

**IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE**

BRECKENRIDGE PHARMACEUTICAL, INC.

Plaintiff,

v.

HETERO USA, INC., HETERO LABS
LIMITED UNIT-III, HETERO LABS LIMITED,
and CAMBER PHARMACEUTICALS, INC.

Defendants.

C.A. No. 1:24-cv-00571-GBW

DEFENDANTS' FIRST SUPPLEMENTAL INVALIDITY CONTENTIONS

Pursuant to the Court's Scheduling Order (D.I. 31) and Paragraph 4(d) of the Default Standard for Discovery, Defendants Hetero USA, Inc., Hetero Labs Limited Unit-III, Hetero Labs Limited, and Camber Pharmaceuticals, Inc. (collectively "Defendants") provide their first supplemental invalidity contentions ("First Supplemental Invalidity Contentions") and produce documents herewith related to their Invalidity Contentions.

Plaintiff Breckenridge Pharmaceutical, Inc. ("Plaintiff" or "Breckenridge") assert claims 1–7 and 10–18 of U.S. Patent No. 11,013,729 ("the '729 patent") and claims 1–20 of U.S. Patent No. 11,752,142 ("the '142 patent") (collectively, "the Asserted Claims") against Defendants, pursuant to Plaintiff's Initial Infringement Contentions and Claim Charts served on November 15, 2024.

While Plaintiffs identified the Asserted Claims in their Contentions, Plaintiff has not amended its Complaint to limit the claims asserted in this case. Indeed, Plaintiff's Contentions say that their identification of asserted claims is an "initial" identification. Defendants reserve the

right to amend, modify, and/or supplement these contentions if Plaintiff asserts new infringement theories, patents, or claims.

Each of the Asserted Claims is invalid under at least 35 U.S.C. §§ 102, 103 and/or 112, as described in further detail below.

I. PRELIMINARY STATEMENT

Defendants' discovery and investigation regarding the Asserted Patents and potential grounds for invalidity is ongoing, and these disclosures are made in good faith based on Defendants' current knowledge and understanding of the Asserted Patents, Plaintiff's Initial Contentions, the prior art, and other facts and information available at this early date in the action. Defendants' Invalidity Contentions are based on information reasonably available at this time with respect to the Asserted Claims, and are necessarily preliminary and may require subsequent amendment, modification, and/or supplementation including as required and permitted by Local and Federal Rules as well as the Court's Scheduling Order, further including, but not limited to, if Defendants obtain additional or different information; if new prior art is discovered; if expert discovery is obtained; in response to any argument of validity or infringement advanced by Plaintiff in this case; if Plaintiff asserts/attempts to assert claim constructions that are different from any assumptions that were compelled to be made herein; if Plaintiff asserts/attempts to assert additional or different infringement allegations or claims at a later date; as provided under or in accordance with the Delaware Default Standard for Discovery ("Default Standard") or the Pretrial Scheduling Order; if Plaintiff asserts an interpretation of the prior art different from that used herein; in light of any response Plaintiff makes to these contentions or any written discovery propounded by Defendants; based on information produced in another action involving any of the patents at issue in this litigation; based on any discovery materials that have not yet been produced or provided to Defendants (whether by Plaintiff or a

Defendants reserve the right to supplement, modify, and/or amend the definition, qualification, and/or criteria of a POSA to the '729 and '142 patents as this litigation progresses.

II. IDENTIFICATION OF PRIOR ART

Relevant prior art includes, without limitation, the following as understood in the context of what was known as of the priority date of the '729 and '142 patents:

1. U.S. Patent Publication No. 2006/0183779, published on August 17, 2006 (“the '779 publication”)
2. PRADAXA® Prescribing Information, published on November 29, 2010, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000Lbl.pdf, last accessed October 25, 2024 (“the PRADAXA 2010 Label”)
3. U.S. Patent Publication No. 2003/0195220, published on October 26, 2003 (“the '220 publication”)
4. U.S. Patent Publication No. 2004/0109890, published on June 10, 2004 (“the '890 publication”)
5. International Patent Publication No. WO 2012/001156, published on January 2, 2012 (“the '156 publication”)
6. Eisert, W.G. *et al.*, “Dabigatran: An Oral Novel Potent Reversible Nonpeptide Inhibitor of Thrombin,” *Arterioscler. Thromb. Vasc. Biol.*, 30:1885–1889 (2010) (“Eisert”)
7. Hankey, G.J. and Eikelboom, J.W., “Dabigatran Etexilate: A New Oral Thrombin Inhibitor,” *Circulation*, 123:1436–1450 (2011) (“Hankey”)
8. International Patent Publication No. WO 2011/107427, published on September 9, 2011 (“the '427 publication”)

9. Center for Drug Evaluation and Research, Clinical Pharmacology and Biopharmaceutics Review(s) of Application Number 22-512 (Pradaxa), published on November 29, 2010 (“Clinical Pharmacology Review”)
10. Center for Drug Evaluation and Research, Chemistry Review(s) of Application Number 22-512 (Pradaxa), published on November 29, 2010 (“Chemistry Review”)
11. International Patent Publication No. WO 2009/118322, published on October 1, 2009 (“the ’322 publication”)

Defendants intend to rely upon each reference in its entirety to the extent relevant and/or appropriate, including references cited in, referenced within, or incorporated-by-reference by the references identified above. Defendants also incorporate, in full, all prior art references cited in the patents-in-suit and their prosecution histories. Defendants also intend to rely on admissions by Plaintiff’s witnesses during depositions in this case.

Defendants expressly reserve the right to modify and/or supplement the prior art discussed herein.¹ In addition to the art summarized herein, Defendants reserve the right to rely

¹ Each of the disclosed references is prior art to the ’729 and ’142 patents. To the extent that Plaintiff attempts to swear behind or otherwise remove as prior art any of the prior art identified herein, Defendants specifically reserve their right to, *inter alia*, add additional prior art to the list. Additionally, as previously noted, Defendants reserve the right to, *inter alia*, modify and/or supplement their list of prior art references based upon, *inter alia*, the patentee’s disclosure of the asserted claims; the patentee’s disclosure of its alleged infringement proofs; disclosure of any additional proposed construction of the claims of the ’729 and ’142 patents by Plaintiff; issuance of any further claim construction ruling by a court; Plaintiff’s response to any of Defendants’ defenses, including, but not limited to, Plaintiff’s interpretation of the prior art; additional fact or expert discovery; and/or further investigation. Moreover, Defendants do not admit, or otherwise concede, that the claims of the ’729 and ’142 patents are entitled to an effective filing date earlier than the patent’s filing date, and therefore reserve the right to, *inter alia*, challenge the effective filing date of the patent and to assert additional prior art references and/or products based on any such challenge. Nevertheless, as discussed herein, each claim of the patent is invalid even if the ’729 and ’142 patents had made a proper claim of priority to an earlier-filed application.

on art identified during prosecution of the '729 and '142 patents, as well as any other art that would have provided useful background information to the POSA.

Description of exemplary prior art references are provided below:

1. The '779 Publication

U.S. Patent Publication No. 2006/0183779 (“the '779 publication”) published on August 17, 2006, and is entitled, “Administration form for the oral application of 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1h-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethyl ester and the salts thereof.” The '779 publication, therefore, qualifies as prior art to the '729 and '142 patents under 35 U.S.C. § 102(b) (pre-AIA).

The '779 publication is directed to a formulation for the oral use of dabigatran etexilate. The '779 publication, ¶ [0006]. The '779 publication reports that the “use of pharmaceutically acceptable organic acids with a water solubility of > 1 g/250 ml at 20° C., preferably > 1 g/160 ml at 25° C., in solid oral preparations leads to a significantly improved formulation” of dabigatran etexilate. *Id.* at ¶ [0007].

The '779 publication discloses a formulation in which an organic acid-containing core is coated with an insulating layer, followed by a dabigatran etexilate layer, which may be further coated. *Id.* at ¶ [0010]. According to the '779 publication, “[o]ne advantage of the formulation thus constructed is the spatial separation of the organic acid and active substance by the insulating layer.” *Id.* at ¶ [0011]. Another advantage is “that the organic acid does not go into solution until after the preparation has been taken and then produces an acid microclimate in which the active substance can dissolve.” *Id.*

2. The PRADAXA 2010 Label

PRADAXA[®] Prescribing Information, published on November 29, 2010 (“the PRADAXA 2010 Label”). PRADAXA 2010 Label, therefore, qualifies as prior art to the ’729 and ’142 patents under 35 U.S.C. § 102(b) (pre-AIA).

The PRADAXA 2010 Label that PRADAXA[®] (dabigatran etexilate mesylate) is “indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.” The PRADAXA 2010 Label, 2. PRADAXA is supplied as 150 mg and 75 mg capsules for oral administration. *Id.*

PRADAXA contains 172.95 mg or 86.48 mg of dabigatran etexilate mesylate, which is equivalent to 150 mg or 75 mg of dabigatran etexilate, respectively. *Id.* at 4. PRADAXA also contains acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. *Id.* PRADAXA’s capsule shell is composed of carageenan, FD&C Blue No. 2, FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink. *Id.*

3. The ’220 publication

U.S. Patent Publication No. 2003/0195220, published on October 16, 2003, and is entitled, “Preparation for oral administration.” The ’220 publication, therefore, qualifies as prior art to the ’729 and ’142 patents under 35 U.S.C. § 102(b) (pre-AIA).

The ’220 publication is directed to a “preparation for oral administration containing a medicinal substance having cGMP-specific phosphodiesterase inhibitory activity and showing [a] decrease of solubility in the neutral and alkaline regions, wherein an acidic substance is compounded [to] promote the dissolution of the medicinal substance in digestive tract and thus the efficacy can be expressed at the early stage after administration.” The ’220 publication, Abstract.

The '220 publication provides examples of the acidic substance that may be used, which includes “any substance on [the] condition that it shows pH 4.0 or below when dissolved in water and does not interfere with the efficacy of a medicinal substance as an active ingredient.” *Id.* at ¶ [0029]. Such acid substances includes organic acids, “such as fumaric acid, tartaric acid, succinic acid, malic acid, ascorbic acid, [and] aspartic acid.” *Id.*

The '220 publication discloses that the oral solid pharmaceutical compositions may be powders, granules, tablets, and capsules. *Id.* at ¶ [0035]. Tablets comprising a “medicinal substance and an acidic substance separately in respective granules” are preferred. *Id.* The compositions “can be prepared in accordance with a conventional method for preparing pharmaceutical solid formulations.” *Id.* at ¶ [0044]. For example, granules may be prepared by known methods such as wet granulation, dry granulation, layer granulation, melt granulation, and impregnated-granulation. *Id.* at ¶ [0046]. The '220 publication discloses that its composition “can achieve rapid expression of efficacy of the active ingredient even when the preparation is administered to a subject who is suffering from anacidity or who intends to take the same just after eating.” *Id.* at ¶ [0007]; *see also id.* at ¶ [0130].

