IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., PHARMACIA & UPJOHN COMPANY, PHARMACIA & UPJOHN COMPANY LLC, SUGEN, INC., C.P. PHARMACEUTICALS INTERNATIONAL C.V., PFIZER PHARMACEUTICALS LLC, and PF PRISM C.V.,	)	C.A. No. 10-528-GMS
Plaintiffs,	)	
v.	)	
MYLAN PHARMACEUTICALS INC.,	)	
Defendant.	)	

MEMORANDUM

I. INTRODUCTION

In this patent infringement action, plaintiffs Pfizer Inc., Pharmacia & Upjohn Company, Pharmacia & Upjohn Company LLC, Sugen, Inc., C.P. Pharmaceuticals International C.V., Pfizer Pharmaceuticals LLC, and PF Prism C.V. (collectively, "Pfizer") allege that pharmaceutical products proposed by defendant Mylan Pharmaceuticals Inc. ("Mylan") infringe the asserted claims of the patents-in-suit. (D.I. 1.) The court held a four-day bench trial in this matter on November 26 through November 29, 2012. (D.I. 148–151.) Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the patents-in-suit, specifically whether the asserted claims are invalid as obvious under 35 U.S.C. § 103. (D.I. 152, 153.)

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: (1) all asserted claims of the patents-in-suit are not invalid due to obviousness; and (2) Pfizer's Rule 52(c) motion is granted,

and Mylan's Rule 52(c) motion is denied. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Pfizer Inc. is a corporation organized and existing under the laws of Delaware and has a place of business at 235 East 42nd Street, New York, New York 10017.

2. Plaintiff Pharmacia & Upjohn Company was a Delaware corporation that was converted into a Delaware limited liability company and changed its name to Pharmacia & Upjohn Company LLC on August 14, 2004. Pharmacia & Upjohn Company LLC has offices located at 7000 Portage Road, Kalamazoo, Michigan 49001.

3. Plaintiff Sugen, Inc. ("Sugen") is a corporation organized under the laws of Delaware and has a place of business at 235 East 42nd Street, New York, New York 10017.

4. Plaintiff C.P. Pharmaceuticals International C.V. ("CPPI CV") is a limited partnership (*commanditaire vennootschap*) organized under the laws of the Netherlands, having its registered seat in Rotterdam, the Netherlands, and registered at the trade register held by the Chamber of Commerce in Rotterdam, under number 24280998. CPPI CV is a wholly owned subsidiary of Pfizer Inc. and has a place of business at 235 East 42nd Street, New York, New York 10017.

5. Plaintiff PF PRISM C.V. ("PF PRISM CV") is a limited partnership (*commanditaire vennootschap*) organized under the laws of the Netherlands, and registered at the trade register held by the Chamber of Commerce in Rotterdam, the Netherlands, under number 51840456.

6. Plaintiff Pfizer Pharmaceuticals LLC is a limited liability company organized under the laws of Delaware and has a place of business at Km 1.9, Road 689, Vega Baja, Puerto Rico 00693. Pfizer Pharmaceuticals LLC is a wholly-owned subsidiary of PF PRISM CV.

7. The plaintiffs will collectively be referred to as "Pfizer."

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 138, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs, corrected some 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 Part III this opinion ("Discussion and Conclusions of Law"), preceded by the phrase "the court finds" or "the court concludes."

8. Defendant Mylan Pharmaceuticals Inc. ("Mylan") is a corporation organized and existing under the laws of West Virginia, and has a place of business located at 781 Chestnut Ridge Road, Morgantown, WV 26505.

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

B. Background

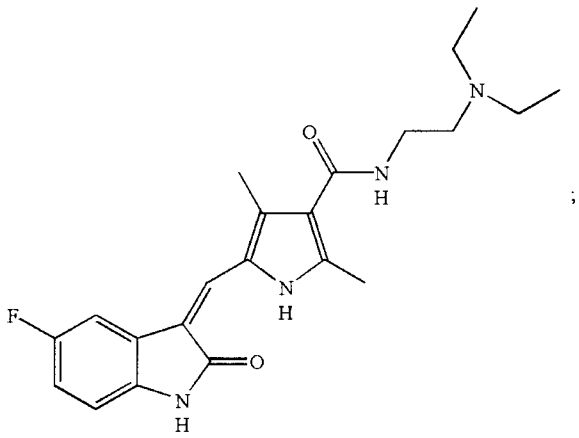
1. The idea of treating cancer by blocking angiogenesis, *i.e.*, the formation of blood vessels, was first suggested in 1971. The concept, however, was still unproven in October 2000, and the FDA had not approved any drug for this purpose.

2. Of the many possible approaches to reduce angiogenesis, one branch of Sugen's research focused on using small molecules to inhibit receptor tyrosine kinases ("RTKs") on the cell surface. Various RTKs bind to external growth factors that promote angiogenesis and tumor growth, such as VEGF (vascular endothelial growth factor), PDGF (platelet derived growth factor), and FGF (fibroblast growth factor).

3. Sugen's first compound to reach clinical studies was SU5416. It was the first small molecule shown to be effective in treating tumors by inhibiting angiogenesis. SU5416 was not orally bioavailable, meaning it could not be administered to a patient orally, and patients required frequent injections. SU5416 went all the way through FDA Phase III clinical trial but was never approved for market.

4. Sugen synthesized SU11248—what came to known as sunitinib—as part of a research project aimed at attacking tumors directly, rather than through angiogenesis inhibition.

