Filed on behalf of: Mylan Pharmaceuticals Inc.
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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. IPR2017-00041
Patent No. 7,157,456

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,157,456

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I. INTRODUCTION

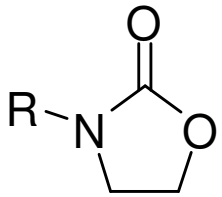
Mylan Pharmaceuticals Inc. ("Petitioner") requests *inter partes* review of U.S. Patent No. 7,157,456 to Straub *et al.* ("the '456 patent," EX1001), which issued on January 2, 2007. PTO records indicate the '456 patent is assigned to Bayer Intellectual Property GmbH ("Patent Owner"). This Petition demonstrates there is a reasonable likelihood that claims 1-8, 10-14, 16-22, 24, 26-28, and 30 of the '456 patent are unpatentable over prior art. Additional Petitions are being filed to address related patents that are terminally disclaimed over the '456 patent.

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. The '456 patent is directed to a class of compounds that bind to and inhibit "factor Xa." Because the crystal structure of factor Xa was known, the art had established the presence of dual binding pockets for inhibitors, termed the S1 and S4 pockets. *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. Many viewed factor Xa inhibitors as attractive drug targets for developing effective oral anticoagulants. *Id.*

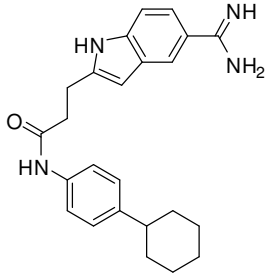
Oxazolidinones are a class of compounds comprising a 5-membered heterocycle (shown), and had long been known in the art to have various pharmacologic activities. EX1008.



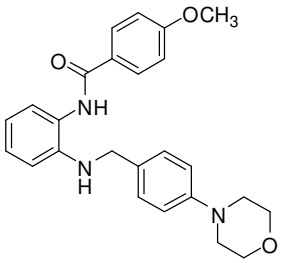
The art described oxazolidinone compounds that inhibited platelet aggregation, and were said to be useful in the treatment of thrombosis and myocardial infarction. *Id.* The "most advanced" oxazolidinone compound, linezolid, was known to have very desirable pharmacokinetic and pharmacologic properties, 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

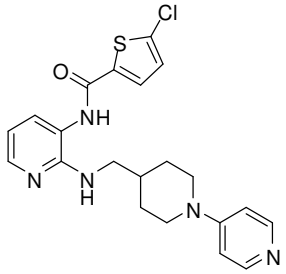
4’-cyclohexyl phenyl moiety found on Ewing’s Compound 49, also a factor Xa inhibitor. EX1007 at 782. Linezolid, Ewing Compound 49, and Examples 1 and 7 of the ’111 publication (shown below), have a two-arm shape and structure consistent with providing a binding moiety for each of the two known binding pockets of factor Xa. *Id.*; EX1008 at 626 (Compound 1); EX1009, 39:1-5; EX1010, 0043:1-5.



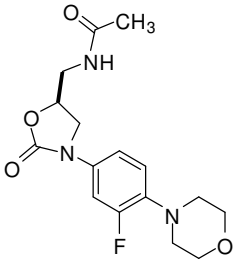
Ewing, EX1007 Compound 49



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 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 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 an 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 leave out linezolid's fluorine atom. This would also have made it possible to use a simpler and less expensive synthetic precursor.

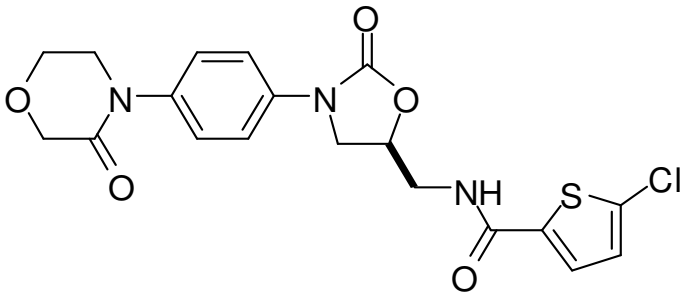
The assessment of known metabolites of a compound intended for pharmaceutical use is considered routine in the art. An assessment of a factor Xa inhibitor compound based on the structure of linezolid would have identified morpholine ring-opened metabolites, as were noted in Chiba (EX1011). The skilled 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 now known as rivaroxaban.

As factor Xa inhibitors were known to be useful in the treatment of thromboembolic disorders, the methods of treatment using a compound such as rivaroxaban for myocardial infarct, pulmonary embolism, or deep venous thrombosis would have likewise been readily apparent and obvious uses. Further, synthetic routes and formulations for linezolid were already well established in the art, and these could have been easily applied to the synthesis and formulation of rivaroxaban, making obvious the pharmaceutical compositions and synthetic routes recited in the remaining claims.

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

A. Brief Overview of the '456 Patent

The '456 patent is entitled "Substituted Oxazolidinones and their Use in the Field of Blood Coagulation." The '456 patent is directed to rivaroxaban, genuses of oxazoldidinones that include rivaroxaban, and methods of formulation, processes to make them, and methods to administer them to patients with various thromboembolic disorders. The patent describes these compounds as factor Xa inhibitors. Claims 6 and 16 are directed to rivaroxaban (structure shown below), or pharmaceutically acceptable salts or hydrates thereof:



Claims 1-5 and 10 recite genuses of oxazolidinones that include rivaroxaban. Claim 7 is directed to two different proccess alternatives (A and B) for synthesizing these compounds. Claims 11, 12, and 20-22 depend directly or indirectly from claim 7 and recite various process specifics.

Claims 8, 17, 18, and 19 recite pharmaceutical compositions comprising a compound of claims 1, 6, 14, and 16, respectively. Claims 27 and 28 recite pharmaceutical composition of enantiomerically pure rivaroxaban.

Claims 13, 24, 26, and 30 recite methods of treating myocardial infarct, pulmonary embolism, or deep venous thrombosis, by administering to a patient in need thereof an effective amount of the compounds or compositions recited in claims 1, 17, 18, or 28, respectively.

B. Brief Overview of the Prosecution History

U.S. Patent Application 10/181,051 ("the '051 application") was filed on June 24, 2002 as a national stage entry of PCT/EP00/12492, filed on December 11, 2000, and claims priority to German Application No. 199 62 924, filed on

December 24, 1999. The '051 application issued on January 2, 2007 as the '456 patent.

Following a restriction requirement and a subsequent election of a subset of oxazolidinones comprising a phenylmorpholinone subunit (EX1006 at 3463-64), the Office made no rejections over the prior art. Instead, prosecution was primarily directed to issues arising under 35 U.S.C. § 112, first and second paragraphs. In the Notice of Allowability, the Office stated that the closest prior art of record was Hutchinson *et al*., WO 97/09328, a reference not relied upon in the present Petition. *Id.* at 0693-0694. Hutchinson discloses a genus of oxazolidinone compounds. The examiner discussed Hutchinson only as a single reference, and only in terms of structural similarity to the claimed genus.

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 '456 patent under 35 U.S.C. § 102(b). Ewing teaches using anticoagulants for the treatment and prevention of thromboembolic disorders. EX1007 at 771; EX1002, ¶49; EX1003, ¶35. 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*.

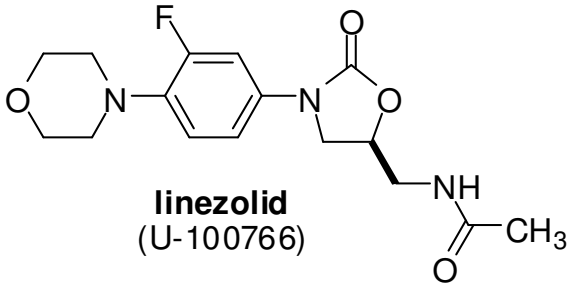
Ewing teaches that developing "safe and effective oral anticoagulants to replace warfarin" with strong pharmacokinetic profiles "may be particularly important since clinical data suggest that long-term and/or prophylactic anticoagulant therapy can provide a significant benefit over current standard treatment." *Id.* at 774; EX1003, ¶36. 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, ¶50; EX1003, ¶37. 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, ¶51.

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, ¶¶52-53. 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, ¶54; EX1003, ¶38. Ewing was not of record during examination of the '456 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 '456 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, ¶56; EX1003, ¶45. 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, ¶57.

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, ¶58. 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, ¶59; EX1003, ¶46. Riedl was not substantively discussed during examination of the '456 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.

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.

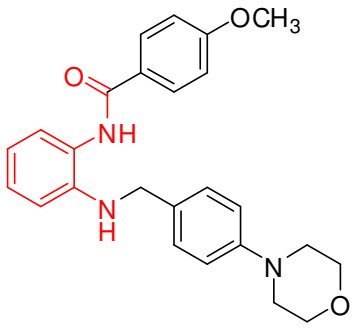
The '111 publication is also entitled to the December 23, 1998 priority date because at least one of its claims has adequate written description in the '778 application under pre-AIA 35 U.S.C. § 112, ¶1. *See Benitec Biopharma Limited v. Cold Spring Harbor Laboratory*, IPR2016-00016, Paper 8, at 7 (March 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, ¶¶66-68 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.

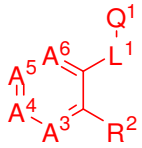
EX1009, 74:15-19; EX1010, 0078:15-19; EX1002, ¶66.

