vitro, rat in vivo and human clinical data relating to an inhibitor of 5α-reductase," the `467 Patent referenced the following publications: "Stoner, E. et al., *J. Steroid Biochem. Molec. Biol.*, 37, 375 (1990); Brooks, J.R. et al., *Steroids*, 47, 1 (1986); and Rasmusson, G.H. et al., *J. Med. Chem.*, 29, 2298 (1986)." *Id.* at 10:27-30.

10. Selectivity to the androgen receptor was known to be a necessary trait for a 5AR inhibitor. (Tr. at 614, Dr. Frye).

11. Merck abandoned a promising 5AR inhibitor candidate because of its "affinity for the androgen receptor[.]" (PTX 242 at 499).

12. Binding with the androgen receptor would interfere with the biological functions of androgens and cause intolerable side effects. (Tr. at 556, Dr. Batchelor; Tr. at 341-42, Dr. Brown).

13. Dutasteride is a 4-azasteroid unsubstituted at the 4-position. *See* `467 Patent, Abstract.

14. The Rasmusson and Brooks references reported that 4-azasteroids unsubstituted at the 4-position would not interfere with the androgen receptor. (DTX 92 at 2298, 2308; *See* PTX 422 at 397).

15. Five out of the thirty-six 4-azasteroids detailed in the Rasmusson reference show moderate-to-high androgen receptor activity. (DTX 652 at 2301-03; Tr. at 922-23).

16. Dr. Batchelor conducted androgen receptor assays on 4-azasteroids in 1994, subsequent to the publishing of the Rasmusson and Brooks references. (DTX at 2356; Tr. at 536-537, 557-558, 561).

17. There is no *in vitro* or *in vivo* evidence in the `467 Patent of whether dutasteride is selective to the androgen receptor.

18. Finasteride and SKF10567 were known 4-azasteroids with both *in vitro* and *in vivo* activity. `467 Patent 10:22-23.

19. Brooks, *Treatment of Hirsutism with 5a-Reductase Inhibitors*, states, "In contrast to in vitro results, relatively few compounds have exhibited in vivo activity." (PTX 422 at 394).

20. Compounds displaying *in vitro* 5AR inhibition activity frequently did not display *in vivo* activity. (Tr. at 325-328, Dr. Brown; DTX 640, 848, 850).

21. GSK memos in 1992 indicated the insufficiency of *in vitro* data to establish *in vivo* activity and the need for confirmatory *in vivo* data. (DTX 42 at 4; DTX 423 at 2).

22. References did not limit the need for *in vivo* results to 6-azasteroids, but indicated the need for *in vivo* results to 5AR inhibitors generally. (*See, e.g.*, DTX 42 at 4; DTX 423 at 2).

23. A small minority of substances with 5AR inhibitory *in vitro* activity achieved *in vivo* results.

24. The *in vivo* section of the `467 Patent lacked numerical data. `467 Patent, 10:03-14; (Tr. at 386-88, Dr. Brown).

25. It was not possible to ascertain from the `467 Patent whether the reported reduction in rat prostate size in the `467 Patent was a statistically significant reduction. (Tr. at 386-88, Dr. Brown).

26. The `467 Patent does not disclose the existence of any experimental controls used during the chronic rat assay to determine whether prostate shrinkage was a result of dutasteride's activity on the androgen receptor, rather than the inhibition of 5AR. (Tr. at 892-94, Dr. Andersson).

27. Prostate shrinkage may occur for reasons other than 5AR inhibition, including a compound's effect on the hypothalamic pituitary axis, a compound's alteration of steroid metabolism, or toxicity of the compound. (Tr. at 891-92, Dr. Andersson).

28. There is nothing inherently unbelievable in regard to the `467 Patent's statements concerning dutasteride's *in vivo* efficacy. `467 Patent, 10:03-14.

29. Dutasteride was approved for human clinical trials during the pendency of the `467 Patent's application, but this data was never submitted to the USPTO. (PTX 423 at 18-19; Tr. at 590-92, Dr. Frye).

30. Dutasteride was proven to not bind with the androgen receptor during the pendency of the `467 Patent, but this data was never submitted to the USPTO. (PTX 419 at 3, 12, 28-29; Tr. at 539-40, Dr. Batchelor).

(B). Legal discussion and conclusions of law.

