Filed on behalf of: Mylan Pharmaceuticals Inc.
By: Steven W. Parmelee
Michael T. Rosato
Jad A. Mills
WILSON SONSINI GOODRICH & ROSATI

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

Bayer Intellectual Property GmbH,
Patent Owner.

Case No. IPR2017-00042
Patent No. 7,585,860

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,585,860

TABLE OF CONTENTS

Page

I. INTRODUCTION

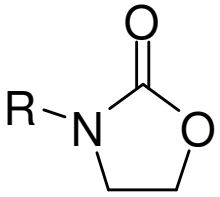
Mylan Pharmaceuticals Inc. ("Petitioner") requests *inter partes* review of U.S. Patent No. 7,585,860 to Straub *et al.* ("the '860 patent," EX1001), which issued on September 8, 2009. PTO records indicate the '860 patent is currently assigned to Bayer Intellectual Property GmbH ("Patent Owner"). This petition demonstrates that there is a reasonable likelihood that claim 1 of the '860 patent is unpatentable over the asserted prior art. Additional petitions are also being filed to address U.S. Patent Nos. 7,157,456 and 7,592,339, over both of which the '860 is terminally disclaimed.

Multiple enzymes are involved in the blood clotting cascade, but one protein known as "factor X," via its active form, "Xa," is called upon at an essential point in both the intrinsic and extrinsic coagulation pathways. EX1014 at 6630. Claim 1 of the '860 patent is directed to a compound or hydrate thereof that is described in the patent as being able to bind to and inhibit factor Xa. The crystal structure of factor Xa was known, and the art had established the presence of dual binding pockets for inhibitors, termed the S1 and S4 pockets, on factor Xa. *Id.*; *see also* EX1015 at 390. The S1 pocket was recognized as a narrow cleft that bound planar aromatic groups, while the S4 pocket was less selective, binding not only planar

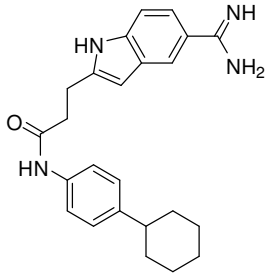
aromatic groups but also non-aromatic rings with heteroatoms, such as nitrogen and oxygen. *Id.*

Based on the detailed knowledge of the factor Xa binding pockets, the art had designed dozens of compounds which fit into these pockets and showed potent inhibition of factor Xa. *See generally*, Ewing, EX1007. What these compounds lacked was not potency, but favorable pharmacokinetic profiles. *Id.* Oral bioavailability was especially sought after, as the art needed new, safe and effective, orally-active anticoagulants. *Id.* Many viewed factor Xa inhibitors as attractive drug targets for developing effective oral anticoagulants. *Id*.

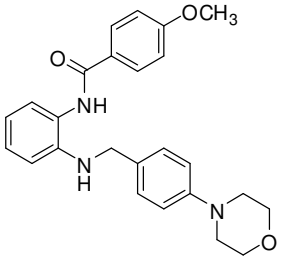
Oxazolidinones are a class of compounds comprising a 5-membered heterocycle (shown), and had long been known in the art to have various pharmacologic activities. EX1008. The art described oxazolidinone compounds that inhibited platelet aggregation, and were said to be useful in the treatment of thrombosis and myocardial infarction. *Id*. The "most advanced" oxazolidinone compound, linezolid, was known to have very desirable pharmacokinetic and pharmacologic properties, including high oral bioavailability and patient tolerability. *Id.* at 626-27. Linezolid was safe in humans and had entered Phase III human clinical trials for antimicrobial uses.



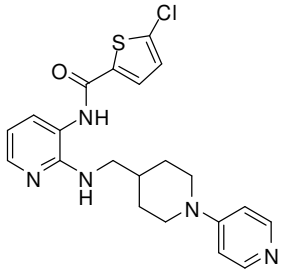
It was known that oxazolidinone-based antibiotics could have dual uses for other indications, and that they could be optimized for other therapeutic activities, including as anti-depressants or as anticoagulants. EX1008 at 630; EX1018 at 136. Linezolid's 4'-morpholinophenyl arm was a known factor Xa binding moiety, and was present on a factor Xa inhibitor disclosed in Example 1 of PCT WO 00/39111 (the '111 publication, EX1009). This binding moiety is structurally similar to the 4-cyclohexyl phenyl moiety found on Ewing's Compound 49, also a factor Xa inhibitor. EX1007 at 782. Linezolid, Ewing Compound 49, and Examples 1 and 7 of the '111 publication (shown below), have a two-arm shape and structure consistent with providing a binding moiety for each of the two known binding pockets of factor Xa. *Id.*; EX1008 at 626 (Compound 1); EX1009, 39:1-5; EX1010, 0043:1-5.



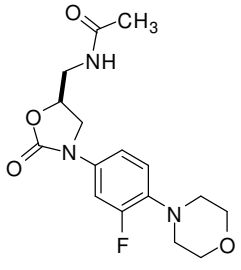
Ewing, EX1007 Compound 49



The '111 Publication; EX1009 Example 1



The '111 Publication; EX1009 Example 7



Riedl, EX1008 Linezolid

Given linezolid's general shape, its 4'-morpholinophenyl arm that was already a known factor Xa binding moiety (*supra*, EX1009), and its excellent

pharmacokinetic properties (*supra*, EX1008), the skilled artisan would have been motivated to exchange the terminal methyl group on the amide arm of linezolid for a known factor Xa binding moiety to optimize its factor Xa binding affinity. In keeping with the known preference for aromatic moieties in the binding pockets of factor Xa, the '111 publication identifies a set of six terminal moieties on the amide-end of a series of compounds that are taught as suitable for factor Xa binding and inhibition. Four of these terminal moieties are attached through the exact same amide linkage that is present in linezolid, and among these four is 5-chlorothiophene, the exact same moiety found in rivaroxaban. EX1009, 47:14-25. Thus, evaluation of each of these four moieties, including 5-chlorothiophene, on the amide arm of linezolid would have been a readily apparent choice by the skilled artisan working to optimize factor Xa inhibition activity.

None of the comparable factor Xa inhibitors taught by the '111 publication had a fluorine atom on the 4'-morpholinophenyl arm as found in linezolid. For this reason, the skilled artisan would have been motivated to omit linezolid's fluorine atom. This would also have made it possible to use a simpler and less expensive synthetic precursor.

The assessment of known metabolites of a compound intended for pharmaceutical use is considered routine optimization in the art. An assessment of

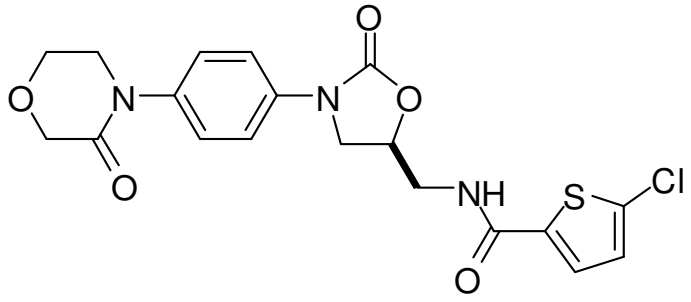
a factor Xa inhibitor compound based on the structure of linezolid by the person of ordinary skill would have identified morpholine ring-opened metabolites, as noted in Chiba (EX1011). The artisan would have been motivated to block that metabolism by installing a carbonyl adjacent to the nitrogen in the morpholine ring so as to block or slow its degradation into a ring-opened metabolite. This would directly result in the compound recited in claim 1 of the '860 patent.

Evidence in support of the forgoing analysis is presented and discussed in detail below.

A. BRIEF OVERVIEW OF THE '860 PATENT

The '860 patent is entitled "Substituted Oxazolidinones and their Use in the Field of Blood Coagulation," and has only two claims. EX1001. The '860 patent is directed to rivaroxaban (structure shown below), describing it as a factor Xa inhibitor. Independent claim 1 of the '860 patent recites:

1. A compound of the formula:



or a hydrate thereof.

B. BRIEF OVERVIEW OF THE PROSECUTION HISTORY

U.S. Patent Application 12/027,553 ("the '553 application") was filed on February 7, 2008 and claims priority through a series of continuations to PCT/EP00/12492, filed on December 11, 2000, which claims priority to German Application No. 199 62 924, filed on December 24, 1999. The '533 application issued on September 8, 2009 as the '860 patent.

The Examiner first rejected the claims for lack of enablement under 35 U.S.C. § 112 with regard to a prodrug claim limitation, as well as for nonstatutory double patenting over U.S. Patent No. 7,157,456. EX1006 at 0053-58. No rejections based on prior art were made by the Office. Applicants subsequently removed the prodrug claim limitations and filed a terminal disclaimer over the '456 patent. *Id.* at 0048-49. A Notice of Allowance was mailed shortly thereafter. *Id.* at 0023-28.

