IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER INTELLECTUAL PROPERTY GMBH, et al.,	:	**CIVIL ACTION**
Plaintiffs,	:	
v.	:	**NO. 15-902**
AUROBINDO PHARMA LIMITED, et al.,	:	
Defendants.	:	

Findings of Fact, Conclusions of Law and Verdict

STENGEL, C.J.[1] **July 13, 2018**

I. Introduction

This is a consolidated patent infringement action arising under the Hatch-Waxman Act. The plaintiffs, Bayer Intellectual Property GMBH, Bayer Pharma AG, and Janssen Pharmaceuticals, Inc. (collectively "Bayer") allege infringement of claim 16 of U.S. Patent No. 7,157,456 (the "'456 patent"), which claims the compound rivaroxaban. The parties concede infringement. Defendants, Mylan Pharmaceuticals Inc. and Sigmapharm Laboratories, LLC submit that the patent is invalid as obvious. I held a four-day bench trial beginning on March 5, 2018 through March 9, 2018.[2]

Presently before me are the parties' proposed findings of fact and conclusions of law. Pursuan t to Federal Rule of Civil Procedure 52(a), having considered the entire

[1] Chief Judge Lawrence F. Stengel of the Eastern District of Pennsylvania is sitting by designation in this case filed in Delaware District Court pursuant to the provisions of 28 U.S.C. § 292(b), and by Order of Chief Judge D. Brooks Smith of the Third Circuit. (Doc. No. 268.)
[2] The Court was closed due to inclement weather on March 7, 2018.

record and the relevant law, I find that the asserted claim of the ’456 patent is not invalid due to obviousness. The findings of fact and conclusions of law are set forth in further detail below.

II. Procedural History

On October 9, 2015, plaintiffs filed a complaint alleging infringement of the ’456, ’860, and ’339 patents. (Doc. No. 1.) Sigmapharm filed its answer on October 30, 2015, alleging that the patents were invalid. (Doc. No. 26.) On January 19, 2016, Mylan filed its answer, also asserting as an affirmative defense that the patents were invalid. (Doc. No. 66.)

The parties filed separate stipulations stating that the products that are the subject of defendants’ ANDAs infringe any valid claims of the ’456, ’860, and ’339 patents, including claim 16 of the ’456 patent. (Doc. Nos. 232, 236.) Plaintiffs later notified defendants that, for purposes of narrowing the issues for trial, they would only assert claim 16 of the ’456 patent. (Doc. No. 286 at ¶ 8; Doc. No. 287 at ¶ 15.)

Beginning on March 5, 2018, I held a four-day bench trial. The parties submitted post-trial briefing and on April 25, 2018 I heard closing arguments.

III. Findings of Fact

A. The parties

1. The Bayer plaintiffs are corporations organized and existing under the laws of the Federal Republic of Germany. (Doc. No. 286-1, Ex. 6, ¶¶ 6-7.)

2. Janssen is a corporation organized and existing under the laws of the Commonwealth of Pennsylvania. (Id. at ¶ 8.)

3. Mylan is a corporation organized and existing under the laws of the State of West Virginia. (Id. at ¶ 18.)

4. Sigmapharm is a limited liability company organized and existing under the laws of the Commonwealth of Pennsylvania. (Id. at ¶ 14.)

5. Janssen is the holder of approved New Drug Application No. 22406 for Xarelto® (rivaroxaban). (Id. at ¶ 12.)

6. Xarelto® is a factor Xa inhibitor which is indicated to (1) reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; (2) for the treatment of deep vein thrombosis (DVT); (3) for the treatment of pulmonary embolism (PE); (4) for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months; and (5) for the prophylaxis (prevention) of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery. (Id. at ¶ 10.)

B. The patent-in suit

7. The ’456 patent is entitled “Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation.” (Id. at ¶ 1.)

8. The named investors are Alexander Straub, Thomas Lampe, Jens Pohlmann, Susanne Roehrig, Elisabeth Perzborn, Karl-Heinz Schlemmer, and Joseph Pernerstorfer. (Id.)

9. The patent was issued on January 2, 2007, expires on August 28, 2024, and is currently assigned to Bayer Intellectual Property GmbH. (Id. at ¶¶ 1, 2.) The priority date for the patent is December 24, 1999. (3/5/18 a.m. Tr. 33:12-19.)

C. ANDA No. 208546

10. Sigmapharm submitted Abbreviated New Drug Application ("ANDA") No. 208546 to the FDA seeking approval of its proposed rivaroxaban tablets under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act ("Paragraph IV Certification") that the claims of the '456 patent and U.S. patent Nos. 7,585,860 (the "'860 patent") and 7,592,339 (the "'339 patent") were invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Sigmapharm's proposed rivaroxaban tablets. (Doc. No. 286-1, Ex. 6, ¶ 16.)

11. By letter dated August 31, 2015, Sigmapharm notified plaintiffs that it submitted ANDA No. 208546. (Id. at ¶ 15.)

D. ANDA No. 208561

12. Mylan submitted ANDA No. 208561 also seeking approval of its proposed rivaroxaban tablets contained in a Paragraph IV Certification that the '456, '860, and '339 patents were invalid, unenforceable, and/or would not be infringed by the commercial manufacture, use, or sale of Mylan's proposed rivaroxaban tablets. (Id. at ¶ 20.)

13. On September 15, 2015, Mylan notified plaintiffs that it submitted ANDA No. 208561. (Id. at ¶ 19.)

E. Expert Witnesses

14. Dr. Steven Brickner, defendants' medicinal chemistry expert, received a Ph.D.

in organic chemistry from Cornell University; worked in the pharmaceutical industry as a medicinal chemist for 27 years, and has another nine years' experience as a medicinal chemistry consultant and is a named inventor on thirty (30) U.S. Patents and Patent Applications. (Defs. FF. ¶ 12 (citing 3/5/18 a.m. Tr. 9:20-11:11; 12:14-13:7; DTX-1266).) Dr. Brickner is accredited with discovering linezolid. (Id. (citing 3/5/18 a.m. Tr. 10:12-11:13).)

