IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER PHARMA AG, BAYER INTELLECTUAL PROPERTY GMBH, and BAYER HEALTHCARE PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 12-cv-517 (GMS) CONSOLIDATED
WATSON LABORATORIES, INC., et al.	)	
Defendants.	)	

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiffs Bayer Pharma AG, Bayer Intellectual Property GmbH, and Bayer HealthCare Pharmaceuticals Inc. (collectively "Bayer") allege that defendants Watson Laboratories, Inc., Actavis, Inc., and Actavis Pharma, Inc. (collectively "Watson") infringed the asserted claims of U.S. Patent Nos. 8,613,950 ("the '950 patent"), 6,362,178 ("the '178 patent"), and 7,696,206 ("the '206 patent"). (D.I. 1); (C.A. No. 14-760-GMS, D.I. 1.)[1] The court held a six-day bench trial on April 6, 2015 through April 14, 2015. (D.I. 156-161.) At the close of trial, the court ruled that the asserted claims of patents '178 and '206 were not obvious. Tr. 1171:7-9, 1172:4-16 (Court). The court also rejected Watson's indefiniteness defense at the close of trial. Tr. 1175:20-1176:1 (Court).

[1] The parties filed a Stipulation and Order on May 28, 2013, concerning Watson's infringement of claims 1-5 and 7-8 of the '178 patent and claims 1-6 of the '206 patent. (D.I. 38.) The court entered the Stipulation and Order on June 3, 2013. (D.I. 40.) Subsequently, during the post-trial briefing process, the parties stipulated to infringement of claims 9 and 11 of the '950 patent. (D.I. 145.) The court entered the Stipulation and Order on May 20, 2015. (D.I. 146.)

Presently before the court are Bayer's post-trial proposed findings of fact and conclusions of law concerning validity of the asserted claims of the '178 patent and the '206 patent. (D.I. 147.)[2] Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that the asserted claims of the '178 and '206 patent are not invalid due to obviousness. The findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[3]

A. The Parties

1. Plaintiff Bayer Pharma AG is a corporation organized and existing under the laws of the Federal Republic of Germany, with a place of business at Müllerstrasse 178, 13353 Berlin, Germany.

2. Plaintiff Bayer Intellectual Property GmbH is a corporation organized and existing under the laws of the Federal Republic of Germany, with a place of business at Alfred-Nobel-Strasse 10, 40789 Monheim, Germany.

3. Plaintiff Bayer HealthCare Pharmaceuticals Inc. is a corporation organized and existing under the laws of the State of Delaware, with a place of business at 6 West Belt, Wayne, New Jersey.

4. Defendant Watson Laboratories, Inc. is a corporation organized and existing under the laws of the State of Nevada, having a place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054. Watson Laboratories, Inc. is a wholly-owned subsidiary of Actavis, Inc.

5. Defendant Actavis, Inc. is a Nevada corporation having a place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054.

---

[2] At the close of trial, the court invited Bayer's post-trial proposed findings of fact and conclusions of law concerning validity of the asserted claims of the '178 patent and the '206 patent, but did not invite Watson to submit post-trial briefing on this issue. Tr. 1178:39:52-1179:40:27 (court).

[3] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 133, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. Where necessary, the court has overruled objections to the inclusion of these facts. The court has also reordered and renumbered some paragraphs, corrected some spelling and formatting errors, and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in the Discussion and Conclusions of Law section of this opinion, preceded by the phrase "the court finds" or "the court concludes."

6. Defendant Actavis Pharma, Inc. is a Delaware corporation having a place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054.

7. The court has subject matter jurisdiction, as well as personal jurisdiction over all parties.

B. The Patents-in-Suit

8. United States Patent No. 6,362,178 ("the '178 patent"), entitled "2-Phenyl Substituted Imidazotriazinones as Phosphodiesterase Inhibitors," naming Ulrich Niewöhner, Mazen Es-Sayed, Helmut Haning, Thomas Schenke, Karl-Heinz Schlemmer, Jörg Keldenich, Erwin Bischoff, Elisabeth Perzborn, Klaus Dembowsky, Peter Serno, and Marc Nowakowski as inventors, issued on March 26, 2002. The '178 patent claims priority to a German patent application that was filed on November 12, 1997.