5. Sunitinib has the following chemical structure:



C. The Patents-in-Suit

1. U.S. Patent Number 6,573,293 ("the '293 patent")—"Pyrrole Substituted 2- Indolinone Protein Kinase Inhibitors"—issued on June 3, 2003, to Sugen and Pharmacia & Upjohn Company, as assignees. Sugen is the current owner of the '293 patent.

2. U.S. Application Number 09/783,264 ("the '264 application"), which issued as the '293 patent, was filed on February 15, 2001 with the United States Patent and Trademark Office ("the PTO").

3. The expiration date of the '293 patent is February 15, 2021.

4. The '293 patent lists ten inventors on its face: Peng Cho Tang, Todd A. Miller, Xiaoyuan Li, Li Sun, Chung Chen Wei, Shahrzad Shirazian, Congxin Liang, Tomas Vojkovsky, Asaad S. Nematalla, and Michael Hawley.

5. The '293 patent claims priority back to provisional applications filed on February 15, 2000, July 6, 2000, and October 27, 2000, as Provisional Application Numbers 60/182,710, 60/216,422, and 60/243,532, respectively.

6. Pfizer is asserting infringement of claims 5 and 21 of the '293 patent against Mylan. For purposes of this action, the priority date for asserted claims 5 and 21 is October 27, 2000.

7. U.S. Patent Number 7,125,905 ("the '905 patent")—"Pyrrole Substituted 2- Indolinone Protein Kinase Inhibitors"—issued on October 24, 2006. Sugen is the current owner of the '905 patent.

8. U.S. Application Number 11/028,477 ("the '477 application"), which issued as the '905 patent, was filed on January 4, 2005 with the PTO. The '477 application is a continuation of Application Number 10/412,690, filed with the PTO on April 14, 2003, now abandoned, which is a division of the '264 application.

9. The expiration date of the '905 patent is February 15, 2021.

10. The '905 patent lists ten inventors on its face: Peng Cho Tang, Todd A. Miller, Xiaoyuan Li, Li Sun, Chung Chen Wei, Shahrzad Shirazian, Congxin Liang, Tomas Vojkovsky, Asaad S. Nematalla, and Michael Hawley.

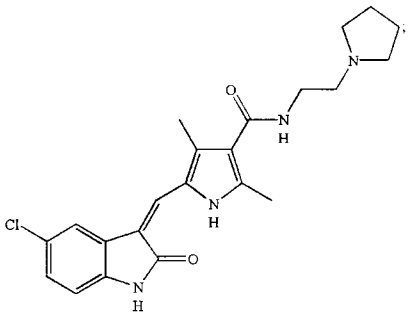
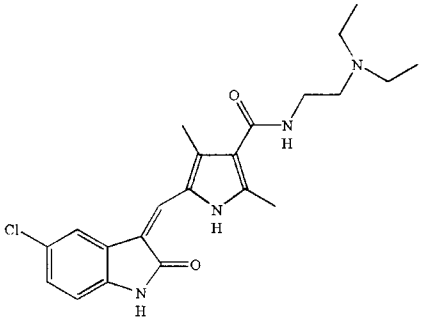
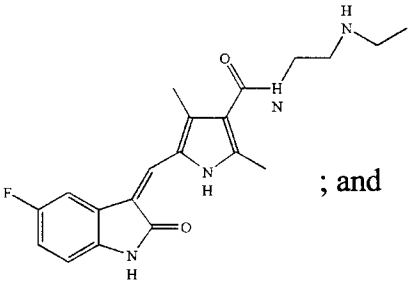
11. The '905 patent also claims priority back to provisional applications filed on February 15, 2000, July 6, 2000, and October 27, 2000, as Provisional Application Numbers 60/182,710, 60/216,422, and 60/243,532, respectively.

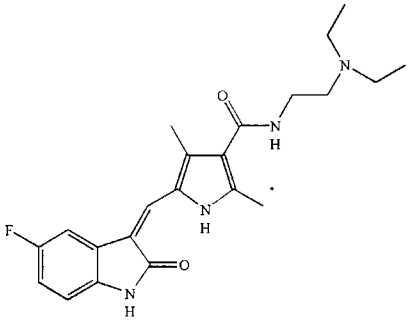
12. Pfizer is asserting infringement of claims 1 and 2 of the '905 patent against Mylan. For purposes of this action, the priority date for asserted claims 1 and 2 is October 27, 2000.

1. The Asserted Claims

a. '293 Patent, Claim 5

1. Claim 5 of the '293 Patent reads: The compound or salt of claim 1, wherein the compound is selected from the group consisting of:




; and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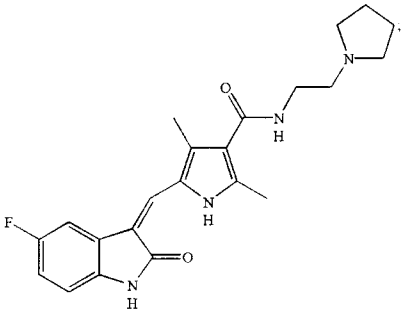
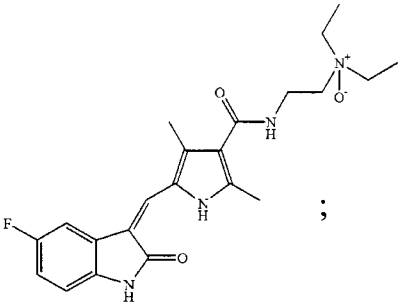
;

or an L-malate salt thereof.