The '220 publication discloses the following process for preparing a composition with two different types of granules:

Further, in the process wherein a drug mixture is granulated, a drug mixture containing a medicinal substance and a pharmaceutical additive(s) without an acidic substance can be granulated. The resulting granules are then mixed with an acidic substance and, if necessary, a carbonate, a disintegrant and a lubricant, and then subjected to compression molding. In this process, granules of an acidic substance prepared by the granulation method above can be used, whereby tablets comprising different granules each containing a medicinal substance and an acidic substance separately are prepared.

Id. at ¶ [0058]. The '220 publication also discloses a working example in which drug substance-containing granules were prepared separately from fumaric acid granules before being mixed with extra-granular excipients and compressed into tablets. *Id.* at ¶¶ [0111]–[0113], Example 13.

4. The '890 publication

U.S. Patent Publication No. 2004/0109890 (“the '890 publication”), published on June 10, 2004, and is entitled, “Tablets that quickly disintegrated in oral cavity.” The '890 publication, therefore, qualifies as prior art to the '729 and '142 patents under 35 U.S.C. § 102(b) (pre-AIA).

The '890 publication is directed to an “intraorally rapidly disintegrating tablet containing a medicinal substance being hardly water-soluble under neutral or alkaline conditions and being highly water-soluble under acidic conditions yet presenting [an] unpleasant taste, and a process for preparing the same.” The '890 publication, ¶ [0009].

5. The '156 Publication

International Patent Publication No. WO 2012/001156 (“the '156 publication”), published on January 2, 2012, and is entitled, “PHARMACEUTICAL ORAL DOSAGE FORMS COMPRISING DABIGATRAN ETEXILATE AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS.” The '156 publication, therefore, qualifies as prior art to the '729 and '142 patents under 35 U.S.C. § 102(b) (pre-AIA).

The '156 publication is directed to pharmaceutical oral dosage forms of dabigatran etexilate. The '156 publication, Abstract. The '156 publication discloses that dabigatran etexilate is “strongly dependent on the pH value, with increased solubility at acidic pH,” while also “chemically instable in acidic environment and particularly susceptible to hydrolysis of the pro-drug forming moieties, as well as polymorphic form transformations.” *Id.* at 3. The '156 publication disclose formulating the dabigatran etexilate with an organic acid to provide an

“acidic micro environment,” while keeping the organic acid separate from the “acid sensitive” dabigatran etexilate. *Id.* at 10–11. The ’156 publication discloses that a “simple mixture of isolated pellets and dabigatran is filled into capsules or sachets.” *Id.* at 14.

6. Eisert

Eisert, W.G. *et al.*, “Dabigatran: An Oral Novel Potent Reversible Nonpeptide Inhibitor of Thrombin,” *Arterioscler. Thromb. Vasc. Biol.*, 30:1885–1889 (“Eisert”) published in October 2010. Eisert, therefore, qualifies as prior art to the ’729 and ’142 patents under 35 U.S.C. § 102(b) (pre-AIA).

Eisert reviews the properties of dabigatran etexilate, an oral direct thrombin inhibitor that was submitted to the FDA for approval to prevent stroke in patients with atrial fibrillation. Eisert, 1885. Dabigatran etexilate has low oral absolute bioavailability; only about 7% of the drug is absorbed when administered orally. *Id.* at 1887. Eisert explains that dabigatran etexilate is more consistently absorbed in an acidic environment in the gastrointestinal tract. *Id.* As such, the drug was formulated with tartaric acid to increase its bioavailability. *Id.* By formulating the drug with tartaric acid, the drug’s absorption is “not dependent on the gastrointestinal acidity of the patient but brings its optimal pH environment with it, reducing variability even with proton pump inhibitor coadministration.” *Id.* at 1888.

7. Hankey

Hankey, G.J. and Eikelboom, J.W., “Dabigatran Etexilate: A New Oral Thrombin Inhibitor,” *Circulation*, 123:1436–1450 (“Hankey”) published in 2011. Hankey, therefore, qualifies as prior art to the ’729 and ’142 patents under 35 U.S.C. § 102(b) (pre-AIA).

Hankey is a review article directed to dabigatran etexilate, a new oral thrombin inhibitor. Hankey discloses the dabigatran etexilate is formulated with tartaric acid “to reduce the variability of dabigatran etexilate absorption, which is dependent on an acid environment.”

Hankey, 1436. Hankey explains that by incorporating tartaric acid in the dabigatran formulation, “dabigatran etexilate absorption is independent of gastrointestinal tract acidity and is not materially affected by coadministration of a proton pump inhibitor.” *Id.* at 1436–1437. Hankey also discloses that the absolute bioavailability after oral administration of dabigatran etexilate is only about 6.5%. *Id.* at 1437. Hankey further discloses that dabigatran etexilate is approved in more than 75 countries for the prevention of venous thromboembolism after elective hip or knee replacement, and is approved in the U.S. for stroke prevention in patients with atrial fibrillation. *Id.* at 1442–1443, 1446.

8. The '427 Publication

International Patent Publication No. WO 2011/107427 (“the '427 publication”) published on September 9, 2011. The '427 publication, therefore, qualifies as prior art to the '729 and '142 patents under 35 U.S.C. § 102(b) (pre-AIA).

The '427 publication is directed to an oral pharmaceutical composition containing dabigatran etexilate. The '427 publication, Abstract. The '427 publication explains that dabigatran etexilate “has a strong pH-dependent solubility that is greatly increased in the acidic environment.” *Id.* at 1. According to the '427 publication, this “leads to the problem that conventional oral pharmaceutical compositions have large variations in the bioavailability since the solubility of the active ingredient depends on the pH value in the patient's stomach.” *Id.* To address this solubility issue, the '427 publication discloses adding an inorganic acid excipient to the dabigatran-containing composition. *Id.* at 2. The '427 publication further explains that it is advantageous to “spatially separate” the inorganic acid component from the drug substance, which can be achieved by micro-encapsulating the inorganic acid. *Id.* at 5.

9. Clinical Pharmacology Review

Center for Drug Evaluation and Research, Clinical Pharmacology and Biopharmaceutics Review(s) of Application Number 22-512 (Pradaxa) (“Clinical Pharmacology Review”) published on November 29, 2010. Clinical Pharmacology Review, therefore, qualifies as prior art to the ’729 and ’142 patents under 35 U.S.C. § 102(b) (pre-AIA).

Clinical Pharmacology Review is a document published by the Food and Drug Administration related to their review of New Drug Application 22-512 (PRADAXA[®]). Clinical Pharmacology Review discloses that the solubility of dabigatran etexilate mesylate is “strongly pH dependent with increase solubility at acidic pH.” Clinical Pharmacology Review, 16. Dabigatran etexilate was formulated with tartaric acid “[b]ased on the physicochemical and biopharmaceutical properties of dabigatran etexilate mesilate and the clinical requirements for a reliable drug release.” *Id.* at 67.

10. Chemistry Review

Center for Drug Evaluation and Research, Chemistry Review(s) of Application Number 22-512 (Pradaxa) (“Clinical Pharmacology Review”) published on November 29, 2010. Chemistry Review, therefore, qualifies as prior art to the ’729 and ’142 patents under 35 U.S.C. § 102(b) (pre-AIA).

Chemistry Review is a document published by the Food and Drug Administration related to their review of New Drug Application 22-512 (PRADAXA[®]). Chemistry Review discloses that the solubility of dabigatran etexilate mesylate is “pH dependednt [sic] (higher at pH < 3).” Chemistry Review, 3. Chemistry Review also discloses that dabigatran is acid sensitive. *Id.* Chemistry Review also discloses that PRADAXA contains tartaric acid. *Id.*

11. The '322 Publication

International Patent Publication No. WO 2009/118322 (“the '322 publication”) published on October 1, 2009. The '322 publication, therefore, qualifies as prior art to the '729 and '142 patents under 35 U.S.C. § 102(b) (pre-AIA).

The '322 publication is directed to an improved process for preparing dabigatran etexilate mesylate. The '322 publication, Abstract. The '322 publication discloses the use of tartaric acid cores in a dabigatran etexilate formulation. *Id.* at 2:17–23. The '322 publication goes on to explain that “for acid-sensitive actives substances such as for example dabigatran etexilate, in which defects in the isolation caused by satellites that have broken off or by the excessively rough surface of over-large particles of tartaric acid powder may lead to significantly impaired storage stability and hence durability of the finished product. For this reason, with acid-sensitive active substances it is also essential to apply the isolating layer as such with high reproducibility and consistently high quality.” *Id.* at 2:28–34.

III. U.S. PATENT NO. 11,013,729 (“THE '729 PATENT”)

The '729 patent, which issued on May 25, 2021, from U.S. Patent Application No. 14/379,613 (“the '613 application”), which is a national stage application of International Patent Application No. PCT/EP2013/053426 (“the '426 application”), filed on February 21, 2013. The '426 application claims priority to Indian Patent Application 461/MUM/2012, filed on February 21, 2012. As such, any art that was published or demonstrates public use or sale of the subject matter claimed in the '729 patent from before February 21, 2012, qualifies as prior art under 35 U.S.C. § 102(b). *See* 35 U.S.C. § 119(a) (pre-AIA).

Pratibha S. Pilgaonkar, Maharukh T. Rustomjee, and Anilkumar S. Gandhi are identified as the purported inventors on the face of the '729 patent. The USPTO identifies Breckenridge

17. The capsule according to claim 16 containing from 50 mg to 200 mg of dabigatran etexilate mesylate.

18. The capsule according to claim 16, wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.

B. Obviousness

The obviousness of the Asserted Claims 1–7 and 10–18 of the '729 patent is set forth in detail below, and within the claim charts contained in Appendices A and B. The following analysis is exemplary only. Providing this analysis in view of certain of the prior art cited herein and within Appendices A and B does not waive any future assertion of any art or any combination of art, and also does not imply that there are no other combinations, or that any of the combinations set forth herein or in Appendices A and B are the only combinations upon which Hetero intends to rely.

Well before the earliest February 21, 2013 priority date of the '729 patent for the purposes of determining 102(b) art, dabigatran etexilate was marketed to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and to prevent venous thromboembolism after elective hip or knee arthroplasty. *See, e.g.*, the PRADAXA 2010 Label, 2; Hankey, 1442–1443. Much was known in the art about dabigatran etexilate's pH-dependent solubility and absorption. For example, dabigatran etexilate's absorption was well known in the art to be inconsistent and variable in neutral or basic pH environments in the gastrointestinal tract. *See, e.g.*, Eisert, 1887; Hankey, 1436; Clinical Pharmacology Review, 16; the '427 publication, 1. To improve dabigatran etexilate's bioavailability, those in the field formulated the drug in such a way as to provide an acidic microenvironment to improve its solubility and absorption. Eisert, 1887–1888; Hankey, 1436; the '427 publication, 2; the '779 publication, ¶ [0011]. One way prior art formulations achieved this was to incorporate an organic

or inorganic acid, such as tartaric acid or phosphoric acid, in the oral dabigatran etexilate formulations. The PRADAXA 2010 Label, 4; Eisert, 1887; Hankey, 1436; the '427 publication, 2, 7; the '779 publication, ¶ [0007], Clinical Pharmacology Review, 67; Chemistry Review, 3; the '156 publication, 10–11.