9. United States Patent No. 7,696,206 ("the '206 patent"), entitled "2-Phenyl Substituted Imidazotriazinones as Phosphodiesterase Inhibitors," naming Ulrich Niewöhner, Maria Niewöhner (as legal representative), Mazen Es-Sayed, Helmut Haning, Thomas Schenke, Karl-Heinz Schlemmer, Jörg Keldenich, Erwin Bischoff, Elisabeth Perzborn, Klaus Dembowsky, Peter Serno, and Marc Nowakowski as inventors, issued on April 13, 2010. The application that matured into the '206 patent was filed on September 29, 2009 and is a continuation through several other intermediate patent applications of Application No. 09/554,162, which matured into the '178 patent.

10. Bayer Intellectual Property GmbH is the assignee of the '178 and '206 patents.

11. The '178 and '206 patent are listed in the Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") at the U.S. Food and Drug Administration ("FDA") in connection with STAXYN® and LEVITRA®.

C. Bayer and STAXYN®

12. On June 17, 2010, Bayer HealthCare Pharmaceuticals, Inc. received approval from the FDA to market vardenafil hydrochloride orally disintegrating tablets, 10 mg, under the trade name STAXYN® for the treatment of erectile dysfunction.

13. Bayer has asserted claims 1-5 and 7-8 of the '178 patent, and claims 1-6 of the '206 patent. These claims cover, among other things, the compound vardenafil hydrochloride trihydrate. Vardenafil hydrochloride trihydrate is the active ingredient in LEVITRA® and STAXYN®.

D. ANDA No. 203689 Submitted by Watson

14. Watson submitted an Abbreviated New Drug Application ("ANDA") No. 203689 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) seeking approval to sell a generic version of STAXYN®, vardenafil hydrochloride orally disintegrating tablets, 10 mg, prior to the expiration of the '178 and '206 patents.

15. Watson sent Bayer a letter dated March 12, 2012 ("First Paragraph IV Notice Letter"), stating that Watson had submitted an Abbreviated New Drug Application ("ANDA") No. 203689 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) seeking

approval to engage in the commercial manufacture, use, and sale of vardenafil hydrochloride orally disintegrating tablets, 10 mg, prior to the expiration of the '178 and '206 patents. Watson's First Paragraph IV Notice Letter stated that the claims of the '178 and '206 patents are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the product described in ANDA No. 203689.

16. Bayer brought suit against Watson alleging infringement of the '178 and '206 patents under 35 U.S.C. § 100 et seq., including § 271(e)(2)(A) on April 25, 2012, within 45 days of receipt of Watson's First Paragraph IV Notice Letter. (D.I. 1.)

17. Subsequently, Watson sent Bayer a letter dated February 6, 2014 ("Second Paragraph IV Notice Letter"), stating that Watson had submitted ANDA No. 203689 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of vardenafil hydrochloride orally disintegrating tablets, 10 mg, prior to the expiration of the '950 patent. Watson's Second Paragraph IV Notice Letter stated that the claims of the '950 patent are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the product described in ANDA No. 203689.

18. Bayer brought suit against Watson alleging infringement of the '950 patent under 35 U.S.C. § 100 et seq., including § 271(e)(2)(A) on March 21, 2014, within 45 days of receipt of Watson's Second Paragraph IV Notice Letter.

E. Procedural History

19. On April 25, 2012, Bayer filed a complaint alleging infringement of the '178 and '206 patents by Watson. (D.I. 1.) Watson counterclaimed for declaratory judgment of noninfringement and invalidity of the '178 and '206 patents on June 25, 2012. (D.I. 13.) Watson filed an amended answer and counterclaims on April 5, 2013. (D.I. 31.) Bayer filed an answer to Watson's first amended counterclaims on April 29, 2013. (D.I. 32.)

20. The parties filed a Stipulation and Order on May 28, 2013, stipulating to infringement of claims 1-5 and 7-8 of the '178 patent and claims 1-6 of the '206 patent, provided that the claims are valid and enforceable. (D.I. 38.) The court entered the Stipulation and Order on June 3, 2013. (D.I. 40.)

21. On March 21, 2014, Bayer filed a complaint alleging infringement of the '950 patent by Watson. (C.A. No. 14-760-GMS, D.I. 1.) Watson counterclaimed for declaratory judgment of noninfringement and invalidity of the '950 patent on April 23, 2014. (C.A. No. 14-760-GMS, D.I. 15.) Bayer filed an answer to Watson's counterclaims on May 19, 2014. (C.A. No. 14-760-GMS, D.I. 27.)

