

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MSN Pharmaceuticals, Inc. and MSN Laboratories Private Limited,

Petitioners,

v.

Breckenridge Pharmaceutical, Inc.,

Patent Owner.

U.S. Patent No. 11,013,729

Title: Oral Pharmaceutical Compositions of Dabigatran Etexilate

Case No.: IPR2025-01107

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,013,729**

TABLE OF CONTENTS

	Page
I. INTRODUCTION	1
II. MANDATORY NOTICES	4
A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))	4
B. Related Matters (37 C.F.R. § 42.8(b)(2)).....	5
C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)).....	5
D. Service Information (37 C.F.R. § 42.8(b)(4))	5
E. Payment of Fees	5
F. Certification of Word Count	6
III. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104	6
A. Grounds for Standing	6
B. Identification of Claims Being Challenged.....	6
IV. CLAIM CONSTRUCTION.....	6
A. “particles”	7
B. “a protective coating layer”	7
C. “consisting of”	8
V. BACKGROUND	9
A. Technology Overview	9
1. Dabigatran Etexilate.....	9
2. Oral Solid Dosage Forms	10
B. The ’729 Patent and its Prosecution History	11
VI. Level of Ordinary Skill in the Art.....	21
VII. Overview of the Prior Art.....	21
A. U.S. Patent Publication No. 2006/0183779 (“Brauns”).....	21
B. U.S. Patent Publication No. 2006/0115525 (“Leane”)	26
C. U.S. Patent Publication No. 2004/0109890 (“Sugimoto”).....	31
VIII. DETAILED EXPLANATION OF GROUNDS (37 C.F.R. § 42.104(b)(4))	34

A.	Motivation to Combine the Prior Art	34
B.	Ground 1: Claims 1-18 are Obvious Over Brauns in view of Leane	37
1.	Independent Claim 1	37
2.	Independent Claims 11 and 16, and Dependent Claims 2, 10, and 14	41
3.	Dependent Claims 3, 5, 12, 15, and 17	43
4.	Dependent Claim 4	44
5.	Dependent Claims 6-9	45
6.	Dependent Claims 13 and 18	50
C.	Ground 2: Claims 1-18 are Obvious Over Brauns in View of Sugimoto	51
1.	Independent Claim 1	51
2.	Independent Claims 11 and 16, and Dependent Claims 2, 10, and 14	54
3.	Dependent Claims 3, 5, 12, 15, and 17	56
4.	Dependent Claim 4	57
5.	Dependent Claims 6-9	58
6.	Dependent Claims 13 and 18	61
D.	No Objective Indicia of Non-Obviousness	62
IX.	PTAB DISCRETION SHOULD NOT PRECLUDE INSTITUTION	68
X.	CONCLUSION	68

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Amgen Inc. v. F. Hoffman-La Roche Ltd.</i> , 580 F.3d 1340 (Fed. Cir. 2009)	46
<i>Atl. Thermoplastics Co. v. Faytex Corp.</i> , 970 F.2d 834 (Fed. Cir. 1992)	46
<i>Breckenridge Pharmaceutical, Inc. v. Hetero USA Inc. et al.</i> , No. 24-cv-571 (GBW) (D. Del.).....	5
<i>Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus.</i> , 145 F.3d 1303 (Fed. Cir. 1998)	67
<i>Cochrane v. BASF</i> , 111 U.S. 293 (1884).....	46
<i>Genentech Inc. v. Hospira, Inc.</i> , 946 F.3d 1333 (Fed. Cir. 2020)	44
<i>Kao Corp. v. Unilever U.S., Inc.</i> , 441 F.3d 963 (Fed. Cir. 2006)	64
<i>In re Peterson</i> , 315 F.3d 1325 (Fed. Cir. 2003)	44
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005) (<i>en banc</i>)	7
<i>In re Taylor</i> , 445 F. App'x 343 (Fed. Cir. 2011)	8
<i>In re Theripion, Inc.</i> , 2023 WL 5125187 (Fed. Cir. Aug. 10, 2023)	64
<i>Wellman, Inc. v. Eastman Chem. Co.</i> , 642 F.3d 1355 (Fed. Cir. 2011)	7

Statutes

35 U.S.C. § 102(b)	21, 26, 31
35 U.S.C. § 103	6, 13
35 U.S.C. § 311 <i>et seq.</i>	1

Other Authorities

37 C.F.R. § 1.132	13, 14, 16
37 C.F.R. § 42.8(b)(1)	4
37 C.F.R. § 42.8(b)(2)	5
37 C.F.R. § 42.8(b)(3)	5
37 C.F.R. § 42.8(b)(4)	5
37 C.F.R. § 42.15	5
37 C.F.R. § 42.15(a)	5
37 C.F.R. § 42.24	6
37 C.F.R. § 42.24(a)(1)(i)	6
37 C.F.R. § 42.100(b)	7
37 C.F.R. § 42.100 <i>et seq.</i>	1
37 C.F.R. § 42.104	6
37 C.F.R. § 42.104(a)	6
37 C.F.R. § 42.104(b)	6
37 C.F.R. § 42.104(b)(1)	6
37 C.F.R. § 42.104(b)(4)	34
https://uspto.cosocloud.com/p9xpz6s4jn75	68

https://www.uspto.gov/about-us/events/learnaboutnew-interim- processes-relating-institution-aia-proceedings (April 24, 2025).....	68
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EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 11,013,729
1002	File History of U.S. Appl. No. 14/379,613
1003	File History of U.S. Appl. No. 17/241,793
1004	File History of U.S. Appl. No. 18/356,642
1005	Declaration of Maureen D. Donovan, Ph.D.
1006	Curriculum Vitae of Maureen D. Donovan, Ph.D.
1007	U.S. Patent Publication No. 2006/0183779 (“Brauns”)
1008	File History of U.S. Appl. No. 11/381,890
1009	U.S. Patent Publication No. 2006/0115525 (“Leane”)
1010	U.S. Patent Publication No. 2004/0109890 (“Sugimoto”)
1011	<i>Pharmaceutics: The Science of Dosage Form Design</i> , M.E. Aulton, Ed. (2d. edition 2002) pp. 247-248 (“Aulton”)
1012	K. Lavanya <i>et al.</i> “Pelletization Technology: A Quick Review,” <i>Int’l J. Pharm. Sci. & Res.</i> 2(6):1337-55 (June 2011) (“Lavanya”)
1013	Reserved
1014	FDA Approved Label for Pradaxa (October 2010)
1015	J. Stangier, “Clinical Pharmacokinetics and Pharmacodynamics of the Oral Direct Thrombin Inhibitor Dabigatran Etexilate,” <i>Clin. Pharmacokinet.</i> 47(5):285-95 (2008) (“Stangier”)
1016	FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms (August 1997)
1017	FDA Dissolution Methods for Dabigatran Etexilate Mesylate (09/22/2011)
1018	Australian Public Assessment Report for Dabigatran etexilate mesylate (May 2011)
1019	FDA Paragraph IV Patent Certifications (06/15/2020)
1020	USPTO Assignments for U.S. Appl. No. 14/379,613
1021	U.S. Patent Publication No. 2008/0069891 (“Habib”)
1022	International Patent App. Pub. No. WO 2012/001156 A2 (“Krka”)
1023	Remington, <i>The Science and Practice of Pharmacy</i> , 21st Ed. (2006) (“Remington”)
1024	Steward Memorandum, Interim Processes for PTAB Workload Management (March 26, 2025)