15. Dr. Spada, plaintiffs' medicinal chemistry expert, was the medicinal chemistry head of a factor Xa inhibitor program from 1993 through 1999; he is the co-author/inventor on numerous publications and patent applications in the factor Xa space, including the Ewing II article, discussed infra; and was familiar with the factor Xa field in December of 1999 including by reviewing the literature and attending conferences. (Pltffs. FF. ¶ 16 (citing 3/8/18 a.m. Tr. 57:2-59:1; PTX-9).)

16. Although both Dr. Spada and Br. Brickner are experienced medicinal chemists, I find that Dr. Spada's testimony is credible and reliable and it informs my obviousness analysis.[3]

F. The Person of Ordinary Skill in the Art

17. The POSA pertaining to the '456 patent as of December 24, 1999 (the priority date), is defined as follows,

> A scientist with a Ph.D. in organic chemistry, or an equivalent discipline, with approximately seven (7) years of experience with the synthesis of organic

[3] In reaching my conclusions, I also considered the expert testimony of Dr. Neil Doherty, III and Ivan Hofmann on behalf of the defendants. Likewise, I considered the testimony of Dr. George Zhanel, Dr. Jeffrey Olin, and Dr. Christopher Vellturo on behalf of plaintiffs. Finally, I considered the testimony of all fact witnesses.

compounds; the purification of organic compounds; and designing pharmaceutical compounds. The POSA would also understand the general principles of drug design and delivery, including pharmacology, pharmacokinetics, metabolism, toxicology and formulation, as well as the role of compounds that inhibit the enzyme factor Xa and other anticoagulants in the treatment and prevention of thromboembolic disorders and the ability to understand work presented by others in these fields.

(Defs. FF ¶ 22 (citing 3/5/18 a.m. Tr. 34:16-35:20).)[4]

G. Scope and Content of the Prior Art

18. As of the priority date, there were 18 companies and hundreds of researchers working in the factor Xa field. (3/8/18 a.m. Tr. 70:5-15.)

19. Among the hundreds of articles published in the field, plaintiffs rely on four review articles published in 1999 that summarize the state of the art: Al-Obeidi, Ewing III, Zhu, and Fevig. (Id. at 71:4-9; PTX-3 (Al-Obeidi); PTX-4 (Ewing III); PTX-6 (Zhu); PTX-325A (Fevig).)

20. Anticoagulants are compounds that prevent or treat problematic blood clots.[5] (3/5/18 a.m. Tr. 16:17-23.)

21. Anticoagulants work by suppressing either the synthesis or function of various clotting factors. (Id.)

22. A factor Xa inhibitor is one such anticoagulant that prevents blood clot

[4] Plaintiffs submit that the definition also requires experience with factor Xa inhibitors. (Pltffs. FF ¶ 4 (citing 3/8/18 a.m. Tr. 66:6-67:4).) Notwithstanding, the parties' experts agree that the invalidity analysis is the same regardless of whether the POSA requires experiences with factor Xa. (3/5/18 a.m. Tr. 36:1-4; 3/8/18 p.m. Tr. Part 1 79:10-14.)

[5] Blood clot formation is a complex series of enzymatic events triggered by an injury to a blood vessel. (3/5/18 a.m. Tr. 15: 8-20.) Following an injury to a blood vessel, platelets aggregate at the injury site to form a plug, which can develop into a blood clot. (Id. at 15:16-20.) Blood clots become problematic when they form in a vessel by blocking blood flow or moving to another area of the body, causing fatal consequences. (Id. at 16:2-10.)

formation. Factor Xa inhibitors bind to factor Va, which prevents the formation of a prothombinase complex that converts prothrombin to thrombin. (Id. at 20: 10-16.) By preventing the formation of thrombin, there is no thrombin to convert fibrinogen to fibrin. (Id.) Without fibrin, a clot cannot form. (Id.)

23. Factor Xa inhibitors have two key binding sites: the S1 and S4 pockets. (Id. at 22: 11-16.)

24. The portion of the factor Xa inhibitor that interacts with the S1 site is known as the "P1 group," and the portion that interacts with the S4 pocket is known as the "P4 group." (Pltff. FF. ¶ 20.) The central scaffold is known as the "core." (Id.)

25. The conventional wisdom in December of 1999 was that in order to be a potent factor Xa inhibitor a compound required a basic P1 group and an aromatic or basic P4 group. (3/8/18 a.m. Tr. 60:12-17; 60:22-61:4, 77:25-81:15; see PTX-3 at 949; see also PTX-325A at 89, 93, 95.)

26. The conventional wisdom for designing factor Xa inhibitors was based on the knowledge of the structure of S1 and S4 pockets. The S1 pocket was known to contain a negatively charged aspartic acid and the idea was to use a positively charged residue with at least some basicity[6] to interact with the negatively charged aspartic acid, like opposite magnetic poles attracting to each other. (3/8/18 a.m. Tr. 77:25-79:4.)

[6] Defendants argue that the prior art taught that "basic moieties were being replaced with non-basic moieties for binding to the S1 site of thrombin inhibitors." (Defs. FF. ¶ 10). In support of this argument, defendants cite Dr. Brickner's testimony stating,

> The prior art taught that things were changing. Medicinal chemists were learning that you no longer needed to have a highly basic group that bound in the S1 site. In fact, removal of basic moiety could be accommodated in this site completely.

27. The S4 pocket was known to have three aromatic rings with a strong affinity for other aromatic rings, and also had a cation hole. (Id. at 79:5-81:5.) Conventional wisdom taught that "aromatic and/or basic residues were tolerated and important for binding in the P4 pocket." (Id. 80:13-15.)

IV. Conclusions of Law

1. Subject matter jurisdiction over this matter is proper pursuant to 28 U.S.C. §§ 1331, 1338, and 2201.

2. "The presumption that all patents are valid is the starting point for any obviousness determination." Impax Labs., Inc. v. Lannett Holdings Inc., 246 F. Supp. 3d 1024, 1035-36 (D. Del. 2017) (citing 35 U.S.C § 282).

3. A party challenging a patent based on obviousness bears the burden of demonstrating by clear and convincing evidence that "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." Bayer Pharma AG v. Watson Laboratories, Inc., 183 F.Supp. 3d 579, 584 (D. Del. 2016) (quoting 35 U.S.C. § 103(a)); see Impax Labs., Inc., 246 F. Supp. 3d at 584-85.

4. The standard requires "a reasonable expectation of success." Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting In re O'Farrell, 853 F.2d 894, 903-04 (Fed. Cir. 1988)).