C. BRIEF OVERVIEW OF THE SCOPE AND CONTENT OF THE PRIOR ART

In obviousness cases, *Graham v. John Deere Co. of Kansas City* requires an evaluation of any differences between the claimed subject matter and the asserted prior art. 383 U.S. 1, 17-18 (1966). As noted *in KSR Int'l Co. v. Teleflex Inc.*, the obviousness inquiry may account for inferences that would be employed by a person of ordinary skill in the art. 550 U.S. 398, 418 (2007).

1) Ewing, W. R., *et al*., *Progress in the design of inhibitors of coagulation factor Xa*, 24 DRUGS OF THE FUTURE 771-87 (1999) ("Ewing," EX1007).

Ewing was published in July 1999 and is prior art to the claims of the '860 patent under 35 U.S.C. § 102(b). Ewing teaches using anticoagulants for the treatment and prevention of thromboembolic disorders. EX1007 at 771; EX1002, ¶48. Ewing teaches, "The formation of an occlusive thrombus is causally related to the pathology of" myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism, and that, "[a]s such, antithrombotic therapy is a crucial component in both acute intervention procedures and chronic prevention strategies for treatment and management of these diseases." *Id.* Ewing teaches that antithrombotic therapy includes an anticoagulant. *Id*.

Ewing teaches that developing "safe and effective oral anticoagulants to replace warfarin" with strong pharmacokinetic profiles "may be particularly important since clinical data suggest that long-term and/or prophylactic anticoagulant therapy can provide a significant benefit over current standard treatment." *Id.* at 774. Ewing identifies several advantages of using factor Xa inhibitors as anticoagulants, including the advantage of increased efficiency by "[i]nhibiting the source of thrombin generation rather than its catalytic activity."

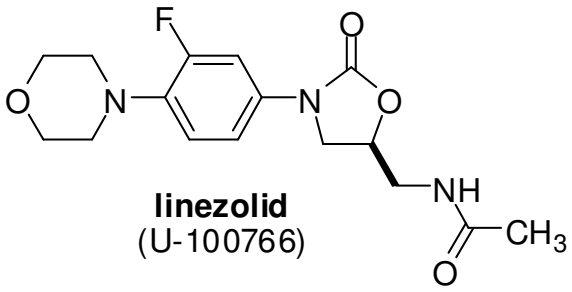
Id. Additionally, Ewing states that "the risk of bleeding complications might be minimized" by using factor Xa inhibitors. *Id*; EX1002, ¶49. Ewing states "[t]he risk of provoking prothrombotic rebound episodes observed with heparin and thrombin inhibitors would be minimized as well." *Id.* Ewing thus teaches that "direct inhibition of factor Xa activity should provide a potent anticoagulant devoid of the potentially limiting side effects observed with thrombin inhibitors." *Id.*; EX1002, ¶50.

Ewing identifies two main binding pockets for factor Xa, "[t]he specificity or S1 binding pocket" and "[t]he aromatic or S4 binding pocket." *Id.* at 775. Ewing describes factor Xa inhibitors that generally have two arms connected via various linkers. Many of these factor Xa inhibitors have aryl rings or heteroaryl rings at one terminal end, and aryl rings or saturated heterocyclic or cycloalkane moieties at the opposing end. *Id.* at 777-83 (Compounds 11-57); EX1002, ¶¶51-52. Ewing also notes that "The discovery of factor Xa inhibitors which lack highly basic functions (i.e., amidines) holds considerable promise for future design since similar advances in the thrombin inhibitor field is what ultimately led to the discovery of orally effective factor IIa [thrombin] inhibitors." *Id.* at 783. Regarding thrombin inhibitors, Ewing states that "[m]any highly potent and selective inhibitors have been described," but that it had been difficult to combine potency and selectivity

"with strong oral pharmacokinetic properties." *Id.* at 773-74; EX1002, ¶53. Ewing was not of record during examination of the '860 patent.

2) Riedl, B. *et al.*, *Recent Developments with Oxazolidinone Antibiotics*, 9 EXP. OPIN. THER. PATENTS 625-633 (1999) ("Riedl," EX1008).

Riedl was published in May 1999 and is prior art to the claims of the '860 patent under 35 U.S.C. § 102(b). Riedl discloses an oxazolidinone compound called linezolid:



linezolid
(U-100766)

Riedl teaches linezolid as "[t]he most promising representative" of an antibacterial oxazolidinone series due to its "advantageous pharmacokinetic profile" and "favourable safety profile," making it notably "well-tolerated in humans at clinically relevant doses," and allowing for its advancement into Phase III clinical trials. EX1008 at 626; EX1002, ¶55. Riedl notes: "In addition to the antimicrobial activity, other pharmacological activities of the oxazolidinones have been reported," noting "[n]ovel oxazolidinone derivatives which inhibit platelet aggregation . . .

and may be useful in the treatment of thrombosis and myocardial infarction." EX1008 at 630, 633; EX1002, ¶56.

Riedl teaches that the antibacterial activity of oxazolidinones, including linezolid, was significantly affected by the terminal moiety of the methylamino acyl arm: "The SAR of the methylamino acyl group in the 5-position of the oxazolidinone seemed to be narrowed down to acetyl amino methyl in this position." *Id.* at 629; EX1002, ¶57. Riedl notes that most compounds "in the field of oxazolidinones with antibacterial activity, use this substituent preferentially," or else use groups that are similarly "unpolar and rather small." *Id.* at 629. Riedl additionally notes the availability of pharmaceutical compositions for both oral and intravenous administration of linezolid. *Id.* at 627; EX1002, ¶58. Riedl was not substantively discussed during examination of the '860 patent.

3) International Patent Publication No. WO 00/39111 to Beight *et al.* ("the '111 publication," EX1009).

The '111 publication published in English on July 6, 2000 based on International Application No. PCT/US99/29832, filed on December 15, 1999. EX1009 at cover. The '111 publication claims priority to U.S. Provisional Application No. 60/113,778 ("the '778 application," EX1010), filed December 23, 1998. EX1009. The '111 publication was not of record during examination of the '860 patent.

Subject matter "carried forward" from the '778 application into the '111 publication is entitled to the benefit of the December 23, 1998 priority date of the '778 application. *See In re Giacomini*, 612 F.3d 1380, 1382-83 (2010) (Under pre-AIA 35 U.S.C. § 102(e)(2), "an applicant is not entitled to a patent if another's patent discloses the same invention, which was carried forward from an earlier U.S. provisional application[.]"). Throughout this petition the teachings of the '111 publication are supported by concurrent citations to both the '111 publication and the '778 application.

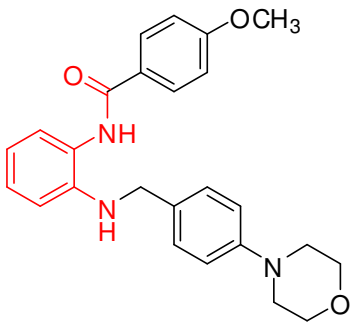
The '111 publication is also entitled to the December 23, 1998 priority date because at least one of its claims has adequate written description in the '778 application under pre-AIA 35 U.S.C. § 112, ¶1. *See Benitec Biopharma Limited v. Cold Spring Harbor Laboratory*, IPR2016-00016, Paper 8, at 7 (March 31, 2016) (priority claim of an issued patent to a U.S. provisional application as prior art under 35 U.S.C. § 102(e)(2) is established if petitioner demonstrates that the provisional "provide[s] written descriptive support for at least one claim of the [issued] patent.") (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1381 (Fed. Cir. 2015)).

As explained by Dr. Lepore, the '778 application provides written description support for at least one claim of the '111 publication. EX1002, ¶¶66-67. For example, claim 13 of the '111 publication is identical to claim 13 of the '778 application, and provides:

Claim 13 of the '778 Application and the '111 Publication
13. A novel compound of formula I substantially as herein before described with reference to any of the examples.

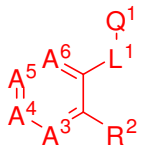
EX1009, 74:15-19; EX1010, 0078:15-19; EX1002, ¶65.