I. INTRODUCTION

MSN Pharmaceuticals, Inc. and MSN Laboratories Private Limited (“MSN” or “Petitioners”) request *inter partes* review pursuant to 35 U.S.C. § 311 *et seq.* and 37 C.F.R. § 42.100 *et seq.* of claims 1-18 of U.S. Patent No. 11,013,729 (Ex. 1001 (“the ’729 patent”)).

The ’729 patent claims a pharmaceutical composition containing the thrombin inhibitor dabigatran etexilate with a pharmaceutically acceptable organic acid, wherein the dabigatran etexilate and acid are in separate particles and the acid-containing particles have a protective coating.

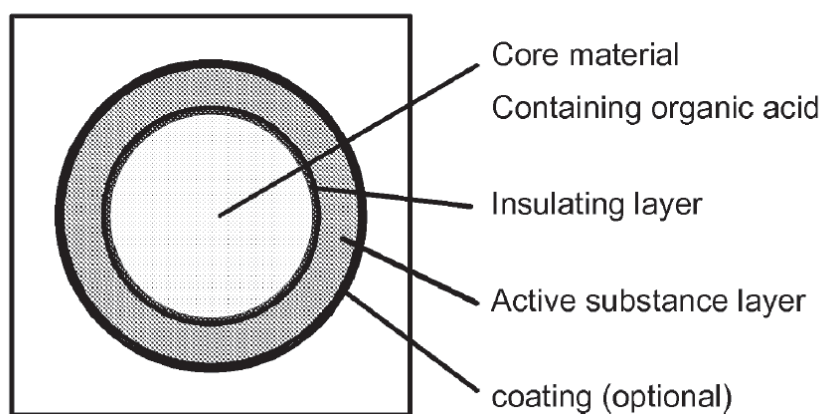
As discussed in the declaration of Dr. Donovan (Ex. 1005), it has long been known that acids can be added to pharmaceutical dosage forms to improve the solubility of weakly basic drugs, like dabigatran etexilate, and other materials exhibiting pH-dependent solubility. Ex. 1005, ¶74. Once ingested, dissolution of the acid lowers the pH of the dosage form’s local environment thereby enhancing the solubility of the weakly basic drug. *Id.*, ¶73.

Dabigatran etexilate was first approved by the United States Food & Drug Administration (“FDA”) in October 2010 under Boehringer Ingelheim’s New Drug Application (“NDA”) No. 022512 and marketed under the tradename Pradaxa[®] to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. *Id.*, ¶71. The Pradaxa[®] oral capsule product contained 75 mg or 150 mg

dabigatran etexilate as the mesylate salt and certain inactive ingredients including tartaric acid (an organic acid). *Id.*, ¶¶72-73. Dabigatran etexilate's solubility was known to be pH dependent. *Id.*, ¶69. It was also specifically known that tartaric acid enhances the solubility of dabigatran etexilate. *Id.*, ¶73. Because dabigatran etexilate was also known to be acid sensitive, the Pradaxa[®] drug product was formulated as multilayer pellets in which the dabigatran etexilate layer is separated from the tartaric acid core by an insulating layer. Ex. 1007, Figure 1 (copied below).

Figure 1:

Schematic structure of the pharmaceutical composition:



Shortly after Pradaxa[®]'s FDA approval, more than 15 generic drug companies were developing generic versions of Pradaxa[®]. Ex. 1019, p. 16. A person of ordinary skill in the art would have been aware of Boehringer Ingelheim's pending patent application that covered the Pradaxa[®] oral capsule formulation (i.e., U.S. Appl. No. 11/381,890, published as U.S. Patent Pub. No. 2006/0183779 (Ex. 1007, "Brauns")),

and would have been motivated to “design around” Brauns’ pending claims. Ex. 1005, ¶¶187-88.

Rubicon Research Private Limited (“Rubicon”), based in Mumbai, India, was one such company developing a generic version of Pradaxa[®] in 2011-2012, and pharmaceutical formulators at Rubicon designed around the Pradaxa[®] oral capsule formulation by placing the dabigatran etexilate mesylate and tartaric acid in separate pellets in the capsule. In February 2012, Rubicon filed a patent application in India (Appl. No. 461/MUM/2012), which served as a priority document for a PCT Appl. No. PCT/EP2013/053426 that entered national phase in the United States and eventually issued as the ’729 patent. Ex. 1002, pp. 627-652.

During prosecution of the ’729 patent, the pending claims were repeatedly rejected over Brauns in view of U.S. Patent Pub. No. 2008/0069891 (Ex. 1021, “Habib”). Habib disclosed abuse-proof opioid formulations comprising a first particle with an active substance and a coating and a second particle with a fat/wax material. Ex. 1002, pp. 152-153 (discussing Habib, Abstract, ¶[0018], ¶[0020]). The PTAB reversed the Examiner’s rejection and found “that Examiner has not articulated a sufficient rationale for combining the two particle composition taught in Habib to modify the single particle composition taught in Brauns.” *Id.*, p. 87. Indeed, the PTAB noted that Habib’s composition was intended to “*inhibit* dissolution of the drug,” i.e., “the opposite result” of the two particle system

described in Brans. *Id.*, pp. 87-88. Thus, the PTAB found that the all of the claim limitations had been addressed, and the sole issue was whether a POSA would have viewed a two-particle system as a viable alternative to the one-particle system of Brauns.