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



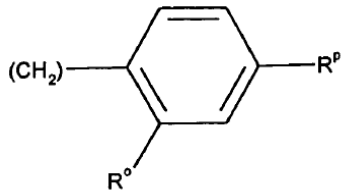
Example 1
The '111 Publication; EX1009
and the '778 Application; EX1010

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

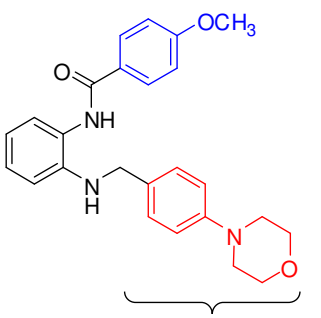
EX1009, 3:5-9; EX1010, 0007:5-9. Example 1 is a compound of formula I, shown above, when A^3, A^4, A^5 and A^6 are CR^3, CR^4, CR^5, and CR^6, respectively, wherein R^3, R^4, R^5, and R^6 are all identically hydrogen, L^1 is NHCO, Q^1 is phenyl, wherein the phenyl bears a 4-methoxy group, and R^2 is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



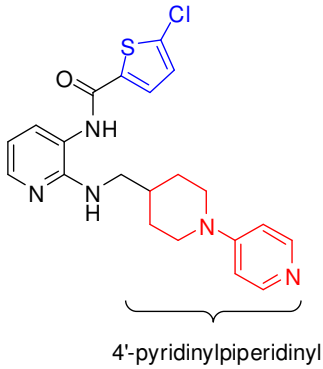
wherein R^o is hydrogen and R^p is a 4-morpholino group. EX1009, 3:5-6:10; EX1010, 0007:5-0010:10; EX1002, ¶67. Likewise, Examples 2-15 of the '111 publication are identical to Examples 2-15 of the '778 application and each is a compound of formula I. EX1009, 39:1-65:5; EX1010, 0043:1-0069:5; EX1002, ¶67. Thus, the '778 application provides written description support for at least one claim of the '111 publication. EX1002, ¶68.

The '111 publication teaches the role of factor Xa in the blood coagulation cascade, noting it as a target for anticoagulant therapy. EX1002, ¶62; EX1003, ¶41. 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, ¶61; EX1003, ¶¶40, 42. The '111 publication discloses 15 specific direct factor Xa inhibitors, each comprising one of three modules (*e.g.*, 4'-morpholinophenyl, 4'-pyridinylpiperidinyl, or 4'-

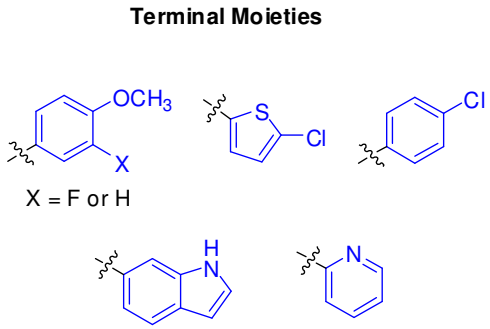
isopropylpiperidinyl) on one arm and one of a small set of terminal moieties on the other arm. EX1009, 39:1-65:5; EX1010, 0043:1-0069:5; EX1002, ¶¶63-64.



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, ¶65. The ’111 publication also describes assays commonly used to measure factor Xa activity. EX1009, 27:7; EX1010, 0031:7; EX1003, ¶43. The ’111 publication was not of record during examination of the ’456 patent.

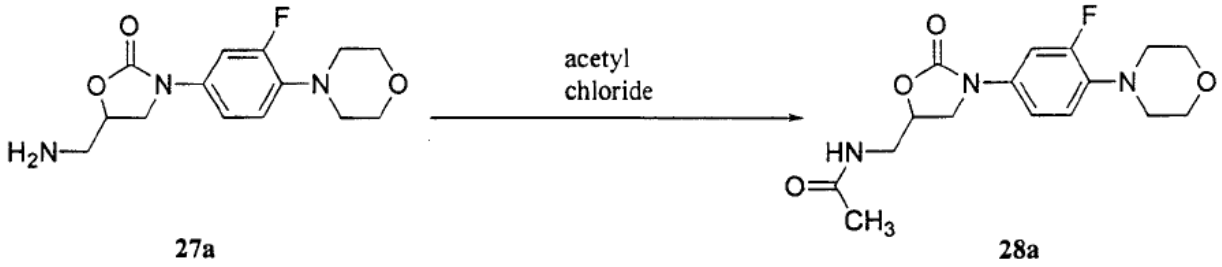
4) Chiba, K., *et al.*, *Absorption, Distribution, Metabolism, and Excretion of the Oxazolidinone Antibiotic Linezolid (PNU-100766) in the Sprague Dawly Rat*, ICAAC, SAN DIEGO, CA September 24-27, 1998 (“Chiba,” EX1011).

Chiba is prior art to the claims of the ’456 patent under 35 U.S.C. § 102(b). Chiba discloses pharmacokinetic properties of linezolid, including 100% oral

bioavailability. EX1011 at 39; EX1002, ¶71; EX1003, ¶48. 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. *Id.*; EX1002, ¶71. Chiba was not of record during examination of the '456 patent.

5) WO 99/37630, to Gordeev *et al.*, filed January 22, 1999 ("the '630 publication," EX1012).

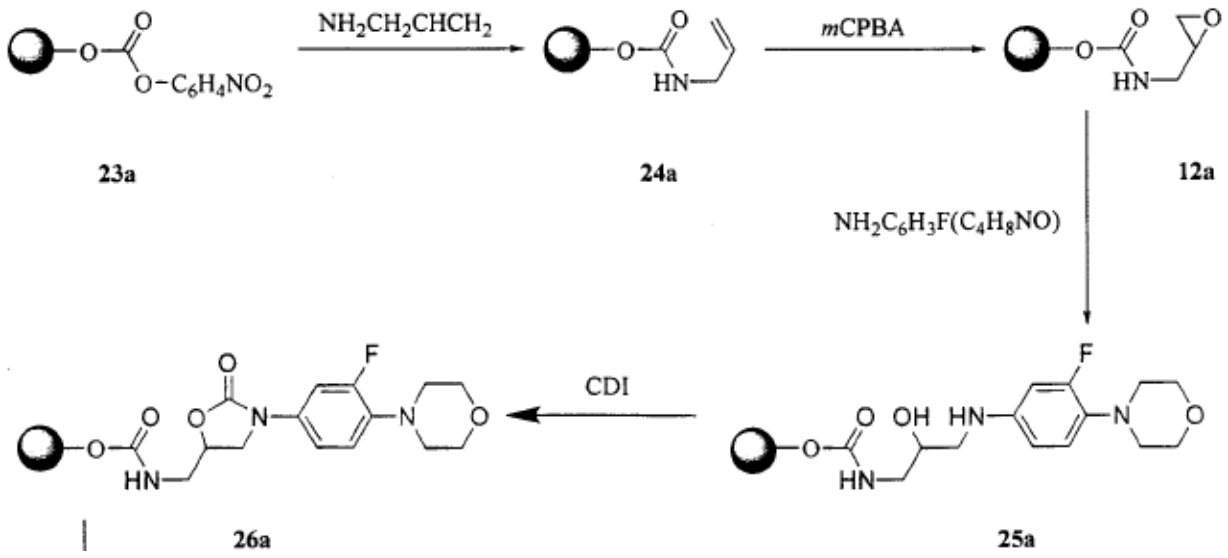
The '630 publication published on July 29, 1999 and qualifies as prior art under 35 U.S.C. 102(b). The '630 publication teaches acylation of the free amine precursor of linezolid with a carbonyl chloride, as shown below:



27a 28a

EX1012 at Figure 25, 0194; EX1002, ¶¶73-74.

The '630 publication also teaches that linezolid and its (*S*)-isomer may be synthesized via epoxidation of an alkene, followed by amine-based nucleophilic attack and subsequent cyclization with the phosgene equivalent CDI, as shown below:



EX1012 at Figure 25, 0194; EX1002, ¶¶74-75.

The '630 publication was not substantively discussed during examination of the '456 patent.

6) U.S. Patent No. 5,817,671 to Filla *et al.*, filed November 14, 1997 ("the '671 patent," EX1013).

The '671 patent issued on October 6, 1998 and qualifies as prior art under 35 U.S.C. 102(b). The '671 patent teaches the acylation of the free amine of a substituted 5-aminopyrrolo[3,2,-b]pyridine with 5-chloro-2-thiophenecarbonyl chloride, in pyridine, to yield the corresponding acylated derivative in high yield. EX1013 at 34:40-53; EX1002, ¶77. The '671 patent was not of record during examination of the '456 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 '456 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, ¶¶23-24; EX1003, ¶¶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; EX1005.

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 ¶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.

Dr. Jack Hirsh has over 50 years of experience in the field of treating blood coagulation disorders. EX1003, ¶1. Dr. Hirsh is currently a Professor Emeritus in the Department of Medicine at McMaster University in Ontario, Canada. EX1003, ¶3. Dr. Hirsh received a Bachelor of Medicine, Bachelor of Surgery degree, and a

subsequent M.D. from Melbourne University in 1958 and 1962, respectively. *Id.* at ¶2. Dr. Hirsh has authored or co-authored many peer-reviewed journal articles and book chapters and has been the recipient of numerous awards. *Id.* at ¶5. A summary of his education, experience, awards and honors, publications, and presentations is provided in his CV, submitted as EX1005; *see also*, EX1003, ¶¶ 1-6.

Dr. Hirsh is a well-qualified expert in the field of blood coagulation disorders, possessing the necessary scientific, technical, and other specialized knowledge to assist in an understanding of the evidence presented herein, as well as possessing 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. EX1005; *see also*, EX1003, ¶¶1-6.

II. GROUNDS FOR STANDING

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '456 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the '456 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 7,585,860 and 7,592,339 are being been filed by the present Petitioner as IPR2017-00042 and IPR2017-00043, respectively.

Petitioner and other entities are involved in litigation over the '456 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 '456 patent against Petitioner was served no earlier than October 9, 2015. Petitioner also identifies the following pending actions involving the '456 patent: *Bayer GmbH v. Breckenridge Pharmaceutical, Inc.*, No. 1:16-cv-00628, in the District of Delaware; and *Bayer GmbH v. InvaGen Pharmaceutical Inc.*, No. 1:16-cv-00064, 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

Petitioners request review of claims 1-8, 10-14, 16-22, 24, 26-28, and 30 of the '456 patent under 35 U.S.C. § 311 and AIA § 6 and that each of the claims be canceled as unpatentable:

Ground	Claims	Obvious under §103 over
1	1-6, 8, 10, 13-14, 16-19, 24, 26-28, and 30	Ewing, Riedl, the '111 publication, and Chiba
2	7, 11-12, and 20-22	Ewing, Riedl, the '111 publication, Chiba, the '630 publication, and the '671 patent

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, ¶25; EX1003, ¶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 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 ¶27. 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, ¶28. 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, ¶29. 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, ¶¶28-29.

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, ¶¶30-31. 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.