A patent may not be granted to an invention unless substantial or practical utility for the invention has been discovered and disclosed. *Fujikawa v. Wattan*, 93 F.3d 1559, 1563 (Fed. Cir.

1996). The utility requirement prevents mere ideas, such as a research proposal or an object of research, from being patented. *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009). In the pharmaceutical arts, "practical utility may be shown by adequate evidence of any pharmacological activity." *Fujikawa*, 93 F.3d at 1563. "It may be difficult to predict, however, whether a novel compound will exhibit pharmacological activity, even when the behavior of analogous compounds is known to those skilled in the art. Consequently, testing is often required to establish practical utility." *Id.* The test results need not absolutely prove that the compound is pharmacologically active; all that is required is that they be reasonably indicative of the desired response. *Id.* This requires a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior. *Id.*

The utility analysis starts with the patent itself. The `467 Patent begins with the statement that dutasteride is "a surprisingly potent and selective dual inhibitor of type 1 and 2 human 5α-reductase." `467 Patent at 1:7-10. The ensuing "Utility" section of the patent begins with the following:

> The steroid 5α-reductase inhibitor of the present invention is useful in the treatment of androgen responsive diseases, e.g., benign and malignant diseases of the prostate, especially benign prostatic hyperplasia, in a manner similar to that for other 5α-reductase inhibitors such as finasteride and SKF105657.

Id. at 10:17-23. The `467 Patent also discloses dutasteride's effective dosage range of "about 0.001 to about 2mg/kg body weight per day, preferably in the range of about 0.005 to about 1 mg/kg per day." *Id.* at 10:45-47. To support these statements, the `467 Patent includes *in vitro* data. *See id.* at 9:57-67 ("Table 1"). This data shows that less than one nanomolar of dutasteride

may effectively inhibit both isozymes of 5AR. (Tr. at 527-30, Dr. Batchelor); `467 Patent at 9:57-67 ("Table 1"). It also shows that dutasteride is selective against 3BHSD at dosages greater than 1000 nanomolars. (Tr. at 527-30, Dr. Batchelor); `467 Patent at 9:57-67 ("Table 1"). The `467 Patent also contains a section entitled, "In vivo Evaluation of Steroid 5α-Reductase Inhibitors." *Id.* at 10:01-02. This section discusses the use of the "chronic rat model" to determine the *in vivo* activity of 5AR inhibitors, citing an article referred to as Brooks by the parties. *Id.* at 10:03-05. The chronic rat model is described as involving the use of castrated male rats, dosed daily with testosterone and the test compound. *Id.* at 10:05-08. The rats were then sacrificed and their prostates weighed. *Id.* at 10:09-10. A reduction in prostate weight was found, and this is said to have signaled the 5AR reductase inhibition activity of the compound. *Id.* at 10:10-11. There is, however, no actual experimental data included in the `467 Patent supporting this findings. *See id.* Finally, the `467 Patent also references the "Stoner," "Rasmusson," and the same "Brooks" articles to substantiate the "correlation of in vitro, rat in vivo and human clinical data relating to an inhibitor of 5α-reductase[.]"[22]

Roxane argues that this disclosure fails to meet the utility requirement for a number of reasons. First, Roxane argues that the *in vitro* activity alone is not sufficient data to find dutasteride useful, and there is no reasonable correlation between the *in vitro* and *in vivo* activity of dutasteride. This is because many compounds tested by the inventors were found to be active *in vitro* but useless *in vivo*, and further the lack of data supporting the *in vivo* chronic rat model renders that section meaningless to a person skilled in the art. Thus, according to Roxane, a person skilled in the art would not find the `467 Patent as disclosing anything more than a

[22] The full titles of these articles are as follows: "Stoner, E. et al., *J. Steroid Biochem. Molec. Biol.*, 37, 375 (1990); Brooks, J.R. et al., *Steroids*, 47, 1 (1986); and Rasmusson, G.H. et al., *J. Med. Chem.*, 29, 2298 (1986)." `467 Patent at 10:27-30.

hypothesis that dutasteride would be an effective 5AR inhibitor. Second, Roxane argues that there is no information in the specification showing that dutasteride is selective to the androgen receptor, and the lack of such selectivity would make a drug compound completely useless to a person skilled in the art. This is because interference with the androgen receptor causes severe health effects in males.