Example 1 of the '111 publication is identical to Example 1 of the '778 application, and is shown below:



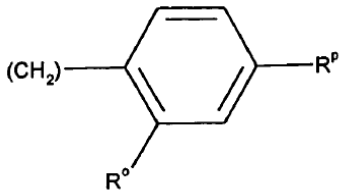
Example 1
The '111 Publication; EX1009
and the '778 Application; EX1010

EX1009, 39:1-5; EX1010, 0043:1-5. Formula 1 of the '111 publication is also identical to Formula 1 of the '778 application, and is shown below:



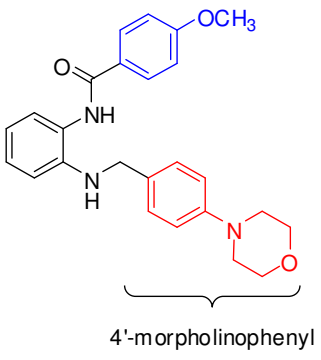
Formula 1
The '111 Publication; EX1009
and the '778 Application; EX1010

EX1009, 3:5-9; EX1010, 0007:5-9. Example 1 is a compound of formula I, shown above, when A^3, A^4, A^5 and A^6 are CR^3, CR^4, CR^5, and CR^6, respectively, wherein R^3, R^4, R^5, and R^6 are all identically hydrogen, L^1 is NHCO, Q^1 is phenyl, wherein the phenyl bears a 4-methoxy group, and R^2 is $NHCH_2Q^2$, wherein Q^2 is Q^{2B}, and Q^{2B} is as shown below (also showing the methylene unit to which Q^{2B} is attached):

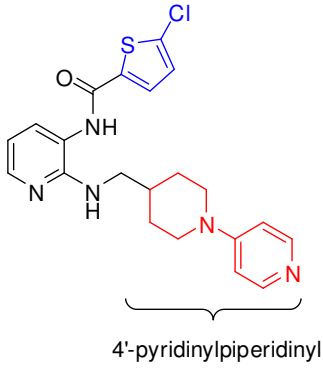


wherein R^o is hydrogen and R^p is a 4-morpholino group. EX1009, 3:5-6:10; EX1010, 0007:5-0010:10; EX1002, ¶66. Likewise, Examples 2-15 of the '111 publication are identical to Examples 2-15 of the '778 application and each is a compound of formula I. EX1009, 39:1-65:5; EX1010, 0043:1-0069:5; EX1002, ¶66. Thus, the '778 application provides written description support for at least one claim of the '111 publication. EX1002, ¶67.

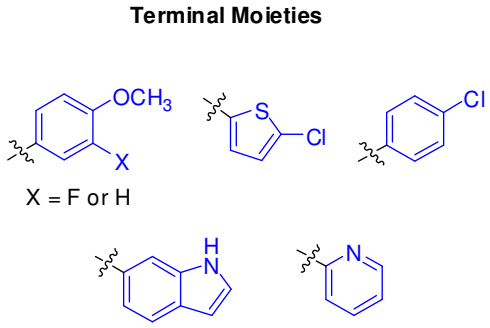
The ’111 publication teaches the role of factor Xa in the blood coagulation cascade, noting it as a target for anticoagulant therapy. EX1002, ¶61. The ’111 publication teaches factor Xa inhibitors for administration “as anticoagulants for prophylaxis and treatment of thromboembolic disorders such as venous thrombosis, pulmonary embolism, arterial thrombosis, in particular myocardial ischemia, myocardial infarction and cerebral thrombosis.” EX1009, 1:16-20; EX1010, 0005:12-16; EX1002, ¶60. The ’111 publication discloses 15 specific direct factor Xa inhibitors, each comprising one of three modules (*e.g.*, 4’-morpholinophenyl, 4’-pyridinylpiperidinyl, or 4’-isopropylpiperidinyl) on one arm and one of a small set of terminal moieties on the other arm. EX1009, 39:1-65:5; EX1010, 0043:1-0069:5; EX1002, ¶¶62-63.



Example 1
The '111 Publication; EX1009



Example 7
The '111 Publication; EX1009



Examples 1-15
The '111 Publication; EX1009

The ’111 publication states that these compounds may be prepared as single enantiomers when a source of chirality is present, and that they may be purified

and formulated using methods known to those in the art. EX1009, 18:16-29; 21:31-22:2; EX1010, 0022:16-29; 0025:31-0026:2; EX1002, ¶64. The '111 publication also describes assays commonly used to measure factor Xa activity. EX1009, 27:7; EX1010, 0031:7.

Chiba, K., *et al.*, *Absorption, Distribution, Metabolism, and Excretion of the Oxazolidinone Antibiotic Linezolid (PNU-100766) in the Sprague Dawly Rat*, ICAAC, SAN DIEGO, CA September 24-27, 1998 ("Chiba," EX1011).

Chiba is prior art to the claims of the '860 patent under 35 U.S.C. § 102(b). Chiba discloses pharmacokinetic properties of linezolid, including 100% oral bioavailability. EX1011 at 39; EX1002, ¶70. Chiba highlights linezolid as being "bioavailable and widely distributed," after which it is excreted "primary in urine as parent drug, or as carboxylic acid metabolites that have low antibacterial potency." Chiba teaches that these metabolites are formed via morpholine ring oxidation. EX1011; EX1002, ¶70. Chiba was not of record during examination of the '860 patent.

D. BRIEF OVERVIEW OF THE LEVEL OF SKILL IN THE ART

At the time of the invention, a person having ordinary skill in the art of the claims of the '860 patent would include an individual or a team of individuals having some combination of the following skills and experience: (i) experience

with the synthesis of organic compounds; (ii) experience designing pharmaceutical compounds; (iii) an understanding of general principles of drug design and delivery, including pharmacology, pharmacokinetics, toxicology, and formulation; (iv) an understanding of the role of anticoagulants, including factor Xa inhibitors, in the treatment and prevention of thromboembolism disorders; and (v) the ability to understand work presented or published by others in the field, including the publications discussed in this petition. EX1002, ¶¶22-23.

Typically, a person of ordinary skill in the relevant field as of the earliest alleged priority date, *i.e.*, December 24, 1999, would have, or be a member of a team with a member having, an advanced degree (*e.g.*, a Ph.D.) in organic chemistry, medicinal chemistry, or a related field. The skilled artisan may also have, or be a member of a team having, a medical degree (*e.g.*, an M.D.) with experience treating thromboembolism disorders using anticoagulants. Alternatively, a person of ordinary skill in the relevant field might have less education but considerable professional experience in one or more of these fields. EX1004.

Dr. Salvatore Lepore is a medicinal chemist who began his career in pharmaceutical research and drug development nearly 20 years ago, and worked in the development of factor Xa inhibitors in the late 1990s and early 2000s. EX1002,

¶¶1-2. Dr. Lepore is currently a Professor of Chemistry and Biochemistry at Florida Atlantic University where he teaches courses on organic chemical reactions and drug design, and leads research efforts focused on the development of new synthetic organic reaction methodology and their application to the total synthesis of compounds of therapeutic interest. EX1002, ¶3. Dr. Lepore earned his Ph.D. in 1997 from Purdue University, after which he conducted research as a postdoctoral fellow at Eli Lilly and Company. EX1002, ¶2. Dr. Lepore has authored or co-authored many peer-reviewed journal articles and book chapters and has been the recipient of numerous awards. *Id.* at ¶¶4-5. A summary of his education, experience, awards and honors, patents, publications, and presentations is provided in his CV, submitted as EX1004. *See also*, EX1002, ¶¶ 1-6.

Dr. Lepore is a well-qualified expert in the field of drug design, and possesses the expertise necessary to determine and explain the level of ordinary skill in the art during the relevant time frame, *i.e.*, prior to December 24, 1999. EX1002, ¶¶1-6; *see also* EX1004.

II. GROUNDS FOR STANDING

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '860 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the '860 patent on the grounds identified.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)): The following real parties-in-interest are identified: Mylan Pharmaceuticals, Inc., which is the Petitioner in this matter and a wholly owned subsidiary of Mylan Inc.; Mylan Inc., which is an indirectly wholly owned subsidiary of Mylan N.V.; and Mylan N.V.

Related Matters (37 C.F.R. § 42.8(b)(2)):

IPR petitions for related 7,157,456 and 7,592,339 are being filed by the present Petitioner as IPR2017-00041 and IPR2017-00043, respectively.

Petitioner and other entities are involved in litigation over the '860 patent and related patents in the action styled CA No. 1:15-cv-00902-SLR, filed by Bayer Intellectual Property GmbH et al. in the District of Delaware. (EX1016). A complaint asserting the '860 patent against Petitioner was served no earlier than October 9, 2015. Petitioner also identifies the following pending actions involving the '860 patent: *Bayer GmbH v. Breckenridge Pharmaceutical, Inc.*, No. 1:16-cv-00628, in the District of Delaware; *Bayer GmbH v. InvaGen Pharmaceutical Inc.*, No. 1:16-cv-00064, in the District of Delaware; and *Bayer GmbH v. Micro Labs Ltd.*, No. 1:16-cv-00242, in the District of Delaware.

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b) (3)):

Lead Counsel: Steven W. Parmelee (Reg. No. 31,990)

Back-Up Counsel: Michael T. Rosato (Reg. No. 52,182)

Back-Up Counsel: Jad A. Mills (Reg. No. 63,344)

Service Information (37 C.F.R. § 42.8(b) (4)):

Petitioner hereby consents to electronic service.