b. '293 Patent, Claim 21

2. Claim 21 of the '293 Patent reads: A pharmaceutical composition, comprising a compound or salt of claim 5 and, a pharmaceutically acceptable carrier or excipient.

c. '905 Patent, Claim 1

3. Claim 1 of the '905 Patent reads: A compound that is the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide.

d. '905 Patent, Claim 2

4. Claim 2 of the '905 Patent reads: A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

D. Sutent® and Mylan's ANDA

1. The '293 and '905 patents cover, *inter alia*, the compound sunitinib malate. Pfizer sells pharmaceutical capsules containing sunitinib malate under the trade name Sutent®, pursuant to a New Drug Application that has been approved by the United States Food and Drug Administration ("FDA"). Sutent® is indicated for the treatment of "advanced renal cell carcinoma," "gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate," and "progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease." The FDA has approved Sutent® in 12.5 mg, 25 mg, 37.5 mg, and 50 mg dosage strengths.

2. Mylan has submitted to the FDA Abbreviated New Drug Application ("ANDA") No. 201-275, seeking approval to sell generic versions of drug products containing sunitinib malate in 12.5 mg, 25 mg, 37.5, and 50 mg dosage strengths ("Mylan's ANDA Products"). ANDA No. 201-275 contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the '293 and '905 patents asserting that the '293 and '905 patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, or sale of Mylan's ANDA products.

3. Mylan has since stipulated that the manufacture, use, sale, offer for sale, or importation of Mylan's ANDA Products, as well as the active ingredient contained therein, infringes claims 5 and 21 of the '293 Patent, and claims 1 and 2 of the '905 Patent.[2]

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). The only issue remaining is whether the asserted claims of the patents-in-suit are invalid due to obviousness. After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that: (1) none of asserted claims of the patents-in-suit are invalid due to obviousness; and (2) Pfizer's Rule 52(c) motion is granted, and Mylan's Rule 52(c) motion is denied. The court's reasoning follows.

[2] (D.I. 106, 107.)

A. Obviousness

The defendants challenge the validity of each of the asserted claims, arguing that they are obvious in light of the prior art. The court finds, for the reasons that follow, that the defendants have failed to establish by clear and convincing evidence that the patents-in-suit are obvious.

1. The Legal Standard

35 U.S.C. § 103(a) provides that 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 patent shall be presumed valid." 35 U.S.C. § 282. A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence"[3] 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. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Intern. Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining

[3] "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)).

obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *See KSR*, 550 U.S. at 415. The *KSR* Court acknowledged, however, the importance of identifying "'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1356–57 (Fed. Cir. 2007) (quoting *KRS*, 550 U.S. at 418).

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See 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, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

2. <u>The Level of Ordinary Skill in the Art</u>

A person of ordinary skill in the art with respect to the patents-in-suit would have: (1) the skills of a Ph.D.-educated medicinal chemist, with knowledge and experience regarding kinase targets and chemical scaffolds as they relate to anti-angiogenesis drugs;[4] or (2) the skills of a

[4] Pfizer's identification of a person of ordinary skill in the art is derived from Drs. Lydon and Denny. (D.I. 153 at 3 (citing Tr. 306:19–307:13 (Lydon); Tr. 77:22–78:8 (Denny).)

Ph.D. or M.D. with experience in the fields of kinase inhibitor compounds and cancer treatment, with one to five years of post-doctoral experience in drug development.[5] The court concludes that the parties' definitions of a person of ordinary skill in the art do not differ in a meaningful way.

3. The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

Although there are four asserted claims in the patents-in-suit, the controlling question for each of the claims is whether synthesizing sunitinib malate would have been obvious to one skilled in the art as of the priority date. Mylan argues that the asserted claims are obvious for two reasons: (1) a nearly identical analog of sunitinib was disclosed in Patent Application WO 99/61422 ("the '422 application"); and (2) the lead compounds available as of the priority date would have motivated one skilled in the art to derive the claimed sunitinib malate. The court addresses each of these arguments in turn.

a. The '422 Application

Mylan argues that the '422 Application discloses a "generic preparation" for a "large number of potential oxindoles," among which is a structurally similar analog of sunitinib: dimethyl sunitinib.[6] (D.I. 152 at 27–29; Tr. at 158–59 (Denny).) The difference between dimethyl sunitinib and sunitinib is simply that dimethyl sunitinib has a dimethylamine solubilizing group whereas the claimed compound has a diethylamine group. Although the '422 Application discloses approximately 1200 possible combinations, Mylan asserts that the '422 Application instructs that each of the combinations *will work*, and therefore the "routine" steps of going from dimethyl sunitinib to sunitinib and finally to sunitinib malate were obvious. (D.I. 152 at 28–29.)

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[5] Mylan's description of a personal of ordinary skill in the art is found in DTX-1021.

[6] Pfizer refers to this compound as the "Hypothetical '422 Compound," whereas Mylan uses the shorthand "dimethyl sunitinib." The court adopts Mylan's phraseology for convenience only.

Mylan relies on *Merck & Co. v. Biocraft Laboratories, Inc.* for this proposition. 874 F.2d 804 (Fed. Cir. 1989). In *Merck*, the Federal Circuit distinguished between compounds that are merely "obvious to try"—which are not barred by § 103—versus compounds with an expectation of success, *i.e.*, compounds that *will work* for their intended purpose. *Id.* at 807. When a prior art reference lists a number of combinations, all of which should achieve the desired result, "routine" alterations or optimization will not preclude a finding of obviousness. *Id.* at 809.