GSK disagrees, arguing that the *in vitro* data alone is sufficient to show utility, and that in any event the combined *in vitro* and *in vivo* results conclusively show the utility of dutasteride to treat androgen responsive diseases, especially considering its structural similarity to finasteride, a selective 5AR inhibitor approved by the FDA and available to the public at the time of filing. GSK next argues that dutasteride had entered clinical human trials while the patent was pending, an accomplishment that should serve as presumptive proof of the drug's utility, and that dutasteride has since been proven to be an extremely effective selective 5AR inhibitor, garnering great commercial success. GSK further argues that the `467 Patent need not demonstrate dutasteride's selectivity to the androgen receptor, as that is a mere side effect, and the existence of side effects does not render a drug compound useless. Finally, GSK argues that dutasteride is a type of steroid known as 4-azasteroids, which are generally known in the art to be selective to the androgen receptor.

In response, Roxane argues that GSK should not be permitted to rely on the clinical testing of dutasteride in support of its utility argument, as it never disclosed any such contention during fact or expert discovery, or in the Pretrial Order. Roxane further argues that in any event, such information is irrelevant, as utility is only assessed on what was submitted to the Patent Office. Finally, Roxane argues that selective 5AR inhibition is the lone pharmacological activity

asserted in the specification, and for this activity to be reasonably supported, selectivity to the androgen receptor must be established.

(i). Selectivity to the androgen receptor.

The Court begins with Roxane's assertion that the `467 Patent is invalid due to a failure to show dutasteride's selectivity to the androgen receptor. Roxane argues that a person skilled in the art would expect a selective 5AR inhibitor to show such selectivity, and the `467 Patent's specification fails to make this showing. Turning to the specification, it states that dutasteride is a "surprisingly potent and selective dual inhibitor of type 1 and type 2 5α-reductase," although it only contains *in vitro* data on the drug's selectivity to 3BHSD, and is bereft of *in vitro* assays testing the drug's selectivity to the androgen receptor. `467 Patent at 1:7-10, 9:9-67.

The Court agrees with Roxane's initial point that selectivity to the androgen receptor was known to be a necessary trait for a 5AR inhibitor. Dr. Frye, one of the dutasteride inventors, admitted as much on cross examination. (Tr. at 614). Merck even abandoned a promising 5AR inhibitor candidate because of its "affinity for the androgen receptor[.]" (PTX 242 at 499). This is because binding with the androgen receptor would interfere with the biological functions of androgens and cause intolerable side effects. (Tr. at 556, Dr. Batchelor; Tr. at 341-42, Dr. Brown). The Court, however, does not agree that a person skilled in the art would require explicit assurance of such selectivity for a 4-azasteroid unsubstituted at the 4-position, which is the specific steroid class to which dutasteride belongs. This is because it was known in the art that this type of steroid showed no affinity for the androgen receptor. A 1986 reference by Rasmusson discussed the pharmacological activity of this drug class on the androgen receptor: "Azasteroids unsubstituted at the 4-position show greatly diminished receptor activity" and that "by leaving the 4-nitrogen unsubstituted it is possible to prepare 5α-reductase inhibitors that will

not interfere with the receptor action." (DTX 92 at 2298, 2308). This reference is cited in the specification. *See* n.22 *supra*. A contemporaneous reference by Brooks, also cited in the specification, made similar findings. (*See* PTX 422 at 397; *see* n.22 *supra*). A person skilled in the art would be expected to take these references into account when reading the `467 Patent.

Roxane counters that because both GSK and Merck conducted *in vitro* androgen assays on 4-azasteroids subsequent to the publishing of the above references, GSK cannot now maintain that a person skilled in the art would have no expectation that the class of compounds were selective to the androgen receptor.[23] Roxane further argues that it effectively cross-examined Dr. Andersson, GSK's expert on utility, and he admitted that there was some correlation between 4-azasteroids and binding on the androgen receptor. GSK's and Merck's conducting of androgen receptor assays for this class of steroids subsequent to the publishing of the cited references, however, does not alter what was generally recognized in the field. Even if it was known in the art that these types of steroids generally exhibited minimal androgen receptor activity, it would make complete sense for drug researchers to do comprehensive testing in anticipation of submitting the drug for human clinical trials and eventual FDA approval. The FDA requires a more exacting standard for drug approval than the PTO requires for a showing of utility.