Email: sparmelee@wsgr.com; mrosato@wsgr.com; jmills@wsgr.com

Post: WILSON SONSINI GOODRICH & ROSATI

701 Fifth Avenue, Suite 5100, Seattle, WA 98104-7036

Tel.: 206-883-2542 Fax: 206-883-2699

IV. STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioner requests review of claim 1 of the '860 patent under 35 U.S.C. § 311 and AIA § 6 and that this claim be canceled as unpatentable:

Ground	Claim	Obvious under §103 over
1	1	Ewing, Riedl, the '111 publication, and Chiba

V. CLAIM CONSTRUCTION

In an *inter partes* review, a claim in an unexpired patent is given its broadest reasonable construction in light of the specification. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 15-446, slip op. at 2 (U.S. June 20, 2016). Claims terms are also "generally given their ordinary and customary meaning,"

which is the meaning that the term would have to a person of ordinary skill in the art at the time of the invention in view of the specification. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); EX1002, ¶24. Under either standard, there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claims. No terms are believed to require special construction at this time for the purposes of this *inter partes* review proceeding.

VI. BACKGROUND KNOWLEDGE IN THE ART PRIOR TO DECEMBER 24, 1999

The background publications below reflect knowledge skilled artisans would bring to bear in reading the prior art at the time of the invention, *i.e.*, the earliest claimed German priority date of December 24, 1999, and thereby assist in understanding why one would have been motivated to combine or modify the references as asserted in this petition. *Ariosa Diagnostics v. Verinata Health, Inc.*, No. 15-1215, slip op. 1, 11-12 (Fed. Cir. Nov. 16, 2015). As established in *KSR*, 550 U.S. at 406, the knowledge of a skilled artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

Prior to December 24, 1999, it was known that anticoagulants were useful in the treatment of thromboembolic disorders, which arise from malfunctions in the

blood coagulation cascade. Kamata, K., *et al*., *Structural basis for chemical inhibition of human blood coagulation factor Xa*, 95 PROC. NATL. ACAD. SCI. USA (1998) 6630-35 ("Kamata," EX1014); EX1002 at ¶26. While Kamata teaches that multiple targets in the coagulation cascade contribute to the formation of blood clots, Kamata notes that one particular component of the blood coagulation cascade, "factor Xa, which is also essential for both the intrinsic and extrinsic pathways of the coagulation process, is thought to be a better target of antithrombotic drugs because many thrombin inhibitors have been shown to increase the risk of abnormal bleeding." EX1014 at 6630; EX1002, ¶27. Kamata describes factor Xa binding sites, including an S1 pocket and an "aryl binding site," also known in the art as an S4 pocket. EX1014 at 6630; EX1002, ¶28. These pockets were identified as capable of binding planar aromatic groups and saturated heterocycles, respectively. *Id.* at 6632; *see also*, Katakura, S. *et al*., M*olecular model of an interaction between factor Xa and DX-9065a, a novel factor Xa inhibitor: contribution of the acetimidoylpyrrolidine moiety of the inhibitor to potency and selectivity for serine proteases*, 30 EUR. J. MED. CHEM. (1995) 387-94 ("Katakura," EX1015); EX1002, ¶¶27-28.

Prior to December 1999, linezolid was known to have impressive pharmaceutical properties, including 100% oral bioavailability. Stalker, D.,

Linezolid Pharmacokinetics, OXAZOLIDINONES: A NEW CLASS OF ANTIBIOTICS SYMPOSIUM, 1998 ("Stalker," EX1017); EX1002, ¶¶29-30. Linezolid belongs to a class of compounds known as oxazolidinones, which were identified in the mid-1990s as useful antimicrobials and antithrombotics. U.S. Patent No. 5,532,255, to Raddatz *et al.*, filed April 29, 1994 ("Raddatz," EX1019); *see also*, U.S. Patent No. 5,614,535, to Juraszyk *et al.*, filed August 18, 1995 ("Juraszyk," EX1020); EX1002, ¶31. Though linezolid entered clinical trials because of its antimicrobial properties, it was recognized that modifications to the two pendant groups off the oxazolidinone ring allowed for optimization of different therapeutic activities, including anticoagulant properties. Gante, J. *et al*., *New Peptidomimetics in the Chemistry of Fibrinogen Receptor Antagonists,* 2 LETT. PEPT. SCI., (1995) 135-40 ("Gante," EX1018); EX1002, ¶¶29-30.

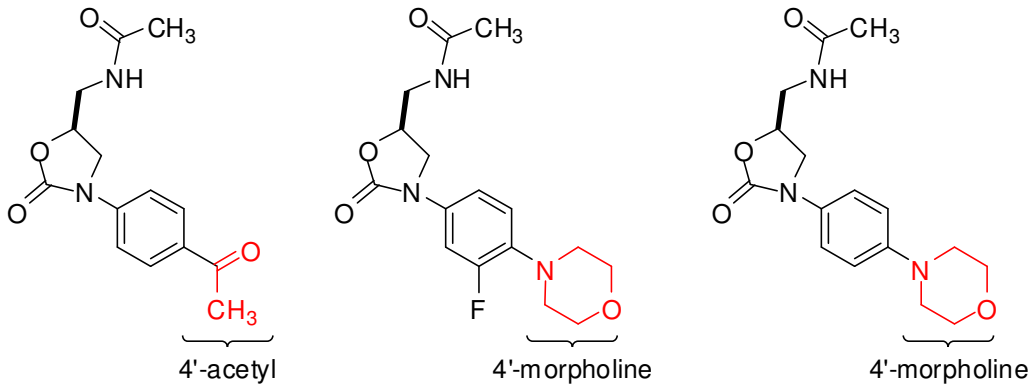
Linezolid was known to be highly accessible from commercially-available starting materials through a straightforward synthetic process. Brickner, S. J., *Oxazolidinone Antibacterial Agents* 2 CURR. PHARM. DES. 175-194 (1996) ("Brickner I," EX1021) at 183; *see also*, Brickner, S. J., *et al.*, *Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections* 39 J. MED. CHEM. 673-79 (1996) ("Brickner II,"

EX1023); EX1002, ¶35. Brickner II describes linezolid's synthesis as easily adaptable to "widely divergent 3-(4-substituted-aryl)-2-oxazolidinones," and highlights that the synthesis "proceeds with high efficiency from commercially available reagents." EX1023 at 674-75.

Given linezolid's favorable properties, it was advanced into clinical trials, and was found to be well-tolerated by humans. EX1021. Linezolid was also identified as being "rapidly and extensively absorbed after oral dosing" in humans, as well as being administrable via intravenous routes. EX1017 at 0002; EX1002, ¶33. The 100% oral bioavailability of linezolid, coupled with its dual administration routes allowed for linezolid to "be given orally without a dose adjustment in patients who are able to receive oral medication." *Id.* As explained by Dr. Lepore, this allowed doctors to "easily switch between intravenous and oral formulations of linezolid without performing calculations to identify the change in dosage required to alter administration routes." EX1002, ¶33. Linezolid was also known to have limited drug-drug interaction concerns, and remained 100% orally bioavailable in the presence of food. EX1017 at 0002, 0004; EX1002, ¶34.

Notably, the morpholine ring on linezolid abated toxicity concerns, which had arisen in the development of a related structural analogue (Dup-721) which comprised a 4'-acetyl group off the phenyl ring. EX1021 at 191*; see also* Gleave,

D. M. *et al.*, *Synthesis and Antibacterial Activity of [6,5,5] and [6,6,5] Tricyclic Fused Oxazolidinones*, 8 BIOORG. MED. CHEM. LETT. (1998) 1231-36 ("Gleave," EX1022) at 1231 (showing both linezolid and *des*-fluorolinezolid); EX1002, ¶32. The structure of Dup-721 is shown below with linezolid, and a *des*-fluorolinezolid bioisostere (discussed further below) which was also known in the art:



Dup-721
Brickner, EX1021

Linezolid
Riedl, EX1008

***Des*-fluorolinezolid**
Gleave, EX1022

Brickner II discloses that the fluorine in the 3'-position of linezolid was added late in development of oxazolidinone antibacterial analogues to enhance antibacterial potency both *in vitro* and *in vivo*. EX1023 at 674; EX1021 at 187; EX1022 at 1231; EX1002, ¶36. As referenced in the figure above, Gleave reported the existence and activity of the *des*-fluoro bioisostere of linezolid. As explained by Dr. Lepore, the commercially-available precursor for the synthesis of *des*-fluorolinezolid is seven times less expensive than the compound required to make

the 3'-fluoro moiety. EX1002, ¶37; SIGMA-ALDRICH PRODUCT CATALOGUE 1995-96 ("Sigma-Aldrich Catalogue," EX1024) at 529 and 733.