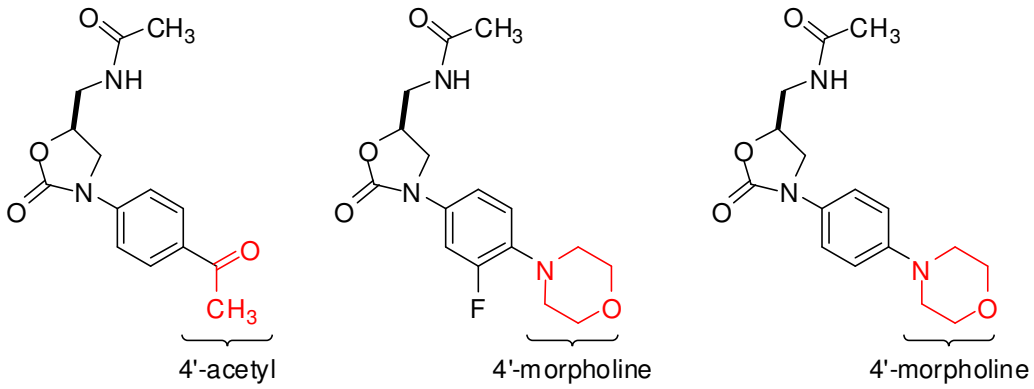
5,614,535, to Juraszyk *et al.*, filed August 18, 1995 ("Juraszyk," EX1020); EX1002, ¶32. Though linezolid entered clinical trials because of its antimicrobial properties, it was recognized that modifications to the two pendant groups off the oxazolidinone ring allowed for optimization of different therapeutic 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, ¶31.

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, ¶36. 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, ¶34. 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, ¶34. 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, ¶35.

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, ¶33. 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

Both linezolid and *des*-fluorolinezolid have the same terminal morpholine ring that was shown to have solved the toxicity concerns associated with the 4'-acetyl on Dup-721.

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, ¶37. 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, ¶38; SIGMA-ALDRICH PRODUCT CATALOGUE 1995-96 ("Sigma-Aldrich Catalogue," EX1024) at 529 and 733.

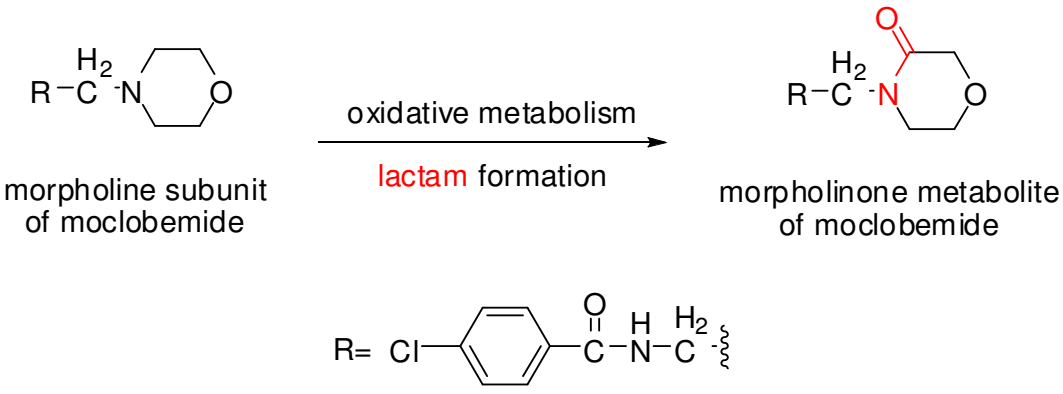
The 5-acetamidomethyl side chain of linezolid was also known to be an important locus for its antimicrobial activity. EX1002, ¶39. For example, Brickner

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 those in 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, ¶40.

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. 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, ¶41. 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,* 360 ACTA PSYCHIATR. SCAND. SUPPL. 87 (1990) ("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, ¶¶42-44. 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, ¶45.

Prior to December 1999, those in the art understood the contribution of thrombus formation to thromboembolic disorders. Carville, D. G. M., *et al., Thrombus precursor protein (TpP™): marker of thrombosis early in the*

pathogenesis of myocardial infarction, 42 CLIN. CHEM. (1996) 1537-41 ("Carville," EX1035); EX1003, ¶26. Carville teaches that a thrombus is an insoluble deposit made primarily of fibrin and blood cells, which may form an embolism (blockage) in the veins or arteries of the body. *Id.* at 1537. Carville notes that thrombi are known to contribute to myocardial infarction, as well as unstable angina and deep vein thrombosis. *Id.* at 1537-38; EX1003, ¶26-28.

Thus, anticoagulants were administered to treat and prevent acute ischemic syndromes and reduced the risk of thromboembolic events. Anand, S. S., *et al.*, *Long-Term Oral Anticoagulant Therapy in Patients with Unstable Angina or Suspected Non-Q-Wave Myocardial Infarction* 98 CIRCULATION (1998) 1064-1070 ("Anand," EX1035); EX1003, ¶29. Though anticoagulants were known to be effective in treating or preventing myocardial infarction, ischemic stroke, and unstable angina, anticoagulants such as heparin and warfarin were associated with a wide range of risks and potential complications. Taylor, F. C., *et al.*, *Evaluation of patients' knowledge about anticoagulant treatment*, 3 QUALITY IN HEALTH CARE 79-85, at 79 (1994) ("Taylor," EX1037); EX1003, ¶30. In addition to drug-drug interactions, food-drug interactions, and patient variability, bleeding was identified as the "most serious complication of oral anticoagulation in the prevention and treatment of thromboembolic complications." Palareti, G., *et al.*, *Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective*

collaborative study (ISCOAT) 348 LANCET 423-28 (1996) ("Palareti," EX1038) at 423; EX1003, ¶31.

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. EX1003, ¶32.

VII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. [Ground 1] Claims 1-6, 8, 10, 13-14, 16-19, 24, 26-28 and 30 are Obvious Under 35 U.S.C. § 103 Over Ewing, Riedl, the '111 Publication and Chiba.

Ground 1 establishes the obviousness of the compound known as rivaroxaban and claims which encompass this compound 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, ¶82.

The discussion below first addresses claim 16, directed to the rivaroxaban compound itself, whereas claims 1-6, and 10 recite genuses that include rivaroxaban. EX1002, ¶¶10, 81. Claims 8, 14, 17-19, and 27-28 recite pharmaceutical compositions that include rivaroxaban. Claims 13, 24, 26, and 30 recite using rivaroxaban, a genus of compounds that includes rivaroxaban, or formulations thereof, to treat thromboembolic disorders including myocardial

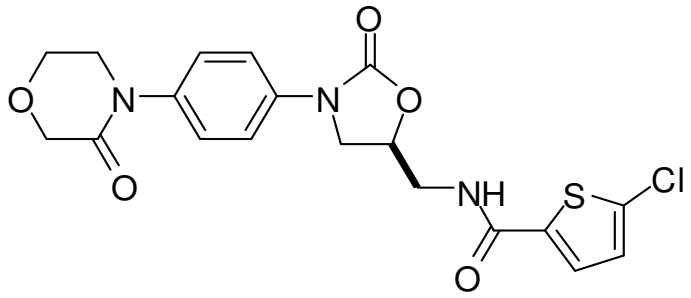
infarction, pulmonary embolism or deep vein thrombosis. Because the compound of claim 16, rivaroxaban, is within the scope of each of the claimed genuses, as established below, a demonstration of the obviousness of the compound of claim 16 is sufficient to render obvious the claimed genera. *In re Muchmore*, 433 F.2d 824, 824-25 (C.C.P.A. 1970) ("Since we agree with the board's conclusion of obviousness as to these narrow claims, the broader claims must likewise be obvious."); *accord Soverain Software LLC v. Victoria's Secret Direct Brand Mgmt., LLC*, 778 F.3d 1311, 1315 (Fed. Cir. 2015) (a broader claim cannot be valid if a narrower claim is invalid).

i. Claim 16

Claim 16 is drawn to a factor Xa inhibitor referred to herein for convenience as "rivaroxaban," and recites the following:

Claim 16:

A compound having the following formula:



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 ¶83.

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, ¶84. 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:

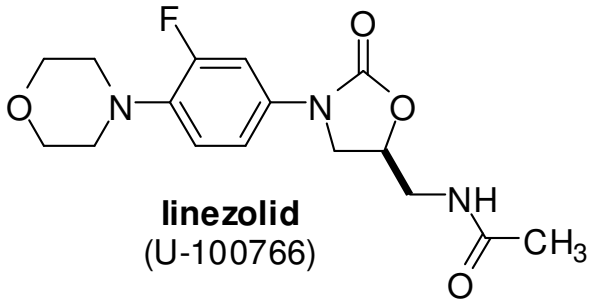
> Direct inhibition of factor Xa activity in the prothrombinase complex blocks the single physiological source of thrombin generation. Inhibiting the source of thrombin generation rather than its catalytic activity offers several potential mechanistic advantages that could afford superior anticoagulant 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, ¶84.

Ewing describes compounds that act as factor Xa inhibitors. They generally comprise two "arms" connected via a linker scaffold. EX1007 at 777-83; EX1002, ¶85. 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, ¶85. 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, ¶85. 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, ¶85.

Linezolid is an oxazolidinone known to have 100% oral bioavailability and low toxicity. EX1008 at 625-26; EX1011 at 39; EX1002, ¶86. The structure of linezolid is shown below:



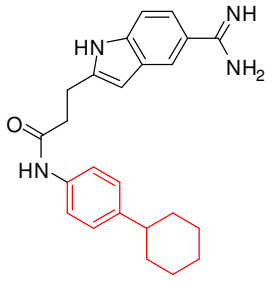
linezolid
(U-100766)

EX1008 at 626.

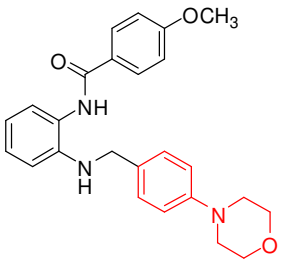
By December, 1999, linezolid had entered Phase III clinical trials based on its antibiotic activity, and had been established to possess a wide array of desirable pharmacokinetic properties. EX1008 at 626; EX1002, ¶87. Linezolid's high volume of distribution, rapid absorption after oral dosing, and relatively 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, ¶88.

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, ¶89.