The court finds, however, that Mylan's reliance on *Merck* goes too far. In *Merck*, the prior art reference disclosed individual diuretic agents that could be co-administered to achieve the desired properties. *Id.* at 807. The Federal Circuit found the patent-in-suit obvious in light of the prior art reference because the patentee had merely followed the instructions and optimized the dosage levels. *Id.* at 808–09. Similarly, in Mylan's other cited case, the claimed compound was simply a salt form of one of the compounds disclosed in the prior art, a step which was in fact suggested by the prior art reference. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007) ("[T]he prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing.") The court is not convinced that the steps needed to go from dimethyl sunitinib ultimately to sunitinib malate constituted "routine optimization" on par with that in *Merck* or *Pfizer*. (D.I. 152 at 27–29.) Although Mylan states matter-of-factly that "the optimization of dimethyl to diethyl is even more routine and therefore obvious" than the steps taken in *Merck* and *Pfizer*, those cases involved little more than following clearly delineated steps outlined by the prior art. (*Id.* at 28.) Critical to the Federal Circuit's decision in *Merck* was the fact that "success [was] not dependent upon random variation of numerous parameters." *Merck*, 874 F.2d at 807. The court finds that the process of going from dimethyl sunitinib to sunitinib to sunitinib malate would have required significant

guesswork and variation of parameters to achieve the end result. The '422 Application did not indicate that these steps would yield better angiogenesis inhibition, nor is the court convinced that the one skilled in the art would have found these "optimization" steps obvious without some data to support it. (Tr. at 227 (Denny).) The court recognizes that *Merck* predates *KSR*, and there is no requirement that the prior art offers an explicit teaching, suggestion, or motivation for the court to make an obviousness determination. *See KSR*, 550 U.S. at 415. But given the sheer volume of possible combinations and the additional subsequent chemical alterations necessary to arrive at the claimed compound, the court cannot say that one skilled in the art would have had a reason to alter dimethyl sunitinib as Mylan suggests. Thus, the asserted claims are not obvious in light of the '422 Application.[7] *See Takeda*, 492 F.3d at 1356–57.

b. Lead Compounds

Pfizer and Mylan both provide a list of "lead" compounds—compounds known in the art that would have served as logical "starting points[] for further development efforts." *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012); *see also Takeda*, 492 F.3d at 1357–60. To establish a *prima facie* case of obviousness, Mylan must first establish that one skilled in the art would have selected a given lead compound. *See Takeda*, 492 F.3d at 1360; *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006). If one skilled in the art would have chosen the lead, Mylan must then prove that modification of the lead compound to arrive at the claimed compound would have been obvious to one skilled in the art. *Takeda*, 492 F.3d at 1360–63.

Pfizer argues that its proffered leads—Compounds 11f, 9a, and 9b; SU6668; PTK-787; ZD 4190; PD-74 and PD-85—take into account the entire state of the art, including compounds

[7] To remain consistent with the parties' briefing, the court also discusses the '422 Application and dimethyl sunitinib below, in the context of lead compounds.

developed by other companies, and best illustrate trends in anti-angiogenesis research at the time. (D.I. 153 at 4–6; Tr. at 321–25 (Lydon).) Compounds 11f, 9a, and 9b were Sugen's "second-generation" oxindole compounds, developed on the heels of SU5416, which had gone to clinical trials with mixed success. (D.I. 153 at 4–5.) Sugen believed these second-generation compounds would overcome the shortcomings of SU5416; in particular, these second-generation compounds improved VEGFR potency and addressed solubility and oral bioavailability problems. (*Id.*) Based on Sugen's structural-activity relationship research, each of these compounds incorporated a propionic acid group on the pyrrole ring, which Sugen believed was "required" for potency. (*Id.*; JTX-113 at 7; Tr. at 648 (Sun).)

Pfizer next highlights SU6668 as a possible lead. (D.I. 153 at 5.) SU6668 was Sugen's second-generation clinical candidate. Like Compounds 11f, 9a, and 9b, it incorporated a propionic acid group on the pyrrole ring and solved several of the problems that plagued SU5416: "The molecular modification of SU5416 provided significant improvements in pharmacokinetics, oral bioavailability, efficacy, preclinical safety, and pharmaceutical properties of SU6668." (*Id.*; PTX-632 at 2; Tr. at 445–46 (Lyons) ("[SU]5416 was an early first generation compound, at which, in the early '90s, was interesting, there is no doubt about that. However, [SU]6668 had already addressed multiple problems that that molecule had."))

Finally, Pfizer provides several non-oxindole compounds that were developed by competitor companies to address angiogenesis in tumors. (D.I. 153 at 5–6.) PTK-7878 (developed by Novartis), ZD 4190 (developed by AstraZeneca), and PD-75 and PD-85 (developed by Parke-Davis) all showed notable improvements over SU5416. (*Id.*) Given the apparent success of these compounds, Pfizer argues that one skilled in the art would not have limited the scope of potential leads to only oxindole compounds.