22. The actions were consolidated for purposes of trial on August 5, 2014. (D.I. 76). These cases had also been consolidated for purposes of trial with C.A. No. 13-845-GMS, in which Bayer alleged infringement by Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc. (collectively "Par") of the '178 and '206 patents (D.I. 59), and C.A. No. 14-761-GMS, in which Bayer alleged infringement by Par of the '950 patent. (D.I. 76). The actions against Par were dismissed without prejudice in September 2014. (D.I. 82, 83).

23. The court held a six-day bench trial in this matter on April 6 through April 14, 2015. (D.I. 156-161). The court rejected Watson's indefiniteness defense at the close of trial. Tr. 1175:20-1176:1 (Court). The court also ruled that the asserted claims of patents '178 and '206 were not obvious. Tr. 1171:7-9, 1172:4-16 (Court).

24. Subsequently, during the post-trial briefing process, the parties stipulated to infringement of the '950 patent. (D.I. 145.)

25. The court issued a memorandum on April 27, 2016 finding that the asserted claims of the '950 patent are not invalid due to obviousness. (D.I. 172.)

III. DISCUSSION AND CONCLUSIONS OF LAW

These consolidated actions arise under the patent laws of the United States, 35 U.S.C. The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, 2201 and 2202. Venue is proper in this court under 28 U.S.C. §§ 1391(b) and (c), and 1400(b). Watson challenges the validity of the '178 and '206 patents as obvious in light of the prior art. After having considered the entire record in this case, the substantial evidence in the record, Bayer's post-trial submission, and the applicable law, the court concludes that Watson has not proven that the asserted claims of the '178 and '206 patents would have been obvious to a person of ordinary skill in the art as of November 12, 1997. The asserted claims of the '178 and '206 patents are valid under 35 U.S.C. § 103. Bayer's Rule 52(c) motion is granted. The court's reasoning follows.

A. Obviousness

A patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such

as commercial success, long-felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

A party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence[4] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. "Obviousness does not require absolute predictability of success," but rather requires "a reasonable expectation of success." *Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (analyzing and applying the flexible obviousness inquiry announced in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 414-16 (2007)). To establish obviousness in cases involving new chemical compounds, the accused infringer must identify a known "lead" compound, a reason for selecting that compound, and "some reason that would have led a chemist to modify a known compound" in a way that leads to the claimed invention. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014)

[4] "Clear and convincing evidence is evidence that places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Alza Corp v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

(1) The Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to the '178 and '206 patents would be: (1) a clinician who had experience in treating erectile dysfunction ("ED"); (2) a pharmacologist; and (3) a medicinal chemist with a Ph.D. in organic chemistry or medicinal chemistry and several years of postgraduate experience in designing and preparing compounds for medicinal purposes, or equivalent training and experience. With respect to medicinal chemistry issues, the POSA would be generally familiar with, or would spend the time to learn about, literature relating to selective PDE5 inhibitors and the state of the art as of November 12, 1997. The POSA would also be familiar with the in vitro, cell-based, and in vivo assays and tests used to evaluate compounds, including PDE inhibitors, for potency, selectivity, efficacy, toxicity, and clinical uses for which PDE inhibitors had been disclosed.[5]

(2) The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

The court will first consider whether Watson has established a *prima facie* case of obviousness in light of the evidence adduced at trial. Bayer argues that the claimed subject matter was not obvious to a POSA because (1) a POSA would not have selected sildenafil as a lead compound (D.I. 147 at 8-10); and (2) a POSA would not have modified sildenafil in the way the claimed invention requires. (D.I. 147 10-22.) The court addresses each of these arguments in turn.

i. A POSA Would Not Have Selected Sildenafil as a Lead Compound

First, Bayer argues that a POSA would not have considered sildenafil to be an optimal lead compound to use as a starting point in designing a new PDE5 inhibitor. (D.I. 147 at 8-10). The court agrees. As of the priority date, there were about 200 scientists researching PDE5 inhibitors

[5] The description of a person of ordinary skill in the art is derived from Dr. Brown's Expert Report. Expert Report of David Brown, Ph.D. at ¶¶ 20-22. The parties stipulated to this definition and the court adopted it. (D.I. 138, 139.)