As to the cross-examination of Dr. Andersson, it similarly does not undermine the published references that dictate what was known in the art. Dr. Andersson relied in part on the Rasmusson reference on direct for the opinion that 4-azasteroids unsubstituted at the 4-position do not bind to the androgen receptor. (Tr. at 849-50). On cross-examination, Dr. Andersson admitted that five out of 36 compounds detailed in the Rasmusson reference show moderate-to-

[23] Dr. Batchelor, one of the inventors, conducted androgen receptor assays on this class of drugs in 1994, subsequent to the publishing of the cited references. (DTX at 2356; Tr. at 536-537, 557-558, 561).

high androgen receptor activity. (DTX 652 at 2301-03; Tr. at 922-23). This does not show enough of a relationship between androgen activity and this class of drugs to undermine Dr. Andersson's reliance on Rasmusson. More than 86% of the 4-azasteroids listed in Rasmusson demonstrated the selectivity, and that was not the only reference relied upon in the specification. A person skilled in the art would accept the fact that this class of steroids would not trigger the androgen receptor, and thus not cause the dangerous side effects, for the purpose of the utility analysis. The lack of *in vitro* evidence on this point does not provide clear and convincing evidence of no utility where the activity at issue is a side effect reported in the art as generally not a factor with this particular class of drugs.[24] For these reasons, the Court holds that the `467 Patent is not invalid due to its failure to explicitly identify dutasteride's selectivity to the androgen receptor.

(ii). The sufficiency of *in vitro* data alone to show dutasteride's inhibition of 5AR.

The next issue is whether the *in vitro* data alone is sufficient to show dutasteride's 5AR inhibition activity. Roxane argues that it is not, as there was no established correlation between the *in vitro* data and efficacy *in vivo*, while GSK asserts that the *in vitro* data alone is sufficient to establish the utility of dutasteride. *In vitro* data by itself may be sufficient to show utility in certain circumstances: "[W]here the disclosed *in vitro* utility is supplemented by the similar *in vitro* and *in vivo* pharmacological activity of structurally similar compounds...*in vitro* utility is sufficient to establish utility." *Fujikawa*, 93 F.3d at 1565. The `467 Patent discloses dutasteride's significant *in vitro* activity. *See* `467 Patent at Table 1; (Tr. at 528-530, Dr. Batchelor; Tr. at 378, Dr. Brown). This disclosure by itself, however, is not enough to confirm a

[24] The Brooks article reported "A striking characteristic of these inhibitors is their relative inability to compete with DHT for binding sites on the androgen receptor." (PTX 422 at 04).

finding of utility. There must also a known correlation between *in vitro* results and *in vivo* activity in similar 5AR inhibitors generally.

GSK argues that dutasteride's similarity to finasteride and SKF10567, two 5AR inhibitors proven to have both *in vitro* and *in vivo* activity, provided the basis to conclude that dutasteride's *in vitro* activity would also lead to *in vivo* activity. The Court disagrees. Roxane points to convincing evidence that no such correlation exists. For example, Dr. Brown, Roxane's utility expert, referenced various articles published by researchers with experience attempting to develop effective 5AR inhibitors. (Tr. at 325-328; DTX 640, 848, 850). These articles describe many compounds that displayed *in vitro* 5AR inhibition activity, but produced nothing *in vivo*. (*See id.*). Another article discussing 5AR inhibitors is by Brooks, *Treatment of Hirsutism with 5a-Reductase Inhibitors*, and unmistakably states, "In contrast to in vitro results, relatively few compounds have exhibited in vivo activity." (PTX 422 at 394). This suggests that *in vitro* results do not reasonably correlate with *in vivo* activity among 5AR inhibitors. Several internal GSK documents confirm this finding, indicating the insufficiency of *in vitro* data and the need for confirmatory *in vivo* data. A GSK memo circulated among the 5AR inhibitor project team from May 1992 referenced a meeting between GSK and Marion Merrell Dow personnel to discuss the latter company's 5AR inhibitors. (DTX 42 at 4). The GSK memo stated, "Insufficient in vivo data was available to evaluate their leads at this time although they do appear to be potent in vitro and when given [subcutaneously] in an acute rat model." (*Id.*). There is also a June 1992 memo from this same team. (DTX 423). The minutes state as follows:

> Clearly, as compounds which meet the in vitro criteria (low nanomolar potency against both human isozymes) are progressed through the chronic assay, consideration of pharmacokinetics in the rat and the relative potency against the rat enzyme will become crucial to interpreting results of this assay.