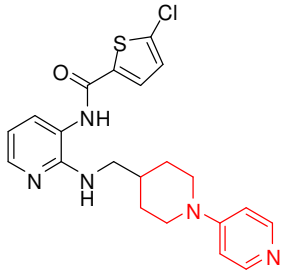
Many factor Xa inhibitors taught in the art had the same general size and shape as linezolid, as illustrated below:



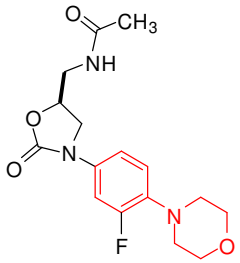
Compound 49
Ewing, EX1007



Example 1
The '111 Publication; EX1009



Example 7
The '111 Publication; EX1009



Linezolid
Riedl, EX1008

EX1002; ¶90. 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, ¶91 (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, ¶93. As explained by Dr. Lepore, such structural changes would ideally also avoid unnecessary synthetic steps and additional costs. EX1002, ¶¶93-94.

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, ¶92. 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, ¶95.

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 undesired antimicrobial activity. 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, ¶95, 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, ¶95; EX1024 at 529 and 733 (noting a 7-fold decrease in cost of 4-fluoro-nitrobenzene as compared to 3,4-difluoro-nitrobenzene).

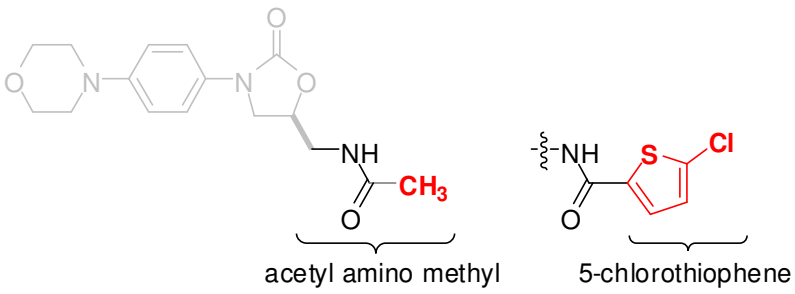
As *des*-fluorolinezolid had been previously synthesized in the art, the skilled artisan would have a reasonable expectation of producing this 4'-morpholinophenyl bioisostere of linezolid using the less expensive reagent. EX1022 at 1235 (Compounds 3a (linezolid) and 3b (*des*-fluorolinezolid) in Table I); EX1002, ¶96.

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, ¶97. 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.

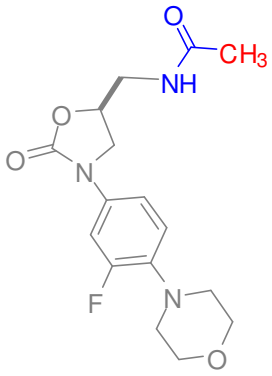
EX1008 at 629; EX1002, ¶98.



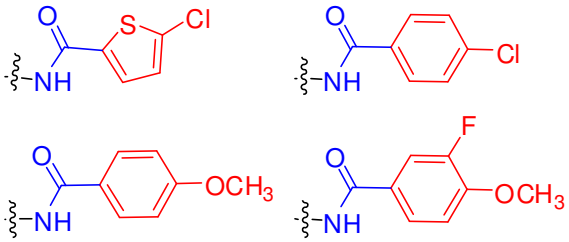
To increase selectivity of linezolid as a factor Xa inhibitor (by, *e.g.*, increasing factor Xa binding affinity and decreasing antibacterial activity), the skilled artisan would have looked to replace the terminal methyl moiety that contributes to the unneeded antibacterial activity with a functional group that was known to bind to factor Xa. *See* EX1008 at 629; EX1002, ¶¶98-99.

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, ¶¶98-99. 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, ¶99. 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, ¶¶99-100.

The '111 publication describes a handful of 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:



Linezolid
Riedl, EX1008

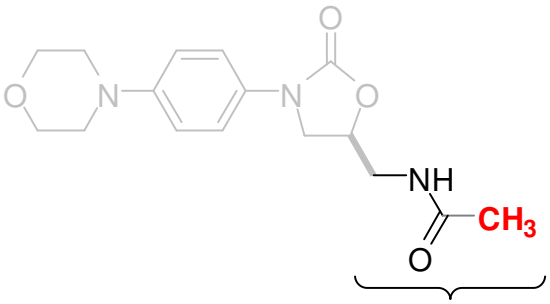


Factor Xa Terminal Amides
The '111 Publication, EX1009

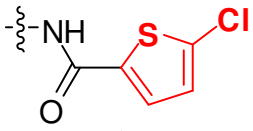
The skilled artisan would have had reason to evaluate each of these planar aromatic factor Xa binding moieties on a *des*-fluoro bioisostere of linezolid because they are taught by the '111 publication to be factor Xa binding moieties and to be present on factor Xa binding inhibitors that are otherwise structurally similar to linezolid. EX1002, ¶¶100-01. 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, ¶68.

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, ¶102. Each of these moieties was known to bind factor Xa, and the chemistry required to make the substitution was routine. EX1002, ¶100. Further, 5-chlorothiophene moieties were known in the art to be common terminal moieties in 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, ¶102.



5-methylamino acyl group



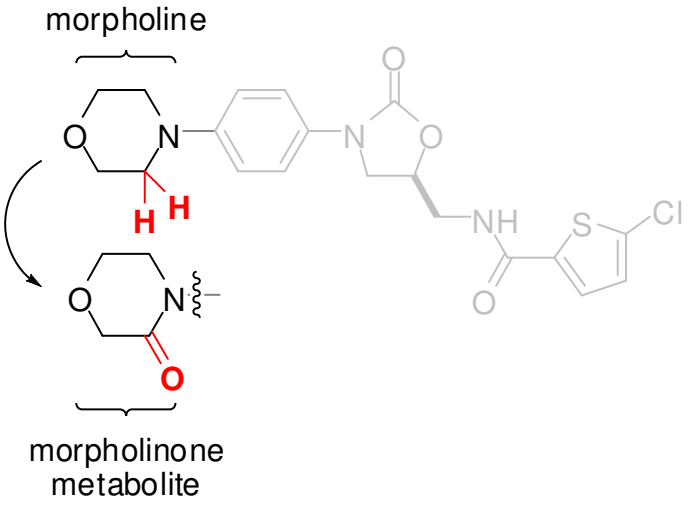
5-chlorothiophene; Example 7, The '111 publication, EX1009

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, ¶103. 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, ¶103. 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, ¶¶104-05 (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, ¶105.



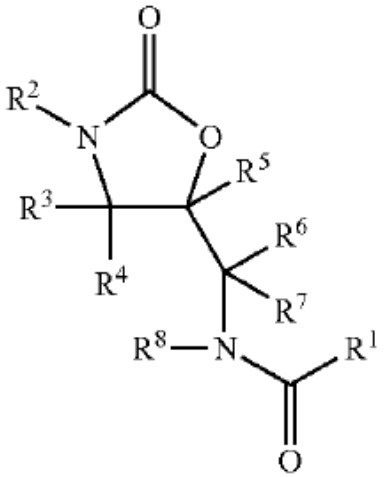
As noted by Dr. Lepore in his declaration, the skilled artisan would have produced the morpholinone analogue using any one of several standard synthetic protocols. *See*, *e.g.*, Kojima, T., *et al.*, *Synthesis of (±)-2-[(Inden-7-yloxy)methyl]morpholine Hydrochloride 9YM-08054, Indeloxazine Hydrochloride) 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, ¶104. The morpholinone derivative of 5-chlorothiophene *des*-fluorolinezolid, is identical to the structure recited in claim 16.

Based on the foregoing evidence and explanation, claim 16 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, ¶106.

ii. Claims 1-6 and 10

Claims 1-6 and 10 each recite a genus of compounds that includes the structure recited in claim 16. Because the structure recited in claim 16 is a species of the genuses recited in claims 1-6 and 10, the genuses recited in claims 1-6 and 10 would have been obvious for the same reasons that the species recited in claim 16 would have been obvious. *Soverain Software LLC*, 778 F.3d at 1315; *Muchmore*, 433 F.2d at 824. The discussion below identifies the criteria for each of claims 1-6 and 10 that establish the genuses of those claims includes the species of claim 16. For example, claim 1 recites:

1. A compound of the formula (I)



characterized in that

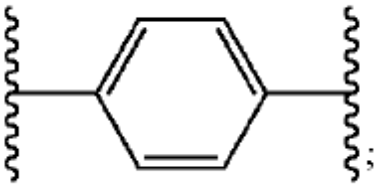
R^1 represents an optionally benzo-fused thiophene group which may optionally be mono- or polysubstituted by a radical

selected from the group consisting of halogen; cyano; nitro; amino; aminomethyl; (C_1-C_8)-alkyl which for its part may optionally be mono- or polysubstituted by halogen; (C_3-C_7)-cycloalkyl; (C_1-C_8)-alkoxy; imidazolinyl; —C(==NH)NH_2; carbamoyl; and mono- and di-(C_1-C_4)-alkyl-aminocarbonyl,

R^2 represents

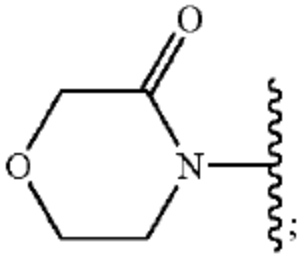
D-M-A-,

where



the radical "A" represents optionally substituted

the radical "D" represents



and

the radical "M" represents a covalent bond;

where

the group "A" defined above may optionally be mono- or polysubstituted by a radical selected from the group

consisting of halogen; trifluoromethyl; cyano; nitro; carbamoyl; (C_1-C_6)-alkanoyl; —OR^{30}; —$NR^{30}R^{31}$, and (C_1-C_6)-alkyl

where

R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, or C(O)R^{33},

where

R^{33} represents (C_1-C_4)-aminoalkyl, or (C_1-C_8)-alkyl,

R^3, R^4, R^5, R^6, R^7, and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

or a pharmaceutically acceptable salt or hydrate thereof

except for compounds of the formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7, and R^8 are each simultaneously hydrogen.

The genus recited in claim 1 includes the species recited in claim 16 with the following group selections: R^1 is a 5-chloro-2-thiophene radical, R^2 is DMA, where A is a phenyl ring, D is a morpholinone, and M is a covalent bond, and R^3, R^4, R^5, R^6, R^7, and R^8 are all identically hydrogen. EX1002, ¶107.