in at least eighteen different companies. Tr. 224:16-226:16 (Heathcock). Sildenafil was one of the well-known PDE5 inhibitors, however, as Dr. Donald Maurice testified, a POSA would have expected that the potency and selectivity of sildenafil were lacking compared to other compound leads. Tr. 733:23-734:7 (Maurice). Multiple review papers had been published by November 1997 that discussed the properties of various PDE5 inhibitors, Tr. 529:4-7 (Brown); Tr. 742:22-743:20 (Maurice), but no review paper described sildenafil as a "lead compound." Tr. 743:24-744:3 (Maurice). There were other examples of compounds that were more potent than sildenafil, more selective than sildenafil, or both, such as Eisai's E-4021, Glaxo's DMPPO, "Compound 59", GF196960, and Sterling Winthrop's Compounds 1(b) and 16. Tr. 734:12-744:7 (Maurice) (discussing E-4021), 744:8-749:16 (discussing DMPPO), 746:4-749:16 (discussing Compound 59) 749:17-756:6 (discussing GF 196960), 757:22- 759:1 (discussing compounds 1(b) and 16)) (Maurice). Thus, as Dr. Maurice testified, sildenafil would have been less desirable than these other compounds. Tr. 720:17-721:6, 722:17-25, 724:12-25 (Maurice). Moreover, according to Dr. Maurice, sildenafil did not have the desirable selectivity for PDE5 versus PDE1. Tr. 727:22-730:13 (Maurice). The lack of selectivity would have concerned a POSA developing an ED treatment. Tr. 728:19-730:13 (Maurice). Thus, a POSA would have understood that sildenafil, when it was invented, was not intended as a therapy for ED. Tr. 726:6-16 (Maurice).

Watson's expert chemist, Dr. Clayton Heathcock, testified that, as of November 12, 1997, a POSA would want to copy sildenafil because it was going to be a success. Tr. 164:2-165:4; 184:18-185:8. The court does not find this testimony credible because it is significantly impacted by hindsight bias. While today sildenafil has an established track record for safety and efficacy, this safety profile did not exist as of November 12, 1997. At that time, a POSA would not have been motivated to copy it. Tr. 730:14-732:20 (Maurice). In further support of its obviousness

argument, Watson points to the structural similarity of vardenafil to sildenafil. The argument does have at least some surface appeal. There are, however, at least two problems: (1) the comparison is offered in a two-dimensional representation; and (2) the two compounds differ with respect to one of the substituents—chemical groups attached at various locations to a molecule's core. Tr. 165:5-14 (Heathcock). Put simply, Watson's evidence does not clearly and convincingly establish that a POSA would have expected the two molecules to bind to PDE5 similarly. Tr. 552:3-10 (Brown).

In conclusion, Watson's argument that the claimed invention would have been obvious to one of ordinary skill in the art depends on impermissible hindsight. *KSR Int'l Co.*, 550 U.S. at 421 (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). Watson fails to demonstrate that a POSA would have selected sildenafil as a "lead compound[], or starting point[], for further development efforts." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). *See also Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed.Cir.2008) ("[P]ost-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.").

ii. A POSA Would Not Have Made Vardenafil Hydrochloride Trihydrate

Bayer next contends that even if a POSA selected sildenafil as a lead compound, development of vardenafil was not the result of an obvious path. Specifically, Bayer asserts that there are seven independent choices that would be necessary to make vardenafil hydrochloride trihydrate. (D.I. 147 at 10-22.) The court agrees. The evidence presented at trial supports the conclusion that modifying sildenafil did not involve trying a "finite number of identified, predictable solutions." *Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir.

2008.) Each layer of decision-making would have required a lengthy research and development process that would not have provided predictable results. *See* Tr. 1173:31:29-32:37 (court).