(3/5/18 a.m. Tr. 22:18-24.) Defendants fail to reference any prior art demonstrating a shift in the conventional wisdom, and I do not find this testimony credible. The overwhelming evidence demonstrates that the prior art in December of 1999 taught the use of a basic P1 group and an aromatic and/or basic moiety at P4. (3/8/18 a.m. Tr. 60:12-17; 60:22-61:4, 77:25-81:15; see PTX-3 at 949; see also PTX-325A at 89, 93, 95.)

5. Obviousness is a question of law that requires consideration of four factual inquiries,

> (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.

Id. (citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)).

6. In the context of chemical compounds, courts acknowledge that this is an "unpredictable art," but the Federal Circuit has concluded that a "'finite number of identified, predictable solutions' or alternatives 'might support an inference of obviousness.'" Bayer Pharma AG, 183 F. Supp.3d at 585 (citing Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008)).

7. To that end, the Federal Circuit announced a two-party test to analyze chemical compounds under the third Graham factor. Otsuka Pharmaceutical Co., Ltd. V. Sandoz, Inc., 678 F.3d 1280, 1291-92 (Fed. Cir. 2012).

8. Under this test, a party seeking to invalidate a chemical compound patent for obviousness must, (1) identify a compound that the POSA would have been motivated to select as the "lead" compound; and (2) provide "a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." Id. at 1292; see Bayer Pharma AG, 183 F. Supp. 3d at 585 (citing Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967, 973 (Fed. Cir. 2014)).

9. I find that the POSA would not have selected linezolid as a lead compound.

10. I find that the POSA would not have modified linezolid to obtain rivaroxaban.

11. Therefore, defendants failed to establish a prima facie case of obviousness by clear and convincing evidence.

12. "[O]nce 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." Bayer Pharma AG, 183 F. Supp. 3d at 589.

13. These considerations include "evidence of commercial success, long-felt but unsolved needs, and/or the failure of others." Id.

14. "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." Id. (citing In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998)).

15. These secondary considerations must be taken into account in the obviousness analysis, but they do not control the conclusion. Id. (citing Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1372 (Fed. Cir. 2007)).

16. There is a nexus requirement that must be met between the "merits of the claimed invention and evidence of secondary considerations" in order for the evidence to be given "substantial weight" in the obviousness analysis. Id. (citing Muniauction, Inc. v. Thomson Corp., 532 F.3d 1318, 1327 (Fed. Cir. 2008)) (quoting Ruiz v. A.B. Chance Co., 234 F.3d 654, 668 (Fed. Cir. 2000)). Stated differently, the secondary considerations

"must be commensurate in scope—"coextensive"—with the claimed features of the invention." Id. (citing Muniauction,532 F.3d at 1327).

17. Even if defendants established a prima facie case of obviousness, I find that the secondary considerations weigh in favor of non-obviousness and a nexus exists between the objective indicia of non-obviousness and the claimed invention.

18. Therefore, I find that claim 16 of the '456 patent is not invalid due to obviousness.

V. Discussion

To invalidate claim 16 of the '456 patent as obvious, the defendants must demonstrate by clear and convincing evidence that the POSA would have been motivated to select linezolid as a lead compound and also that the POSA would have been motivated to make the necessary structural changes to linezolid to arrive at rivaroxaban. For the reasons discussed in detail below, I find that defendants fail to meet their burden on both elements. I further find that the secondary considerations weigh in favor of non-obviousness.

A. The POSA would not have selected linezolid as a lead compound

Defendants assert that a POSA would have selected linezolid as a lead compound because (1) it was the most advanced oxazolidinone in Phase III clinical trials; (2) linezolid had an excellent pharmacokinetic profile and more specifically, 100% oral bioavailability; and (3) linezolid possesses structural motifs characteristic of existing factor Xa inhibitors. I find that defendants fail to demonstrate by clear and convincing evidence that the POSA would have selected linezolid as a lead compound.

At the outset, there were attractive lead compounds in the factor Xa field in December of 1999. Dr. Spada identified seven promising lead compounds that all had activity against factor Xa. (PDX-306; 3/8/18 a.m. Tr. 87:18- 89:9.) Three of these compounds[7] had anticoagulant activity and "good" oral bioavailability. (PDX-306; 3/8/18 a.m. Tr. 87:25- 88:9.) The other four[8] were active factor Xa inhibitors that were used as lead compounds in other factor Xa programs prior to December 1999. (PDX-306; 3/8/18 a.m. Tr. 89:10-90:19.)

Based on the prior art as of December of 1999, I find that the POSA would have selected one of these seven compounds as the lead compound.[9] However, even if there was a dearth of attractive lead compounds in the factor Xa field, the defendants fail to

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[7] The three compounds are YM60828, Fevig 77, and ZK807834.

[8] These four compounds are DX9065a, DABE, BABCH, and TPAM.

[9] Defendants argue that the POSA would not have selected any of these compounds because they did not have 100% oral bioavailability, they contained a basic benzamidine substituent, and because none had reached phase III clinical trials. (Defs. Br. at 12.) These arguments are meritless.

First, the testimony at trial demonstrated that 100% oral bioavailability was not necessary for a factor Xa inhibitor. (3/8/18 p.m. Tr. Part 1 106:17-25 ("The POSA is not striving to achieve a hundred percent bioavailability. At the end of the program, one is bringing forward a molecule that has efficacy that was sufficient enough to take into the clinical trial . . . irrespective of . . . [one] hundred percent bioavailability.")

Next, I find that the fact that six of these seven compounds contain a benzamidine is not inconsistent with conventional wisdom. (PTX-325A; 3/8/18 a.m. Tr. 76:18-81:15.) While there was a shift away from the use of a highly basic benzamidine at P1 to a less basic P1 structure, this was done to improve oral bioavailability. (3/8/18 a.m. Tr. 94:25-97:3.) However, two of the seven compounds (YM60828 and ZK807834) that contained a basic benzamidine also had good oral bioavailability. (3/8/18 a.m. Tr. 94:25-97:3.) Therefore, defendants' argument for using a less basic moiety at P1 does not apply to those two compounds.

Finally, defendants argue that unlike linezolid, none of Dr. Spada's proposed lead compounds had reached Phase III clinical trials. I find that whether linezolid had reached phase III trials would have been irrelevant to the POSA because linezolid had no activity against factor Xa. (Id. at 86:19-87:3.)

demonstrate by clear and convincing evidence that the POSA would have selected linezolid.