However, it was also well-known in the art that dabigatran etexilate was acid-labile and chemically unstable in an acidic environment. *See, e.g.*, the '156 publication, 3; Clinical Pharmacology Review, 15; Chemistry Review, 3; the '322 publication, 2:28–34. To prevent degradation of the dabigatran etexilate in the presence of an acid, prior art formulations separated the acid from the drug. *See, e.g.*, the '779 publication, ¶ [0011]; the '156 publication, 11; the '427 publication, 5; the '322 publication, 2:28–34. Several ways of addressing dabigatran's acid sensitivity were within the skill of a POSA and were evidenced in the art at the time, including, for example (1) preparing pellets with a tartaric acid core, an isolating layer, and a drug layer, or (2) formulating the dabigatran etexilate separately from the acid (e.g., in different pellet populations). In fact, this latter approach was recognized by several different drug developers. *See, e.g.*, Indian Patent Application No. 438/CHE/2013, filed on January 31, 2013, by Dr. Reddys Laboratories Limited and Indian Patent Application No. 1318/MUM/2013, filed on April 5, 2013, by V-Ensure Pharma Technologies Private Limited; the '156 publication, 14. Accordingly, as of the priority date of the '729 patent, a POSA simply needed to use one of the well-known formulation approaches that had been described in the art for addressing acid sensitivity to resolve the known acid sensitivity of dabigatran. In addition, as of the priority date of the '729 patent, it would have been obvious to try any one of the well-known formulation approaches that had been described in the art for addressing acid sensitivity, given that there was

a design need or market pressure to resolve dabigatran's known acid sensitivity and there were a finite of identified, predictable solutions that had been described in the art.

1. The Asserted Claims would have been obvious over the '779 publication in combination with the '220 publication and/or the '890 publication in view of the general knowledge in the art

a. Claim 1

Claim 1 is directed, *inter alia*, to a composition comprising at least two distinct types of particles wherein the first type of particles comprise dabigatran etexilate and is free of organic or inorganic acids, and the second type of particles comprise at least one organic acid, is coated with a protective coating layer, and is free of dabigatran etexilate.

A formulation comprising dabigatran etexilate and an organic acid, as was known in the prior art, would have been obvious to a POSA. Moreover, a formulation comprising two different types of granules would have immediately been obvious to a POSA who was developing a dabigatran etexilate formulation.

The '779 publication is directed to a dabigatran etexilate formulation for oral use. The '779 publication, ¶ [0006]. The '779 publication reports that the “use of pharmaceutically acceptable organic acids with a water solubility of > 1 g/250 ml at 20° C., preferably > 1 g/160 ml at 25° C., in solid oral preparations leads to a significantly improved formulation” of dabigatran etexilate. *Id.* at ¶ [0007]. Examples of such organic acids include tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, and aspartic acid. *Id.* at ¶ [0012].

The '779 publication discloses a formulation in which an organic acid-containing bead is coated with an insulating layer, followed by a dabigatran etexilate layer, which may be further coated. *Id.* at ¶ [0010]; *see also* Example 1. According to the '779 publication, “[o]ne advantage of the formulation thus constructed is the spatial separation of the organic acid and active substance by the insulating layer.” *Id.* at ¶ [0011]. Another advantage is that the organic acid

does not go into solution until after the preparation has been taken and then produces an acid microclimate in which the active substance can dissolve. *Id.*

The '779 publication, which is assigned to Boehringer Ingelheim Pharma, was undergoing prosecution at the U.S. Patent and Trademark office when PRADAXA[®], the commercial embodiment of the '779 publication, was approved by the FDA. Drug developers, such as generic pharmaceutical companies, would have realized that when the '779 publication issued as a patent, that patent would have likely been listed in the Orange Book for PRADAXA[®] and would have blocked drug companies from manufacturing the formulations disclosed in the '779 publication.² As such, generic companies would have had a reason to develop alternative dabigatran etexilate formulations.

A POSA looking to develop a dabigatran etexilate formulation that would have avoided those being pursued in the claims of the application that published as the '779 publication would have looked to the '220 and/or '890 publications. The '220 and/or '890 publications both relate to increasing the solubility and absorption of a drug (e.g., a PDE-V inhibitor) that has reduced solubility in neutral or basic regions by formulating the drug with an acidic substance. The '220 publication, Abstract; the '890 publication, Abstract. Sildenafil, an exemplary PDE-V inhibitor, has a 23-fold higher solubility at an acidic pH of 1.2 (2.52 mg/mL) than at a neutral pH of 6.8 (0.11 mg/mL). The '220 publication, ¶ [0003]; *see also* the '890 publication, ¶ [0031] (“Examples of such medicinal substances include those of which solubility in water at 25° C. is not greater than 0.1 mg/mL at pH of 7 or above and is not less than 1 mg/mL at pH of 2 or below, preferably those of which solubility in water (25° C.) at pH 1.2 is not less than 10-fold,

² In fact, the '779 publication issued as U.S. Patent No. 9,925,174, and was subsequently listed in the Orange Book.

preferably not less than 100-fold compared to the solubility in water (25° C.) at pH 7.”). The ’220 publication discloses formulating the PDE-V inhibitor with an “acidic substance” to “exert drug efficacy rapidly after administration.” The ’220 publication, ¶ [0008]; *see also* the ’890 publication, ¶ [0025].

Examples of an appropriate “acidic substance” include “any substance on condition that it shows pH 4.0 or below when dissolved in water and does not interfere with the efficacy of a medicinal substance as an active ingredient.” The ’220 publication, ¶ [0029]; *see also* the ’890 publication, ¶ [0026]. Preferred acidic substances include organic acids, such as fumaric acid, tartaric acid, succinic acid, malic acid, ascorbic acid, and aspartic acid. The ’220 publication, ¶ [0029]; the ’890 publication, ¶ [0026].

The ’220 and/or ’890 publications disclose formulating the drug substance separately from the acidic substance in respective granule populations. The ’220 publication discloses that “tablets comprising a medicinal substance and an acidic substance separately in respective granules are preferred.” The ’220 publication, ¶ [0035]; *see also* ¶ [0058]. The ’220 and/or ’890 publications both disclose working examples in which a PDE-V inhibitor and fumaric acid is granulated separately as two different granule populations. The ’220 publication, Example 13; the ’890 publication, Example 1.

The ’220 publication also discloses coating the formulations to prevent abrasion and improve stability. The ’220 publication, ¶ [0061]. Coatings can be used “in a conventional manner,” in a “coating amount ... that does not disturb the dissolution of a medicinal substance.” *Id.* The fumaric acid granules in the ’890 publication’s Example 1 are also coated with hydroxypropylmethyl cellulose. The ’890 publication, Example 1.

A POSA looking for an alternate dabigatran etexilate formulation would have had a reason to combine the '779 publication with the '220 and/or '890 publications because these publications disclose formulations for improving the solubility and absorption of a pH-dependent drug similar to dabigatran etexilate. Following the '220 and/or '890 publications' teachings, a POSA would have had a reason to prepare a formulation comprising separate granule populations of the dabigatran etexilate and an organic acid. A POSA would have recognized the importance of coating the organic acid granules, as taught by the '220 and/or '890 publications, to prevent the organic acid from coming into contact with the dabigatran etexilate. A POSA would have had a reasonable expectation of success in preparing such a dabigatran etexilate formulation based on the disclosures of the '779 publication, the '220 publication, and the '890 publication, in light of the common knowledge and skill in the art.

The Applicants seems to have argued during prosecution of the '729 patent that a food effect would have existed if the dabigatran etexilate and organic acid were formulated in two different particles. *See* the '729 patent File History, Applicant Remarks filed June 1, 2016, 8. However, the '220 publication discloses that a composition comprising an active agent and organic acid in separate granules which “achieve[s] rapid expression of efficacy of the active ingredient even when the preparation is administered to a subject who is suffering from an acidity or who intends to take the same just after eating.” The '220 publication, ¶ [0007]; *see also* ¶ [0130]. As such, a POSA would have reasonably expected a formulation comprising dabigatran etexilate and an organic acid in separate granules to not exhibit a food effect, as taught by the '220 publication. And, in fact, the Applicant's own bioavailability data demonstrates that there was no difference between the bioavailability of a two granule

formulation compared to a one granule formulation when administered under fed conditions. *See* the '729 patent File History, Declaration of Zhengguo Xu filed June 1, 2016, 2.

The prior art combination of the '779 publication in combination with the '220 publication and/or '890 publication is different from the art raised by the Examiner during prosecution of the '729 patent. During prosecution, the Examiner rejected the pending claims over the '779 publication in combination with U.S. Patent Publication No. 2008/0069891 ("the '891 publication"). The Applicants overcame this combination on Appeal by arguing, in part, that the '891 publication was "not related at all to, or concerned with, the necessity of a close proximity between an acid and active ingredient to obtain a desired result, *i.e.*, an acidic environment that allows for diffusion." *See* the '729 patent File History, Appeal Brief filed December 6, 2019, 10.

In fact, while the '891 publication discloses two types of particles, wherein the first particle comprises an active agent, the second particle comprises a "fat/wax material present in an amount *sufficient to inhibit administration abuse of the API from the first particle.*" The '891 publication, ¶ [0020]. On the contrary, the acid-containing particle in the composition disclosed in the '220 and/or '890 publications is meant to improve the solubility and absorption of a pH-dependent drug, such as dabigatran.

Accordingly, claim 1 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

b. Claims 2, 6, and 10

Claim 2 depends from claim 1 and specifies that the composition of claim 1 further comprises at least one pharmaceutically acceptable excipient. Claim 6 depends from claim 2 and recites, "[a] process for the preparation of the composition according to claim 2, comprising the

step of mixing the first type of particles and the second type of particles with the at least one pharmaceutically acceptable excipient.” Claim 10 depends from claim 2 and further recites, “wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.” The analysis with respect to claim 1 is incorporated herein.

Claims 2 and 10 would have been obvious. The ’220 and/or ’890 publications both disclose incorporating additional excipients in the different granule populations. Both publications disclose the oral formulations “may contain additives generally used in the pharmaceutical solid preparations,” including binders, disintegrants, and lubricants. The ’220 publication, ¶ [0034]; the ’890 publication, ¶¶ [0057], [0081]. The ’220 and/or ’890 publications disclose working examples in which the drug substance is mixed with mannitol before granulation with hydroxypropylcellulose or polyvinylpyrrolidone. The ’220 publication, Example 13; the ’890 publication, Example 1. A POSA, therefore, would have had a reason to include at least one pharmaceutically acceptable excipient selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof and arrive at the compositions of claims 2 and 10 with a reasonable expectation of success.