In contrast, Mylan proposes three possible lead compounds: SU5416, SU5408, and dimethyl sunitibin. As already noted, SU5416 was Sugen's first-generation compound and the first small molecule demonstrating RTK inhibition to reach clinical trials. (D.I. 152 at 8–9.) Mylan argues that Sugen itself had used SU5416 as a scaffold in developing other possible formulations, including SU6668, thus confirming its status as a lead compound, notwithstanding its oral bioavailability and metabolism concerns. (*Id.* at 10)

Mylan also lists SU5408 as a possible lead compound. (*Id.* at 10.) SU5408 was another first-generation compound, structurally similar to both SU5416 and SU6668. It demonstrated strong VEGF potency, and its electronic-withdrawing ethyl ester group at C-4' position of the pyrrole ring would have helped reduce metabolism in the body. (*Id.* at 11.) Mylan argues that one skilled in the art would have recognized the promising base properties of SU5408 and would have modified it to achieve additional improvements. (*Id.*)

Finally Mylan suggests one skilled in the part would have selected dimethyl sunitinib as a lead compound. (*Id.* at 11–12.) As noted above, this compound is drawn from the '422 Application, which provided a list of oxindoles and aldehydes that could be combined to create a possible RTK inhibitor. (*Id.*; Tr. at 158–59 (Denny).) The list provides for approximately 1200 distinct combinations. Mylan argues that dimethyl sunitinib would have been selected as a lead compound from among the various possible combinations contemplated by the '422 Application because of the common core structure it shared with SU5416 and SU6668, and also because it would have addressed the metabolism and solubilization problems. (D.I. 152 at 12.)

Mylan bears the burden in proving that one skilled in the art would have considered its proposed lead compounds. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 654 (D. Del. 2013). To avoid the possibility of hindsight bias, "the patent

challenger must point to more than mere structural similarity as a reason to select a compound as a lead." *Id.* (citing *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). Moreover, even if the compounds Mylan suggests are shown to be viable leads, Mylan must then establish that one skilled in the art would have found it obvious to modify the lead compounds to arrive ultimately at claimed compound: sunitinib malate. After considering the parties' submissions and the evidence on the record, the court is not convinced that any of Mylan's proffered compounds would have constituted lead compounds as of the October 2000 priority date.

i. SU5416

The court finds that, although SU5416 represented a breakthrough in anti-angiogenesis cancer treatment at the time it was first disclosed, as of the priority date in October 2000, one skilled in the art would have acknowledged its shortcomings and looked to more recent advances in the field. Sugen published its SU5416 data in 1998, but already by 1999 Sugen had published research on second-generation compounds that addressed SU5416's lack of oral bioavailability. By October 2000, SU6668 had also reached clinical trials and demonstrated improvements over SU5416 in several respects. (Tr. at 383 (Lydon).) Sugen's publications disclosed that the presence of a propionic acid group was a necessary element for potency, and therefore taught away from SU5416, which lacked a propionic acid group. In considering lead compounds, one skilled in the art would not ignore these teachings and discount the improvements and progress that had been made in the field in favor of SU5416, simply because it was *first*. The art had advanced beyond SU5416 by October 2000. The court concludes one skilled in the art would not have chosen SU5416 as a lead compound.

ii. SU5408

The court finds that SU5408 also would not have been selected by one skilled in the art as a lead compound. Mylan's choice of SU5408 as a lead compound appears largely the result of hindsight. SU5408, like SU5416, was one of Sugen's first-generation compounds. Although it demonstrated strong potency against VEGF *in vitro*, there is no *in vivo* data available for SU5408; indeed Mylan's expert Dr. Denny acknowledged that "[v]ery little work was done with SU5408." (Tr. at 207 (Denny).) Mylan once again relies on a snapshot of the state of the art as it existed in 1998 when Sugen disclosed its first-generation compounds. (Tr. at 151 (Denny).) But as already stated, the field moved forward, and one skilled in the art would have kept pace with such progress in selecting lead compounds. Whereas SU5416 at least made it to clinical trials and yielded significant data, SU5408 never made it out of the lab. The data are very limited. One skilled in the art would not have had any particular motivation for selecting SU5408, especially in light of the second-generation compounds and their much more promising and complete data, which was widely available as of October 2000.

iii. Dimethyl Sunitinib

Finally Mylan argues that dimethyl sunitinib—a hypothetical compound listed as one of approximately 1200 possible combinations in the '422 Application—would have been a lead compound for one skilled in the art. The court finds that Mylan's choice of dimethyl sunitinib as a lead compound cannot be characterized by anything other than hindsight bias. The compound, which is referred to here as dimethyl sunitinib only for the sake of convenience, had no name, had no chemical structure, had never actually been synthesized, and of course had no data demonstrating its properties. The only hint that this compound could exist came from the '422 Application's list of components, and there was nothing to suggest that this particular

combination would yield promising results as a lead. (Tr. at 201–02 (Denny).) Dr. Denny's choice of dimethyl sunitinib as a lead was informed by a "logic chain." (*Id.* at 202–03.) The court finds, however, that one skilled in the art would not have ignored actual, synthesized compounds with actual data in favor of a hypothetical, never-created compound as a lead.

In the previous discussion, the court explained that the claimed sunitinib malate is not obvious in light dimethyl sunitinib because more than routine optimization would have been needed to achieve the claimed compound. Similarly, the court now concludes that, under a lead compound analysis, one skilled in the art also would not have chosen dimethyl sunitinib as a lead compound. As quoted above, "the patent challenger must point to more than mere structural similarity as a reason to select a compound as a lead." *Bristol-Myers Squibb*, 923 F. Supp. 2d at 654. The court is not persuaded by Dr. Denny's "logic chain" rationale that resulted in selecting the almost identical structural analog of sunitinib malate. The court concludes that this post-hoc reconstruction of events is entirely informed by hindsight bias.

iv. Modifying the Lead Compounds

Even accepting Mylan's choices as lead compounds, the court finds that Mylan has not established by clear and convincing evidence that modifying the leads to yield sunitinib malate would have been obvious to one skilled in the art or that one skilled in the art would have had a reasonable expectation of success. *See Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010) ("Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select *and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation* that the new compound would have similar or improved properties compared with the old." (emphasis added)).