It is well established that a lead compound is "a compound in the prior art that would be the most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." Otsuka, 678 F.3d at 1291 (internal citations and quotations omitted). The court in Otsuka explained,

> In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties. Such properties may include positive attributes such as activity and potency, adverse effects such as toxicity, and other relevant characteristics in evidence . . . . Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection.

Id. at 1292.

1. A POSA would not select a compound that was the most advanced oxazolidinone in antibiotics as a lead compound for factor Xa inhibitors.

Defendants argue that the prior art disclosed various anticoagulants including factor Xa inhibitors with oxazolidinones,[10] but that the prior art was devoid of a factor Xa inhibitor that had entered clinical trials. (Defs. FF. ¶ 44 (citing 3/6/18 a.m. Tr. 38:7-39:13, 40:8-10).) The fact that linezolid was known as the "most advanced oxazolidinone" and was in Phase III clinical trials in December of 1999, defendants urge, demonstrate that the POSA would have selected linezolid as a lead compound. (Defs. FF. ¶¶ 45, 46.)

[10] "Oxazolidinones are a class of compounds that includes a five-membered ring containing an oxygen atom, a carbon atom, and a nitrogen atom, such that the carbon atom between the oxygen atom and the nitrogen atom is double-bound to another oxygen atom, also known as a carbonyl moiety." (Defs. FF. ¶ 15.)

At the outset, defendants' argument is a red herring. Linezolid was the most advanced oxazolidinone antibiotic and it was in Phase III trials for antibiotic indications. The relevant issue here, however, is whether the prior art taught that oxazolidinones were useful in factor Xa inhibitors. It did not. There was no evidence that a factor Xa inhibitor with an oxazolidinone core could have potent activity against factor Xa. (3/8/18 a.m. Tr. 63:10-19; 3/8/18 p.m. Tr. 9:9-13.) In fact, the '092 publication was the only one reference to factor Xa inhibitors with oxazolidinone cores in the prior art.[11] This publication discloses compounds with an oxazolidinone core, but it contains no data that these compounds are potent factor Xa inhibitors. (DTX 1080; 3/8/18 p.m. Tr. Part 2 44:24-47:14.) Dr. Bricker did not rely on this reference (3/8/18 p.m. Tr. Part 2 47:14-18), and the POSA would not have relied on it either.

Equally unpersuasive is defendants' argument that the Riedl publication disclosed oxazolidinones for the treatment of thrombosis. (Defs. FF. ¶ 46 ("Riedl teaches that oxazolidinones have non-anti-infective activity, including platelet inhibition activity, which allows oxazolidinones to 'be useful in the treatment of thrombosis and myocardial infarction.'").) Riedl does not address factor Xa inhibitors. (See DTX 1265 at 630; 3/8/18 a.m. Tr. 106:13-19.) It describes oxazolidinone antiplatelet activity. (See DTX 1265 at 630; 3/8/18 a.m. Tr. 107:4-16.) This reference actually teaches away from the selection of linezolid because a factor Xa inhibitor with antiplatelet activity creates an increased risk

[11] Dr. Brickner also relied on the '371 publication (DTX-1133) as prior art disclosing oxazolidinones in factor Xa inhibitors. However, this reference disclosed oxazolidinones as a substituent and not as a core structure. (3/5/18 p.m. Tr. 81:3-15.) A POSA would not be motivated to selected linezolid as a lead compound based on this reference.

for bleeding. (3/8/18 a.m. Tr. 108:15-20.) I find that the prior art taught away from the selection of linezolid as a lead compound.

2. 100% oral bioavailability, by itself, is an insufficient reason to select a lead compound.

Defendants also assert that a POSA would have selected linezolid because it had 100% oral bioavailability. This argument fails for several reasons. First, 100% oral bioavailability is meaningless without activity against factor Xa. Dr. Spada testified,

> [W]hen one starts with a lead, one starts with a molecule that has some activity against the target itself, and in this case we're talking about Factor Xa. And if I could digress . . . I've been a medicinal chemist for 33 years, and in my entire career, I cannot recall one single example in interactions with my colleagues, either in the United States or in other locations, where someone had proposed starting a program with a lead that didn't have activity on the target. It's just simply not the way medicinal chemistry is done.

(3/8/18 a.m. Tr. 61:10-21.) I find Dr. Spada's testimony credible and I conclude that the POSA would not select a lead compound with no known activity against factor Xa.

This argument also fails because100% oral bioavailability, without more, is an insufficient basis for selecting linezolid as a lead compound. Although oral bioavailability was a factor that was considered in selecting a lead compound, a POSA would not need that level of oral bioavailability for a factor Xa inhibitor. In fact, Zhu teaches that 20 percent oral bioavailability is "good." (PTX-6; see 3/8/18 a.m. Tr. 101:19-25 (Zhu indicates that "you don't need 100 percent oral bioavailability and that you can get effective, efficacious compounds with oral bioavailability in the 20 percent range.").) Indeed there were two compounds that were known in the prior art that had "good" oral

bioavailability.[12] Defendants have failed to demonstrate that the POSA would have selected linezolid as a lead compound rather than one of these two compounds.

Finally, the prior art taught chemists to address bioavailability by incorporating less basic P1 replacements into factor Xa inhibitors to obtain "good" oral bioavailability. (3/8/18 a.m. Tr. 98:16-99:9, 102:1-6; PTX-325A; PTX-4.) Conventional wisdom did not teach the use of compounds with no activity against the target and 100% oral bioavailability. I find that defendants failed to demonstrate by clear and convincing evidence that the POSA would have selected linezolid because it maintained 100% oral bioavailability.