However, prior art not previously before the Office teaches that using two distinct types of particles, as required by the claims of the '729 patent, *was* a well-known and commonly employed formulation strategy for providing controlled pH-dependent solubility. And, following the prior art discussed here, a person of ordinary skill in the art would have reasonably expected success in preparing the dabigatran etexilate compositions of claims 1-18 of the '729 patent. Further, the claims of the '729 patent provide no unexpected or surprising results concerning dabigatran etexilate solubility or stability, or that the claimed pharmaceutical formulation is bioequivalent with Pradaxa[®]. Thus, claims 1-18 of the '729 patent are obvious over the prior art of Grounds 1 and 2 discussed here.

II. MANDATORY NOTICES

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties in interest are MSN Pharmaceuticals, Inc., a Delaware corporation, with its business address at 20 Duke Road, Piscataway, NJ 08854, and MSN Laboratories Private Limited, a corporation organized under the laws of India, with its business address at MSN House, Plot No. C-24, Industrial Estate,

Sanathnagar, Hyderabad, 500018, Telangana, India.

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

The '729 patent is currently the subject of litigation in *Breckenridge Pharmaceutical, Inc. v. Hetero USA Inc. et al.*, No. 24-cv-571 (GBW) (D. Del.), filed on May 10, 2024 (D.I. 1). Petitioners are not a party to that pending district court litigation.

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

Lead Counsel	Back-Up Counsel
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D. Service Information (37 C.F.R. § 42.8(b)(4))

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. MSN consents to service by electronic mail at the email addresses set forth above.

E. Payment of Fees

All required fees have been paid with the filing of this Petition. If there are any additional or outstanding fees, Petitioner further authorizes the U.S. Patent & Trademark Office to charge Deposit Account No. 50-1814 for these fees, including the fee set forth in 37 C.F.R. § 42.15(a) for this Petition.

F. Certification of Word Count

Petitioners certify that the word count in this Petition, including all footnotes and annotations, is 13,831 words as counted by the word-processing program used to generate this Petition, excluding those portions identified in 37 C.F.R. § 42.24(a). This Petition is in compliance with the 14,000-word limit set forth in 37 C.F.R. § 42.24(a)(1)(i).

III. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

A. Grounds for Standing

Petitioners certify that the '729 patent is available for *inter partes* review. Petitioner is not barred or estopped from requesting an *inter partes* review of the '729 patent claims on the grounds identified in this Petition. 37 C.F.R. § 42.104(a).

B. Identification of Claims Being Challenged

Pursuant to 37 C.F.R. §§ 42.104(b) and (b)(1), MSN requests *inter partes* review and cancellation of claims 1-18 of the '729 patent based on the following grounds:

Ground	Prior Art	Basis	Claims Challenged
1	Brauns in view of Leane	§ 103	1-18
2	Brauns in view of Sugimoto	§ 103	1-18

IV. CLAIM CONSTRUCTION

In an IPR proceeding, claims are to be given their ordinary and customary meaning as understood by a person of ordinary skill in the art in view of the patent

and file history. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-1313 (Fed. Cir. 2005) (*en banc*). “Claim terms need only be construed to the extent necessary to resolve the controversy.” *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (internal quotation omitted).

A. “particles”

Independent claims 1, 11, and 16 require “a mixture of at least two distinct types of particles.” Dependent claims 6, 7, 9, 13, and 18 also recite the term “particles.” The ’729 patent states that “[t]he term ‘particle’ as used herein is intended to mean any solid or semi-solid portion of a substance or a composition having defined physical boundaries. Examples of particles include, but are not limited to, powder, granules, pellets, beads, minitabets or the like.” Ex. 1001, 8:62-66. Thus, the term “particles” should be construed as “any solid or semi-solid portions of a substance or a composition having defined physical boundaries, such as powder, granules, pellets, beads, and minitabets.” Ex. 1005, ¶¶54-56.

B. “a protective coating layer”

Claims 1, 8, 9, 11, and 16 require “a protective coating layer” on the second type of particles that comprise at least one organic acid and are free from dabigatran etexilate. This limitation was added in an amendment dated November 9, 2017, so that the claims were commensurate in scope with “the Examples presented, [wherein] the acid containing particles are coated but the active agent containing

particles are not coated.” Ex. 1002, pp. 349-351.

The ’729 patent states that “[t]he term ‘protective coating layer’ as used herein is intended to mean a layer of a polymeric or a non-polymeric material disposed on the surface of a particle core in order to avoid direct contact of the particle core with its environment.” Ex. 1001, 5:39-43. Applicants also argued during prosecution that “[t]he insulating layer [of Brauns] just acts as a protective layer between the acid core and active substance layer on storage, but once in the stomach it permits the diffusion of the acid to the active substance layer immediately.” Ex. 1002, p. 137 (Reply Br. dated Apr. 15, 2020).

In view of the definition provided for this limitation in the specification and applicants’ statements during prosecution, “a protective coating layer” should be construed to mean “a coating layer that prevents the organic acid from contacting dabigatran etexilate until after the composition is administered.” Ex. 1005, ¶¶57-61.

C. “consisting of”

Claims 11 and 16 require a “composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient.”

The transitional phrase “consisting of” should be given its plain and ordinary meaning, which closes the composition to ingredients other than the “two distinct types of particles and at least one pharmaceutically acceptable excipient.” *See In re Taylor*, 445 F. App’x 343, 345-46 (Fed. Cir. 2011).

V. BACKGROUND

A. Technology Overview

1. Dabigatran Etexilate

Pradaxa[®] (dabigatran etexilate mesylate) was first approved by the FDA in October 2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Ex. 1005, ¶¶71-72. The Pradaxa[®] oral capsule product contained 86.48 mg and 172.95 mg of the mesylate salt of dabigatran etexilate (equivalent to 75 mg or 150 mg dabigatran etexilate) along with acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid (an organic acid). *Id.*, ¶73.

Dabigatran etexilate was known to dissolve relatively well in water at low acidic pH levels, while being “virtually insoluble” at pH levels higher than 5. *Id.*, ¶100. Tartaric acid was known to improve dabigatran etexilate’s bioavailability by increasing its solubility independent of the gastric pH and to prevent malabsorption. *Id.*, ¶131. Dabigatran etexilate was also known to be prone to chemical degradation and polymorphic form transformation in an acidic environment. *Id.*, ¶76; Ex. 1022, p. 3. Thus, the Pradaxa[®] drug product was prepared by a powder layering process producing pellets that contained an insulating layer separating the tartaric acid core from the layer containing dabigatran etexilate. Ex.