Id. at 2. Dr. Brown interpreted these memos as suggesting that compounds with potency against 5AR needed to be progressed to the rat model to ensure activity *in vivo*. (Tr. at 336). GSK's own skepticism of potential 5AR inhibitors for the lack proof of *in vivo* activity belies its argument that such correlation could be assumed.

GSK points to Table 1 of the '467 Patent, which shows the strong *in vitro* potency of dutasteride. GSK further argues that dutasteride is a 4-azasteroid, and none of the references show that a person of ordinary skill in the art would question the correlation between *in vitro* and *in vivo* activity for a 4-azasteroid 5AR inhibitor. The Court disagrees, as many of the references expressing a need for *in vivo* testing refer to 5AR inhibitors generally, without drawing the distinction between 4-azasteroids and 6-azasteroids. (*See, e.g.*, DTX 42 at 4; DTX 423 at 2). Moreover, the fact that both of the 5AR inhibitors that showed *in vivo* activity (finasteride and SKF10567) were 4-azasteroids does not constitute evidence that a correlation was generally known in the field, and little evidence was further provided.[25] The Court agrees that the data in Table 1 show *in vitro* potency, but it is not sufficient to show correlation between *in vitro* and *in vivo* activity. This evidence here contrasts sharply with the circumstances of *Fujikawa*, where credible testimony was given that the "*in vivo* activity [was] typically highly correlatable to a compound's *in vitro* activity" in the field of the cholesterol inhibiting drugs. 93 F.3d at 1565. The relevant scholarly articles expressly stated that *in vitro* potency paralleled the *in vivo* activity for most substances in that field. *Id.* at 1566. That is far different from the evidence here, which repeatedly and consistently demonstrated that only a small minority of substances with 5AR inhibitory *in vitro* activity also achieved *in vivo* results. Roxane has established by clear and

[25] This is unlike the relationship between 4-azasteroids unsubstituted at the 4-position and the lack of binding on the androgen receptor, where the references explicitly stated no relationship was found.

convincing evidence that a person skilled in the art would not believe that the *in vitro* activity of a 5AR inhibitor was correlated with *in vivo* results at the time the `467 Patent was filed.

(iii). The specification's statements of *in vivo* activity.

The `467 Patent's failure to provide *in vitro* data sufficient to establish the utility of dutasteride does not end the Court's inquiry on this subject, as the `467 Patent's specification also discusses *in vivo* experimentation. The entire discussion, entitled "In vivo Evaluation of Steroid 5α-Reductase Inhibitors," follows:

> The in vivo activity of steroid 5α–reductase inhibitors may be determined in a chronic rat model (Brooks, J.R. et al., *Steroids*, 47, 1 (1986)). The chronic model utilizes castrated male rats that are dosed daily with testosterone (20 μg/rat) subcutaneously and with test compound (.01-10mg/kg) or vehicle orally for 7 days. The animals are then sacrificed and their prostates weighed. Reduction in the size of testosterone-stimulated prostate weight demonstrated activity of the test compound. Known steroid 5α–reductase inhibitors were tested in parallel to ensure consistency of the assay method.

`467 Patent, 10:03-14.

The value of this *in vivo* discussion is hotly contested. GSK argues that the specification's statements that dutasteride caused a reduction in the size of the rat prostates should be taken at face value as true, absent some objective reason fostering disbelief. GSK further argues that human clinical trials were approved while the `467 Patent application was pending, and that dutasteride has since been proven to be an extremely effective selective 5AR inhibitor, garnering considerable commercial success. According to GSK, all of this demonstrates the trustworthiness of the *in vivo* statements as well as the actual *in vivo* activity of dutasteride, establishing its utility. Roxane argues that the lack of any numerical data or indication of experimental controls renders this portion of the specification not credible to a

person skilled in the art. Roxane further argues that GSK failed to provide any information on human clinical trials in discovery or in the pre-trial order, thus waiving that argument, and in any event such information, which was never submitted to the Patent Office, is irrelevant for the purpose of the utility inquiry.