3. Linezolid does not have structural motifs characteristic of factor Xa inhibitors.

Defendants next argue that linezolid has structural motifs characteristic of factor Xa inhibitors. This argument fails for several reasons. First, Ewing II taught the use of a pyrrolidinone scaffold, which defendants argue is similar to an oxazolidinone scaffold in factor Xa inhibitors. (Def. FF. ¶ 49 (citing 3/5/18 p.m. Tr. 4:24-6:8) (also citing DTX 1081 at 3559-60).) However, Ewing II does not teach using an oxazolidinone or linezolid as a lead. (3/8/18 p.m. Tr. Part 3:22-4:18.) What is more, Ewing provided no reason to use an oxazolidinone core instead of a pyrrolidinone. (Id. at 4:19-5:5.) This argument is further weakened by the fact that Ewing actually discloses data for two pyrrolidinone core structures, and the one closer in structure to an oxazolidinone was 40-fold less

[12] ZK807834 demonstrated oral bioavailability of 20 percent and Fevig 77 demonstrated oral bioavailability of 53percent. (PTX-6 at 70, 72-73; PTX-325A at 95.)

potent. (Id. at 6:16-9:13.) A POSA simply would not have selected linezolid as a lead based on this prior art.

Next, defendants argue that "Quan teaches that a factor Xa inhibitor containing two six membered rings linked via a single bond, similar to that found in linezolid, would fit into the S4 site of factor Xa." (Def. FF. ¶ 50 (citing 3/5/18 a.m. Tr. 46:21-47:1; 3/5/18 p.m. Tr. at 6:9-22, 7:15-8:25; 3/6/18 a.m. Tr. at 19:3-11; DTX-1129 at 2764).) Quan does not stand for this proposition. Quan teaches the use of two aromatic rings at P4 that happen to be 6-membered rings. (3/8/18 p.m. Tr. Part 1 15:1-14.) The morpholine in linezolid is not aromatic and a POSA would not have selected linezolid as a lead compound based on the ring shape. (Id. at 15:15-16:3.) Defendants submit that "there is no requirement that a factor Xa inhibitor must include an aromatic and/or basic moiety that can fit into the P4 pocket of the factor Xa active site." (Defs. Br. at 11 (citing Defs. FF. ¶ 55.) However, this runs contrary to the conventional wisdom which taught the use of aromatic and/or basic groups at P4, and defendants fail to cite to any prior art that would convince me otherwise.

I find that linezolid does not have structural motifs characteristic of factor Xa inhibitors, and the POSA would not have selected linezolid as a lead compound.

4. The prior art taught away from the selection of linezolid as a lead compound.

Even if any one of the three reasons set forth by defendants were supported by clear and convincing evidence, the fact remains that the prior art taught away from the selection of linezolid as a lead compound. It is undisputed that linezolid has no activity

against factor Xa.[13] (3/8/18 a.m. Tr. 61:5-21; 3/5/18 a.m. Tr. 38:11-15.) Dr. Spada testified that chemists would not select a lead compound with no activity against the target. (3/8/18 a.m. Tr. 61:5-21) ("[that is] simply not the way medicinal chemistry is done."). Dr. Bricker was unable to cite a single example to the contrary. I find that defendants fail to demonstrate by clear and convincing evidence that a POSA would have selected a lead compound with no activity against factor Xa.

What is more, the prior art taught away from the selection of linezolid because it had several adverse effects. See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1326 (2009) (An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). These adverse effects included linezolid's potent antibacterial effect. Specifically, the use of linezolid would have promoted antibiotic resistance which would have been unacceptable to the POSA. (3/8/18 a.m. Tr. 61:22-62:4; 3/5/18 p.m. Tr. 70:23-71:5.)

The POSA would also have been concerned with the common antibacterial side effects, such as diarrhea. (3/9/18 a.m. Tr. 21:23-23-24.) These side effects are reasonably tolerated for acute treatment. (Id.) However, such side effects would not be acceptable for chronic, long-term treatment, as was intended for a factor Xa inhibitor. (Id.); see also,

[13] Defendants concede that there was no "published information about linezolid exhibiting anti-factor Xa activity," but urge that a "POSA would not have concluded that linezolid possessed no activity in light of the structural motifs previously discussed." (Def. Br. at 11.) At the outset, as discussed above, linezolid does not possess structural motifs similar to factor Xa inhibitors. Regardless, the POSA would not select linezolid as a lead compound because the prior art did not teach that linezolid had activity against factor Xa. (Pltff. FF ¶ 12.)

Takeda Chemical Industries, Ltd. V. Alphapharm Pty., Ltd., 492 F.3d 1350, 1358 (Fed. Cir. 2007) ("[b]ecause diabetes is a chronic disease and thus would require long term treatment . . . researchers would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects."). For these same reasons, the prior art taught away from linezolid due to its non-antibacterial toxicities including thrombocytopenia (a reduction in platelet counts that can lead to bleeding), liver toxicity, and bone marrow toxicity.

Defendants argue that factor Xa inhibitors are administered at lower doses than linezolid which would decrease the anti-bacterial and non-antibacterial side effects. (Def. FF. ¶ 55; Defs. Br. at 12.) This argument relies on improper hindsight. This argument necessarily assumes that an oral factor Xa inhibitor existed in December of 1999 and that there were known dosages as a frame of reference. This argument also fails because the POSA would have understood that a weaker antibiotic is more likely to promote resistance than a potent antibiotic. (3/9/18 a.m. Tr. 14:10-15:14.)

In sum, plaintiffs argue that to select linezolid a POSA would have had to make the following decisions:

> (1) select a compound with no activity against factor Xa; (2) prioritize oral bioavailability (as Defendants do) as the single most important characteristic of a lead compound; (3) select a molecule that was still in clinical trials—with all the associated risks that some unidentified toxicity could appear—rather than one of many approved drug products; (4) select a molecule that was intended for short-term use, rather than chronic administration; (5) accept the need to design out the antibacterial activity; (6) accept the need to design out thrombocytopenia; (7) accept the need to design out liver toxicity; and (8) accomplish all these changes while maintaining the high oral bioavailability.

(Pltffs. FF. ¶ 21.) Plaintiffs submit that the POSA would not make any one of these decisions, let alone all eight decisions required to arrive at the selection of linezolid as a lead compound. I agree. I find that the defendants failed to demonstrate by clear and convincing evidence that the POSA would have selected linezolid as a lead compound, and the '456 patent is not obvious.

B. The POSA would not have modified linezolid to obtain rivaroxaban

Even assuming the POSA would have selected linezolid as a lead compound, the POSA would have not made the modifications necessary to arrive at rivaroxaban. Plaintiffs submit that there are at least three independent choices necessary to modify linezolid to make rivaroxaban. I find based on the evidence presented at trial, that the development of rivaroxaban from linezolid was not an obvious path because it did not involve a "finite number of identified, predictable solutions." Bayer Pharma AG, 183 F. Supp.3d at 587 (citing Eisai Co. Ltd., 533 F.3d at 1359). Instead, "[e]ach layer of decision-making would have required a lengthy research and development process that would not have provided predictable results." Id.