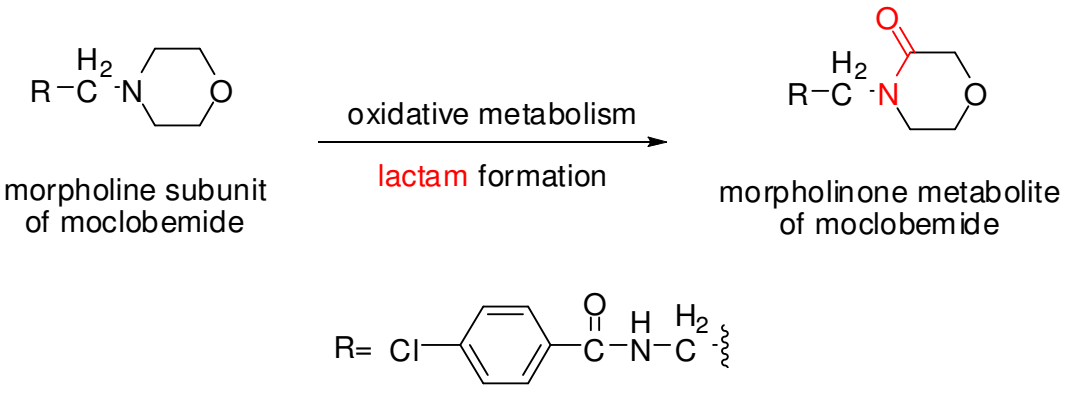
The 5-acetamidomethyl side chain of linezolid was also known to be an important locus for its antimicrobial activity. EX1002, ¶38. For example, Brickner I teaches that the antimicrobial "binding site is very sensitive to the steric environment about the 5-position of the oxazolidinone, and not tolerant of drastic deviation." EX1021 at 186.

While the art identified the 5-acetamidomethyl side chain as a binding moiety for antimicrobial activity, terminal 5-chlorothiophene moieties were known binding moieties for factor Xa. *See e.g.,* US Patent No. 5,958,918 to Ewing *et al.* ("the '918 patent," EX1026) at 9:23-25; US Patent No 5,925,635 to Maduskuie, Jr. *et al.* ("the '635 patent," EX1027) at 8:60-61, 62:31. Terminal 5-chlorothiophene moieties had already been known to be useful in inhibiting blood platelet aggregation for decades. U.S. Patent No. 4,075,340, to Maffrand *et al.*, filed June 2, 1976 ("Maffrand," EX1025); EX1002, ¶39.

Pharmaceutical development has long routinely included an evaluation of metabolites of drug candidates to "guide structural modifications, thereby improving the activity and/or bioavailability" of the structure that was originally designed. *See, e.g.*, Korfmacher *et al.*, *HPLC API/MS/MS: a powerful tool for*

integrating drug metabolism into the drug discovery process, 2 DRUG DISC. TODAY 532 (1997) ("Korfmacher," EX1028); EX1002, ¶40. Korfmacher specifically teaches, "future lead compounds might be a metabolite identified from the previous lead drug or an analog of the previous drug designed to block the major route of metabolism." EX1028 at 534.

Pharmaceutical compounds containing morpholine subunits were known to be metabolized oxidatively to yield morpholinone derivatives as well as oxidatively-ring opened compounds. Jauch, R. *et al.*, *Biotransformation of moclobemide in humans,* Suppl. 360 ACTA PSYCHIATR. SCAND. (1990) 87-90 ("Jauch," EX1029). Jauch teaches the metabolism of morpholine-containing moclobemide proceeds via a "general pattern" of morpholine ring oxidation, consistent with the known metabolic pathway of other morpholine-containing drugs:



Id. at 89; EX1002, ¶¶41-43. Jauch also teaches that it is routine to screen these metabolites in order to assess any changes in biological activity that may arise. *Id.;* EX1002, ¶44.

Thus, there remained in 1999 a need for improved anticoagulants with improved pharmacokinetic and pharmaceutic properties, and decreased risks of bleeding and other complications associated with anticoagulant therapy

VII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

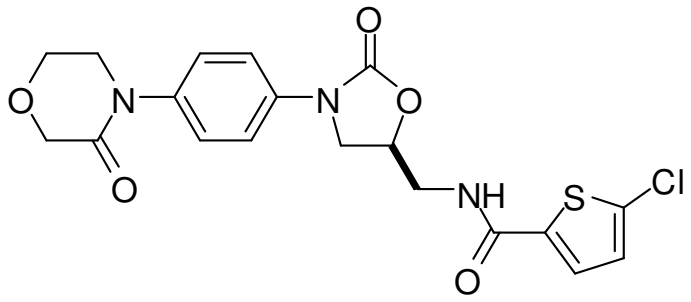
A. [Ground 1] Claim 1 is Obvious Under 35 U.S.C. § 103 Over Ewing, Riedl, the '111 Publication and Chiba.

Ground 1 establishes the obviousness of the compound of claim 1 based on the combined teachings of Ewing (EX1007), Riedl (EX1008), the '111 publication (EX1009), and Chiba (EX1011), when appropriately considered in view of the knowledge of a person of ordinary skill in the art. EX1002, ¶74.

Claim 1 is drawn to a factor Xa inhibitor referred to herein for convenience as "rivaroxaban," and recites the following:

Claim 1:

A compound of formula:



or a hydrate thereof.

Well prior to December 1999, the art recognized additional anticoagulant therapies were needed beyond heparin and warfarin. Though these were regarded as "mainstay" anticoagulants, the art acknowledged their narrow therapeutic windows, as well as concerns about drug-drug and food-drug interactions associated with their administration. EX1007 at 771, 773-74; EX1002 at ¶75.

Ewing teaches that factor Xa was a desirable target for anticoagulant therapy because it lies at the convergence of the two coagulation pathways. *Id.;* EX1002, ¶76. Both the intrinsic and extrinsic pathways are "capable of being activated in response to different stimuli" yet "ultimately converge upon the formation of factor X and its conversion to factor Xa in the prothrombinase complex." EX1007 at 771. Ewing states: "[D]irect inhibition of factor Xa activity should provide a potent anticoagulant devoid of the potentially limiting side effects observed with thrombin inhibitors." EX1007 at 771. Ewing states:

> Direct inhibition of factor Xa activity in the prothrombinase complex blocks the single physiological source of thrombin generation.

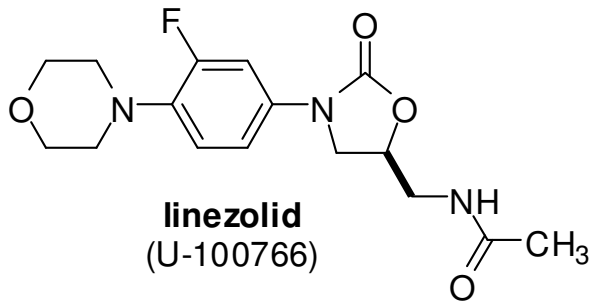
> Inhibiting the source of thrombin generation rather than its catalytic activity offers several potential mechanistic advantages that could afford superior anticoagulant agents.

Id. at 774. Ewing also states that direct inhibition of factor Xa would have minimal impact on normal hemostatic response/regulation processes and would minimize the risk of bleeding complications. EX1007 at 774; EX1002, ¶76.

Ewing describes compounds that act as factor Xa inhibitors. They generally comprise two "arms" connected via a linker scaffold. EX1007 at 777-83; EX1002, ¶77. The two arms bind in the two primary binding pockets of factor Xa, known in the art as "the specificity or S1 binding pocket" and "[t]he aromatic or S4 binding pocket." EX1007 at 775. Ewing depicts dozens of factor Xa inhibitors where the terminal end of one arm comprises aryl or heteroaryl rings, and the other arm comprises aryl, saturated heterocyclic, or cycloalkane moieties. EX1007 at 777-83 (compounds 11-57); EX1002, ¶77. While Ewing teaches that a variety of potent factor Xa inhibitors had been developed either by modifying previously identified factor Xa inhibitors or through *de novo* design, Ewing also states that "[t]he discovery of factor Xa inhibitors which lack highly basic functions (i.e., amidines) holds considerable promise for future design since similar advances in the thrombin inhibitor field is what ultimately led to the discovery of orally effective factor IIa [thrombin] inhibitors." EX1007 at 783; EX1002, ¶77. Ewing's reference

to similar advances in thrombin inhibitors is notable because Ewing states that combining potent inhibition with strong oral pharmacokinetic properties had remained elusive. EX1007 at 773-74; EX1002, ¶77.

Linezolid is an oxazolidinone known to have 100% oral bioavailability and low toxicity. Riedl, EX1008 at 625-26; Chiba, EX1011 at 39; EX1002, ¶78. The structure of linezolid is shown below:



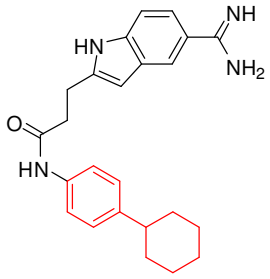
linezolid
(U-100766)

EX1008 at 626.