Claim 2 depends from claim 1 and limits the genus of claim 1 by removing the "optionally benzo-fused" claim limitation, as well as limiting the functional group substitutions on the R^1 thiophene group to include only mono or

polysubstititution with "halogen, amino, aminomethyl or (C1-C8)-alkyl, where the (C1-C8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen." EX1001 at 126:24-28; EX1002, ¶¶107-08. As noted above with regard to claim 1, the species recited in claim 16 is encompassed by the genus recited in claim 2 with the following group elections: R^1 is a 5-chloro-2-thiophene radical, R^2 is DMA, where A is a phenyl ring, D is a morpholinone, and M is a covalent bond, and R^3, R^4, R^5, R^6, R^7, and R^8 are all identically hydrogen. EX1002, ¶108.

Claim 3 depends from claim 1 and again limits the substitution pattern on the R1 thiophene moiety, reciting that the thiophene "may optionally be mono- or polysubstituted by halogen or by (C_1-C_8)-alkyl, where the (C_1-C_8)-alkyl for its part may optionally be mono- or polysubstituted by halogen," as well as limiting the optional substitution on the R^2, Group A phenyl ring. *Id.* at 127:6-49. The genus recited in claim 3 includes the species recited in claim 16 with the following group selections: R^1 is a 5-chloro-2-thiophene radical, R^2 is DMA, where A is a phenyl ring, D is a morpholinone, and M is a covalent bond, and R^3, R^4, R^5, R^6, R^7, and R^8 are all identically hydrogen. EX1002, ¶108.

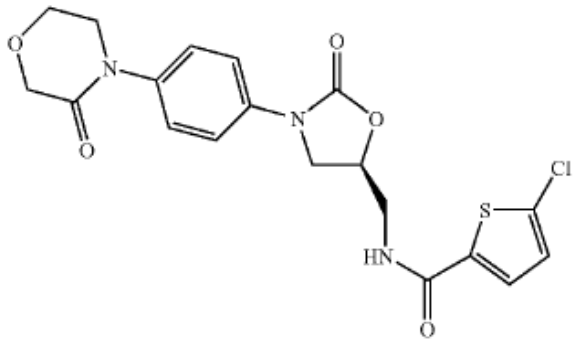
Claim 4 depends from claim 1 and further limits the genus described in claim 1 in that the thiophene of R^1 "may optionally substituted in the 5-position by a radical selected from the group consisting of chlorine, bromine, methyl and trifluoromethyl." *Id.* at 127: 52-55. The species recited in claim 16 is encompassed

within the genus recited in claim 4 with the following group elections: R^1 is a 5-chloro-2-thiophene radical, R^2 is DMA, where A is a phenyl ring, D is a morpholinone, and M is a covalent bond, and R^3, R^4, R^5, R^6, R^7, and R^8 are all identically hydrogen. EX1002, ¶109.

Claim 5 depends from claim 1 and further limits the genus of claim 1 in restricting substitution on the R^2 Group A phenyl ring to occur at the meta position with respect to the point of attachment to the oxazolidinone, and to one of the group consisting of "fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano." The genus recited in claim 5 includes the species recited in claim 16 with the following group selections: R^1 is a 5-chloro-2-thiophene radical, R^2 is DMA, where A is a phenyl ring, D is a morpholinone, and M is a covalent bond, and R^3, R^4, R^5, R^6, R^7, and R^8 are all identically hydrogen. EX1002, ¶109.

Claim 6 is an independent claim and recites:

6. The compound having the following formula

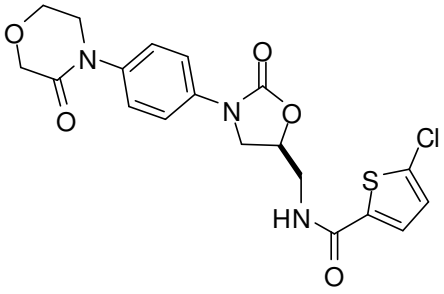
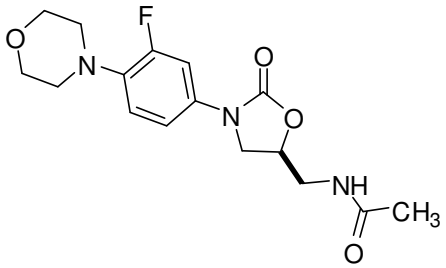


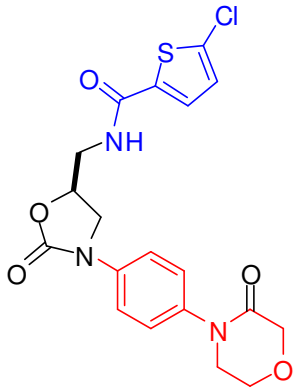
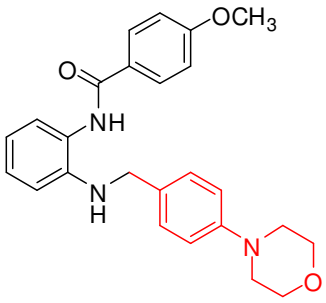
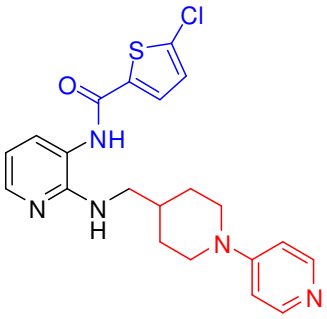
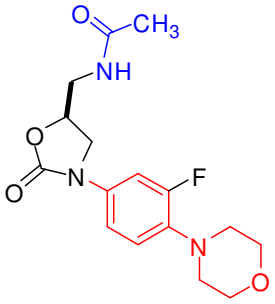
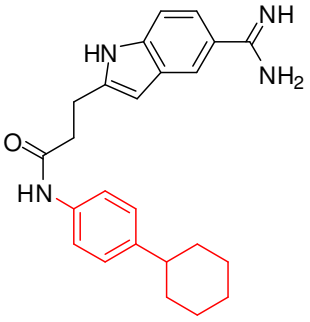
or a pharmaceutically acceptable salt or hydrate thereof.

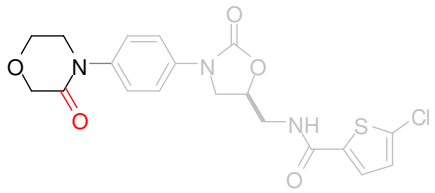
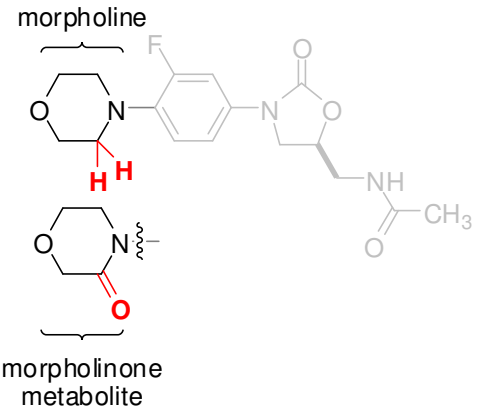
Claim 6 recites the identical structure recited in claim 16. The genus of rivaroxaban and its pharmaceutically acceptable salts and hydrates recited in claim 6 includes the species recited in claim 16. EX1002, ¶110.

Claim 10 recites, "The compound of claim 2 or 3 wherein R^1 represents an optionally substituted 2-thiophene group, and wherein said halogen substituent is chlorine or bromine, and said (C_1-C_8)-alkyl substituent is methyl, where the methyl radical for its part optionally may be mono- or polysubstituted by fluorine." *Id.* at 132:1-6. As the compound of claim 16 comprises a 5-chlorothiophene group for R^1, and as the (C1-C8) alkyl substituent recited in claim 10 is optional in both claims 2 and 3, the genus recited in claim 10 includes the species recited in claim 16. EX1002, ¶108.

Thus, each of claims 1-6 and 10 would have been obvious for the same reasons that claim 16 would have been obvious. The claim chart below uses claim 16 as a representative claim and identifies where the specific elements of this claim are found in the asserted references and in the declaration of Dr. Lepore, utilizing claim 16 as an exemplary claim for claims 1-6 and 10.

Exemplary '456 Patent Claims	Obvious over Ewing, Riedl, the '111 publication, and Chiba
16. A compound having the following formula:  	"In Phase III clinical trials, linezolid appears to be highly efficacious and well-tolerated." EX1008 at 630; EX1002, ¶88. "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, ¶89. "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, ¶98. "absolute bioavailability was 109%." EX1011 at 39; EX1002, ¶71.

The compound of claim 16: 	"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, ¶103; *see also* EX1029 at 89 (providing a "general pattern" of metabolic morpholine oxidation). 

iii. Claims 14 and 27

Claim 14 depends from independent claim 6 of the '456 patent, which recites rivaroxaban or a corresponding salt or hydrate thereof. Claim 14 adds the limitation that the compound is both purified and isolated. Independent claim 27 recites a composition comprising rivaroxaban or a salt or hydrate thereof, "wherein the composition is substantially free of the enantiomer of the compound of formula (a) and substantially free of the salts and hydrates of the enantiomer" of rivaroxaban. EX1001 at 134:8:33.

As discussed above with regard to claim 16, the structure of rivaroxaban would have been obvious to a person of ordinary skill in the art in light of the combined prior art teachings of Ewing, Riedl, the '111 publication, and Chiba. The

purification and isolation of this compound, including purification from the compound's own enantiomer, would have been routine prior to December 1999. EX1002, ¶¶110-11. For example, each factor Xa inhibitor described by the '111 publication is noted to be "purified by chromatography" and isolated to give a final overall reaction yield. *See*, *e.*g., EX1009, 39:14-17; EX1010, 0043:14-17. The '111 publication also notes that the disclosed factor Xa inhibitors may be present "in the form of an individual enantiomer . . . it being well known in the art how to prepare or isolate particular forms." EX1009, 9:14-17; EX1010, 0013:14-17; EX1002, ¶114. The '111 publication continues by noting that enantiomers may be separated "by resolving the racemic mixtures. This resolution can be carried out by derivatization with a chiral reagent followed by chromatography or repeated crystallization. Removal of the chiral auxiliary by standard methods affords substantially optically pure isomers of the compounds[.]" EX1009, 18:20-25; EX1010, 0022:20-25; EX1002, ¶¶114-15.