1. The POSA would have modified the oxazolidinone core.

If the POSA selected linezolid as the lead compound, the first decision would be whether to maintain or modify the oxazolidinone core of linezolid. (3/8/18 p.m. Tr. Part 1 30:16-31:7.) Plaintiffs urge, and I agree, that the POSA would have every reason to replace the core with a factor Xa inhibitor that shows potent activity. (Pltffs. FF. ¶ 23.) This decision would have been motivated, at least in part, by the need to eliminate

linezolid's antibacterial activity to avoid creating resistant bacteria.[14] (3/8/18 a.m. Tr. 102:7-20; 3/5/18 p.m. Tr. 71:6-72-5.) Were the POSA to modify the oxazolidinone core, it would not have led to rivaroxaban. (3/8/18 p.m. Tr. Part 1 31:14-16.)

2. The POSA would not have incorporated a 5-chlorothiophene at P1.

Assuming the POSA would have chosen to maintain the oxazolidinone core, which a POSA would not, the POSA would not have incorporated a 5-chlorothiophene at P1. First, a 5-chlorothiophene at P1 was unprecedented and is unsupported by the prior art. (3/8/18 p.m. Tr. Part 1 32:9-11.) Absent data demonstrating that the placement of a 5-chlorothiophene at P1 could confer potent factor Xa inhibitory activity, the POSA would have no reason to make this decision. Rather, the POSA would have incorporated a functional group with known activity against factor Xa. (3/8/18 a.m. tr. 64:16-65:6.)

Not only was there no support in the prior art, but also the placement of a 5-chlorothiophene at P1 was inconsistent with the conventional wisdom in December of 1999. The conventional wisdom in the factor Xa art was to use a basic group at P1 (preferably a weakly basic group) to form a positive-negative interaction with the negatively charged aspartic acid in the S1 pocket. (3/8/18 a.m. Tr. 60: 12-17.) The use of a neutral 5-chlorothiophene would not have a positive charge to interact with the negatively charged aspartic acid. (3/8/18 p.m. Tr. Part 1 33:2-23; see 3/5/18 p.m. Tr. 93:21-25.)

[14] Defendants' own expert, Dr. Brickner, teaches that the oxazolidinone core of linezolid was "essential" to the antibacterial activity, and agreed that the POSA would want to eliminate antibacterial activity to the extent possible to form an antithrombotic. (3/5/18 p.m. Tr. 72:2-5; 75:1-12.)

Defendants argue that there was a shift in the conventional wisdom and that non-basic groups, such as a 5-chlorothiophene, demonstrated improvements in potency in factor Xa inhibitors. (Defs. FF. ¶ 31.) However, the defendants fail to point to any data demonstrating this change in the conventional wisdom and I find that this argument lacks credibility.[15] In fact, Dr. Spada testified that the only examples where a highly basic P1 substituent was replaced with a neutral substituent exhibited poor factor Xa activity, producing micromolar potency values that were a thousand-fold less active. (3/8/18 p.m. Tr. Part 2 57:12-58:16; PTX-3 at 936.) The POSA would simply not have been motivated to add a neutral group at P1.

Also unpersuasive is defendants' argument that 5-chlorothiophene is a "privileged structure" for factor Xa inhibitors. A privileged structure is a "structure that provides some advantage to a compound that contains it." (3/5/18 p.m. Tr. 10:12-18.) The prior art contains no reference to a 5-chlorothiophene as a privileged structure, and the review articles published in 1999 do not provide any data demonstrating that it has desirable properties.[16] (3/8/18 p.m. Tr. Part 1 32:12-33:1.) Defendants also rely on the '304 publication to no avail. (Def. FF. ¶ 62.) This reference used the 5-chlorothiophene at the P4 position (and not at P1), which was consistent with the conventional wisdom. (3/8/18 p.m. Tr. Part 1 36:12-16; 39:3-43:18.)

[15] Defendants' reliance on Zhu is misplaced because Zhu's findings are punctuated with the caveat that "biological activities were not disclosed." (PTX-6 at 79.) Absent data demonstrating that a 5-chlorothiophene at P1 would improve factor Xa activity, the POSA would not have made this modification.

[16] Defendants' reliance on Medicamentos is unavailing because this pertains to warfarin compounds, not factor Xa inhibitors. (DTX-1127 at 383-84; 3/8/18 p.m. Tr. Part 1 44:8-45:3.)

Finally, defendants' argument that the placement of 5-chlorophiene at P1 would reduce antibacterial activity also fails. (Defs. FF. ¶ 64 (citing 3/5/18 p.m. Tr. 16:9-15) (also citing DTX-1122).) The POSA would want to eliminate antibacterial activity, not merely reduce it. (3/8/18 p.m. Tr. Part 1 25:13-15; 3/5/18 p.m. Tr. 71:6-72:5.) This is because a reduction in antibacterial activity would generate antibiotic resistant bacteria, which the POSA would want to avoid. (3/8/18 p.m. Tr. Part 2 28:1-15.)

There was no suggestion in the prior art for substituting a 5-chlorothiophene at P1. Conventional wisdom in December of 1999 taught away from the use of a neutral substituent at P1. I find that the POSA would not have any reason to substitute a 5-chlorothiophene at P1 and would not have arrived at rivaroxaban.

3. The POSA would not have used a phenyl-morpholinone at P4.

Next, defendants suggest that the POSA would have used a phenyl-morpholinone at P4. This requires two changes to linezolid: adding an oxo (carbonyl) group to the morpholinone and removing the fluorine from the phenyl. I find that the POSA would not have had a reason to incorporate a phenyl-morpholinone at P4.

At the outset, the prior art did not suggest that a phenyl-morpholinone would be useful at P4.[17] (3/8/18 p.m. Tr. Part 1 54:8-15.) Absent data demonstrating that a phenyl-morpholinone at P4 would have potent factor Xa activity, a POSA would not have made this change. In fact, the prior art taught away from using phenyl-morpholinone as a P4 substituent because it was neither aromatic nor basic, and was contrary to the

[17] Defendants reliance on the '371 publication is misplaced. That reference only disclosed morpholinones generally, and did not teach the use of morpholinones at the P4 position. (3/8/18 p.m. Tr. Part 1 at 9:14-10:7.)

conventional wisdom. (3/8/18 p.m. Tr. Part 1 54:24-55:10; see 3/8/18 a.m. Tr. 60: 12-17; 60:22-61:4.)