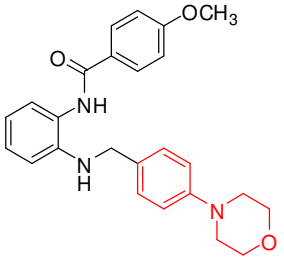
By December, 1999, linezolid had entered Phase III clinical trials based on its antibiotic activity, and had been established to possess a wide array of desirable pharmacokinetic properties. EX1008 at 626; EX1002, ¶79. Linezolid's high volume of distribution, rapid absorption after oral dosing, and relatively low serum binding, were properties that made it regarded as "bioavailable and widely distributed." EX1011 at 39. Linezolid did not have toxicity issues that had been observed in other oxazolidinone-based antimicrobial agents, such as a compound referred to as "Dup-721." EX1008 at 626-27; EX1002, ¶80.

Riedl also notes "[i]n addition to the antimicrobial activity, other pharmacological activities of the oxazolidinones have been reported." Among these oxazolidinone activities are those "which inhibit platelet aggregation . . . and [thus] may be useful in the treatment of thrombosis and myocardial infarction." EX1008 at 626, 630; EX1002, ¶81.

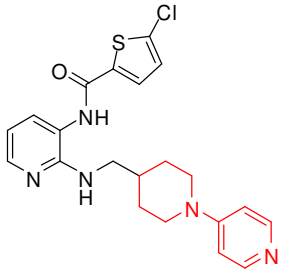
Many factor Xa inhibitors taught in the art had the same general size and shape as linezolid, as illustrated below:



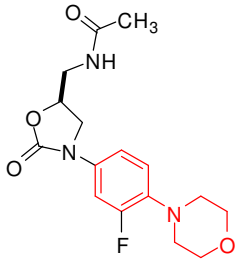
Compound 49
Ewing, EX1007



Example 1
The '111 Publication; EX1009



Example 7
The '111 Publication; EX1009



Linezolid
Riedl, EX1008

EX1002; ¶82. For example, the 4'-morpholinophenyl arm of linezolid (colored red in the structure above) is physically and chemically similar to the corresponding arm in each of of Ewing's Compound 49, and Examples 1 and 7 of the '111 publication (also colored in red). EX1009 at 39, 47; EX1010 at 43, 51; EX1002, ¶83 (discussing EX1031 and identifying hydrogen and fluorine, and methylene, nitrogen and oxygen, respectively, as bioisosteres). Indeed, the '111 publication teaches a binding arm in the factor Xa inhibitor of Example 1 that is identical to

that of linezolid with the sole exception of the bioisosteric hydrogen at the 3' position instead of a fluorine. *Id., see also* EX1031 at 20.

As explained in detail below, the person of ordinary skill would have good reasons to use the scaffold provided by linezolid to implement structural changes to optimize factor Xa binding activity. These reasons would have included achieving improved factor Xa inhibition efficacy, retaining linezolid's desirable pharmacokinetic properties, and abating linezolid's antimicrobial activity. EX1002, ¶85. As explained by Dr. Lepore, such structural changes would ideally also avoid unnecessary synthetic steps and additional costs. EX1002, ¶¶85-86.

As the *des*-fluoro-4'-morpholinophenyl arm, which is identical to that present in linezolid (minus the 3'-fluorine), was a known factor Xa binding moiety (EX1009, 39:1-5; EX1010, 0043:1-5), a person of ordinary skill in the art would have retained the 4'-morpholinophenyl arm of linezolid minus the 3'-fluorine to function as a factor Xa binding moiety. EX1002, ¶84. The person of ordinary skill would also reasonably understand that the 3'-fluorine of linezolid likely was not necessary in the design of a potent factor Xa inhibitor because none of Examples 1-15 (including Example 1) of the '111 publication contained a 3'-fluorine. *See e.g.*, EX1009, 39:1-65:3 (Examples 1-15); EX1010, 0043:1-0069:3; *see also* EX1007 at 782 (Compound 49); EX1002, ¶87.

As it was known that the fluorine was a late-stage add-on included to increase linezolid's antimicrobial potency, the skilled artisan would have expected that omitting the fluorine would mitigate the dual antimicrobial activity that would not have been desired in a factor Xa inhibitor. EX1023 at 674. A synthetic precursor was readily available to make the *des*-fluoro compound, and was substantially less expensive than the otherwise identical precursor for making the fluorinated compound. *See* EX1002, ¶87, referring to the 1995-96 Sigma Aldrich Chemical Catalogue (EX1024). Indeed, the commercial precursor to install the fluorinated phenyl ring cost seven times more than the precursor to install its *des*-fluoro analogue. EX1002, ¶87; *E.g.*, EX1024 at 529 and 733 (noting a 7-fold decrease in cost of 4-fluoro-nitrobenzene as compared to 3,4-difluoro-nitrobenzene).

As *des*-fluorolinezolid had been previously synthesized in the art, the skilled artisan would have a reasonable expectation of producing this 4'-morpholinophenyl bioisostere of linezolid using the less expensive reagent. EX1022 at 1235 (Compounds 3a (linezolid) and 3b (*des*-fluorolinezolid) in Table I); EX1002, ¶88.

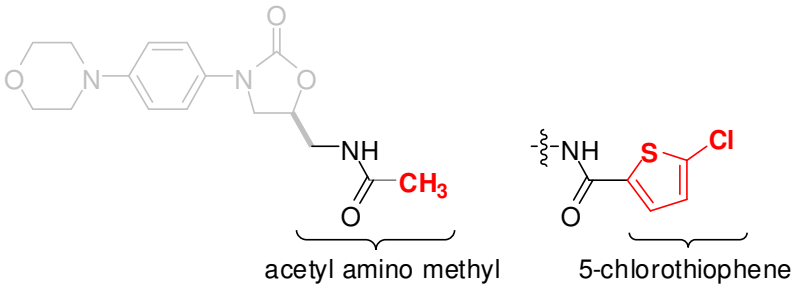
A person of ordinary skill also would have reasonably expected that the *des*-fluoro-4'-morpholinophenyl arm on linezolid would have factor Xa binding

activity because Ewing teaches a similar factor Xa binding arm comprised of a 4'-cyclohexylphenyl moiety (Compound 49). EX1007 at 782. As discussed above, the '111 publication specifically discloses the 4'-morpholinophenyl arm (Example 1) for use as a factor Xa binding moiety. EX1009, 39:1-5; EX1010, 0043:1-5. In addition, the skilled artisan would have had a reasonable expectation that the *des*-fluorolinezolid compound would be non-toxic given the presence of the 4'-morpholine ring, which was known in the art to be associated with the low toxicity of linezolid. EX1021 at 191.

Due to the two-arm structure of factor Xa inhibitors corresponding with the S1 and S4 binding pockets of factor Xa, the skilled artisan would have looked to the 5-methylamino acyl arm of linezolid for further modification. EX1002, ¶89. Riedl also identifies the 5-methylamino acyl arm of linezolid, shown in the depiction below, as a key locus for antibacterial activity:

> The SAR of the methylamino acyl group in the 5-position of the oxazolidinone seemed to be narrowed down to acetyl amino methyl in this position. Most of the companies, which are active in the field of oxazolidinones with antibacterial activity use this substituent preferentially.

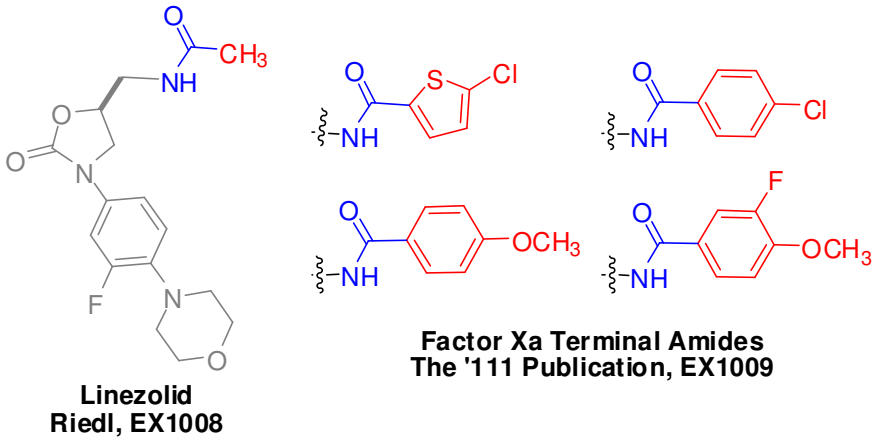
EX1008 at 629; EX1002, ¶90.