Roxane did establish that there is no numerical data in the `467 Patent from which one skilled in the art could verify the truth of the conclusion that dutasteride caused the shrinkage of the rat prostates and thus demonstrated *in vivo* activity. Dr. Brown testified to the lack of "quantitative data there to show how much reduction there was in the prostate weight," and Dr. Andersson was impeached as to his testimony that one could divine a statistically significant reduction in prostate weight from the face of the patent. (Tr. at 386-88; Tr. at 888-890).[26] Roxane also established that the `467 Patent does not disclose the existence of any control group to determine whether prostate shrinkage was a result of dutasteride's activity on the androgen receptor, rather than the inhibition of 5AR. (Tr. at 892-94, Dr. Andersson). It was shown that prostate shrinkage may occur for a variety of reasons, including a compound's effect on the hypothalamic pituitary axis, a compound's alteration of steroid metabolism, or toxicity of the compound. (Tr. at 891-92, Dr. Andersson).

Thus, Roxane established that there was no numerical data or control information from which a person skilled in the art could verify the statements regarding *in vivo* activity. The legal significance of these omissions, however, is not as easily resolved, and raises an important question: how much support do the statements of utility within a patent require, and how much

[26] The observation that there is no numerical data from which one could evaluate statistical significance is obvious on the face of the patent. Whether such information is necessary for the patent to survive utility scrutiny is a different question.

scrutiny do those statements deserve? The Federal Circuit has stated that deference is owed to the utility statements in a patent absent a reason to disbelieve them:

> [A] specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented *must* be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter *unless* there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

In re Langer, 503 F.2d 1380, 1391 (CCPA 1974) (emphasis in original); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 924 (Fed. Cir. 2011); *see also In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (explaining that teachings in patent as to enablement should be taken in compliance with §112 absent reason to doubt the objective truth of those statements).

The question thus is whether the `467 Patent's failure to disclose statistical evidence detailing the degree of rat prostate size reduction, and the failure to provide any information as to control groups to confirm the size reduction was indeed due to the activity of dutasteride justifies ignoring the statement that the experiment showed *in vivo* activity. The Court does not believe so. Such a decision would entail imposing an unjustified level of scrutiny to a patentee's statements that were accepted as credible by the Patent Office. The Federal Circuit has stated that "results from animal tests or in vitro experiments may be sufficient to satisfy the utility requirement." *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324-25 (Fed. Cir. 2009). Here, the animal test "result" is that "[r]eduction in the size of testosterone-stimulated prostate weight demonstrated activity of the test compound." Roxane criticizes this statement as mere conclusion, but cites nothing indicating that conclusory statements of test results should be disbelieved absent a full disclosure of the underlying data and test controls. There is no reason to question the "objective truth" of the statement that dutasteride caused prostate shrinkage in rats, as the disclosure is not "on its face, contrary to generally accepted science principles." *In re*

Marzocchi, 439 F.2d 220, 223 (CCPA 1971). Although 5AR inhibitors showing *in vivo* activity were certainly rare, they were not unprecedented, as two other such compounds showed *in vivo* activity: finasteride and SKF10567.[27] It is also fair to assume that trained researchers obtained their test results via scientifically sound methods, absent some evidence to the contrary. No evidence was cited indicating that the dutasteride inventors actually arrived at their results via scientifically compromised methods; only that it was preferable that the controls described by Dr. Brown be used, and that it was possible that the prostate shrinkage was caused by other means. "Rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *Id.* at 1325. In light of the significant *in vitro* data combined with the statements indicating *in vivo* activity, the Court finds that Roxane has not met its burden of proving a lack of utility by clear and convincing evidence.

(iv). The relevance of post-filing experimental data not filed with the PTO need not be decided here.

GSK argues that the Court should take into account additional data of the approval of human clinical trials and other experimental data that, although never submitted to the PTO, shows that the patentee possessed voluminous evidence of dutasteride's utility during the pendency of the `467 Patent. The logic behind this argument is that the patentee would have been free to submit this information to the PTO had it been thought necessary to do so. Since the Examiner did not maintain the rejection of the `467 Patent for lack of utility, there is no particular public interest in invalidating a useful patent for a reason that could have been cured with no change to the claims and their scope. Roxane argues that GSK failed to disclose this

[27] The fact that this was not common enough to warrant finding *in vitro* activity of dutasteride alone sufficient to show utility does not mean that a showing of *in vitro* activity along with statements indicating *in vivo* results should be similarly discounted.

data during discovery and in the Pre-trial Order, and that GSK's argument is thus waived. Roxane argues that, in any event, that the evidence is irrelevant, as it is improper to consider information that was never submitted to the PTO.