As rivaroxaban would have been prepared as a factor Xa inhibitor and thus with the specific purpose of serving as a pharmaceutical, it would have been additionally obvious to purify and isolate the compound, including identifying and purifying the separate enantiomer (and salts or hydrates thereof) to evaluate if one enantiomer has more favorable properties than the other. EX1002, ¶114, citing EX1009 and EX1010. Thus, the purification and isolation of rivaroxaban as recited

in each of claims 14 and 27 of the '456 patent would have been obvious in view of the routine practices taught by the '111 publication and general knowledge of a person of ordinary skill in the art. EX1002, ¶114.

iv. Claims 8, 17-19, 28

Claim 8 depends from claim 1 and recites:

> **8. A pharmaceutical composition comprising at least one compound of the formula (I) according to claim 1 and one or more pharmacologically acceptable auxiliaries or excipients.**

Claims 17-19 and 28 depend respectively from claims 6, 14, 16, and 27, and similarly recite rivaroxaban in a pharmaceutical composition comprising one or more pharmacologically acceptable auxiliaries or excipients. As discussed above in the context of claims 1, 6, 14, 16, and 27, the compound rivaroxaban would have been obvious in view of the combined teachings of the prior art Ewing, Riedl, the '111 publication, and Chiba references. As the skilled artisan would have developed rivaroxaban as a factor Xa inhibitor with the specific purpose of serving as a pharmaceutical, the artisan would have been motivated to formulate rivaroxaban in a pharmaceutical composition, including a formulation comprising one or more auxiliaries or excipients. EX1002, ¶¶112-13, 115.

Moreover, pharmaceutical formulations of oxazolidinones were already known in the art. For example, Riedl notes the preparation of oxazolidinones for

administration to patients, highlighting "an appropriate iv formulation already in use" for linezolid. EX1008 at 627. The '111 publication similarly teaches the routine formulation of factor Xa inhibitors using one or more pharmacologically acceptable auxiliaries or excipients. EX1009, 21:31-22:2; EX1010, 25:31-26:2. Based on the prior art disclosure of formulations for linezolid and the structurally similar factor Xa inhibitors from the '111 publication, the skilled artisan would have had a reasonable expectation of success in formulating rivaroxaban in a pharmaceutical composition comprising at least one excipient or auxiliary agent as recited in claims 8, 17-19, and 28. EX1002 at ¶¶112-13, 115.

v. Claims 13, 24, 26, and 30

Claims 13, 24, 26, and 30 depend respectively from claims 1, 17, 18, and 28 and recite methods of treating thromboembolic disorders, including myocardial infarct, pulmonary embolism, and deep venous thrombosis, via the administration of rivaroxaban or the genus that includes rivaroxaban (claim 13) to a patient in need thereof. For example, claims 13 and 24 specifically recite:

Claim 13:

A method for the treatment of a thromboembolic disorder comprising administering to a patient in need thereof an effective amount of a compound of claim 1, wherein the thromboembolic disorder is myocardial infarct, pulmonary embolism or deep venous thrombosis.

Claim 24:

A method for the treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 17 to a patient in need thereof.

Claims 26 and 30 are identical to claim 24, except they depend from claims 18 and 28, respectively.

It was well established prior to December 1999 that factor Xa inhibitors were useful as anticoagulants for the treatment and prevention of thromboembolic disorders. As noted by Dr. Hirsh, Ewing highlights antithrombotic agents as "crucial component[s] in both acute intervention procedures and chronic prevention strategies for treatment and management" of thromboembolic-based disorders, including myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism. EX1007 at 771; EX1036 at 1068; EX1003, ¶¶53-54. Ewing specifically urges the development of factor Xa inhibitors to provide anticoagulants for the treatment and prevention of these disorders. EX1007 at 771; EX1003, ¶55.

The '111 publication similarly teaches "inhibitors of factor Xa . . . are useful anticoagulants in mammals," and can be used "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, 1:9-20; EX1010, 0005:5-16; EX1003, ¶56.

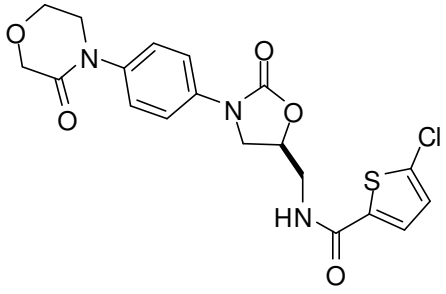
As discussed above with regard to claim 16, it would have been obvious to develop the compound rivaroxaban, which is the compound incorporated in claims 24, 26 and 30 and is encompassed by the genus incorporated in claim 13, as a factor Xa inhibitor. As rivaroxaban would have been obvious to a person of ordinary skill seeking to develop a factor Xa inhibitor in view of Ewing, Riedl, the '111 publication, and Chiba, administering an effective amount of rivaroxaban to a patient in need thereof for the treatment of a thromboembolic disorder, including myocardial infarct, pulmonary embolism or deep venous thrombosis, as recited in claims 13, 24, 26, and 30 would have been obvious to the skilled artisan.

As rivaroxaban would have been developed by the skilled artisan with the purpose of creating a factor Xa inhibitor, and in view of the teachings of Ewing and the '111 publication that factor Xa inhibitors are useful in the treatment of thromboembolic disorders such as myocardial infarction, pulmonary embolism, and deep venous thrombosis, a person of ordinary skill would have a reasonable expectation that an effective amount of factor Xa inhibitor such as rivaroxaban would be effective in the treatment of such disorders. EX1003, ¶¶57-58.

Determining an effective amount of a factor Xa inhibitor such as rivaroxaban would have been a routine matter to a person of ordinary skill prior to

December 1999. EX1003, ¶57. For example, the '111 publication teaches, "an effective and orally active factor Xa inhibitor may be evaluated in one or more of the following assays or in other standard assays known to those in the art." EX1009, 27:4-7; EX1010, 0031:4-7. The '111 publication also describes the routine nature of determining an appropriate dosage level of a factor Xa inhibitor for a given patient and indication. EX1009, 20:27-32; EX1010, 0024:27-32*; see also*, EX1009, 20:33-21:7; EX1010, 0024:33-0025:7. Thus, determining an effective dose of rivaroxaban would have been a routine matter for the skilled artisan. EX1003, ¶57.

For the reasons discussed above, the methods of treatment recited in claims 13, 24, 26, and 30 would have been obvious in view of the teachings of Ewing, Riedl, the '111 publication and Chiba. The claim chart below uses claim 30 as a representative for claims 13, 24, and 26, and shows where the specific elements of these claims are found in the asserted references.

Exemplary '456 Patent Claims	**Obvious over Ewing, Riedel, the '111 publication, and Chiba**
27. A composition comprising a compound having formula (a):  (a)	*See* structural obviousness claim chart, above.

or a pharmaceutically acceptable salt or hydrate thereof,	
[27a.] wherein the composition is substantially free of the enantiomer of the compound of formula (a) and substantially free of the salts and hydrates of the enantiomer of the compound of formula (a).	"[I]somers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. This resolution can be carried out by derivatization with a chiral reagent followed by chromatography or repeated crystallization. Removal of the chiral auxiliary by standard methods affords substantially optically pure isomers of the compounds[.]" EX1009 at 18:19-25; EX1010 at 0022:19-25; EX1002, ¶¶114-15.
28. A pharmaceutical composition comprising the composition of claim 27 and one or more pharmacologically acceptable auxiliaries or excipients.	"A pharmaceutical composition of the invention comprises an effective factor Xa inhibiting amount of a compound of formula I in association with a pharmaceutically acceptable carrier, excipient or diluent." EX1009 at 21:31-22:2; EX1010 at 0025:31-0026:2; EX1002, ¶¶114-15.
30. A method for the treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering . . . to a patient in need thereof.	"[I]nhibitors of factor Xa . . . are useful anticoagulants in mammals," and can be used "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, 1:9-20; EX1010, 0005:12-16; EX1003, ¶56. "**Myocardial infarction**, stroke, **deep vein thrombosis** and **pulmonary embolism** accounted for approximately 2 million deaths in the United States in 1996. The formation

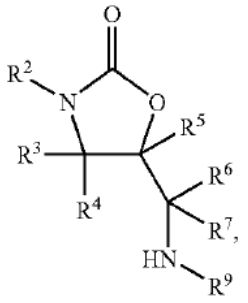
	of an occlusive thrombus is causally related to the pathology of these conditions. As such, antithrombotic therapy is a crucial component in both acute intervention procedures and chronic prevention strategies for **treatment and management of these diseases**." EX1007 at 771; EX1003, ¶¶53-55.
[30a]. . . . an effective amount . . .	"[A]n effective and orally active factor Xa inhibitor may be evaluated in one or more of the following assays or in other standard assays known to those in the art." EX1009 at 27:4-7; EX1010 at 0031:4-7; *see also*, EX1009 at 20:27-32; EX1010 at 0024:27-32; EX1002, ¶68; EX1003, ¶57.
[30b] . . . . of the composition of claim 28 . . . [.]	*See* discussion of claim 28, above.

B. [Ground 2] Claims 7, 11-12, and 20-22 are Obvious under 35 U.S.C. § 103 over Ewing, Riedl, the '111 Publication, Chiba, the '630 Publication, and the '671 patent.