1005, ¶77. But, in practice, it was difficult to prepare an intact insulating layer, which was required for storage stability and durability of the finished product. *Id.*, ¶78.

2. Oral Solid Dosage Forms

By February 2012, the most used oral solid dosage forms included tablets and capsules, such as capsules. Ex. 1005, ¶¶80-81. Further, it was known that the dissolution rate of a poorly soluble hydrophobic drug from a capsule formulation can be increased by including hydrophilic diluent particles, which increase the rate at which gastrointestinal fluids can penetrate the contents of a capsule to aid dispersion and subsequent dissolution of the drug particles. Ex. 1011, p. 3.

Solid dosage forms containing pellets were also known in the art. Ex. 1012, Abstract. These dosage forms were popular because they had several advantages, such as improved flow and packing properties, and ease of coating. *Id.*; *see also id.*, 2. Further, preparing different pellets was known as a “convenient way” to separate chemically incompatible substances that needed to be delivered in a single dose. *Id.*, p. 2. Prior art also taught methods for preparing pellets, including drug layering and compaction, which were “the most widely used” techniques. *Id.*, p. 3. “Of the compaction techniques used, extrusion and spheronization [wa]s the most popular method.” *Id.*

It was also well-known that a pharmaceutically acceptable excipient can be added to pellets to prepare a finished dosage form, such as a hard capsule. Ex. 1005,

¶¶82-83. Indeed, a POSA would have known that glidants, lubricants, binders, and/or diluents/fillers are commonly combined with pellets to aid in manufacturing. Ex. 1005, ¶¶84-86. For example, glidants and lubricants can be used to improve the flow properties of pellets by preventing sticking and assist with the capsule filling process. Ex. 1005, ¶86. Binders are “adhesive materials that can be incorporated into pellet formulations to bind powders and maintain integrity” of the pellets. Ex. 1012, p. 10. And a filler/diluent can be added to add bulk to the dosage form and provide uniform and reproducible capsule fill. Ex. 1005, ¶84. Finally, it was known that pellets can be coated, for example, to control drug release from the pellets or to mask pellets’ taste. Ex. 1012, p. 8.

B. The ’729 Patent and its Prosecution History

The ’729 patent is directed to compositions for the oral administration of dabigatran etexilate “comprising” (claims 1-5, and 10) or “consisting of” (claims 11-18) “two distinct types of particles” wherein the first type of particles comprise dabigatran etexilate in the form of a free base or a pharmaceutically acceptable salt or polymorph and “is free from organic and inorganic acids,” and the second type of particles comprise at least one pharmaceutically acceptable organic acid, “is coated with a protective coating layer,” and “is free from dabigatran etexilate.” Claims 6-9 are directed to processes for preparing the composition of claim 2. Claims 8, 9, and 15-18 require that the compositions are in the form of a capsule.

Example 1 of the '729 patent discloses preparing capsule dosage forms having separate dabigatran etexilate mesylate and tartaric acid pellets in which a protective coating layer of hydroxypropyl methylcellulose and talc is applied to the tartaric acid pellets. Ex. 1001, 11:30–12:67. Example 3 compares the in vitro dissolution profiles of a composition having separate dabigatran etexilate and coated tartaric acid pellets (Formulation A) versus Example 1 of Brauns (Formulation B), as shown below.

Time (minutes)	% release	
	Formulation A (two types of particles/pellets)	Formulation B (one type of particles/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

Id., 14:30–16:6. The '729 patent states that “formulations of the present invention having two types of particles/pellets can provide faster dissolution particularly at earlier time points as compared to formulation having one type of particles/pellets. Such a faster dissolution at earlier time points can ensure availability of more amount of active especially when (a) absorption of the active is rapid with faster T_{max} (~45 minutes-1 hour), (b) significant bioactivation is involved and (c) negligible and variable absorption at higher pH.” *Id.*, 15:65–16:6.

The '729 patent issued on May 25, 2021, from U.S. Patent Appl. No. 14/379,613 (“’613 application”), which entered national stage in the United States on August 19, 2014 from PCT Appl. No. PCT/EP2013/053426, filed on February 21, 2013. *Id.*, p. 1; Ex. 1002, pp. 551-681. The '729 patent claims priority to Indian Patent Appl. No. 461/MUM/2012, filed on Feb. 21, 2012. Ex. 1001, p. 2; Ex. 1002, pp. 614-652.

The '613 application was consistently rejected by the Office under, *inter alia*, 35 U.S.C. § 103 as obvious over Brauns in view of Habib. *See, e.g.*, Ex. 1002, pp. 491-504 (Sept. 30, 2015 Office Action). In response, applicants amended the only pending independent claim at that time to recite:

21. (currently amended) A composition comprising a mixture of at least two distinct types of particles 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 salts, ~~polymorph~~[[s,]] ~~solvates or hydrates~~ thereof; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein at least one type of particles is coated with a protective coating layer.

Id., p. 480. Applicants also submitted a Declaration Under 37 C.F.R. § 1.132 from inventor Anilkumar S. Gandhi, Ph.D. that compared “the stability of compositions comprising dabigatran etexilate particles and coated organic acid particles (according to the present invention) and compositions without said coating.” *Id.*, p. 485. In testing at 40°C and 75% relative humidity, the uncoated organic acid (tartaric acid) pellets formed a sticky agglomerate, whereas the coated tartaric acid pellets

did not. *Id.* The compositions with the coated tartaric acid pellets were also more stable, forming less dabigatran impurities after four weeks. *Id.*, pp. 485-486.

In making the rejection over Brauns and Habib final, the Office found, *inter alia*, that:

- [T]he instant tested examples are directed to one specific coating material, hydroxypropyl cellulose and talc, whereas the instant claims are broadly directed to protective coating layer, and thus are not commensurate in scope.
- [T]he use of a coating layer containing the hydroxypropyl cellulose was known to stabilize the acid in the formulation (citing Brauns, ¶[0011], ¶[0013], ¶[0015]).
- Applicant has not compared the closest prior art to the claimed invention, as the closest prior art comprises the coating layers, wherein the active agent and the acid are in different layers of the same particles. Therefore, the difference is in the particle being layered vs. two separate particles, and is not regarding the protective layer being present.

Ex. 1002, pp. 456-469 (March 23, 2016 Final Office Action).