Claim 6 would have been obvious. The ’220 and/or ’890 publications also disclose mixing the two different granule populations (i.e., the drug-containing granules and organic acid-containing granules) with pharmaceutically acceptable excipients before tableting. For example, the ’220 publication discloses mixing the different granules with low-substituted hydroxypropylcellulose, precipitated calcium carbonate, and magnesium stearate before tableting. The ’220 publication, ¶ [0113]. The ’890 publication discloses mixing the different granules with aspartame before tableting. The ’890 publication, ¶ [0133]. The ’729 patent defines

hydroxypropylcellulose as a binder, calcium carbonate as a diluent, and magnesium stearate as a lubricant. The '729 patent, 8:–6, 8:22–30, 8:35–36. In light of the art, a POSA would have had a reason to combine dabigatran etexilate-containing granules, organic acid-containing granules, and at least one pharmaceutically acceptable excipient, such as a binder, diluent, or lubricant, before manufacturing the final dosage form, with a reasonable expectation of success in arriving at the composition of claim 6.

Accordingly, claims 2, 6, and 10 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

c. Claims 3 and 5

Claims 3 and 5 depend from claim 1 and further specify that the composition of claim 1 comprises “from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate” (claim 3) and that the composition of claim 1 comprises “from 50 mg to 200 mg of dabigatran etexilate mesylate” (claim 5). The analysis with respect to claim 1 is incorporated herein.

Claim 3 would have been obvious. The '779 publication also discloses that the amount of dabigatran etexilate mesylate in the formulation is “5 to 60%, preferably 10 to 50%” and the amount of organic acid in the formulation is “usually between 20 and 90%, preferably between 20 and 80%.” The '779 publication, ¶ [0021]. The dabigatran etexilate mesylate in the working examples accounts for 20% and 40% of the total composition, respectively. *Id.* at Examples 1–2. The '220 publication discloses a formulation comprising two different granule populations in which the drug substance accounts for about 15 wt % of the formulation. The '220 publication, Example 13. The '890 publication discloses a formulation comprising two different granule populations in which the drug substance accounts for about 3 wt % of the formulation. The '890 publication, Example 1.

A POSA would have also known that the weight percent of the dabigatran etexilate mesylate in the formulation is a result-effective variable. As such, a POSA would have had a reason to routinely optimize the amount of drug to arrive at a composition comprising 0.01 wt % to 90 wt % of dabigatran etexilate mesylate, with a reasonable expectation of success in arriving at the composition of claim 3. Indeed, the '729 patent does not indicate that the claimed range is critical. Defendants are also not aware of any evidence that the claimed range was taught away from in the prior art, the claimed range is critical to the purported invention, led to unexpected results, or other objective indicia of nonobviousness exist with a connection to the claimed range.

Claim 5 would have been obvious. As discussed above, the '779 publication discloses formulating dabigatran etexilate with an organic acid to improve the solubility and absorption of the active. The '779 publication discloses that the “preferred” salt of the dabigatran etexilate is the mesylate salt. The '779 publication, ¶ [0014]. The '779 publication discloses several examples of dabigatran etexilate mesylate formulations, as well as a process for preparing dabigatran etexilate mesylate. *Id.* ¶¶ [0028], [0033], Examples 1–3.

The working examples of the '779 publication comprise 57.7 mg, 115.3 mg, or 173 mg of dabigatran etexilate mesylate. *Id.* ¶¶ [0028], [0033], Examples 1–2. These doses are encompassed by the claimed dosing range, rendering the claimed limitation obvious. As such, a POSA would have had a reason to use the mesylate salt of dabigatran etexilate in amounts of 50 mg to 200 mg, with a reasonable expectation of success in arriving at the composition of claim 5.

Accordingly, claims 3 and 5 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

d. Claim 4

Claim 4 depends from claim 1 and further specifies that the composition of claim 1 comprises “2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.” The analysis with respect to claim 1 is incorporated herein.

As discussed above, the ’779 publication discloses formulating dabigatran etexilate with an organic acid to improve the solubility and absorption of the active. The ’779 publication discloses that the “content of the pharmaceutically acceptable organic acid is usually between 20 and 90%, preferably between 20 and 80%.” The ’779 publication, ¶ [0021]. The organic acid (i.e., tartaric acid) in the working examples of the ’779 publication accounts for 61.3% and 38.5% of the total composition, respectively. *Id.* at Examples 1–2. As such, the ’779 publication discloses amounts of organic acid which overlap with the claimed range, rendering the limitation obvious.

The ’220 publication discloses a formulation comprising two different granule populations in which the organic acid (i.e., fumaric acid) accounts for about 36% of the formulation. The ’220 publication, Example 13. The ’890 publication discloses a formulation comprising two different granule populations in which the organic acid (i.e., fumaric acid) accounts for about 14% of the formulation. The ’890 publication, Example 1.

A POSA would have also known that the weight percent of the organic acid in the formulation is a result-effective variable. As such, a POSA would have had a reason to routinely optimize the amount of organic acid to arrive at a dabigatran etexilate mesylate composition comprising 2 wt % to 95 wt % of an organic acid, with a reasonable expectation of success in arriving at the composition of claim 4. Indeed, the ’729 patent does not indicate that the claimed range is critical. Defendants are also not aware of any evidence that the claimed range was taught away from in the prior art, the claimed range is critical to the purported invention, led to

unexpected results, or other objective indicia of nonobviousness exist with a connection to the claimed range.

Accordingly, claim 4 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

e. Claim 7

Claim 7 depends from claim 6 and further specifies that the first type of particles (i.e., the drug particles) in the composition of claim 1 are prepared by granulation. The analysis with respect to claims 1 and 6 are incorporated herein.

As discussed above, a POSA would have had a reason to prepare a formulation comprising separate granule populations of the dabigatran etexilate and an organic acid, with a reasonable expectation of success in arriving at the compositions of claims 1 and 6. The '220 and/or '890 publications both disclose methods of granulating the drug-containing granules. For example, the '220 publication discloses that the “[g]ranules can be prepared by any one of known methods for preparing granules such as wet granulation, dry granulation, layering granulation, melt-granulation, impregnated-granulation, etc.” The '220 publication, ¶ [0046]. The '890 publication discloses “granulating the ingredients after mixing them successively or granulating the ingredients simultaneously to yield granules for compression.” The '890 publication, ¶ [0076]. The '220 and/or '890 publications both disclose working examples in which drug-containing granules were prepared by granulation. The '220 publication, Example 13; the '890 publication, Example 1. As such, a POSA would have had a reason to prepare the dabigatran etexilate-containing granules by granulation, with a reasonable expectation of success in arriving at the composition of claim 7.

Accordingly, claim 7 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

f. Claim 11

Independent claim 11 recites:

11. A composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

Independent claim 11 is substantially similar to claim 2. Claim 11 only differs from claim 2, which depends from claim 1, by reciting the transitional phrase, "consisting of." The analysis with respect to claims 1 and 2 are incorporated herein.

For at least the reasons as discussed for claims 1 and 2 above, a POSA would have had a reason to develop a formulation consisting of dabigatran etexilate and an organic acid in separate granule populations with at least one pharmaceutically acceptable excipient, with a reasonable expectation of success in arriving at the composition of claim 11. For example, the '220 publication discloses mixing drug granules and organic acid granules with low-substituted hydroxypropylcellulose, precipitated calcium carbonate, and magnesium stearate before tableting. The '220 publication, ¶ [0113].

Accordingly, claim 11 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

g. Claim 12

Claim 12 depends from claim 11 and specifies that the composition of claim 11 comprises “from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.” The analysis with respect to claim 11 is incorporated herein.

As discussed above, the '779 publication discloses formulating dabigatran etexilate with an organic acid to improve the solubility and absorption of the active. The '779 publication discloses that the “preferred” salt of the dabigatran etexilate is the mesylate salt. The '779 publication, ¶ [0014]. The '779 publication discloses several examples of dabigatran etexilate mesylate formulations, as well as a process for preparing dabigatran etexilate mesylate. *Id.* at ¶¶ [0028], [0033], Examples 1–3. As such, a POSA would have had a reason to use the mesylate salt of dabigatran etexilate, with a reasonable expectation of success in arriving at the composition of claim 12.

The '779 publication also discloses that the amount of dabigatran etexilate mesylate in the formulation is “5 to 60%, preferably 10 to 50%” and the amount of organic acid in the formulation is “usually between 20 and 90%, preferably between 20 and 80%.” The '779 publication, ¶ [0021]. The dabigatran etexilate mesylate in the working examples accounts for 20% and 40% of the total composition, respectively. *Id.* at Examples 1–2. The '220 publication discloses a formulation comprising two different granule populations in which the drug substance accounts for about 15 wt % of the formulation. The '220 publication, Example 13. The '890 publication discloses a formulation comprising two different granule populations in

which the drug substance accounts for about 3 wt % of the formulation. The '890 publication, Example 1.

A POSA would have also known that the weight percent of the dabigatran etexilate mesylate in the formulation is a result-effective variable. As such, a POSA would have had a reason to routinely optimize the amount of drug to arrive at a composition comprising 0.01 wt % to 90 wt % of dabigatran etexilate mesylate, with a reasonable expectation of success in arriving at the composition of claim 12. Indeed, the '729 patent does not indicate that the claimed range is critical. Defendants are also not aware of any evidence that the claimed range was taught away from in the prior art, the claimed range is critical to the purported invention, led to unexpected results, or other objective indicia of nonobviousness exist with a connection to the claimed range.

Accordingly, claim 12 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

h. Claims 13 and 14

Claims 13 and 14 each depend from claim 11 and further recite, “wherein the first type of particles comprise at least one pharmaceutically acceptable excipient” (claim 13) and “least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof,” (claim 14) respectively. The analysis with respect to claim 11 is incorporated herein.

Claim 13 would have been obvious. As explained above for claims 2 and 10, the '220 and/or '890 publications both disclose incorporating additional excipients in the different granule populations. Both publications disclose the oral formulations “may contain additives generally used in the pharmaceutical solid preparations,” including binders, disintegrants, and lubricants. The '220 publication, ¶ [0034]; the '890 publication, ¶¶ [0057], [0081]. The '220 and/or '890

publications disclose working examples in which the drug substance is mixed with mannitol before granulation with hydroxypropylcellulose or polyvinylpyrrolidone. The '220 publication, Example 13; the '890 publication, Example 1. A POSA, therefore, would have had a reason to include at least one pharmaceutically acceptable excipient and arrive at the composition of claim 13 with a reasonable expectation of success.