To increase selectivity of linezolid as a factor Xa inhibitor (by, *e.g.*, increasing factor Xa binding affinity and decreasing antibacterial activity), the skilled artisan would have looked to replace the terminal methyl moiety that contributes to the unneeded antibacterial activity with a functional group that was known to bind to factor Xa. *See* EX1008 at 629; EX1002, ¶¶90-91. The skilled worker would have used a larger or more polar functional group than the existing methyl group to mitigate the antibacterial activity that Riedl teaches is associated with smaller, nonpolar functional groups. EX1002, ¶¶90-91. In doing so, the person of skill would have chosen a functionality intended to fit into one of factor Xa's primary binding pockets to increase factor Xa binding affinity. Aromatic moieties were known to bind in both the S1 and S4 pockets of factor Xa. EX1007 at 775; EX1002, ¶91. The S1 binding pocket had also been described as having a narrow cleft and acting as "one of the prime determinants of substrate specificity." *Id.* Thus, the skilled artisan would have had reason to look to an aromatic factor Xa

binding moiety, such as those described in the '111 publication, as planar aromatic groups were known to fit in the S1 binding pocket. EX1002, ¶¶91-92.

The '111 publication describes a handful of planar aromatic factor Xa binding moieties in Examples 1-15 on compounds that are generally structurally similar to linezolid. Four of these moieties could be readily evaluated on the 5-methyl amino acyl arm of linezolid by a simple substitution of the existing protocols for linezolid synthesis because they are installed via an identical amide linkage to that present in linezolid:

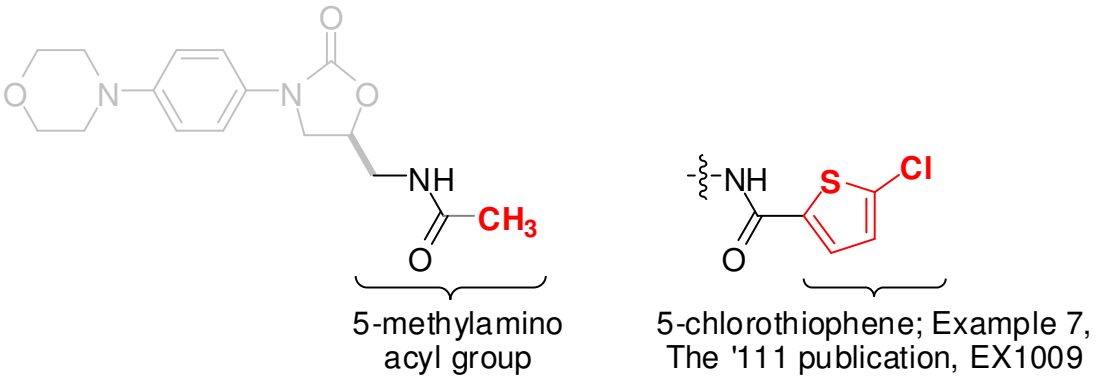


The skilled artisan would have had reason to evaluate each of these planar aromatic factor Xa binding moieties on a *des*-fluoro bioisostere of linezolid, because they are taught by the '111 publication to be factor Xa binding moieties and to be present on factor Xa binding inhibitors that are otherwise structurally similar to linezolid. EX1002, ¶¶92-93. As stated in *KSR*, 550 U.S. at 420-21,

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." Methods for measuring factor Xa inhibition were routine and known in the art. EX1009, 27:7; EX1010, 0031:7; EX1002, ¶67.

The person of ordinary skill would have had a reasonable expectation of success in installing the aromatic amides taught by the '111 publication onto the 5-methyl amino acyl arm of the linezolid scaffold. The synthesis of linezolid was known. EX012 at Figure 25, 0194; *see also* EX1021 at 183. The final step in the synthesis is the acylation of the free amine that consequently becomes the nitrogen in the amide bond linkage shown above. Thus, the process for adding each of the four amide moieties in the '111 publication identified above would have been a straightforward exchange of the acylating reagent used in the final step of the synthesis. EX1021 at 183; EX1002, ¶94. Each of these moieties was known to bind factor Xa, and the chemistry required to make the substitution was considered routine. EX1002, ¶92. Further, 5-chlorothiophene moieties were known in the art to be common terminal moieties in potent factor Xa inhibitors (*e.g.*, EX1009 at [57]; EX1010, 0005:4-21; EX1026, 9:23-25; EX1027, 8:60-61, 62:31). Thus, the

skilled artisan would have had a reasonable expectation that a 5-chlorothiophene analogue of *des*-fluorolinezolid would be a factor Xa inhibitor. EX1002, ¶94.

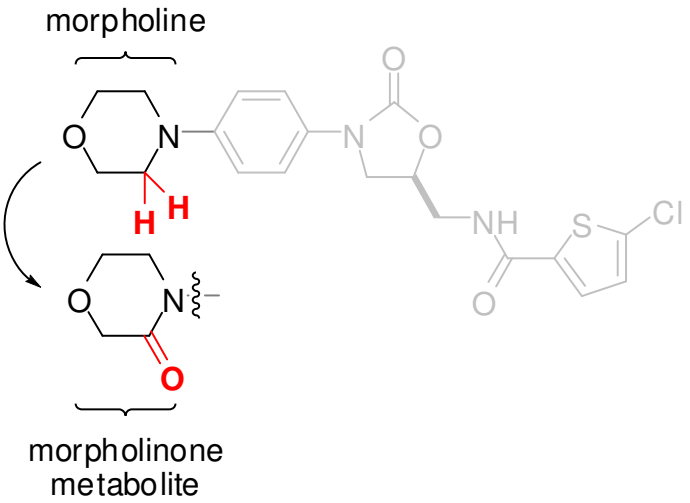


Moreover, it was well known in the art that a drug candidate's metabolites could "guide structural modifications, thereby improving the activity and/or bioavailability" of a given compound. EX1028 at 532. For this reason, in designing a linezolid-based factor Xa inhibitor, one of ordinary skill would have also performed a routine analysis of the compound's metabolites. EX1002, ¶95. The identification of metabolites was known to "provide information on how to improve the metabolic stability of the lead structure. In this way, future lead compounds might be a metabolite identified from the previous lead drug[.]" EX1028 at 534.

Chiba notes that linezolid is often excreted as mostly intact drug, but also identified morpholine ring-oxidized metabolites. EX1011 at 39. This oxidation led to "ring-opened major metabolites" of linezolid. *Id.*; EX1002, ¶95. As explained by

Dr. Lepore, the skilled artisan "would have understood that the morpholinone metabolite would be less susceptible than morpholine to oxidation leading to ring-opened metabolites." EX1002, ¶¶96-97 (discussing the teachings of Chiba, EX1011 and Jauch, EX1029).

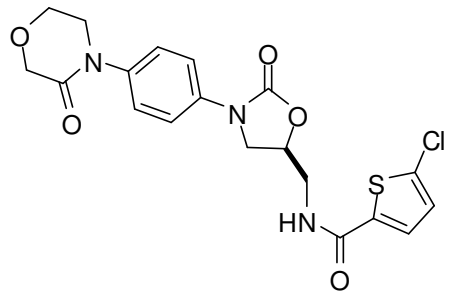
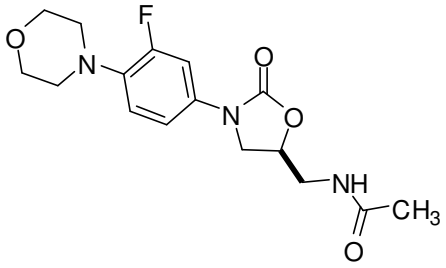
Thus, the person of ordinary skill in the art would have been motivated to make the morpholinone derivative. EX1002, ¶97.

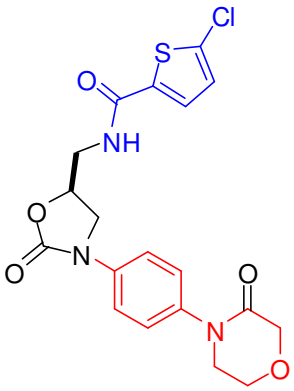
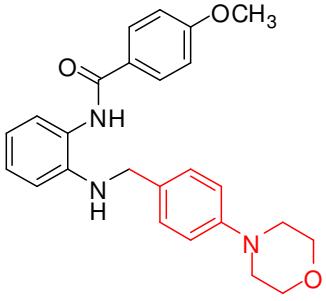
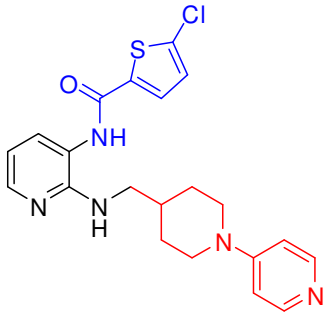
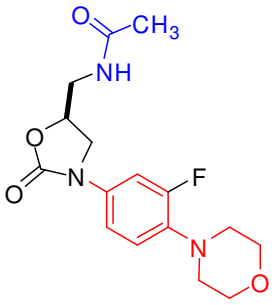
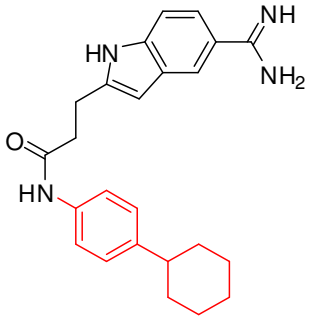