On June 1, 2016, applicants filed a Request for Continued Examination and submitted two further declarations under 37 C.F.R. § 1.132. *Id.*, pp. 427-445. One declaration, from Ziauddin Tyebji, compared the *in vitro* dissolution profiles of a

“formulation of the present invention having two types of particles/pellets” with a formulation of Brauns (having one type of particles/pellets), as discussed in Example 3 of the ’729 patent. *Id.*, pp. 442-445. According to Mr. Tyebji, the dissolution data of Example 3 of the ’729 patent “clearly demonstrate that [compared to] the compositions disclosed in [Brauns], the compositions of the present invention exhibit a faster dissolution profile. The superior properties associated with the compositions of the present invention would not have been predicted based on the teachings of [Brauns].” *Id.* The other declaration, from Zhengguo Xi, compared the relative bioavailability of the formulations in Example 3 of the ’729 patent in fed and fasted healthy adults and showed that the compositions of the ’729 patent were bioequivalent to those of Brauns. *Id.*, pp. 439-441.

In maintaining the rejection over Brauns in view of Habib, the PTO found:

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the oral composition taught by [Brauns] as two distinct particles as [Habib] teaches pharmaceutical composition comprise two distinct types of particles, one of which includes a pharmaceutical agent (abstract, [0018]). One of ordinary skill in the art at the time the invention was made would be motivated to use two distinct particles as [Brauns] teaches the need for spatial separation of the organic acid and the active substance [0010]. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success as [Brauns] teaches the an oral pharmaceutical formulation in the form of particles (Figure 1, [0010]) and [Habib] teaches it was known to formulate active agents

and excipients (fat/wax) for oral dosage forms in separate particles (abstract, [0018], [0167]). It would have been obvious to one of ordinary skill in the art at the time the invention was made that the separation of the organic acid and the active agent described by [Brauns] could be via the layers taught by [Brauns] or through the use of separate particles as taught by [Habib].

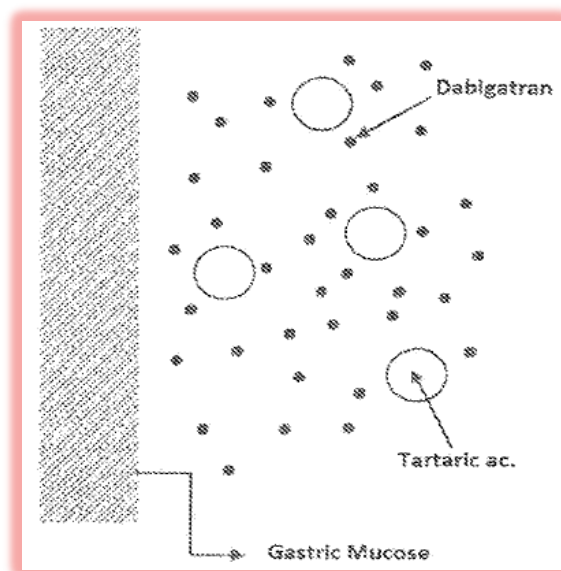
Id., pp. 393-394 (August 11, 2017 Office Action). The PTO also found the declarations insufficient to overcome the obviousness rejection based on Brauns and Habib, noting that “the Formulation A and B cannot be properly compared to each other, as the ratio and amount of tartaric acid and active substance are not the same in [each] ... [and] the comparison is not strictly between the use of two separate particles or a layered particle.” *Id.*, pp. 398-400.

In response, applicants amended the only pending independent claim at that time to recite:

21. (currently amended) A composition comprising a mixture of at least two distinct types of particles 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; and b) the second type of particles comprise at least one pharmaceutically acceptable organic acid, wherein ~~at least one~~ the second type of particles is coated with a protective coating layer.

Ex. 1002, p. 354. Applicants also submitted a further Declaration Under 37 C.F.R. § 1.132 from Ziauddin Tyebji that referred to an *Australian Public Assessment Report for Dabigatran etexilate mesylate* (May 2011) (Ex. 1018) and alleged that “the bioavailability results obtained with one specific formulation cannot be

expected to be maintained when a different formulation is used.” Ex. 1002, p. 359. It was further alleged that “[t]he formulation of the present application would not have been expected to result in a good bioavailability because the acidic microclimate needed for the transportation of dabigatran and absorption through the gastric mucosa cannot be formed at all, as evidenced by the picture shown below representing the formulation of the present invention at the absorption site[]. In spite of that, the formulation of the present invention unexpectedly shows the desired bioavailability.”



Id., p. 361. Further, it was alleged that because Brauns teaches the use of a specific layered-pellet structure, one skilled in the art would not have expected that the bioavailability and dissolution rate obtained with the particles of the invention could be achieved using two distinct types of pellets. *Id.*, pp. 361-362.

The PTO maintained the rejection over Brauns in view of Habib, finding *inter*

alia that:

- the instant claims do not contain limitations directed to the release rate of the drug particles. Additionally, Applicant has demonstrated that release is different between different particle formulations, however this is not considered an unexpected or superior results, as some differences are expected between different formulations.
- the use of acid in a distinct particle mixed with particles which contain the drug would still result in close contact of the drug and acid to create the acid microenvironment after administration.

Id., pp. 334-338 (January 16, 2018 Final Office Action). In response, applicants filed another Request for Continued Examination (*id.*, pp. 285-303), amended claim 21 as follows, and submitted new claims 40-48 (with claims 41 and 46 being new independent claims):

21. (Currently Amended) A composition comprising a mixture of at least two distinct types of particles 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 acids 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.

41. (New) 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.

46. (New) 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.

Id., pp. 294-298. Applicants also pointed to statements made by the Brauns applicants in support of patentability, which stated:

The present formulation was designed to accommodate the specific and unique properties of the prodrug, dabigatran etexilate. An ***acid core layer***, an ***insulating layer*** and an ***active substance layer*** are necessary components of this invention. For example, the acid core layer provides the low-pH microenvironment once the formulation enters the stomach. The insulating layer first acts as a protective layer between the acid core and active substance layer on storage but then permits the diffusion of acid to the active substance layer immediately in passage through the stomach. The active substance layer provides the correct dosage of prodrug.

Id., pp. 300-301. Based on these statements by Brauns, applicants argued that Brauns would not provide a POSA any reason or motivation to modify Brauns' layered

single pellet compositions to provide the dabigatran etexilate and organic acid in separate pellets with any reasonable expectation of success, and a POSA would not have considered modifying Brauns to arrive at the claimed compositions as an identifiable, predictable solution. *Id.*, p. 301.