Ground 2 addresses the claimed synthesis processes for making rivaroxaban. Claim 7 of the '456 patent depends from claim 1 and recites two alternative processes, A and B, for preparing a substituted oxazolidinone as defined by claim 1. Claim 20 depends from claim 7 and limits the claim to preparing rivaroxaban. EX1002, ¶¶117-18. While Petitioner need only demonstrate the obviousness of either one of the two process alternatives, both processes are conventional reactions known in the art to have been previously used in the synthesis of

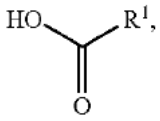
oxazolidinones, as evidenced by the teachings of the '630 publication regarding the synthesis of linezolid. EX1012 at Figure 25, 0194; *see also* EX1021 at 183; EX1002, ¶117. Process alternative A of claim 7 is reproduced below:

> **7. Process for preparing the substituted oxazolidinone of claim 1, where either according to a process alterative (A) a compound of the formula (II)**



in which

the radicals R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in claim 1 is reacted with carboxylic acid of the formula (III)

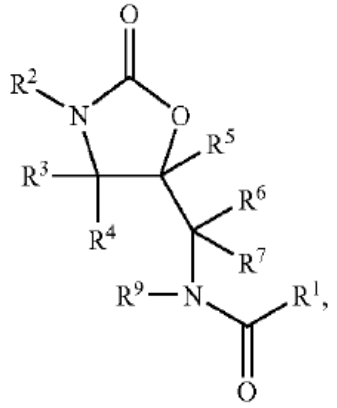


in which

the radical R^1 is as defined in claim 1,

or else with a corresponding carbonyl halide, or else with a corresponding symmetric or mixed carboxylic anhydride of the carboxylic acid of the formula (III) defined above, in an inert solvent, if appropriate in the presence of an activating or coupling agent and/or a base, to give a compound of the

formula (I)



in which

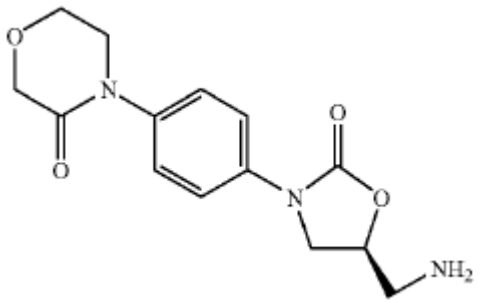
the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in claim 1, . . .

Claims 11 depends from claim 7 and recites that the "corresponding carbonyl halide of carboxylic acid (III) [in Process A] is a carbonyl chloride."

Claim 21 recites:

Claim 21:

A process for the preparation of the compound of claim 6 comprising reacting a compound of the following formula



with 5-chlorothiophene-2-carbonyl chloride in an inert solvent to prepare the compound of claim 6.

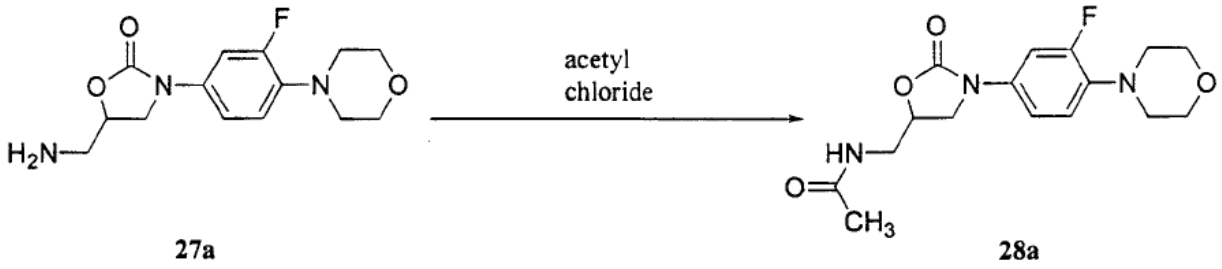
Each aspect of Process A as recited in claims 7, 11, and 20-22 is disclosed by the '630 publication for the acylation of the amine on the 5-position of the oxazolidinone of linezolid. Claim 22 specifies pyridine as the inert solvent of claim 21.

As discussed above in the context of Ground 1, the structure of rivaroxaban would have been obvious in light of the teachings of Ewing, Riedl, the '111 publication and Chiba. The skilled artisan would look to the known synthetic routes for linezolid to identify obvious synthetic routes for rivaroxaban, because linezolid and rivaroxaban share the same oxazolidinone ring and methyl amide structure. Moreover, the known synthetic pathway for linezolid provides ample opportunity to apply these synthetic routes to the synthesis of rivaroxaban with only minor substitutions of widely available reagents. EX1002, ¶119.

In synthesizing rivaroxaban, the skilled artisan readily would have used the same acylation reaction taught in the synthesis of linezolid by simply substituting 5-chlorothiophene-2-carbonyl chloride for the acyl chloride used in linezolid's synthesis. This substitution would have been very straightforward because the amide linkage common to rivaroxaban and linezolid allows for the same chemistry to be used at this sight. EX1002, ¶119. Indeed, this acylation reaction, the same reaction described in claim 21 of the '456 patent, is a textbook reaction taught in

introductory organic textbooks. Atkins, R.C. *et al.*, *Organic Chemistry A Brief Course*, MCGRAW HILL (1997) ("Atkins," EX1032) at 362-64; EX1002, ¶118.

The '630 publication describes a routine preparation of linezolid, in which free amine (27a) is acylated by the carbonyl chloride known as acetyl chloride to yield linezolid (compound 28a):



27a 28a

EX1012 at 34:26-27 ("Addition of acetyl chloride to 27a produce acetamide 28a"); EX1021 at 194; EX1002, ¶119. This reaction proceeds in the presence of dichloromethane, an inert solvent, as recited in claim 21 of the '456 patent. *Id.* at 122:25-123:8; EX1002, ¶118. The '630 publication teaches that the acylation reaction proceeds without regard to stereochemistry at the 5-oxazolidinone position. EX1002, ¶119.

This same reaction was known to proceed as well in another inert solvent, pyridine. EX1013, 34:40-53. The '671 patent describes the acylation reaction of 5-chloro-2-thiophenecarbonyl chloride with a substituted 5-aminopyrrolo[3,2,-b]pyridine in the inert solvent pyridine. EX1013, 34:40-53; EX1002, ¶121. As the acylation reaction with 5-chloro-2-thiophenecarbonyl chloride is taught by the '671

patent to proceed in pyridine, a person of ordinary skill would have readily used 5-chloro-2-thiophenecarbonyl chloride in pyridine to synthesize rivaroxaban. EX1002, ¶¶122-23.

As explained by Dr. Lepore, the skilled artisan would have had a reasonable expectation of success in carrying out this simple acylation reaction between the free amine precursor of rivaroxaban and 5-chlorothiophene-2-carbonyl chloride. EX1002, ¶120. For example, Brickner I notes that the asymmetric synthesis of linezolid "is applicable to the synthesis of widely divergent" oxazolidinones, and describes multiple acylation reactions of this type. EX1023 at 674. International Patent Application WO 98/54161 published December 3, 1998 ("the '161 PCT," EX1033) describes acylation of linezolid's free amine with propionyl chloride (*id.* at 54:14-29), fluoroacetyl chloride (*id.* at 57:5-19), and methyl malonyl chloride (*id.* at 60:30-61:14); as well as the acylation of a Boc-protected piperazine analogue of linezolid with benzyl chloroformate. EX1002, ¶122. These varied acylation reactions illustrate that the 5-methylamine oxazolidinone scaffold shared by linezolid and rivaroxaban was indeed known to be easily modified and that acylation reactions involving halogenated aromatic rings were known. *Id.* at 74:14-29; EX1002, ¶122.

In view of the teachings of the '630 publication and the '671 patent that an acylation reaction can be accomplished using 5-chloro-2-thiophenecarbonyl in

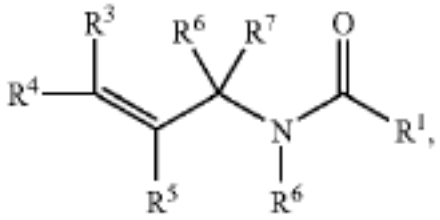
pyridine, using a carbonyl halide (as recited in claim 7), including a carbonyl chloride (claim 11), including 5-chloro-2-thiophenecarbonyl chloride (claim 21), in pyridine (claim 22), to access the structure of rivaroxaban (claim 20) would have been obvious. EX1002, ¶123. These teachings render obvious the process alternative A found in claim 7, and render each of claim 7, 11, and 20-22 obvious.

Process alternative B, recited in claim 7 of the '456 patent, describes a synthetic scheme known in the prior art for the construction of the oxazolidinone scaffold shared by linezolid and rivaroxaban. The Process B alternative of claim 7 is shown below:

(Claim 7 continued)

. . .a compound of the formula (IV)

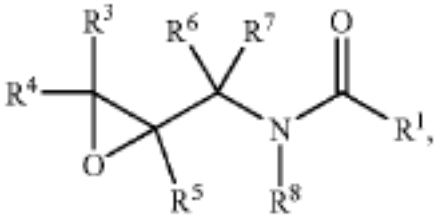
(IV)



in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in claim 1, is converted, using a suitable selective oxidizing agent in an inert solvent, into the corresponding epoxide of the formula (V)

(V)



in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in claim 1,

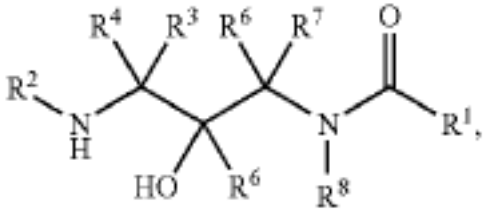
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the formula (VI)

R^2—NH_2 (VI),

in which the radical R^2 is as defined in claim 1,

a compound of the formula (VII)

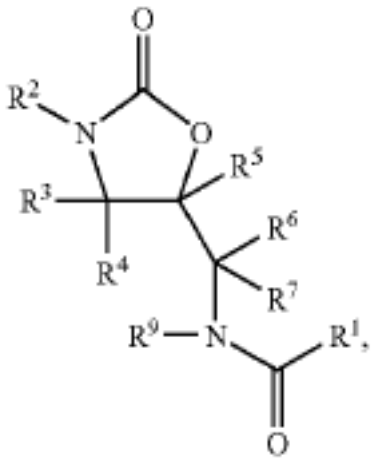
(VII)



in which

the radicals it R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in claim 1, is initially prepared and, subsequently, in an inert solvent in the presence of phosgene or a phosgene equivalent, cyclized to give a compound of formula (I)

(I)