Bayer contends that the first decision the POSA would have needed to make would be to modify the core structure of sildenafil (called a "pyrazolopyrimidinone") to the core of vardenafil (called an "imidazotriazinone"). (D.I. 147 at 11.) Dr. Heathcock testified that a POSA would have been motivated to modify the core of the lead compound to arrive at the claimed invention. Tr. 230:22-233:4 (Heathcock). In contrast, Bayer's expert, Dr. David Brown, testified that he had never heard of selecting a lead compound with desirable properties and then changing its core. Tr. 447:16-448:4 (Brown). He further testified that there is no evidence of anyone using such an approach. Tr. 485:10-486:1 (Brown). According to Dr. Brown, a POSA would have considered changes to the core structure to be radical changes that very often have quite dramatic effects on a compound's activity. Tr. 469:9-20, 532:18-23 (Brown). A POSA would have expected that changing the location of atoms on a molecule would produce different opportunities and properties for binding to targets and different charge distribution, which are critical for PDE5 inhibition. Tr. 532:18-538:19 (Brown); PTX-362 at 1820. The scientific literature concerning sildenafil supported this understanding and taught away from changing sildenafil's core. Tr. 461:1-5 (Brown, discussing PTX-362 at 1820). Rather than making radical changes to the activity of sildenafil by changing its core, Bayer argues that the POSA would have focused on changing the substituents of sildenafil to affect potency. Tr. 460:18-461:5, 482:7-486:1 (Brown). The court finds that a POSA would not have selected sildenafil as a lead compound and then modified the core structure. *See Daiichi Sankyo v. Matrix Labs., Ltd.*, 619 F.3d at 1356 (Fed. Cir. 2010) ("[A POSA] would not select the '902 patent compounds as leads only to disregard one of their distinguishing characteristics, specifically their increased lipophilicity at the 4-position"). The court is particularly

persuaded to reach this result because, as Bayer points out, the core of the compound is significant because it confers the binding properties. (D.I. 147 at 30.)

Even if the court were to agree with Watson's assertion that a POSA would be motivated to utilize the core structure of sildenafil, Bayer asserts that in order to arrive at vardenafil hydrochloride trihydrate, a POSA would need to modify the core structure of sildenafil in a way that changed the left-hand, six-membered ring of sildenafil (the "A ring") to the left-hand, six-membered ring of vardenafil. (D.I. 147 at 14.) The court finds credible Dr. Brown's testimony that the art specifically taught away from this path. Dr. Brown testified that researchers at Sterling Winthrop, Pfizer, Glaxo, and others had made prior art PDE5 inhibitors with different core groups. Tr. 493:20-506:16 (Brown). While these compounds encompassed eleven different core groups, all of the compounds shared the pyrimidinone "A ring." *Id.* (discussing PTX-225, PTX-358, PTX-436). Indeed, Dr. Brown testified: "all the teaching in the art is that the A ring had never been changed until Bayer did so.") Tr. 510:7-14 (Brown). According to Dr. Brown, the conventional wisdom in the art, as reflected in all of the examples of cGMP-mimetic PDE5 inhibitors in the literature, was that the pyrimidinone ring had to be maintained for a mimetic to inhibit PDE5. Tr. 510:2-14 (Brown). The court is persuaded that it would not have been obvious to a POSA to change the pyrimidinone portion of sildenafil's core, a necessary decision to make vardenafil.

Bayer next argues that even if the POSA had a reason to change the pyrimidinone A ring, a POSA would have to modify the core to be the imidazotriazinone core. (D.I. 147 at 17). Dr. Brown testified that there is not a single example in the prior art of a selective PDE5 inhibitor that used an imidazotriazinone core. Tr. 515:13-19, 594:11-17 (Brown). The only prior art compounds with the imidazotriazinone core structure were disclosed in patents by Allen & Hanburys as PDE3 inhibitors and were considered to be toxic. Tr. 205:5-206:1 (Heathcock), Tr. 526:15-527:4, 594:11-

17 (Brown). Dr. Brown demonstrated persuasively that the POSA could have used countless other core groups that did not have the negative history of PDE3 inhibition associated with imidazotriazinone. Tr. 506:23-510:6, 512:14-516:3 (Brown). Thus, the prior art effectively taught away from using the core structure of vardenafil in a PDE5 inhibitor for the treatment of erectile dysfunction. Tr. 527:5-11 (Brown).

Finally, Bayer argues that even if the POSA had changed the sildenafil core to the vardenafil core, the POSA would have to change the substituent to methyl-piperazine. (D.I. 147 at 19.) This decision would have required a research program to study the structure-activity relationship for substituents associated with that core in order to determine which were optimal for PDE5 inhibition. Tr. 559:18-561:6, 560:25, 581:17-25 (Brown). The necessary research would involve over six thousand compounds just to consider substituents from prior art PDE5 inhibitors. Tr. 580:22-581:16 (Brown). What is more, Bayer asserts that the POSA would have had to change from sildenafil's methyl-piperazine to vardenafil's ethyl-piperazine. (D.I. 147 at 19.) Dr. Brown identified two factors that would discourage a POSA from changing the substituent to an ethyl-piperazine: the "lipophilicity" of a molecule—its tendency to dissolve in fat rather than water, Tr. 564:3- 565:3, and molecular weight. Tr. 566:6-12, 568:16-23 (Brown). In addition, Pfizer's patent application concerning the use of various pyrazolopyrimidinone compounds to treat erectile dysfunction does not include ethyl-piperazine 5′-substituent in any of the ten "especially preferred" compounds nor an ethyl-piperazine 5′-substituent in any of the "particularly preferred" compounds. Tr. 575:4-9, 575:20- 576:5 (Brown). The court is persuaded that these changes to vardenafil would not have been obvious to a POSA.