To obtain sunitinib from dimethyl sunitinib, one skilled in the art only would have had to replace the dimethylamine solubilizing group with a diethylamine group. The court is not convinced, however, that even this single modification would have been obvious. Dr. Denny's testimony confirmed that a diethylamine group was similarly susceptible to the problem of dealkylation as a dimethylene group. (Tr. at 258 (Denny).) And Pfizer's expert Dr. Stafford testified that one skilled in art—if faced with a dealkyation problem (referred to as "demethylation" in his testimony)—would not have turned to a diethylamine group for the solution. (Tr. at 538–39 (Stafford).) Rather, several other structural changes, such as creating a cyclic version, would have been appealing next steps. (*Id.* at 539.) The court is not convinced that one skilled in the art—assuming dealkylation were recognized as a problem at all—would have expected the addition of diethylamine to solve the apparent problem.

As for SU5416 and SU5408, both require several sequential modifications to arrive at sunitinib. The modification chain is largely the same for both except than one additional step is needed initially to modify SU5416 to create SU5048. This first step requires adding an electron-withdrawing ester to the pyrrole ring of SU5416. Dr. Denny argues that one skilled in the art would have found it obvious to lower the electron density of the pyrrole ring (by introducing an electron-withdrawing group) in order to improve activity and reduce metabolism. (Tr. at 164 (Denny).) The court disagrees with this conclusion. First, the statement is contrary to the Sugen's explicit teachings that propionic acid, an electron-*donating* group, was "required" for high potency. (JTX 113 at 7.) One skilled in the art would not discount data published by the very researchers working with SU5416. Second, one skilled in the art would not have modified a relatively successful compound like SU5416 simply to recreate SU5408, a compound that had

already been tested and essentially ignored by Sugen as a candidate. Mylan fails to show this first modification of SU5416 would have been obvious.

In addition, the court finds Mylan also fails to show that the remaining modifications from SU5408 to sunitinib would have been obvious. Dr. Denny maintains that one skilled in the art would have replaced the C-5 hydrogen with fluorine to reduce metabolism of the oxindole. (Tr. at 174–75 (Denny).) But both Dr. Denny and Dr. Stafford testified that there were no data available for any oxindole compound with fluorine at the C-5 position. (Tr. 254–55 (Denny); Tr. at 510 (Stafford).) Moreover, it is not clear that metabolism at the C-5 position presented a major problem that required a substitution; after all, in its next clinical candidate, SU6668, Sugen made no substitution to the C-5 position. (Tr. at 503–504 (Stafford).) Even assuming that metabolism was a problem to be addressed, the court is not convinced that choosing fluorine to do so would have been an obvious modification to one skilled in the art, as opposed to any other blocking group placed at the C-5 position. (*Id.* at 556–57.) Mylan only points to the dimethyl sunitinib to support its assertion that a fluorine at the C-5 position would have been an obvious modification; the court is not persuaded that this hypothetical compound in the '422 Application that had never been synthesized is sufficient to render the modification obvious.

Mylan next argues that replacing the ester at the C-4' position with an amide would have been obvious in order to increase stability because of the potential for ester hydrolysis in the bloodstream and liver. (Tr. 153–54 (Denny).) In the context of SU5416, this would require substituting the ester that had just been added in the previous step with an amide, an exercise that defies logic. But even in the SU5408 scenario, the court is not convinced that such a substitution would have been obvious. Many successful drugs have esters, and it would be very difficult to predict whether ester hydrolysis would pose a problem for any particular compound without test

data. (Tr. at 482–83 (Stafford).) As noted above, there was no *in vivo* data for SU5408 to prompt one skilled in the art to worry about ester hydrolysis.

Mylan next contends that after substituting the amide, one skilled in the art would have appended an additional solubilizing group to the C-4' amide in order improve solubility. (Tr. at 167 (Denny).) Dr. Denny testified that a diethylamine would have been the obvious choice because amides were generally preferred over acid solubilizing groups and diethylamine groups were commonly used for this purpose. (*Id.* at 165–67, 171.) But again, Mylan fails to establish that one skilled in the art would have assumed there to be a solubility problem in the first place. Dr. Stafford's testimony reveals that theoretical solubility of the unmodified compound would have fallen within the acceptable range. (Tr. at 490–91 (Stafford).) The court finds that, without data demonstrating a solubility concern, one skilled in the art would have had no reason (and therefore it was not obvious) to add a solubilizing amide. *See Takeda*, 492 F.3d at 1356–57. Moreover, even if one skilled in the art were motivated to address solubility, the court finds that the natural choice would have been to use propionic acid, as taught by Sugen's publications. Dr. Denny acknowledged that acid solubilizing agents could be equally if not more effective than base agents in some cases. (Tr. at 249 (Denny).) The court is not convinced that that one skilled in the art would have found it obvious to select this particular amide side chain as opposed to any of the other possibilities, especially when the art pointed towards propionic acid.