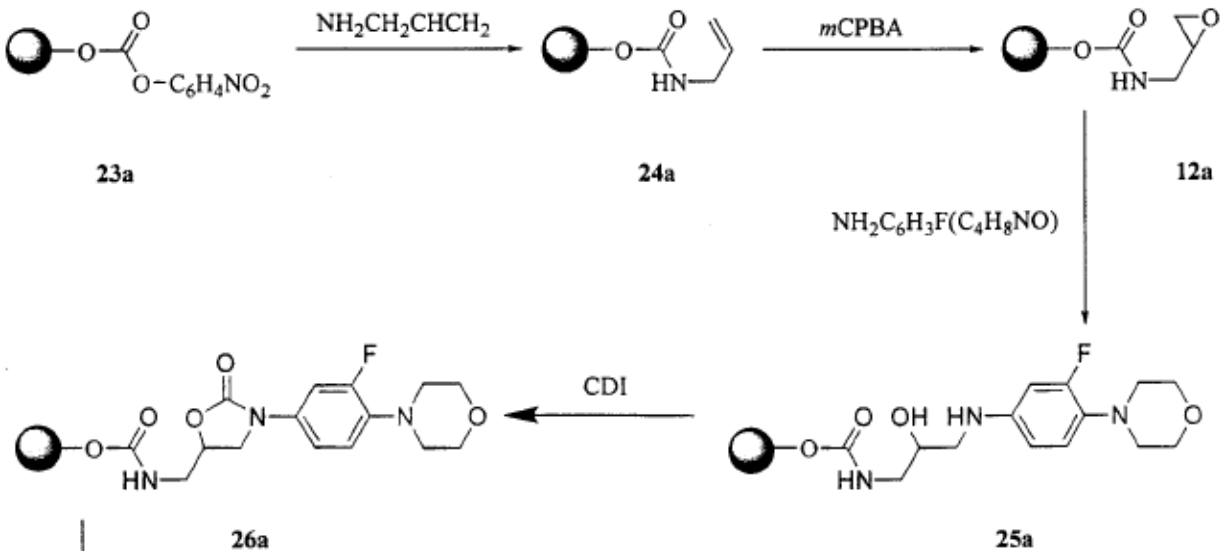


in which

the radicals it R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in claim 1[.]

Claim 7 recites other limitations that do not apply to the synthesis of rivaroxaban. EX1002, ¶¶128-29. Thus, these limitations are not discussed herein. Claim 12 depends from claim 7 and specifies that the phosgene equivalent employed in process alternative B is carbonyldiimidazole (CDI).

The '630 publication teaches using the process B synthetic pathway recited in claim 7 for the synthesis of linezolid. EX1002, ¶124. The '630 publication describes "oxidizing the olefin to provide an epoxide functionality, opening the epoxide with an amine and cyclizing the resulting amino alcohol using a phosgene equivalent." EX1012 at 3:16-19; EX1002, ¶¶124-25. The '630 publication illustrates this synthetic pathway in the figure reproduced below:



EX1012 at Figure 25.

Regarding the scheme outlined in the figure above, the '630 publication teaches, "The terminal olefin of carbamate 24a was oxidized with *m*CPBA ([*meta*-chloroperoxybenzoic acid] to yield immobilized epoxide 12a. Addition of 3-fluoro-4-morpholino aniline to 12a produced amino alcohol 25a, which was cyclized to oxazolidinone 26a upon treatment with CDI [(carbonyldiimidazole)]." EX1012 at 34:23-27; EX1002, ¶125. This process is identical to Process B in claim 7 of the '456 patent.

Because linezolid and rivaroxaban share an identical 5-methylamine-substituted oxazolidinone ring, the skilled artisan would have known that reactions useful to make the oxazolidinone ring for linezolid would also be useful to make the same ring for rivaroxaban. EX1002, ¶119. Thus, the skilled artisan would have

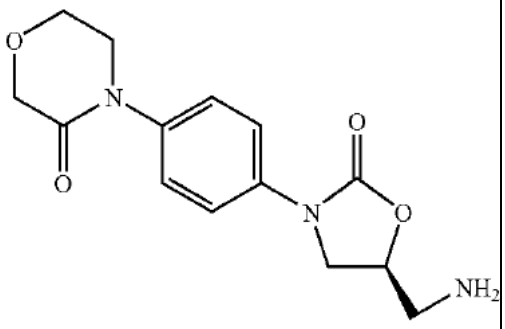
known that the process described in the '630 publication for the construction of linezolid (a terminal alkene is epoxidized with *m*CPBA and subsequently subjected to amine-based nucleophilic attack and then cyclized with CDI), the same process described in process B of claims 7 and 12, would be useful to make rivaroxaban. EX1002, ¶124.

The skilled artisan would have had a reasonable expectation of success in performing this synthesis reaction regardless of whether the reaction is carried out on a solid support resin or freely in a flask. EX1002, ¶126. As explained by Dr. Lepore, the '630 publication describes the reaction sequence being performed on a solid support resin, but the reaction would not be limited to performance on solid report, and the claims do not exclude synthesis on solid support. EX1002, ¶119. Moreover, as explained by Dr. Lepore, the skilled artisan would have a reasonable expectation of success in performing the reaction without the solid support, as such a reaction had previously been reported as successfully executed directly in the flask. *E.g.*, Williams, M. R., *et al*., *A New Synthetic Approach to 1-(Hydroxymethyl)-8-methoxy-1,2,3,4-tetrahydroisoquinolin-4-one*, 52 J. ORG. CHEM. (1987) 2615-2617 ("Williams," EX1034) at 2616, Scheme 1, Step e, wherein an amino alcohol is cyclized with CDI to give an oxazolidinone; *see also* EX1002, ¶126. Thus, regardless of whether solid support resin is used, the skilled

artisan would have had a reasonable expectation of success in synthesizing rivaroxaban using the epoxide reaction described in the '630 publication.

In view of the foregoing, each of claims 7, 11-12, and 20-22 of the '456 patent is rendered obvious under 35 U.S.C. § 103 by the combined teachings of Ewing, Riedl, the '111 publication, Chiba, the '630 publication and the '671 patent. EX1002, ¶127. The claim chart below identifies where the specific elements of the exemplary claims 12 and 20 are found in the asserted references, and where they are addressed by Dr. Lepore.

Exemplary '456 Patent Claims	**Obvious over Ewing, Riedel, the '111 publication, and Chiba**
12. The process of claim 7 wherein in process alternative "B," the phosgene equivalent employed in the cyclization of compound (VII) is carbonyldiimidazole (CDI).	"The terminal olefin of carbamate 24a was oxidized with mCPBA to yield immobilized epoxide 12a. Addition of 3-fluoro-4-morpholino aniline to 12a produced 25 amino alcohol 25a, which was cyclized to oxazolidinone 26a upon treatment with CDI." EX1012 at 34; EX1002, ¶125.
20. A process for the preparation of the compound of claim 6, comprising reacting a compound of the following formula	"Addition of acetyl chloride to 27a produce acetamide 28a" EX1012 at 34:26-27; EX1002, ¶119. "Beginning with 0.3 gm (1.3 mMol) 5-amino-3-(1-methylpiperidin-4-yl)pyrrolo[3,2-b]pyridine and 0.29 gm (1.56 mMol) 5-chloro-2-thiophenecarbonyl chloride, 0.36 gm (75%) of the title compound were prepared essentially by the procedure described in Example 4." EX1013

 with 5-chlorothiophene-2-carbonyl chloride in an inert solvent to prepare the compound of claim 6.	at 34:40-53; EX1002, ¶121.
21. The process of claim 21 wherein the inert solvent comprises pyridine.	"EXAMPLE 4 . . . A solution . . . in 40 mL pyridine . . ." EX1013 at 23:61-24:1; EX1013 at 34:40-53; EX1002, ¶121.

VIII. CONCLUSION

For the reasons set forth above, claims 1-8, 10-14, 16-22, 24, 26-28, and 30 of the '456 patent are unpatentable over the asserted prior art. Petitioners therefore request that an *inter partes* review of these claims be instituted and that they be found unpatentable and canceled.

Respectfully submitted,

Dated: October 7, 2016

/ Steven W. Parmelee /

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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 13,003 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. 7,157,456 to Straub *et al*.
1002	Declaration of Salvatore D. Lepore, Ph.D.
1003	Declaration of Jack Hirsh, M.D.
1004	Curriculum Vitae of Salvatore D. Lepore, Ph.D.
1005	Curriculum Vitae of Jack Hirsh, M.D.
1006	File History of 7,157,456 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 (1999) 771-87.
1008	Riedl, B. *et al*., *Recent Developments with Oxazolidinone Antibiotics*, 9 EXP. OPIN. THER. PATENTS (1999) 625-633.
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	WO 99/37630, to Gordeev *et al*.
1013	U.S. Patent No. 5,817,671 to Filla *et al*.
1014	Kamata, K., *et al*., *Structural basis for chemical inhibition of human blood coagulation factor Xa*, 95 PROC. NATL. ACAD. SCI. USA 6630-35 (1998).
1015	Katakura, S., *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	Gante, J. *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) (exerpts).
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*, 360 ACTA PSYCHIATR. SCAND. SUPPL. 87 (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).
1032	Atkins, R.C. *et al.*, *Organic Chemistry A Brief Course*, MCGRAW HILL (1997).
1033	WO 98/54161 to Hester *et al*.
1034	Williams, R. M., *et al*., *A New Synthetic Approach to 1-(Hydroxymethyl)-8-methoxy-1,2,3,4-tetrahydroisoquinolin-4-one*, 52 J. ORG. CHEM. 2615-2617 (1987).
1035	Carville, D. G. M., *et al., Thrombus precursor protein (TpP^{TM}): marker of thrombosis early in the pathogenesis of myocardial infarction*, 42 CLIN. CHEM. 1537-41(1996).
1036	Anand, S. S., *et al*., *Long-Term Oral Anticoagulant Therapy in Patients with Unstable Angina or Suspected Non-Q-Wave Myocardial Infarction* 98 CIRCULATION 1064-1070 (1998).
1037	Taylor, F. C., *et al.*, *Evaluation of patients' knowledge about anticoagulant treatment*, 3 QUALITY IN HEALTH CARE 79-85 (1994).
1038	Palareti, G., *et al.*, *Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT)* 348 LANCET 423-28 (1996).

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. 7,157,456 (and accompanying Exhibits 1001-1038) by overnight courier (Federal Express or UPS), on this 7 day of October, 2016, on the Patent Owner at the correspondence address of the Patent Owner as follows:

BUCHANAN, INGERSOLL & ROONEY PC
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Respectfully,

Dated: October 7, 2016

/ Steven W. Parmelee /
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