Defendants' argument that adding an oxo group would slow down metabolism is also unconvincing. The crux of defendants' argument for the selection of linezolid is premised on the "advantageous pharmacokinetic profile" including linezolid's half-life. (Defs. Br. at 10.) It is inconsistent to also argue that the oxo group was added to improve metabolism. The POSA would not have seen this as an area that required improvement. (3/8/18 p.m. Tr. Part 1 56:1-16.) This argument also fails because the prior art teaches that adding the oxo group would actually accelerate metabolism, not slow it down. (3/8/18 p.m. Tr. Part 1 56:17-21.)

Likewise, the defendants' argument that the POSA would have replaced the fluorine atom with a hydrogen atom to reduce antibacterial activity is incorrect. As discussed above, the POSA would not merely seek to reduce antibacterial activity, but would have sought to eliminate it entirely. (3/8/18 p.m. Tr. Part 1 25:13-15; 3/5/18 p.m. Tr. 71:6-72:5.)

Defendants bear the burden of demonstrating that "the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." Bayer Pharma AG, 183 F.Supp. 3d at 589. Defendants failed to show by clear and convincing evidence that a POSA would have made any, let alone all, of the necessary modifications to arrive at rivaroxaban. I find that defendants failed to establish a prima facie case that claim 16 of the '456 patent is invalid for obviousness.

C. Objective Indicia of Non-obviousness

Plaintiffs argue that even if defendants established their prima facie case, the objective indicia of obviousness support the validity of claim 16 of the '456 patent. Although I find that defendants failed to meet their burden of demonstrating a prima facie case of obviousness, I will address the secondary considerations including the nexus requirement.

1. Secondary Considerations

a. Rivaroxaban satisfied a long-felt but unmet need.

In December of 1999, there was a long-felt but unmet need for an oral factor Xa inhibitor, evidenced in part by the 18 pharmaceutical companies and hundreds of scientists looking for a solution. (3/8/18 a.m. Tr. 70:5-15; 3/5/18 p.m. Tr. 57:22-58:14.) As of the priority date, there were three main medications used to treat and prevent conditions which Xarelto® was indicated for: unfractionated heparin, low molecular weight heparin, and warfarin. (3/8/18 a.m. Tr. 15:10-16:6, 17:3-8, 18:12-15.) Each of these three medications had known drawbacks. For instance, heparin was administered via injection and side effects included thrombocytopenia (low blood platelet count). (3/8/18 a.m. Tr. 19:13-20:11.) Low Molecular weight heparin was also administered via injection and required once or twice daily blood testing. (3/8/18 a.m. Tr. 20:12-21:17.) Likewise, warfarin required regular blood tests to monitor anticoagulation. (3/8/18 a.m. Tr. 23:22-25:13.)

Xarelto® "revolutionized the field of treating patients with thrombotic disorders; it changed the paradigm of how these patients were treated." (3/8/18 a.m. Tr. 13:23-14:3.)

Xarelto® was at least as effective as Warfarin, and more effective than low molecular weight heparin. (3/8/18 a.m. Tr. 31:11-19.) It had a similar overall safety profile, with a lower rate of dangerous bleeding conditions. (3/8/18 a.m. Tr. 31:24-32:4.) Importantly, Xarelto® did not have the side effects associated with those medications previously on the market. (3/8/18 a.m. Tr. 26:4-27:12.) Specifically, it was an oral factor Xa inhibitor and therefore, did not require injections; it did not require regular monitoring or blood testing; and did not have extensive food and/or drug interactions. (Id.)

Defendants argue that Xarelto® did not satisfy a long-felt need because there were other oral anticoagulants on the market. Specifically, defendants point to Pradaxa®, Eliquis®, and Savaysa®. However, neither Eliquis® nor Savaysa® were available as of the priority date. (Defs. FF. ¶ 91 (conceding that Eliquis® and Savaysa® were approved in 2012 and 2015, respectively.).) And while Pradaxa® was on the market when Xarelto® was approved, it was approved only to treat atrial fibrillation. (3/8/18 a.m. Tr. 28:16-23.) In fact, to date Pradaxa® is not approved for the prevention of deep vein thrombosis or pulmonary embolism after knee replacement surgery. (3/8/18 a.m. Tr. 43:14-44:6.) Therefore, I find that Xarelto® satisfied a long-felt but unmet need for a potent oral factor Xa inhibitor.

b. Rivaroxaban had success where other failed.

As of the priority date, there were approximately 18 companies and hundreds of scientists that tried, but failed, to develop an oral factor Xa inhibitor. (3/8/18 a.m. Tr. 70:5-15; 3/5/18 p.m. Tr. 57:22-58:14.) The anticoagulants that were on the market as of the priority date were either injectable treatments rather than oral or, as with Pradaxa®,

were not factor Xa inhibitors. Defendants' argument that these direct acting anticoagulants were interchangeable is simply without merit. Rivaroxaban was the first successful oral factor Xa inhibitor as of December 24, 1999. I find that rivaroxaban was a success where others had failed.

c. Rivaroxaban received industry praise.

Rivaroxaban received substantial industry praise. For instance, it won the Prix Galien International in 2010 for "groundbreaking basic research."[18] (DTX-1285.) This award "recognizes the technical, scientific, and clinical research skills necessary to develop innovative medicines such as these, and is considered the industry's highest accolade, equivalent to the Nobel Prize." (Id. at BAYX 03295864.) In addition, Dr. Perzborn, one of the named inventors, received the German Futures prize for her work on Rivaroxaban. (PTX-281.)

d. Others were skeptical of Rivaroxaban.

Defendants do not dispute that there was skepticism concerning the safety of Rivaroxaban's structure. In particular, the European Medicines Agency (the European equivalent of the Food and Drug Administration) was skeptical that rivaroxaban would not have antibacterial activity due to its oxazolidinone core, and demanded that Bayer demonstrate that there was no antibacterial effect. (3/6/18 a.m. Tr. 67:13-68:6, 72:25-74:5.) Chemists also expressed concern that the five-chlorothiophene moiety would produce toxic metabolites. (3/6/18 p.m. Tr. 38:2-19.)