Claim 14 would have been obvious. The '220 and/or '890 publications also disclose mixing the two different granule populations (i.e., the drug-containing granules and organic acid-containing granules) with pharmaceutically acceptable excipients before tableting. For example, the '220 publication discloses mixing the different granules with low-substituted hydroxypropylcellulose, precipitated calcium carbonate, and magnesium stearate before tableting. The '220 publication, ¶ [0113]. The '890 publication discloses mixing the different granules with aspartame before tableting. The '890 publication, ¶ [0133]. The '729 patent defines hydroxypropylcellulose as a binder, calcium carbonate as a diluent, and magnesium stearate as a lubricant. The '729 patent, 8:–6, 8:22–30, 8:35–36. In light of the art, a POSA would have had a reason to combine dabigatran etexilate-containing granules, organic acid-containing granules, and at least one pharmaceutically acceptable excipient, such as a binder, diluent, or lubricant, before manufacturing the final dosage form, with a reasonable expectation of success in arriving at the composition of claim 14.

Accordingly, claims 13 and 14 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

i. Claim 15

Claim 15 depends from claim 14, which depends from claim 11, and recites:

15. A capsule unit dosage form prepared from the composition according to claim 14, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

The analysis with respect to claims 11 and 14 is incorporated herein.

A POSA would have had a reason to prepare capsules comprising dabigatran etexilate-containing granules and organic acid-containing granules, with a reasonable expectation of success. The '220 publication discloses that while “tablets comprising a medicinal substance and an acidic substance separately in respective granules are preferred,” the granules may be filled into capsules. The '220 publication, ¶ [0035]. In fact, the '220 publication expressly discloses that “capsules can be manufactured by filling in hard capsules either a drug mixture obtained by mixing a medicinal substance, an acidic substance and, if necessary, a carbonate and a pharmaceutical additive(s) as it is, or in the form of powders, granules or tablets prepared in a manner as described above.” *Id.* at ¶ [0060]. Thus, a POSA would have had a reason to fill capsules with the different granules, as disclosed in the '220 publication, and would have reasonably expected to successfully do so. The '779 publication, for example, also discloses filling capsules with granules. *See, e.g.*, the '779 publication, Example 1.

Also, as discussed above, the '779 publication discloses that the “preferred” salt of the dabigatran etexilate is the mesylate salt. The '779 publication, ¶ [0014]. The '779 publication discloses several examples of dabigatran etexilate mesylate formulations, as well as a process for preparing dabigatran etexilate mesylate. *Id.* at ¶¶ [0028], [0033], Examples 1–3.

The working examples of the '779 publication comprise 57.7 mg, 115.3 mg, or 173 mg of dabigatran etexilate mesylate. *Id.* at ¶¶ [0028], [0033], Examples 1–2. These doses are encompassed by the claimed dosing range, rendering the claimed limitation obvious. As such, a POSA would have had a reason to use the mesylate salt of dabigatran etexilate in amounts of

50 mg to 200 mg, with a reasonable expectation of success in arriving at the composition of claim 15.

Accordingly, claim 15 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

j. Claim 16

Independent claim 16 recites:

16. A capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

Independent claim 16 is substantially similar to claim 11. Claim 16 only differs from claim 11 by specifying the dosage form is a capsule. The analysis with respect to claim 11 is incorporated herein.

A POSA would have had a reason to prepare capsules comprising dabigatran etexilate-containing granules and organic acid-containing granules, with a reasonable expectation of success. As explained above for claim 15, the '220 publication discloses that while “tablets comprising a medicinal substance and an acidic substance separately in respective granules are preferred,” the granules may be filled into capsules. The '220 publication, ¶ [0035]; *see also* ¶ [0058]. In fact, the '220 publication expressly discloses that “capsules can be manufactured by filling in hard capsules either a drug mixture obtained by mixing a medicinal substance, an acidic

substance and, if necessary, a carbonate and a pharmaceutical additive(s) as it is, or in the form of powders, granules or tablets prepared in a manner as described above.” *Id.* at ¶ [0060]. Thus, a POSA would have had a reason to fill capsules with the different granules, as disclosed in the ’220 publication, and would have reasonably expected to successfully do so. The ’779 publication, for example, also discloses filling capsules with granules. *See, e.g.*, the ’779 publication, Example 1.

Accordingly, claim 16 of the ’729 patent would have been *prima facie* obvious over the ’779 publication in combination with the ’220 publication and/or the ’890 publication, in view of the general knowledge in the art.

k. Claim 17

Claim 17 depends from claim 16 and specifies that the capsule contains “from 50 mg to 200 mg of dabigatran etexilate mesylate.” The analysis with respect to claim 16 is incorporated herein.

As discussed above, the ’779 publication discloses formulating dabigatran etexilate with an organic acid to improve the solubility and absorption of the active. The ’779 publication discloses that the “preferred” salt of the dabigatran etexilate is the mesylate salt. The ’779 publication, ¶ [0014]. The ’779 publication discloses several examples of dabigatran etexilate mesylate formulations, as well as a process for preparing dabigatran etexilate mesylate. *Id.* at ¶¶ [0028], [0033], Examples 1–3.

The working examples of the ’779 publication comprise 57.7 mg, 115.3 mg, or 173 mg of dabigatran etexilate mesylate. *Id.* at ¶¶ [0028], [0033], Examples 1–2. These doses are encompassed by the claimed dosing range, rendering the claimed limitation obvious. As such, a POSA would have had a reason to use the mesylate salt of dabigatran etexilate in amounts of

50 mg to 200 mg, with a reasonable expectation of success in arriving at the composition of claim 17.

Accordingly, claim 17 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

I. Claim 18

Claim 18 depends from claim 16 and further recites, “wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.” The analysis with respect to claim 16 is incorporated herein.

As explained above for claims 2, 10, 13, and 14, the '220 and/or '890 publications both disclose incorporating additional excipients in the different granule populations. Both publications disclose the oral formulations “may contain additives generally used in the pharmaceutical solid preparations,” including binders, disintegrants, and lubricants. The '220 publication, ¶ [0034]; the '890 publication, ¶¶ [0057], [0081]. The '220 and/or '890 publications disclose working examples in which the drug substance is mixed with mannitol before granulation with hydroxypropylcellulose or polyvinylpyrrolidone. The '220 publication, Example 13; the '890 publication, Example 1. As such, a POSA would have had a reason to incorporate at least one pharmaceutically acceptable excipient in the dabigatran etexilate-containing granules, with a reasonable expectation of success in arriving at the composition of claim 18.

Accordingly, claim 18 of the '729 patent would have been *prima facie* obvious over the '779 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

2. The Asserted Claims would have been obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication in view of the general knowledge in the art

a. Claim 1

Claim 1 is directed, *inter alia*, to a composition comprising at least two distinct types of particles wherein the first type of particles comprise dabigatran etexilate and is free of organic or inorganic acids, and the second type of particles comprise at least one organic acid, is coated with a protective coating layer, and is free of dabigatran etexilate.

A formulation comprising dabigatran etexilate and an organic acid, as was known in the prior art, would have been obvious to a POSA. Moreover, a formulation comprising two different types of granules would have immediately been obvious to a POSA who was developing a dabigatran etexilate formulation.

Dabigatran etexilate was approved as PRADAXA[®] by the FDA to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The PRADAXA 2010 Label, 2. PRADAXA contains 172.95 mg or 86.48 mg of dabigatran etexilate mesylate and acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid as inactive ingredients. *Id.* at 4.

A POSA would have known from the prior art that dabigatran etexilate's absorption was inconsistent and variable in neutral or basic pH environments in the gastrointestinal tract. *See, e.g.*, Eisert, 1887; Hankey, 1437; Clinical Pharmacology Review, 16; the '427 publication, 1. A POSA would have also known that dabigatran etexilate was acid-labile and chemically unstable in an acidic environment. *See, e.g.*, the '156 publication, 3; Chemistry Review, 3; the '322 publication, 2:28–34.

Thus, a POSA looking to develop a dabigatran etexilate formulation would have understood the need to incorporate an organic acid into the formulation to improve dabigatran etexilate's solubility and absorption while also protecting the drug from the organic acid to prevent stability issues. A POSA would have had a reason to combine the PRADAXA label with the '220 and/or '890 publications and arrive at such a formulation design with a reasonable expectation of success. The '220 and/or '890 publications both relate to increasing the solubility and absorption of a drug (e.g., a PDE-V inhibitor) that has reduced solubility in neutral or basic regions by formulating the drug with an acidic substance. The '220 publication, Abstract; the '890 publication, Abstract. Sildenafil, an exemplary PDE-V inhibitor, has a 23-fold higher solubility at an acidic pH of 1.2 (2.52 mg/mL) than at a neutral pH of 6.8 (0.11 mg/mL). The '220 publication, ¶ [0003]; *see also* the '890 publication, ¶ [0031] ("Examples of such medicinal substances include those of which solubility in water at 25° C. is not greater than 0.1 mg/mL at pH of 7 or above and is not less than 1 mg/mL at pH of 2 or below, preferably those of which solubility in water (25° C.) at pH 1.2 is not less than 10-fold, preferably not less than 100-fold compared to the solubility in water (25° C.) at pH 7."). The '220 publication discloses formulating the PDE-V inhibitor with an "acidic substance" to "exert drug efficacy rapidly after administration." The '220 publication, ¶ [0008]; *see also* the '890 publication, ¶ [0025].

Examples of an appropriate "acidic substance" include "any substance on condition that it shows pH 4.0 or below when dissolved in water and does not interfere with the efficacy of a medicinal substance as an active ingredient." The '220 publication, ¶ [0029]; *see also* the '890 publication, ¶ [0026]. Preferred acidic substances include organic acids, such as fumaric acid, tartaric acid, succinic acid, malic acid, ascorbic acid, and aspartic acid. The '220 publication, ¶ [0029]; the '890 publication, ¶ [0026].

The '220 and/or '890 publications disclose formulating the drug substance separately from the acidic substance in respective granule populations. The '220 publication discloses that “tablets comprising a medicinal substance and an acidic substance separately in respective granules are preferred.” The '220 publication, ¶ [0035]; *see also* ¶ [0058]. The '220 and/or '890 publications both disclose working examples in which a PDE-V inhibitor and fumaric acid is granulated separately as two different granule populations. The '220 publication, Example 13; the '890 publication, Example 1.

The '220 publication also discloses coating the formulations to prevent abrasion and improve stability. The '220 publication, ¶ [0061]. Coatings can be used “in a conventional manner,” in a “coating amount ... that does not disturb the dissolution of a medicinal substance.” *Id.* The fumaric acid granules in the '890 publication's Example 1, for example, are coated with HPMC. The '890 publication, Example 1. A POSA would have understood the importance of isolating the organic acid (via with a coating) from the dabigatran etexilate because of the drug's acid sensitivity. *See, e.g.*, the '322 publication, 2:28–34.