The PTO nonetheless maintained the obviousness rejection over Brauns in view of Habib for the same reasons as previously noted. *Id.*, pp. 260-277 (January 30, 2019 Office Action); *see also id.*, pp. 216-233 (May 30, 2019 Final Office Action). Applicants then filed a notice of appeal (*id.*, p. 202), submitted briefing (*id.*, pp. 173-194 (Appeal Brief); 145-162 (Answer); 137-140 (Reply Brief)), and an oral hearing was held January 7, 2021 (*id.*, pp. 73-81). In reversing the rejection, the PTAB found “that [the] Examiner has not articulated a sufficient rationale for combining the two particle composition taught in Habib to modify the single particle composition taught in Brauns.” *Id.*, p. 87. The PTAB further explained:

It is not clear why one of ordinary skill in the art would have considered Habib’s abuse resistant formulations to be relevant to the layered particle compositions taught in Brauns. Indeed, Brauns teaches that an advantage of the “spatial separation of the organic acid and active substance by the insulating layer” in its layered particle composition is that it increases bioavailability by facilitating the creation of “an acid microclimate in which the active substance can dissolve” when acid from the core diffuses into the drug layer. Brauns ¶11. In contrast, the second particle in Habib’s composition is intended to achieve the opposite result, i.e., to inhibit dissolution of the drug. *See* Habib ¶36 (“It is believed that the combination of particles

according to the present invention produces a barrier relative to the active ingredient-containing particles against solvent access, thereby protecting and preserving the intended controlled release properties of the active particles.”).

Id., pp. 87-88. A Notice of Allowance followed (*id.*, pp. 51-60), and the ’729 patent issued on May 25, 2021.

VI. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (“POSA”) relevant to the challenged claims of the ’729 patent would have an advanced degree (i.e., a doctorate or master’s degree) in pharmaceutical sciences or a related discipline and at least three to seven years of experience formulating and/or characterizing pharmaceutical dosage forms. Ex. 1005, ¶19. This level of education and experience is also commensurate with that of the inventors and other individuals who submitted declarations during prosecution of the ’729 patent. *See* Ex. 1002, pp. 371-374 (Ziauddin Tyebji), 368-370 (Zhenggua Xu), 447-450 (Anilkumar S. Gandhi).

VII. OVERVIEW OF THE PRIOR ART

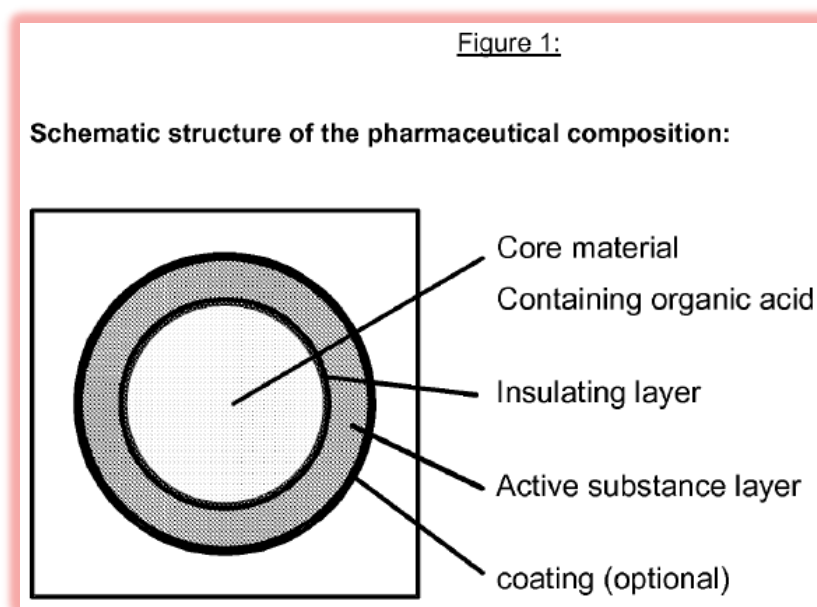
A. U.S. Patent Publication No. 2006/0183779 (“Brauns”)

Brauns was published on August 17, 2006, and is prior art to the ’729 patent under 35 U.S.C. § 102(b) (pre-AIA). Brauns discloses oral dosage forms for dabigatran etexilate and pharmacologically acceptable salts thereof (the “active substance”) in combination with pharmaceutically acceptable organic acids,

preferably tartaric, fumaric, succinic, and citric acids. Ex. 1007, ¶¶[0003], [0007]-[0008]. The preferred ratio of organic acid to active substance is about 0.9:1 to about 4:1, most preferably between about 1:1 and 3:1, with at least one equivalent of acid per mol of dabigatran etexilate. *Id.*, ¶[0037].

The preferred salt of dabigatran etexilate is the mesylate (i.e., methanesulphonate) (*id.*, ¶[0014]), and dosages for oral use comprise 25 mg to 300 mg, preferably 50 mg to 200 mg, and most preferably 75 mg to 150 mg of dabigatran etexilate on a free base basis, administered once or twice daily. *Id.*, ¶[0036]. The compositions in such dosage amounts are useful for preventing post-operative deep-vein thrombosis. *Id.*, ¶[0003].

Brauns discloses preferred compositions having the below structure, whereby the core material comprises the pharmaceutically suitable acid, optionally in combination with 1% to 10% by weight of a suitable binder (*id.*, ¶[0012]), which is coated with an “insulating layer” based on a water-soluble, pharmaceutically acceptable polymer (*id.*, ¶[0013]) that separates the acid core from the active substance:



Id., p. 2 (Figure 1); ¶¶[0009]-[0010]. According to Brauns, advantages of this formulation are “the spatial separation of the organic acid and active substance by the insulating layer” and “the fact 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.*, ¶[0011]. This is important because dabigatran etexilate is virtually insoluble at pH levels above 5, but dissolves “relatively well in water at low pH levels.” *Id.*, ¶[0024]. The spatial separation of the organic acid and active substance by the insulating layer increases the “durability of the finished product” before the drug is taken, (*id.*, ¶[0013]) while allowing the organic acid to create an acidic microclimate to dissolve the active substance after the drug is taken. *Id.*, ¶[0011].