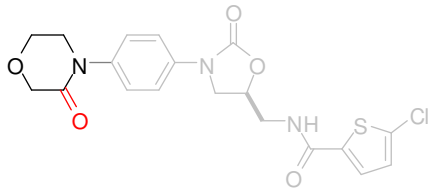
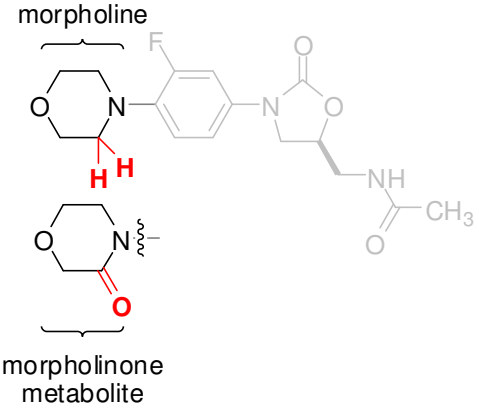
As noted by Dr. Lepore in his declaration, the skilled artisan would have produced the morpholinone analogue using any one of several standard synthetic protocols. *See*, *e.g.*, Kojima, T., *et al.*, *Synthesis of (±)-2-[(Inden-7-yloxy)methyl]morpholine Hydrochloride 9YM-08054, Indeloxazine Hydrochloride) and Its Derivatives with Potential Cerebral-Activating and Antidepressive Properties*, 33 CHEM. PHARM. BULL. (1985) 3766-6774 ("Kojima," EX1030), showing a routine synthesis of a phenylated morpholinone arm. *See also* EX1002,

¶96. The morpholinone derivative of 5-chlorothiophene *des*-fluorolinezolid, is identical to the structure recited in claim 1.

Based on the foregoing evidence and explanation, claim 1 would have been obvious under 35 U.S.C. § 103 in light of the combined teachings of Ewing, Riedl, the '111 publication and Chiba. EX1002, ¶98.

'860 Patent Claim	**Obvious over Ewing, Riedl, the '111 publication, and Chiba**
1. A compound of formula:  **or a hydrate thereof.**	"In Phase III clinical trials, linezolid appears to be highly efficacious and well-tolerated." EX1008 at 630; EX1002, ¶80. "Due to its advantageous pharmacokinetic profile, Upjohn continued the clinical development program with linezolid." EX1008 at 626.  Figure 1, EX1008 at 626. "In addition to the antimicrobial activity, other pharmacological activities of the oxazolidinones have been reported." EX1008 at 626; EX1002, ¶81. "Novel oxazolidinone derivatives which inhibit platelet aggregation . . . act as fibrinogen antagonists and may be useful in the treatment of thrombosis and myocardial infarction." EX1008 at 630; EX1002, ¶90.

	"absolute bioavailability was 109%." EX1011 at 39; EX1002, ¶70.
The compound of claim 1: 	"This invention relates to antithrombotic aromatic amides which demonstrate activity as inhibitors of factor Xa and, accordingly, which are useful anticoagulants in mammals." EX1009, 1:8-11; EX1010, 0005:4-7.  Example 1 EX1009, 39:1-5; EX1010, 0043:1-5  Example 7 EX1009, 47:14-25; EX1010, 0051:14-25  Linezolid, Figure 1 EX1008 at 626  Compound 49, EX1007 at 782

	"Linezolid (po) was excreted mostly as intact drug (32% of dose) and was metabolized by morpholine ring oxidation to ring-opened major metabolites[.]" EX1011 at 39; EX1002, ¶95; *see also* EX1029 at 89 (providing a "general pattern" of metabolic morpholine oxidation). 

VIII. CONCLUSION

For the reasons set forth above, claim 1 of the '860 patent is unpatentable over the asserted prior art. Petitioner therefore requests that an *inter partes* review of this claim be instituted and that it be found unpatentable and canceled.

Respectfully submitted,

Dated: October 7, 2016

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990
Michael T. Rosato, Back-Up Counsel
Reg. No. 52,182
Jad A. Mills, Back-Up Counsel
Reg. No. 63,344
WILSON, SONSINI, GOODRICH & ROSATI

IX. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 7,110 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: October 7, 2016

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990

X. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XI. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 7,585,860 to Straub et al.
1002	Declaration of Salvatore D. Lepore, Ph.D.
1003	*Intentionally Left Blank*
1004	Curriculum Vitae of Salvatore D. Lepore, Ph.D.
1005	*Intentionally Left Blank*
1006	File History of 7,585,860 to Straub et al.
1007	Ewing, W. R., et al., *Progress in the Design of Inhibitors of Coagulation Factor Xa*, 24 DRUGS OF THE FUTURE 771-87 (1999).
1008	Riedl, B. et al., *Recent Developments with Oxazolidinone Antibiotics*, 9 EXP. OPIN. THER. PATENTS 625-633(1999).
1009	WO 00/39111 to Beight et al.
1010	U.S. Provisional Application No. 60/113,778.
1011	Chiba, K., et al., *Absorption, Distribution, Metabolism, and Excretion of the Oxazolidinone Antibiotic Linezolid (PNU-100766) in the Sprague Dawly Rat*, ICAAC, SAN DIEGO, CA SEPTEMBER 24-27, 1998.
1012	*Intentionally Left Blank*
1013	*Intentionally Left Blank*
1014	K. Kamata, *et al*., *Structural basis for chemical inhibition of human blood coagulation factor Xa*, 95 PROC. NATL. ACAD. SCI. USA 6630-35 (1998).
1015	S. Katakura, et al., *Molecular model of an interaction between factor Xa and DX-9065a, a novel factor Xa inhibitor: contribution of the acetimidoylpyrrolidine moiety of the inhibitor to potency and selectivity for serine proteases*, 30 EUR. J. MED. CHEM. 387-94 (1995).
1016	Complaint, *Bayer GmbH v. Mylan Pharmaceuticals Inc. et al.*, CA No. 1:15-cv-00902-SLR.
1017	Stalker, D., *Linezolid Pharmacokinetics*, OXAZOLIDINONES: A NEW CLASS OF ANTIBIOTICS SYMPOSIUM, 1998.
1018	J. Gante et al., *New Peptidomimetics in the Chemistry of Fibrinogen Receptor Antagonists*, 2 LETT. PEPT. SCI. 135-40 (1995).

1019	U.S. Patent No. 5,532,255 to Raddatz et al.
1020	U.S. Patent No. 5,614,535, to Juraszyk et al.
1021	Brickner, S. J., *Oxazolidinone Antibacterial Agents* 2 CURR. PHARM. DES. 175-194 (1996).
1022	Gleave, D. M. et al., *Synthesis and Antibacterial Activity of [6,5,5] and [6,6,5] Tricyclic Fused Oxazolidinones*, 8 BIOORG. MED. CHEM. LETT. 1231-36 (1998).
1023	Brickner, S. J., et al., *Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections* 39 J. MED. CHEM. 673-79 (1996).
1024	Sigma-Aldrich Product Catalogue (1995-96) (excerpts).
1025	U.S. Patent No. 4,075,340, to Maffrand et al.
1026	US Patent No. 5,958,918 to Ewing et al.
1027	US Patent No 5,925,635 to Maduskuie, Jr. et al.
1028	Korfmacher et al., *HPLC API/MS/MS: a powerful tool for integrating drug metabolism into the drug discovery process*, 2 DRUG DISC. TODAY 532 (1997).
1029	Jauch, R. *et al.*, *Biotransformation of moclobemide in humans,* Suppl. 360 ACTA PSYCHIATR. SCAND. 87-90 (1990).
1030	Kojima, T., *et al.*, *Synthesis of (±)-2-[(Inden-7-yloxy)methyl]morpholine Hydrochloride 9YM-08054, Indeloxazine Hydrochloride) and Its Derivatives with Potential Cerebral-Activating and Antidepressive Properties*, 33 CHEM. PHARM. BULL. 3766-6774 (1985).
1031	Silverman, R. B., *The Organic Chemistry of Drug Design and Drug Action*, ACADEMIC PRESS (1992).

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for *inter partes* review of U.S. Patent No. 7,282,860 (and accompanying Exhibits 1001-1031) by overnight courier (Federal Express or UPS), on this 7th day of October, 2016, on the Patent Owner at the correspondence address of the Patent Owner as follows:

BUCHANAN, INGERSOLL & ROONEY PC
P.O. Box 1404
Alexandria, VA 22313-1404

and at other addresses also likely to affect service:

Jack B. Blumenfeld
MORRIS, NICHOLS, ARSHT & TUNNELL LLP
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899

Respectfully,

Dated: October 7, 2016

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990