The Court is able to reach the conclusion that the `467 Patent meets the utility requirement without reliance on the submissions in question. The Court notes that it is an undisputed fact that, during the pendency of the application, human clinical trials were approved for dutasteride, which would have created a presumption of utility at the PTO. (PTX 423 at 18-19; Tr. at 590-92, Dr. Frye). It is further not disputed that dutasteride was proven to not bind with the androgen receptor during this time. (PTX 419 at 3, 12, 28-29; Tr. at 539-40, Dr. Batchelor).[28] All of this data could have thus been presented to the Examiner had the PTO requested additional proof of dutasteride's utility. If considered relevant, that data would show incontrovertible proof of utility.

There is some tension in the recent case law as to this issue of relevance. *Actavis Elizabeth* is a recent Federal Circuit non-precedential opinion, and it allowed post-filing evidence of utility to be considered. 435 F. App'x at 917.[29] In that case, the district court was reversed for finding a lack of utility where data of human clinical trials was available during the pendency of the application. *Id.* at 924. This data was never submitted to the PTO, but additional data was never deemed needed by the Examiner. *Id.* at 925. The decision notes that had such data been requested, it would have sufficed as presumptive proof of the drug

[28] Although the Court is not taking this evidence into account for the purpose of this holding, it is worth noting that Roxane failed to object to the presentation of post-filing evidence of dutasteride's utility at trial, and that objection is thus waived. *See Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 237 F.R.D. 106, 118 (D. Del. 2006).

[29] A non-precedential opinion is not binding precedent. Fed. Cir. R. 32.1(d). It may not "add[] significantly to the body of law," Fed. Cir. R. 32(b), but I do presume it correctly states the law.

compound's utility. *Id.* at 924 (citing MPEP § 2107.03 (8th ed. 2008)). In finding post-filing data relevant, the Court stated the following: "With reference to demonstration of utility, in *Brana*, 51 F.3d at 1567 n.19, the court noted that post-filing evidence 'can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification.'" *Id.* The Court reversed the District Court's decision, stating that "the utility of [the drug compound] is accurately stated in the specification; there is no allegation of falsity in the disclosed utility, and the patent examiner did not require the presentation of additional data." *Id.*[30]

There appears to be, however, some disharmony between *Actavis* and *Janssen Pharmaceutica N.V. v. Teva Pharmaceuticals USA, Inc.* 583 F.3d 1317 (Fed. Cir. 2009). (*See* D.I. 291 at 4-6). Unlike *Actavis*, *Janssen* is a precedential opinion. In *Janssen*, the Court noted, "The results from the `318 patent's proposed animal tests of [the drug compound] for treating symptoms of Alzheimer's disease were not available at the time of the application, and the district court properly held that they could not be used to establish enablement." *Id.* A footnote distinguished *Brana's* allowance of post-filing data on the basis that, in that case, "the [post-filing] testing was submitted to the PTO during prosecution."[31] *Id.* at 1325 n.8. For its part, *Actavis* specifically discussed and factually distinguished *Janssen*, although without dealing with *Janssen's* apparent prohibition against considering data not filed with the PTO. *See Actavis*, 435 F. App'x at 925-26.

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[30] These facts would seem to be on all fours with those of the instant case, as the statements within the `467 Patent have been shown to be accurate.

[31] For an interesting analysis of the Federal Circuit's decisions in *Brana* and *Janssen*, *see* Irving N. Feit, *Does A Utility That Is "Unproved" at the Time of Filing Violate §112? The Federal Circuit Says "Yes" in Janssen Pharmaceutica N.V. v. Teva Pharmaceuticals USA, Inc.*, 93 J. Pat. & Trademark Off. Soc'y 1, 8 (2011).

This Court does not need to decide whether these two cases can be harmonized, as there is enough information within the four corners of the `467 Patent to conclude that dutasteride produced *in vivo* and *in vitro* activity. Were the post-filing evidence proffered by GSK relevant, however, it would provide absolute evidence of dutasteride's utility.

For all these reasons, the Court finds that Roxane has not shown by clear and convincing evidence that the `467 Patent is invalid due to a failure to show utility.

IV. CONCLUSION

The Defendants have not proven by clear and convincing evidence that any of the asserted claims of the `467 Patent are invalid.

GSK should submit an agreed-upon form of final judgment within two weeks.