For attaching the diethylamine solubilizing side chain to the C-4' amide, Mylan argues a two-carbon linker would have been used because it was the minimal stable linker length between the two nitrogens, and it was the most conservative change. (Tr. at 174 (Denny).) But Dr. Denny also testified that the length of the carbon linkage could affect the potency of the compound. (*Id.* at 248.) One skilled in the art would not have arbitrarily chosen a two-carbon chain because it

was the most conservative. Rather, one skilled in the art would have looked to test data to determine the optimal linker length to maximize activity. The court finds that, without any data, there was no reason for one skilled in the art to assume two carbons was the obvious length for the linkage, and there was no way of having a reasonable expectation of success.[8]

The last required modification for each of Mylan's proposed lead compounds—SU5416, SU5408, and dimethyl sunitinib—is to create the malate salt form of sunitinib. The court finds that one skilled in the art would not have found this particular salt form obvious. Assuming one skilled in the art would have been motivated to try a sunitinib salt, there is no explanation for why one skilled in the art would have found malate to be an obvious choice. Dr. Denny testified that in his salt selection experience, he would limit tests to three or four options, and never had he selected malate. (Tr. at 261 (Denny).) He confirmed that malate is one of the rarest salts in pharmaceutical compounds. (*Id.*) Despite this testimony, Mylan asserts that selecting malate would have been the result of routine optimization. The court finds that Mylan misinterprets the case law on this topic. As discussed briefly in the previous section, Mylan's reliance on *Pfizer* is misplaced. 480 F.3d 1348. In *Pfizer*, the Federal Circuit held that the patentee's creation of an acid salt was obvious because it was the result of "routine testing." *Id.* at 1367. But the court was careful to emphasize that its holding was based on the "*particularized facts of this case*" because the prior art had specifically "predicted the results." *Id.* (emphasis in original). Here, unlike in *Pfizer*, there was nothing in the prior art to suggest to one skilled in the art that malate was one of a limited subset of salts to choose, or even that a salt form of sunitinib would be beneficial.[9]

[8] Pfizer additionally argues that one skilled in the art would not have retained the methyl side groups at the C-3' and C-5' position because the prior art taught away from this configuration. The court does not consider retention of lead compound attributes to be a "modification" as contemplated by case law. The court, therefore, does not discuss this as a necessary modification.

[9] The court once again recognizes that an obviousness determination does not require an explicit motivation in the art. *See Daiichi Sankyo Co.*, 619 F.3d at 1352. But because the Federal Circuit's decision in *Pfizer* was

Indeed, malate did not appear on the most current FDA list of approved salt forms. (PTX-328 at 3; Tr. at 263 (Denny).) Despite the inherent unpredictability of acid salts—acknowledged by both parties' experts (Tr. at 264 (Denny); Tr. at 681 (Myerson))—Mylan nonetheless argues that testing essentially all possibilities would have been done as a matter of course. (Tr. at 177–78 (Denny).) The court disagrees and finds that one skilled in the art would not have found the malate salt modification obvious. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008) (upholding the district court's finding of non-obviousness where there were a "wide range of possible outcomes" and a "relative unlikelihood" that the desired results would be obtained).

The court has already explained that Mylan's choice of lead compound would not have been selected by one skilled in the art. Nonetheless, the court also concludes that the requisite modifications needed to go from the lead compounds to sunitinib malate would not have been obvious to one skilled in the art.

4. Secondary Considerations

Pfizer contends that Mylan has failed to make a *prima facie* showing of obviousness under § 103, or, in the alternative, that the secondary considerations of non-obviousness rebut Mylan's *prima facie* showing. *See Graham*, 383 U.S. at 17–18. The court has found that Mylan failed to establish a *prima facie* case of obviousness. Assuming Mylan had satisfied its initial burden, however, the court finds that Pfizer's secondary considerations—unexpected properties, long-felt need, failure of others, commercial success, skepticism, and acceptance and praise—support a determination of non-obviousness.

a. Unexpected Properties

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heavily influenced by the prior art's explicit teachings, the court finds this to be a critical distinction. *See Pfizer*, 480 F.3d at 1367.

The court agrees that the claimed compounds, including sunitinib, possessed unexpected properties, thus weighing in favor of a non-obviousness finding. First, the activity of sunitinib compared with the previous clinical candidates, SU5416 and SU6668, was "certainly much more potent" against each of the target RTKs *in vitro*. (Tr. at 267 (Denny); Tr. at 542 (Stafford).) Considering that sunitinib was synthesized with entirely different goals in mind, the court finds its significant activity to be unexpected. (Tr. at 667–670 (Sun).)

Moreover, the malate salt form of sunitinib solved several manufacturing problems that posed a major barrier to bringing sunitinib to market. (Tr. at 695 (Myerson).) Malate was not among the initial screen of salts. (*Id.* at 691–92.) None of the salts from this screen were selected. (*Id.* at 691.) Researchers, however, discovered that the freebase sunitinib possessed "terrible filtration and drying properties," which persuaded them to do an additional salt screen. (*Id.* at 692.) For this second screen, malate was chosen "just for kicks," and it turned out that sunitinib malate had superior properties across the board compared to other salts; such properties made it possible to commercialize sunitinib. (*Id.* at 695–96.) The court finds that one skilled in the art would not have expected sunitinib malate to outperform the other salts in all categories.

b. Long-Felt Need and Failure of Others

The court also agrees that sunitinib malate satisfied a long-felt need in the market for treatments for renal cell carcinoma ("RCC") and pancreatic neuroendocrine tumors ("PNET"). *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009). This need was caused largely by frequent failures of others to develop an effective treatment for these cancers. (Tr. at 724 (Bukowski) ("[I]f you want to show a new drug to fail, test it in kidney cancer.")) There is no question that others, including Sugent, had tried to address the question of anti-angiogenesis and failed. (Tr. at 544 (Stafford).) The evidence demonstrated that sunitinib

malate provided greatly improved clinical outcomes for RCC patients, and represented a "huge paradigm shift" for the treatment of PNET. (PTX-524 at 1; Tr. at 742–43 (Bukowski); (Tr. at 790–93 (Kulke)). The court finds that, even with the competing drugs available, sunitinib malate satisfied a long-felt need in the treatment of these cancers. (Tr. at 721–24; 730 (Bukowski).)