A POSA developing a dabigatran etexilate formulation would have looked to the '220 and/or '890 publications because these publications disclose formulations using an organic acid to improving the solubility and absorption of a pH-dependent drug, similar to dabigatran etexilate. Following the '220 and/or '890 publications' teachings, a POSA would have had a reason to prepare a formulation comprising separate granule populations of the dabigatran etexilate and an organic acid. A POSA would have recognized the importance of coating the organic acid granules, as taught by the '220 and/or '890 publications, to prevent the organic acid from coming into contact with the dabigatran etexilate. A POSA would have had a reasonable

expectation of success in preparing such a dabigatran etexilate formulation in light of the common knowledge and skill in the art.

The Applicants seems to have argued during prosecution of the '729 patent that a food effect would have existed if the dabigatran etexilate and organic acid were formulated in two different particles. *See* the '729 patent File History, Applicant Remarks filed June 1, 2016, 8. However, the '220 publication discloses that a composition comprising an active agent and organic acid in separate granules which “achieve[s] rapid expression of efficacy of the active ingredient even when the preparation is administered to a subject who is suffering from an acidity or who intends to take the same just after eating.” The '220 publication, ¶ [0007]; *see also* ¶ [0130]. As such, a POSA would have reasonably expected a formulation comprising dabigatran etexilate and an organic acid in separate granules to not exhibit a food effect, as taught by the '220 publication. And, in fact, the Applicant’s own bioavailability data demonstrates that there was no difference between the bioavailability of a two granule formulation compared to a one granule formulation when administered under fed conditions. *See* the '729 patent File History, Declaration of Zhengguo Xu filed June 1, 2016, 2.

The prior art combination of the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or '890 publication is different from the art raised by the Examiner during prosecution of the '729 patent. During prosecution, the Examiner rejected the pending claims over the '779 publication in combination with U.S. Patent Publication No. 2008/0069891 (“the '891 publication”). The Applicants overcame this combination on Appeal by arguing, in part, that the '891 publication was “not related at all to, or concerned with, the necessity of a close proximity between an acid and active ingredient to obtain a desired result,

i.e., an acidic environment that allows for diffusion.” See the ’729 patent File History, Appeal Brief filed December 6, 2019, 10.

In fact, while the ’891 publication discloses two types of particles, wherein the first particle comprises an active agent, the second particle comprises a “fat/wax material present in an amount *sufficient to inhibit administration abuse of the API from the first particle.*” The ’891 publication, ¶ [0020]. On the contrary, the acid-containing particle in the composition disclosed in the ’220 and/or ’890 publications is meant to improve the solubility and absorption of a pH-dependent drug, such as dabigatran.

Accordingly, claim 1 of the ’729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the ’322 publication in combination with the ’220 publication and/or the ’890 publication, in view of the general knowledge in the art.

b. Claims 2, 6, and 10

Claim 2 depends from claim 1 and specifies that the composition of claim 1 further comprises at least one pharmaceutically acceptable excipient. Claim 6 depends from claim 2 and recites, “[a] process for the preparation of the composition according to claim 2, comprising the step of mixing the first type of particles and the second type of particles with the at least one pharmaceutically acceptable excipient.” Claim 10 depends from claim 2 and further recites, “wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.” The analysis with respect to claim 1 is incorporated herein.

Claims 2 and 10 would have been obvious. The ’220 and/or ’890 publications both disclose incorporating additional excipients in the different granule populations. Both publications disclose the oral formulations “may contain additives generally used in the pharmaceutical solid preparations,” including binders, disintegrants, and lubricants. The ’220

publication, ¶ [0034]; the '890 publication, ¶¶ [0057], [0081]. The '220 and/or '890 publications disclose working examples in which the drug substance is mixed with mannitol before granulation with hydroxypropylcellulose or polyvinylpyrrolidone. The '220 publication, Example 13; the '890 publication, Example 1. A POSA, therefore, would have had a reason to include at least one pharmaceutically acceptable excipient selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof and arrive at the compositions of claims 2 and 10 with a reasonable expectation of success.

Claim 6 would have been obvious. The '220 and/or '890 publications also disclose mixing the two different granule populations (i.e., the drug-containing granules and organic acid-containing granules) with pharmaceutically acceptable excipients before tableting. For example, the '220 publication discloses mixing the different granules with low-substituted hydroxypropylcellulose, precipitated calcium carbonate, and magnesium stearate before tableting. The '220 publication, ¶ [0113]. The '890 publication discloses mixing the different granules with aspartame before tableting. The '890 publication, ¶ [0133]. The '729 patent defines hydroxypropylcellulose as a binder, calcium carbonate as a diluent, and magnesium stearate as a lubricant. The '729 patent, 8:–6, 8:22–30, 8:35–36. In light of the art, a POSA would have had a reason to combine dabigatran etexilate-containing granules, organic acid-containing granules, and at least one pharmaceutically acceptable excipient, such as a binder, diluent, or lubricant, before manufacturing the final dosage form, with a reasonable expectation of success in arriving at the composition of claim 6.

Accordingly, claims 2, 6, and 10 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

c. Claims 3 and 5

Claims 3 and 5 depend from claim 1 and further specify that the composition of claim 1 comprises “from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate” (claim 3) and that the composition of claim 1 comprises “from 50 mg to 200 mg of dabigatran etexilate mesylate” (claim 5). The analysis with respect to claim 1 is incorporated herein.

Claim 3 would have been obvious. The '220 publication discloses a formulation comprising two different granule populations in which the drug substance accounts for about 15 wt % of the formulation. The '220 publication, Example 13. The '890 publication discloses a formulation comprising two different granule populations in which the drug substance accounts for about 3 wt % of the formulation. The '890 publication, Example 1. The '322 publication also discloses dabigatran etexilate formulations in which the drug substance accounts for about 40 wt % of the formulations. The '322 publication, 16, Example 5.

A POSA would have also known that the weight percent of the dabigatran etexilate mesylate in the formulation is a result-effective variable. As such, a POSA would have had a reason to routinely optimize the amount of drug to arrive at a composition comprising 0.01 wt % to 90 wt % of dabigatran etexilate mesylate, with a reasonable expectation of success in arriving at the composition of claim 3. Indeed, the '729 patent does not indicate that the claimed range is critical. Defendants are also not aware of any evidence that the claimed range was taught away from in the prior art, the claimed range is critical to the purported invention, led to unexpected results, or other objective indicia of nonobviousness exist with a connection to the claimed range.

Claim 5 would have been obvious. As discussed above, the PRADAXA 2010 Label discloses a dabigatran etexilate mesylate formulation comprising 172.95 mg and 86.48 mg of the drug. The PRADAXA 2010 Label, 4. The '322 publication also discloses dabigatran etexilate mesylate formulations comprising 126.83 mg and 86.48 mg of the drug. The '322 publication,

16, Example 5. These amounts are encompassed by the claimed range, rendering the limitation obvious. As such, a POSA would have had a reason to use the mesylate salt of dabigatran etexilate in amounts of 50 mg to 200 mg, with a reasonable expectation of success in arriving at the composition of claim 5.

Accordingly, claims 3 and 5 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

d. Claim 4

Claim 4 depends from claim 1 and further specifies that the composition of claim 1 comprises “2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.” The analysis with respect to claim 1 is incorporated herein.

As discussed above, the '220 publication discloses a formulation comprising two different granule populations in which the organic acid (i.e., fumaric acid) accounts for about 36% of the formulation. The '220 publication, Example 13. The '890 publication discloses a formulation comprising two different granule populations in which the organic acid (i.e., fumaric acid) accounts for about 14% of the formulation. The '890 publication, Example 1. The '322 publication also discloses dabigatran etexilate formulations in which the organic acid accounts for about 41 wt % of the formulations. The '322 publication, 16, Example 5.

A POSA would have also known that the weight percent of the organic acid in the formulation is a result-effective variable. As such, a POSA would have had a reason to routinely optimize the amount of organic acid to arrive at a dabigatran etexilate mesylate composition comprising 2 wt % to 95 wt % of an organic acid, with a reasonable expectation of success in arriving at the composition of claim 4. Indeed, the '729 patent does not indicate that the claimed range is critical. Defendants are also not aware of any evidence that the claimed range was taught

away from in the prior art, the claimed range is critical to the purported invention, led to unexpected results, or other objective indicia of nonobviousness exist with a connection to the claimed range.

Accordingly, claim 4 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

e. Claim 7

Claim 7 depends from claim 6 and further specifies that the first type of particles (i.e., the drug particles) in the composition of claim 1 are prepared by granulation. The analysis with respect to claims 1 and 6 are incorporated herein.

As discussed above, a POSA would have had a reason to prepare a formulation comprising separate granule populations of the dabigatran etexilate and an organic acid, with a reasonable expectation of success in arriving at the compositions of claims 1 and 6. The '220 and/or '890 publications both disclose methods of granulating the drug-containing granules. For example, the '220 publication discloses that the “[g]ranules can be prepared by any one of known methods for preparing granules such as wet granulation, dry granulation, layering granulation, melt-granulation, impregnated-granulation, etc.” The '220 publication, ¶ [0046]. The '890 publication discloses “granulating the ingredients after mixing them successively or granulating the ingredients simultaneously to yield granules for compression.” The '890 publication, ¶ [0076]. The '220 and/or '890 publications both disclose working examples in which drug-containing granules were prepared by granulation. The '220 publication, Example 13; the '890 publication, Example 1. As such, a POSA would have had a reason to prepare the dabigatran etexilate-containing granules by granulation, with a reasonable expectation of success in arriving at the composition of claim 7.

Accordingly, claim 7 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

f. Claim 11

Independent claim 11 recites:

11. A composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

Independent claim 11 is substantially similar to claim 2. Claim 11 only differs from claim 2, which depends from claim 1, by reciting the transitional phrase, "consisting of." The analysis with respect to claims 1 and 2 are incorporated herein.

For at least the same reasons as discussed for claims 1 and 2 above, a POSA would have had a reason to develop a formulation consisting of dabigatran etexilate and an organic acid in separate granule populations with at least one pharmaceutically acceptable excipient, with a reasonable expectation of success in arriving at the composition of claim 11. For example, the '220 publication discloses mixing drug granules and organic acid granules with low-substituted hydroxypropylcellulose, precipitated calcium carbonate, and magnesium stearate before tableting. The '220 publication, ¶ [0113].

Accordingly, claim 11 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

g. Claim 12

Claim 12 depends from claim 11 and specifies that the composition of claim 11 comprises “from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.” The analysis with respect to claim 11 is incorporated herein.

As discussed above, the PRADAXA 2010 Label discloses a dabigatran etexilate mesylate formulation comprising 172.95 mg and 86.48 mg of the drug. The PRADAXA 2010 Label, 4. The '322 publication also discloses dabigatran etexilate mesylate formulations comprising 126.83 mg and 86.48 mg of the drug. The '322 publication, 16, Example 5. As such, a POSA would have had a reason to use the mesylate salt of dabigatran etexilate, with a reasonable expectation of success in arriving at the composition of claim 12.