[18] Defendants submit that this was an internal award and, therefore, was not indicative of industry praise. This argument is without substance. The fact that Janssen was one of many sponsors for this award does not render it any less prestigious or legitimate.

e. Rivaroxaban has been accepted in the medical community.

Xarelto® revolutionized the treatment of thrombotic disorders and defendants do not dispute that it has been accepted in the medical community as advantageous to unfractionated heparin and low molecular weight heparin. (3/8/18 a.m. Tr. 13:23-14:3, 26:4-12, 33:24-34:11.) The 2014 practice guidelines for treatment of atrial fibrillation state, "All 3 new oral anticoagulents [including Xarelto®] represent important advances over warfarin because they have more predictable pharmacological profiles, fewer drug-drug interactions, an absence of major dietary effects, and less risk of intracranial bleeding than warfarin."[19] (PTX-38 at e23.)

f. Rivaroxaban demonstrated 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 . . . This comparison is made to the closest prior art." Bayer Pharma AG, 183 F. Supp. 3d at 589 (internal citations and quotations omitted).

Defendants submit that the closest prior art is linezolid. Assuming this is true, linezolid is a potent antibiotic and it is not a factor Xa inhibitor. (3/8/18 p.m. Tr. Part 1 71:5-24; 3/6/18 a.m. Tr. 4:12-65:12, 67:2-68:6, 72:25-75:7; 3/6/18 p.m. Tr. 52:24-53:2; PTX-284T; PTX-282T; PTX-306.) Rivaroxaban on the other hand, is not an antibiotic and is a potent factor Xa inhibitor. (Id.) These two compounds are used in unrelated

[19] Xarelto® also has FDA approval which tends to demonstrate acceptance in the medical community and is relevant to the obviousness analysis. See Leo Pharma. Prods., Ltd. v. Rea, 726 F.3d 1346, 1358 (Fed. Cir. 2013).

fields and are approved for unrelated therapeutic indications. (Id.) I find that the POSA would not have expected rivaroxaban to have the same properties or advantages of linezolid. I find credible the testimony of Dr. Spada, Dr. Perzborn, and Dr. Roehrig regarding unexpected results. A POSA would not have expected a compound with rivaroxaban's structure to be a potent factor Xa inhibitor.

g. Xarelto® is a Blockbuster commercial success.

Finally, the Xarelto® sales unquestionably demonstrate that it is a blockbuster drug and marketplace success. Despite defendant's argument that the success of Xarelto® is due to inordinate marketing and advertising, the data shows that Xarelto's® spending on marketing was not out of the ordinary, and was actually even less than some of its competitors. Rather, the testimony of Dr. Olin and Dr. Vellturo demonstrated that Xarelto® is prescribed because it is effective, safe, and easy to administer. (Pltff. FF. ¶ 42.)

Likewise, plaintiffs did not influence or inflate Xarelto's® sales with rebates, discounts, and incentives. Initially, the net sales are inclusive of the discounts and rebates. In addition, while it is true that the rebates off the list price for Xarelto® have increased, the list price itself has also increased. Finally, any rebates on Xarelto® are not materially different from those offered by its competitors.

Therefore, I find that Xarelto® is a marketplace success.

2. A nexus exists between the objective indicia of non-obviousness and the claimed invention.

I may only afford substantial weight to these secondary considerations if there is a

nexus between the merits of the claimed invention and the secondary considerations. This nexus is presumed where "the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1329 (Fed Cir. 2016) (citing J.T. Eaton & Co. v. Atl. Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997)); see Ormco Corp v. Align., Inc., 463 F.3d 1299, 1311-12 (Fed. Cir. 2006); see also Brown & Williamson Tobacco Corp. v. Phillip Morris Inc., 229 F.3d 1120, 1130 (Fed. Cir. 2000).

Here, claim 16 covers rivaroxaban, which is the sole active ingredient that makes Xarelto® an effective drug. (3/8/18 p.m. Tr. Part 1 67:5-15, 71:25-72:17.) Xarelto® would not exist without the claimed invention. (Id.) Likewise, rivaroxaban cannot be separated from the product as a whole. (Id.) I find that a nexus exists between the secondary considerations demonstrating non-obviousness and claim 16. Defendants argue that Xarelto's® once-daily dosing is the only difference between Xarelto® and the other direct acting anticoagulants, which is attributed to the '218 patent. I disagree. Xarelto® is coextensive with rivaroxaban and I find that a nexus exists between the objective indicia of non-obviousness and claim 16. Therefore, the secondary considerations weigh in favor of non-obviousness.[20]

[20] I find even stronger support for the non-obviousness of claim 16 of the '456 patent in the struggles of the inventors to arrive at rivaroxaban. The plaintiffs describe the fortuitous path the inventors took to arrive at rivaroxaban,

> The investors' first lead compound was not an oxazolidinone, because the few oxazolidinone hits (none of which was linezolid) in the high-throughput screen of nearly 200,000 compounds showed only weak potency against factor Xa. The inventors hit a dead end in the efforts to optimize that first lead compound, but in the course of synthesizing hundreds of compounds over many months, discovered that the 5-

VI. Conclusion

I find that claim 16 of the ’456 patent is not invalid due to obviousness. An appropriate order will follow.

> chlorothiophene moiety in their initial lead compound was critical for factor Xa activity. The inventors went back to their hits from the high throughput screen with that information, and noticed that one of the weak oxazolidinone hits had a thiophene moiety. The inventors decided to add a chlorine atom to that compound in the hopes of increasing its activity against factor Xa. The approach worked surprisingly well, and the inventors used this new compound as their new lead.
>
> After switching to the new lead, the inventors synthesized hundreds more oxazolidinones. In total, the team synthesized 700 oxazolidinones, one of which happened to be rivaroxaban. They also had many of these compounds tested for antibacterial activity in light of concerns from management that the use of a compound with an oxazolidinone core would result in antibacterial activity—a concern that was validated by the fact that at least one of the more potent factor Xa inhibitors with a 5-chlorothiophene did have antibacterial activity.

(Pltff. Br. at 34.) I find that this evidence provides further proof that claim 16 of the ’456 patent is non-obvious.