Further, Brauns teaches that the presence of the organic acid “ensures

adequate bioavailability of the active substance, better than that of a conventional pharmaceutical preparation and largely independent of the gastric pH,” thus “it reduces fluctuations in the bioavailability of the active substance and it prevents malabsorption.” *Id.*, ¶[0035]. For example, the presence of organic acid maintains the bioavailability of dabigatran even in subjects pre-treated with pantoprazole (which raises gastric pH levels), while subjects who were administered conventional oral tablets containing no water-soluble organic acid exhibits a relative bioavailability of only 18%. *Id.*, ¶¶[0025]-[0029].

As of the earliest priority date of the '729 patent, Brauns had undergone substantial examination by the PTO. Ex. 1008. For example, claim 1 of Brauns, which recited:

Claim 1 (currently amended): A [[P]]pharmaceutical composition for oral administration comprising:
a) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof and
b) one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 ml at 20° C.

(*id.*, p. 292) was rejected as obvious over U.S. Patent No. 6,387,917 in view of U.S. Patent No. 3,986,111 and JP 58-134033 because “it would have been obvious to one skilled in the art at the time of the invention to make a methanesulphonate salt of

[dabigatran etexilate] because prior art teaches that methane sulphonate salt[s] are non toxic, [and] water soluble ... and AKIRA teaches the use of organic acids such as tartaric acid, citric acid etc. which are organic acids. Motivation has been provided by the prior art to make methanesulphonate salt and adding organic acids for enhanced solubility, stability and non-toxic nature of this salt.” *Id.*, pp. 186-94.

In response, Brauns’ applicants amended claim 1 to recite:

Claim 1 (currently amended): A pharmaceutical composition for oral administration comprising:
a) a substantially spherical core material comprised of one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 mL at 20° C; and
~~a)~~ (b) an active substance layer containing one or more binders and optionally a separating agent, that encloses said core material, wherein said active substance is ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof, and
~~b) one or more pharmaceutically acceptable organic acids with a water solubility of > 1 g / 250 ml at 20° C.~~

Id., p. 173. Following further obviousness rejections (*id.*, pp. 143-56, 103-19), applicants appealed (*id.*, pp. 74-91), and then received a Notice of Allowance on December 14, 2010 (*id.*, pp. 52-57). Rather than pay the issue fee, on March 2, 2011, the Brauns applicants filed a further Information Disclosure Statement along with a Request for Continued Examination. *Id.* at 24-48. Further prosecution of Brauns

would not occur until a non-final rejection was issued by the PTO on June 20, 2013.
See id. at 1-23.

As noted above, Brauns was the primary reference cited by the PTO during prosecution of the '729 patent, and applicants ultimately overcame the Examiner's obviousness rejections over Brauns in view of Habib based on the PTAB's finding that Habib would not have sufficiently motivated a POSA to modify Brauns to develop a composition with the "two distinct types of particles," as required by the claims of the '729 patent. In doing so, the PTAB found that all of the claim limitations had been addressed, and the sole issue was whether a POSA would have viewed a two-particle system as a viable alternative to the one-particle system of Brauns.

B. U.S. Patent Publication No. 2006/0115525 ("Leane")

Leane was published on June 1, 2006, and is prior art to the '729 patent under 35 U.S.C. § 102(b) (pre-AIA). Leane was not cited as prior art during prosecution of the '729 patent.

Leane discloses solid pharmaceutical compositions for oral administration that incorporate the bioadhesive polymer chitosan in order to enhance drug uptake across the intestinal wall. Ex. 1009, ¶¶[0004]-[0005]. Chitosan is a weakly basic substance (pKa 6.5) that is soluble in solutions having acidic pH values but is insoluble in solutions having neutral or basic pH values. *Id.*, ¶[0012]. Because the

human intestine can range from pH 5 to pH 7.5, there are areas in which chitosan is soluble and areas in which it is insoluble. *Id.*, ¶[0013]. Even at low (acidic) pH, chitosan readily hydrates, but adjacent chitosan particles will adhere to one another to form a hydrated gelled layer that inhibits water penetration into the core of the dosage form, resulting in slow dissolution from the surface. *Id.*, ¶[0015]. Thus, Leane discloses an oral solid dosage form that incorporates an organic acid in the form of an agglomerate that provides an acidic microenvironment in a controlled fashion to dissolve chitosan at the pH range found in the intestine. *Id.*, ¶¶[0016]-[0022], [0041].

Leane discloses that suitable organic acids are present in the compositions in the form of an agglomerate, which is “an association of acid particles” (*id.* ¶[0039]), for example, in the form of a pellet, which can be engineered to a specific size using standard techniques such as precipitation, spray drying, or crystallization. *Id.*, ¶¶[0037]-[0039], [0042]-[0043]. Leane provides a list of preferred organic acids that includes tartaric acid. *See id.*, ¶[0037]. Leane discloses that an agglomerate of organic acid allows rapid disintegration of the dosage form by controlling the timing of contact between chitosan and the acid. *Id.*, ¶[0041]. The amount of organic acid is chosen in relation to the amount of chitosan, and the weight ratio of acid:chitosan is preferably 10:1 to 1:1, more preferably 8:1 to 1:1, and most preferably 6:1 to 1:1. *Id.*, ¶[0049].