The '220 publication discloses a formulation comprising two different granule populations in which the drug substance accounts for about 15 wt % of the formulation. The '220 publication, Example 13. The '890 publication discloses a formulation comprising two different granule populations in which the drug substance accounts for about 3 wt % of the formulation. The '890 publication, Example 1. The '322 publication also discloses dabigatran etexilate formulations in which the drug substance accounts for about 40 wt % of the formulations. The '322 publication, 16, Example 5.

A POSA would have also known that the weight percent of the dabigatran etexilate mesylate in the formulation is a result-effective variable. As such, a POSA would have had a reason to routinely optimize the amount of drug to arrive at a composition comprising 0.01 wt % to 90 wt % of dabigatran etexilate mesylate, with a reasonable expectation of success in arriving

at the composition of claim 12. Indeed, the '729 patent does not indicate that the claimed range is critical. Defendants are also not aware of any evidence that the claimed range was taught away from in the prior art, the claimed range is critical to the purported invention, led to unexpected results, or other objective indicia of nonobviousness exist with a connection to the claimed range.

Accordingly, claim 12 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

h. Claims 13 and 14

Claims 13 and 14 each depend from claim 11 and further recite, “wherein the first type of particles comprise at least one pharmaceutically acceptable excipient” (claim 13) and “least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof” (claim 14). The analysis with respect to claim 11 is incorporated herein.

Claim 13 would have been obvious. As explained above for claims 2 and 10, the '220 and/or '890 publications both disclose incorporating additional excipients in the different granule populations. Both publications disclose the oral formulations “may contain additives generally used in the pharmaceutical solid preparations,” including binders, disintegrants, and lubricants. The '220 publication, ¶ [0034]; the '890 publication, ¶¶ [0057], [0081]. The '220 and/or '890 publications disclose working examples in which the drug substance is mixed with mannitol before granulation with hydroxypropylcellulose or polyvinylpyrrolidone. The '220 publication, Example 13; the '890 publication, Example 1. A POSA, therefore, would have had a reason to include at least one pharmaceutically acceptable excipient and arrive at the composition of claim 13 with a reasonable expectation of success.

Claim 14 would have been obvious. The '220 and/or '890 publications also disclose mixing the two different granule populations (i.e., the drug-containing granules and organic acid-containing granules) with pharmaceutically acceptable excipients before tableting. For example, the '220 publication discloses mixing the different granules with low-substituted hydroxypropylcellulose, precipitated calcium carbonate, and magnesium stearate before tableting. The '220 publication, ¶ [0113]. The '890 publication discloses mixing the different granules with aspartame before tableting. The '890 publication, ¶ [0133]. The '729 patent defines hydroxypropylcellulose as a binder, calcium carbonate as a diluent, and magnesium stearate as a lubricant. The '729 patent, 8:3–6, 8:22–30, 8:35–36. In light of the art, a POSA would have had a reason to combine dabigatran etexilate-containing granules, organic acid-containing granules, and at least one pharmaceutically acceptable excipient, such as a binder, diluent, or lubricant, before manufacturing the final dosage form, with a reasonable expectation of success in arriving at the composition of claim 14.

Accordingly, claims 13 and 14 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

i. Claim 15

Claim 15 depends from claim 14, which depends from claim 11, and recites:

15. A capsule unit dosage form prepared from the composition according to claim 14, which comprises from 50 mg to 200 mg of dabigatran etexilate mesylate.

The analysis with respect to claims 11 and 14 is incorporated herein.

A POSA would have had a reason to prepare capsules comprising dabigatran etexilate-containing granules and organic acid-containing granules, with a reasonable expectation of success. The '220 publication discloses that while “tablets comprising a medicinal substance and

an acidic substance separately in respective granules are preferred,” the granules may be filled into capsules. The ’220 publication, ¶ [0035]; *see also* ¶ [0058]. In fact, the ’220 publication expressly discloses that “capsules can be manufactured by filling in hard capsules either a drug mixture obtained by mixing a medicinal substance, an acidic substance and, if necessary, a carbonate and a pharmaceutical additive(s) as it is, or in the form of powders, granules or tablets prepared in a manner as described above.” *Id.* at ¶ [0060]. Thus, a POSA would have had a reason to fill capsules with the different granules, as disclosed in the ’220 publication, and would have reasonably expected to successfully do so. The PRADAXA 2010 Label also specifies that the PRADAXA product is a capsule. The PRADAXA 2010 Label, 1–2, 4. The ’322 publication also discloses dabigatran etexilate capsule formulations. The ’322 publication, 2:22–23; Example 5.

Also, as discussed above, the PRADAXA 2010 Label discloses a dabigatran etexilate mesylate formulation comprising 172.95 mg and 86.48 mg of the drug. The PRADAXA 2010 Label, 4. The ’322 publication also discloses dabigatran etexilate mesylate formulations comprising 126.83 mg and 86.48 mg of the drug. The ’322 publication, 16, Example 5. These amounts are encompassed by the claimed range, rendering the limitation obvious. As such, a POSA would have had a reason to use the mesylate salt of dabigatran etexilate in amounts of 50 mg to 200 mg, with a reasonable expectation of success in arriving at the composition of claim 15.

Accordingly, claim 15 of the ’729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the ’322 publication in combination with the ’220 publication and/or the ’890 publication, in view of the general knowledge in the art.

j. Claim 16

Independent claim 16 recites:

16. A capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient, wherein

a) the first type of particles comprise dabigatran etexilate in the form of the free base or in the form of a pharmaceutically acceptable salt or polymorph thereof, wherein the first type of particles is free from organic and inorganic acids; and

b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein the second type of particles is coated with a protective coating layer and is free from dabigatran etexilate.

Independent claim 16 is substantially similar to claim 11. Claim 16 only differs from claim 11 by specifying that the dosage form is a capsule. The analysis with respect to claim 11 is incorporated herein.

A POSA would have had a reason to prepare capsules comprising dabigatran etexilate-containing granules and organic acid-containing granules, with a reasonable expectation of success. As explained above for claim 15, the '220 publication discloses that while “tablets comprising a medicinal substance and an acidic substance separately in respective granules are preferred,” the granules may be filled into capsules. The '220 publication, ¶ [0035]; *see also* ¶ [0058]. In fact, the '220 publication expressly discloses that “capsules can be manufactured by filling in hard capsules either a drug mixture obtained by mixing a medicinal substance, an acidic substance and, if necessary, a carbonate and a pharmaceutical additive(s) as it is, or in the form of powders, granules or tablets prepared in a manner as described above.” *Id.* at ¶ [0060]. Thus, a POSA would have had a reason to fill capsules with the different granules, as disclosed in the '220 publication, and would have reasonably expected to successfully do so. The PRADAXA 2010 Label, for example, specifies that the PRADAXA product is a capsule. The PRADAXA 2010 Label, 1–2, 4. The '322 publication also discloses dabigatran etexilate capsule formulations. The '322 publication, 2:22–23; Example 5.

Accordingly, claim 16 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

k. Claim 17

Claim 17 depends from claim 16 and specifies that the capsule contains “from 50 mg to 200 mg of dabigatran etexilate mesylate.” The analysis with respect to claim 16 is incorporated herein.

As discussed above, the PRADAXA 2010 Label discloses a dabigatran etexilate mesylate formulation comprising 172.95 mg and 86.48 mg of the drug. The PRADAXA 2010 Label, 4. The '322 publication also discloses dabigatran etexilate mesylate formulations comprising 126.83 mg and 86.48 mg of the drug. The '322 publication, 16, Example 5. These amounts are encompassed by the claimed range, rendering the limitation obvious. As such, a POSA would have had a reason to use the mesylate salt of dabigatran etexilate in amounts of 50 mg to 200 mg, with a reasonable expectation of success in arriving at the composition of claim 17.

Accordingly, claim 17 of the '729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the '322 publication in combination with the '220 publication and/or the '890 publication, in view of the general knowledge in the art.

l. Claim 18

Claim 18 depends from claim 16 and further recites, “wherein the first type of particles comprise at least one pharmaceutically acceptable excipient.” The analysis with respect to claim 16 is incorporated herein.

As explained above for claims 2, 10, 13, and 14, the '220 and/or '890 publications both disclose incorporating additional excipients in the different granule populations. Both publications disclose that the oral formulations “may contain additives generally used in the

pharmaceutical solid preparations,” including binders, disintegrants, and lubricants. The ’220 publication, ¶ [0034]; the ’890 publication, ¶¶ [0057], [0081]. The ’220 and/or ’890 publications disclose working examples in which the drug substance is mixed with mannitol before granulation with hydroxypropylcellulose or polyvinylpyrrolidone. The ’220 publication, Example 13; the ’890 publication, Example 1. As such, a POSA would have had a reason to incorporate at least one pharmaceutically acceptable excipient in the dabigatran etexilate-containing granules, with a reasonable expectation of success in arriving at the composition of claim 18.

Accordingly, claim 18 of the ’729 patent would have been *prima facie* obvious over the PRADAXA 2010 Label and the ’322 publication in combination with the ’220 publication and/or the ’890 publication, in view of the general knowledge in the art.

3. Lack of Secondary Considerations Supporting Non-Obviousness of the ’729 Patent

Breckenridge has so far not come forward with any purported evidence or argument of secondary considerations of non-obviousness, and Defendants are not aware of any such evidence or argument. Hetero reserves the right and ability to amend, supplement, or modify these contentions to address any evidence or argument of secondary considerations that Breckenridge or its experts may raise. But even if Breckenridge does come forward with purported evidence of secondary considerations of non-obviousness, any such evidence or argument would be insufficient to overcome the strong case of obviousness articulated above. *See Leapfrog*, 485 F.3d 1157 (Fed. Cir. 2007); *Newell Cos.*, 864 F.2d at 768-69; *Pfizer*, 480 F.3d 1348 (Fed. Cir. 2007).

The prosecution history of the ’729 patent shows that during prosecution of the ’729 patent, the Applicants argued that the claimed formulation unexpectedly provided a faster

dissolution rate at earlier time points (10 and 15 minutes) compared to the formulation disclosed in the '779 publication. *See* the '729 patent File History, Tyebji Declaration filed June 1, 2016.³ Specifically, the Tyebji Declaration compared the dissolution profiles of the two compositions, as shown below:

Time (minutes)	% Release	
	Formulation A (two types of pellets)	Formulation B (one type of pellets)
10	65.1	19.2
15	79.2	57
20	86.7	86.1
30	92	97
45	95.5	97.6
60	96.8	98.5

To the extent Breckenridge alleges purported unexpected results vis-à-vis the dissolution profile of the claimed formulations, such expected results are not sufficient to support the non-obviousness of the '729 patent for the following reasons. *First*, the Tyebji Declaration shows a comparison between a formulation containing two types of pellets to a formulation containing only one type of pellet.