According to Bayer, the sixth choice a POSA would need to make to arrive at vardenafil hydrochloride trihydrate would have been to prepare the hydrochloride salt of vardenafil. (D.I. 147

at 22.) However, Dr. Brown testified that, at the time, sildenafil was being developed as a citrate salt. Tr. 586:4-7 (Brown). Dr. Heathcock offered no basis to conclude that the POSA would deviate from Pfizer's choice of the citrate salt with sildenafil. Tr. 213:5-15 (Heathcock). Moreover, hydrochloride salt would have been but one option out of between 30 and 50 salt forms that were recognized in the field to be generally regarded as safe. Tr. 586:17-587:2 (Brown). Finally, Bayer argues that a POSA would have to prepare the hydrochloride trihydrate form of vardenafil. (D.I. 147 at 22.) Dr. Heathcock did not affirmatively offer a reason for the POSA to make the trihydrate form. In contrast, Dr. Brown testified that a POSA could not predict which hydrates of a compound would form. Tr. 587:12-19. The court concludes that it would not have been obvious to a POSA to make a hydrochloride trihydrate form of vardenafil.

Obviousness requires "a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). Watson failed to establish by clear and convincing evidence that a POSA would have made the many necessary modifications to obtain vardenafil hydrochloride trihydrate. Far from a clear path, a POSA developing the claimed invention would face an array of decisions. For the foregoing reasons, Watson has not met its burden to establish a prima facie case that the '178 or '206 patent is invalid for obviousness.

(2) Secondary Considerations

Under relevant law, once a *prima facie* case of obviousness has been established, the burden then shifts to the applicant to present evidence of secondary considerations of non-obviousness to overcome this *prima facie* showing. *See, e.g.*, *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). The Supreme Court has made clear that secondary considerations can include, among other things,

evidence of commercial success, long-felt but unsolved needs, and/or the failure of others. *See Graham*, 383 U.S. at 17-18. A plaintiff may also rebut an obviousness contention by demonstrating that there were unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and/or skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998).

"Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer*, 480 F.3d at 1372. Moreover, "[a] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision." *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) (alteration in original) (quoting *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed. Cir. 2000)). In other words, the secondary considerations must be commensurate in scope—"coextensive"—with the claimed features of the invention. *Id.*; *see also MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264–65 (Fed. Cir. 2013).

Here, Bayer argues that, even should the court determine that Watson established a *prima facie* case on this issue, the secondary considerations of unexpected properties and long-felt, but unmet need rebut this *prima facie* case. (D.I. 202 at 137); *see Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1373 n.9 (Fed. Cir. 2004). Although Watson has not established a prima facie case, the court will briefly address each of the two secondary considerations that Bayer raises.

i. Unexpected Properties

Unexpected results may be demonstrated by showing "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989,

994 (Fed. Cir. 2009). This comparison is made to the closest prior art. *In re De Blauwe,* 736 F.2d 699, 705 (Fed. Cir. 1984). Dr. Brown testified that the closest prior art to vardenafil are the imidazotriazinone compounds disclosed in the Allen & Hanburys patents, PTX-409, because those compounds have the same core as vardenafil. Tr. 588:25-590:9 (Brown). This is supported by the position the PTO took during prosecution of the '178 and '206 patents. Tr. 588:23-590:4 (Brown, discussing PTX-0002 & PTX-0005). The court found credible Drs. Brown and Irwin Goldstein's testimony regarding unexpected results. A POSA would not have expected a compound with vardenafil's structure to be a potent and selective PDE5 inhibitor, given that the Allen & Hanburys compounds were known to be PDE3 inhibitors. Tr. 526:15-24, 596:21-25. (Brown).