Mylan makes a false distinction between properties identified in the claims versus the specification. (D.I. 152 at 39.) The patents-in-suit need not specifically identify RCC and PNET in the claims for the purposes of evaluating long-felt need. *See In re Papesch*, 315 F.2d 381, 391 (C.C.P.A 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing.") Mylan's reliance on *Therasense*, which did not discuss chemical compound claims, is inapposite. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325 (Fed. Cir. 2010).

c. Commercial Success

Pfizer and Mylan presented competing experts who testified as to whether Sutent®, Pfizer's brand-name embodiment of sunitinib malate, has been a commercial success. The court finds that Sutent® has indeed been a commercial success. The court notes initially that any success Sutent® has had—whatever it may be—is attributable to the active, claimed compound, sunitinib malate, and not marketing. *See Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392–93 (Fed. Cir. 1988) ("A prima facie case of nexus is generally made out when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent.") Mylan has not rebutted this presumption.

Although the parties presented directly opposing evidence, the court finds Pfizer's testimony was the more compelling. Sutent® remains the dominant drug for RCC treatment,

maintaining nearly fifty percent of the market six years after its launch, with almost twice as much market share as the nearest competitor.[10] (PTX-620.) Sutent® is Pfizer's largest revenue generator among its oncology drugs. (Tr. at 813 (Robertson).) Revenues have exceeded expenses each year Sutent® has been on the market. (*Id.*) Moreover, on average, drugs in the industry tend to take fifteen or sixteen years to break even and recoup the investment; Sutent® is on pace to break even within ten years. (*Id.* at 872– 73.) Mylan presented evidence that Sutent® failed to meet Pfizer's own internal projections and failed to obtain FDA approval for several indications. (*Id.* at 832–33; 836–38.) While it considers these as factors, in the larger picture, the court still finds that Sutent® has been a commercial success. The fact that competitors have entered the market and diminished Sutent®'s overall share does not change the court's conclusion.

d. Skepticism and Praise

Evidence of both initial skepticism and subsequent acceptance and praise after patenting are probative factors for evaluating non-obviousness. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1367–68 (Fed. Cir. 2012). In this case, the court finds these factors also weigh toward a finding of non-obviousness. Several prior failed attempts at creating an effective anti-angiogenesis drug created a general sense of skepticism as to whether the concept could work in practice. *See OSI Pharm., Inc. v. Mylan Pharm. Inc.*, 858 F. Supp. 2d 341 (D. Del. 2012) (noting the "almost insurmountable failure rate for new drug candidates" in evaluating skepticism). Moreover, Pfizer has presented convincing evidence that Sutent® was a breakthrough in the industry, widely praised by researchers and doctors. (PTX-524; PTX-505; Tr. at 746–47 (Bukowski); Tr. at 791 (Kulke).) "Substantial industry praise" is compelling evidence of non-obviousness. *See Crocs., Inc. v. ITC*, 598 F.3d 1294, 1311 (Fed. Cir. 2010).

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[10] The data only went through 2011.

In sum, Mylan has failed to present a *prima facie* case that the asserted claims of the patents-in-suit are invalid as obvious. Moreover, even assuming a *prima facie* case had been made, the court finds that the secondary, objective indicia point towards a finding of non-obviousness. The asserted claims are not invalid as obvious.

IV. CONCLUSION

For the reasons stated above, the court concludes that: (1) none of the asserted claims of the patents-in-suit are invalid due to obviousness; (2) Pfizer's Rule 52(c) motion is granted, and Mylan's Rule 52(c) motion is denied.[11]

Dated: October 22, 2014

UNITED STATES DISTRICT JUDGE

[11] As noted, all parties submitted Proposed Findings of Fact and Conclusions of Law, requesting that the court find in its favor on the issue of obviousness. For the reasons stated above and based on the court's findings, the court grants Pfizer's Rule 52(c) motion and denies Mylan's motion.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., PHARMACIA & UPJOHN COMPANY, PHARMACIA & UPJOHN COMPANY LLC, SUGEN, INC., C.P. PHARMACEUTICALS INTERNATIONAL C.V., PFIZER PHARMACEUTICALS LLC, and PF PRISM C.V.,	)	C.A. No. 10-528-GMS
Plaintiffs,	)	
v.	)	
MYLAN PHARMACEUTICALS INC.,	)	
Defendant.	)	

ORDER

At Wilmington this 22nd day of October, 2014, IT IS HEREBY ORDERED THAT:

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

2. Plaintiffs' Rule 52(c) motion (D.I. 153) is GRANTED;

3. Defendant's Rule 52(c) motion (D.I. 152) is DENIED;

4. The Clerk of Court is directed to enter final judgment in favor of the plaintiffs.

UNITED STATES DISTRICT JUDGE