Second, the dissolution data for Formulation A are not, in fact, superior to Formulation B. As shown in the table above, while Formulation A (which is allegedly embodied by the claims of the '729 patent) has a faster dissolution rate for the first 15 minutes, by the 20-minute time point, the dissolution rates of the two formulations are almost identical (86.7% vs. 86.1). And, in fact, by the 30-minute time point, the '779 publication formulation (Formulation B) has a slightly faster dissolution rate than the Applicant's Formulation A (97% vs. 92%).

³ The Applicants did not alleged any secondary considerations related to long-felt but unmet need, commercial success, skepticism then praise, commercial acquiescence through licensing, industry praise, copying by others, or teaching away.

Third, the data in the Tyebji Declaration would not have been unexpected to a POSA. A POSA would have expected the '729 patent's formulation to release the drug more quickly at the early time point due to the differences between the two formulations. Specifically, the dabigatran etexilate-containing granules in the '729 patent formulation are not coated, while the dabigatran etexilate-containing granules in the '779 publication formulation are coated with hydroxypropylcellulose. The additional coating on the dabigatran etexilate-containing granules would delay the release of the drug slightly as the coating needs to dissolve before the drug is released. However, once the coating dissolves from the '779 publication's formulation, the drug would have been expected to be released quickly, as demonstrated by the dissolution profile data in the Tyebji Declaration. A POSA would have expected the tartaric acid-containing granules in the '729 patent formulation to improve the solubility of the dabigatran etexilate, allowing for a rate of absorption similar to that of the '779 publication's formulation (as shown by their similar blood plasma concentrations after administration to a patient), as demonstrated by the Wu Declaration also submitted by the Applicants during prosecution. *See* the '729 patent File History, Wu Declaration filed June 1, 2016.

In addition, Breckenridge seems to allege that a POSA would not have expected a two pellet formulation (e.g., Formulation A) to be bioequivalent to the '779 publication's formulation (e.g., Formulation B). *See* the '729 patent File History, Wu Declaration filed June 1, 2016. However, this argument is flawed. As explained above, generic drug developers designing around the dabigatran etexilate formulation disclosed in the '779 publication would have wanted to develop a formulation that was bioequivalent to the '779 publication's formulation in order to obtain FDA approval of a generic product.

Fourth, at best, the data in the Tyebji Declaration show a difference in degree not a difference in kind.

Fifth, Breckenridge has not presented any evidence, data, or argument to demonstrate that any evidence of unexpected results is commensurate with the scope of the claims.

Sixth, Breckenridge has not presented any evidence, data or argument to demonstrate a nexus to the claimed subject matter, or that any such unexpected results are coextensive with the claimed subject matter.

Additionally, there are no alleged unexpected results or any other secondary consideration of non-obviousness in view of the near simultaneous invention of dabigatran formulations containing two types of pellets by independent researchers before the '426 application published and became publicly available. Evidence of a simultaneous invention may be relied on to demonstrate the level of ordinary skill in the art and that POSAs understood the problem in the art and developed a solution to that problem. *See Regents of the Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1296 (Fed. Cir. 2018); *see also Ecolochem v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000). Evidence of a simultaneous invention is considered “persuasive” evidence that the claimed invention was the product only of ordinary skill when there is “[i]ndependently made, simultaneous inventions, made within a comparatively short space of time.” *George M. Martin Co. v. Alliance Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010). In this case, evidence of simultaneous invention can be found in the following exemplary patent applications of other companies:

- Indian Patent Application No. 438/CHE/2013, filed on January 31, 2013, by Dr. Reddys Laboratories Limited (“Dr. Reddys Application”)

- Indian Patent Application No. 1318/MUM/2013, filed on April 5, 2013, by V-Ensure Pharma Technologies Private Limited (“V-Ensure Application”)

Both applications disclose capsules comprising dabigatran etexilate granules and coated tartaric acid granules. Dr. Reddys Application, 29–30, Example 6; V-Ensure Application, 13–14, Example 4. Discovery will provide additional evidence of simultaneous invention.

Defendants reserve the right to rebut any secondary considerations of non-obviousness identified, alleged, or otherwise raised by Plaintiff.

C. The Asserted Claims of the ’729 Patent Are Invalid Under 35 U.S.C. § 112 for Lacking Written Description and Enablement

The Asserted Claims of the ’729 patent are directed, in part, to a composition comprising “dabigatran etexilate in the form ... of a pharmaceutically acceptable salt or polymorph thereof.” The ’729 patent, claims 1, 11, and 16. While the ’729 patent states that “[p]harmaceutically acceptable salts are well known in the art,” the ’729 patent provides no written description support for all “pharmaceutically acceptable salt form[s]” of the claimed compound. Rather, the ’729 patent only discloses the mesylate salt. *See, e.g.*, the ’729 patent, 2:4–5, 3:54, 3:64, 4:9, 4:12–22, 4:39–40, Examples 1–3, claims 3, 5, 12, 15, and 17. The working examples of the ’729 patent also only use the mesylate salt of dabigatran etexilate. *Id.* at Examples 1–3. There is no indication that the inventors were in possession of any other pharmaceutically acceptable salt encompassed by claims 1, 2, 4, 6, 7, 10, 11, 12, 14, 16, and 18 of the ’729 patent. Nor does the ’729 patent enable a POSA to make or use any other dabigatran etexilate salt encompassed by the claims, other than the mesylate salt.

Further, the ’729 patent only describes two polymorphic forms of dabigatran etexilate mesylate, with reference to International Patent Publication No. WO2005/028468 (“the WO ’468 publication”), which is not incorporated by reference. The ’729 patent, 2:13–14. This PCT

application discloses two polymorphs: Form I and Form II, as well as a hemihydrate crystal form. However, a later patent application, PCT/EP2007/062415, discloses additional polymorphic forms: anhydrous Form III, anhydrous Form IV, a monohydrate Form I, a monohydrate Form II, and a solvate Form I. *See* WO2008/059029. Furthermore, a later European patent application, EP 2610251A1, published after the '729 priority date, discloses two additional polymorphic forms: Form P and Form Q. Thus, dabigatran etexilate appears to be highly polymorphic, with many polymorphic forms identified and the further characterization of additional forms possible.

However, the '729 patent is silent as to other polymorphic forms of the free base or salts thereof beyond Forms I and II. Thus, the Asserted Claims encompass polymorphic forms that the inventors did not conceive or have possession of as of the filing date of the '729 patent. Moreover, the '729 patent does not teach a POSA how to make and characterize these additional polymorphic forms.

During prosecution, the Examiner rejected pending claims under 35 U.S.C. § 112, first paragraph, alleging that the claims lacked adequate written description for the term polymorph. The '729 patent File History, Non-final Rejection mailed September 30, 2015, 3–5. In response, the Applicant argued that the WO '468 publication discloses anhydrous Forms I and II and “applicant was in possession of polymorphic forms of dabigatran etexilate.” The '729 patent File History, Applicants Remarks filed December 29, 2015, 2–3. However, the Examiner did not consider that polymorphic forms beyond Forms I and II exist. As the claims read on all polymorphic forms, and forms beyond Form I and II, in fact, do exist, the '729 patent would not adequately describe and enable all the polymorphic forms of dabigatran etexilate encompassed by the Asserted Claims.

The Asserted Claims also recite, “wherein the second type of particles is coated with a protective coating layer.” *Id.* at claims 1, 11, and 16. The term “protective coating layer” is expressly defined in the ’729 patent in a broad way to mean “a layer of a polymeric or non-polymeric material disposed on the surface of a particle core in order to avoid direct contact of the particle core with its environment.” *Id.* at 5:40-43. The ’729 patent then provides examples of “protective coating layers” that a POSA would typically consider modified-release coatings, such as ethyl cellulose, acrylic copolymers (e.g., Eudragit RL and RS), and shellac. Thus, the definition would be understood to encompass any coating, including a “protective coating layer” that would modify—by slowing or delaying—the release of the acid.

The purpose of the discrete acid particles in the claimed invention is to create an acidic environment to increase the solubility of the dabigatran. As the dabigatran etexilate is present in an immediate release formulation, the acid must be released rapidly as well. This provides “a quick dissolution particularly at earlier time points.” *Id.* at 3:7-8. The dissolution data presented in the ’729 patent suggests this effect is seen within the first 15 minutes of dissolution, e.g., 79.2% within 15 minutes. *Id.* at 15:44–60. This suggests a release more rapid than the standard definition for an immediate release formulation, i.e., 85% within 30 minutes. As this increase in dissolution happens very rapidly, any “protective coating layer” that delays release of acid, would impede its function. That is, it would not achieve quick dissolution of the dabigatran, mediated by a more acidic environment, as the acid would not be sufficiently released to achieve the dissolution rate relied upon by the patent.

The Asserted Claims of the ’729 patent encompass protective coating layers that would not function as required, e.g., pH-dependent coating layers with a methacrylate enteric coating, which would not release the acid at all in the stomach. Thus, there would be significant

inoperative embodiments, where the release would not precede or be at the same time as the release of the dabigatran from their granules. As such, the '729 patent has not enabled a POSA to make or use the broad scope of the claims.

Accordingly, the Asserted Claims of the '729 patent are invalid under 35 U.S.C. § 112, first paragraph, for lacking written description and enablement support.

D. The Asserted Claims of the '729 Patent Are Invalid Under 35 U.S.C. § 112 as Being Indefinite

The Asserted Claims of the '729 patent require “two distinct types of particles.” Hetero asserts that the phrase, “two distinct types of particles” should be given its plain and ordinary meaning – i.e., a first type of particle that is not in contact with a second type of particle. To the extent that Breckenridge does not agree with Hetero’s construction, and asserts that the term means something different, the claims are indefinite because a POSA would have been unable to determine the scope of the Asserted Claims with reasonable certainty.

The '729 patent does not define “two distinct types of particles,” nor is the word “distinct” found anywhere in the specification. The only support for the meaning of the term is the applicant’s statements during prosecution. However, those statements support Hetero’s construction. Accordingly, if Breckenridge disagrees with the construction that “two distinct types of particles” means a first type of particle that is not in contact with a second type of particle, and asserts that the term has a different meaning, then a POSA would be unable to determine the scope of the Asserted Claims with reasonable certainty as there would be more than one interpretation of the scope of the claims without any guidance as to which interpretation was correct. As such, the Asserted Claims are invalid as indefinite.

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

BRECKENRIDGE PHARMACEUTICAL,
INC.,

Plaintiff,

v.

HETERO USA INC., HETERO LABS
LIMITED UNIT-III, HETERO LABS
LIMITED., and CAMBER
PHARMACEUTICALS, INC.,

Defendants.

Civil Action No. 24-571 (GBW)

NOTICE OF SERVICE

The undersigned hereby certifies that copies of the following document:

DEFENDANTS' FIRST SUPPLEMENTAL INVALIDITY CONTENTIONS

were served upon the attorneys listed below via email on this 14th day of February, 2025 prior to
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