Even if the court considers sildenafil to be the closest prior art as Watson argues, the evidence on the record supports a finding that vardenafil exhibits unexpected desirable properties. Specifically, vardenafil is substantially more potent than sildenafil. Tr. 765:13-767:7 (Maurice, discussing Table 2 of PTX-196). In addition, Vardenafil stays bound to PDE5 much longer than sildenafil. Tr. 768:7-769:25 (Maurice, discussing Figure 5 of PTX-196). It is also more selective than sildenafil as to both PDE1 and PDE6. Tr. 770:1-772:17 (Maurice, discussing Table 2 of PTX-177). These effects were demonstrated in vitro and in vivo in both rat and rabbit animal models of ED. Tr. 772:18-774:15 (Maurice, discussing PTX-194 and PTX-246). The POSA would have considered all of these properties desirable. Tr. 766:11-16, 769:24-25, 772:16-17 (Maurice).

In addition, the evidence demonstrates that vardenafil exhibits unexpected clinical properties relative to sildenafil. One clinical study, known as PROVEN, tested vardenafil in patients with ED who had failed when taking sildenafil, so called "sildenafil non-responders." Tr. 1025:5-1027:16 (Goldstein). Treatment with vardenafil significantly improved erectile function. Tr. 1033:3-1037:8 (Goldstein). Another study, demonstrated that vardenafil provided statistically

significant improvements compared to sildenafil in obtaining an erection hard enough for penetration (question 2), being able to achieve penetration (question 3), being able to maintain an erection after penetration (question 4), being able to maintain an erection through completion of intercourse (question 5), and confidence that the patient could get and keep an erection (question 15). Tr. 1049:5-1053:3 (Goldstein, discussing DTX-626, Table 3). Vardenafil was also shown to be superior to sildenafil in various measures of erectile function in a peer-reviewed "meta-analysis" by Yuan. Tr. 1055:15-1056:7 (Goldstein, discussing DTX-795). Moreover, vardenafil demonstrates superior properties in treating the "hard-to-treat" erectile dysfunction patients like sildenafil non-responders or patients with comorbidities. Tr. 1063:6-24 (Goldstein). While Watson's expert, Dr. Laurence Levine, suggested that vardenafil could not demonstrate improved clinical properties compared to sildenafil without a "large scale placebo controlled head-to-head trial," Tr. 655:16-20, the court was persuaded by Bayer's expert, Dr. Goldstein, who explained that a practicing physician treating patients with erectile dysfunction would rely upon meaningful clinical studies, which show statistically significant results. Tr. 1022:12-1024:7 (Goldstein). Based upon Dr. Goldstein's testimony, the court finds that these beneficial clinical properties would have been unexpected to the POSA as of the priority date. Tr. 1063:25-1065:4 (Goldstein).

ii. Long-felt Need

Second, the court finds that substantial evidence on the record supports a finding that vardenafil serves an unmet need. While sildenafil helped treat large numbers of men with ED, it was not successful in all cases, and for such patients there remained a long-felt need for an effective oral treatment for ED. Tr. 1024:16-1025:10 (Goldstein). Because vardenafil has been shown to work in sildenafil non-responders, vardenafil filled a long-felt but unmet need in such patients. Tr. 1062:25-1063:5 (Goldstein). The evidence showed that vardenafil was coextensive with the

asserted claims of the '206 patent and Watson presented insufficient evidence to rebut the presumption of a nexus. *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) ("If the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus.").

*****

In sum, Watson has failed to present a *prima facie* case that the asserted claims of the patents-in-suit are invalid as obvious. Additionally, the court finds that the secondary, objective indicia point towards a finding of non-obviousness. Thus, the asserted claims are not invalid as obvious.

IV. CONCLUSION

For the reasons stated above, the court concludes that: (1) the '178 and '206 patents are not invalid due to obviousness; (2) Bayer's Rule 52(c) motion is granted. An appropriate order will follow.

Dated: May 2, 2016

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER PHARMA AG, BAYER INTELLECTUAL PROPERTY GMBH, and BAYER HEALTHCARE PHARMACEUTICALS, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 12-cv-517 (GMS) CONSOLIDATED
WATSON LABORATORIES, INC., et al.	)	
Defendants.	)	

ORDER

At Wilmington this 2nd day of May, 2016, IT IS HEREBY ORDERED THAT:

1. The asserted claims of the patents-in-suit are not invalid due to obviousness;

2. The plaintiffs' Rule 52(c) motion (D.I. 147) is GRANTED.

3. The Clerk of Court is directed to enter final judgment in favor of the plaintiffs and against the defendants.

UNITED STATES DISTRICT JUDGE