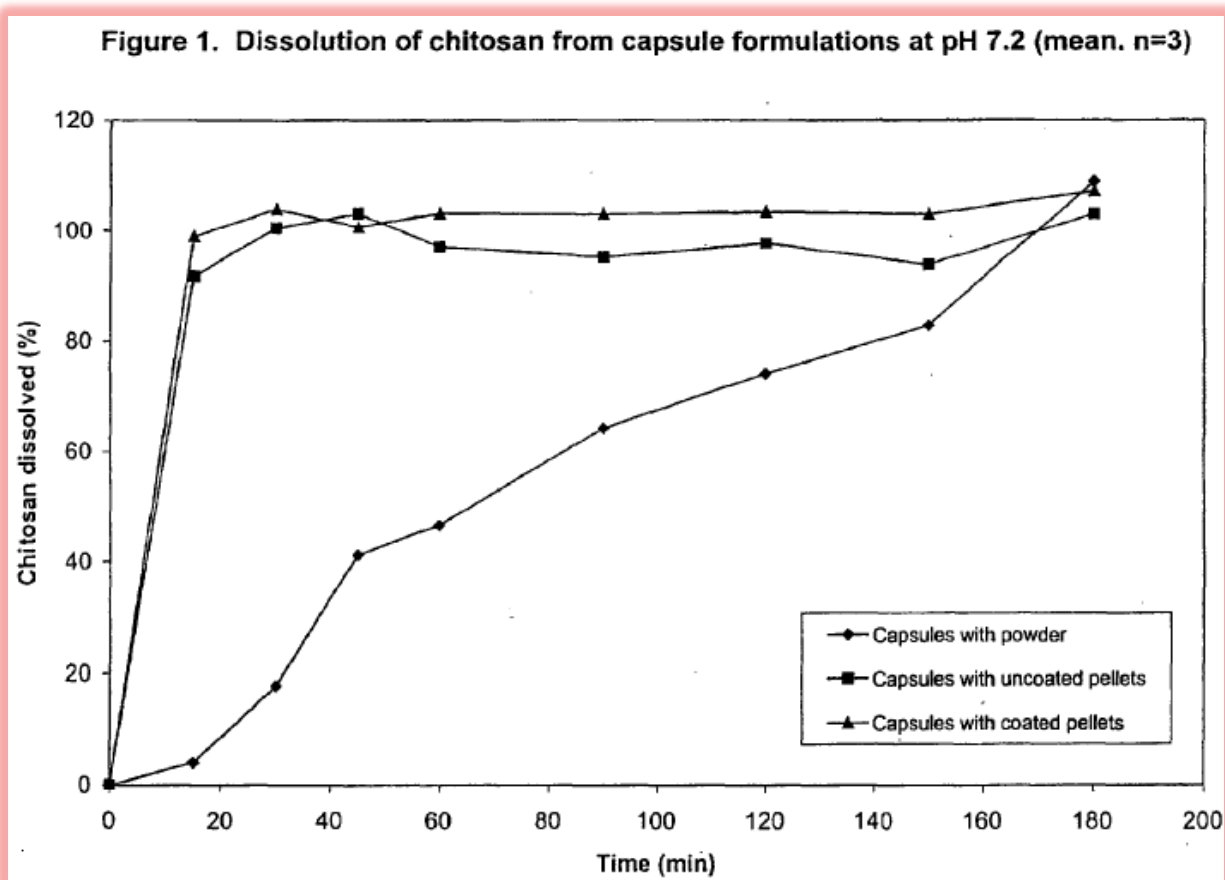
The organic acid agglomerate can include a pharmaceutically acceptable diluent, binder, disintegrant, glidant, and/or lubricant, and can also be coated with a water-soluble or water-permeable coating. *Id.*, ¶¶[0043]-[0044]. Leane teaches coating the acid agglomerates advantageously improves chitosan solubility by controlling the timing of contact between chitosan and the acid. *Id.*, ¶[0044].

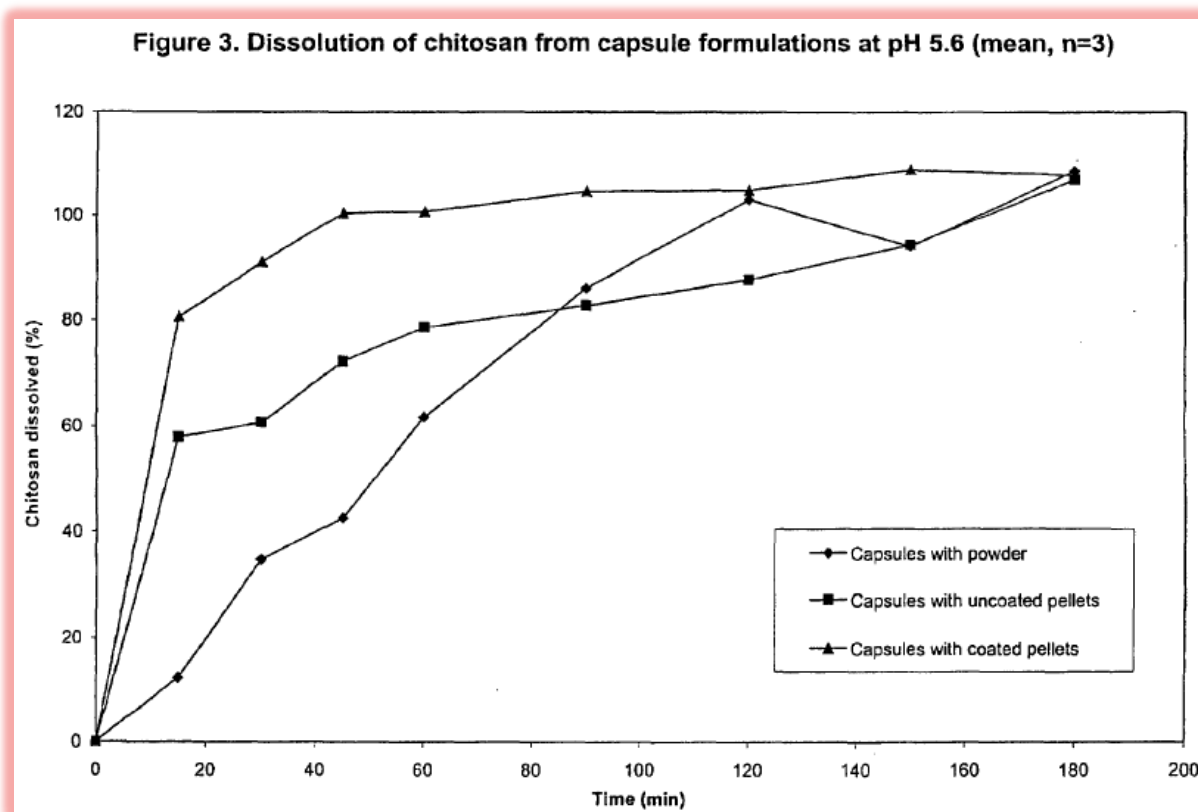
Leane's disclosed compositions include those comprising the (i) drug, chitosan, and an agglomerate of the organic acid (*id.*, ¶[0056]), (ii) an agglomerate of the drug and organic acid, which is mixed with chitosan (*id.*, ¶[0057]), (iii) an agglomerate of the drug, which is mixed with the organic acid agglomerate, and then with chitosan (*id.*, ¶[0058]), and (iv) an agglomerate of the drug and chitosan, which is mixed with the organic acid agglomerate (*id.* at ¶[0059]). In each case, incorporating the acid into agglomerates spatially separates the acid from the acid-sensitive component, chitosan. These compositions can be in tablet forms or placed into capsules using standard pharmaceutical procedures. *Id.*, ¶¶[0060]-[0061].

Leane's exemplary embodiments disclose the preparation of pellets containing succinic acid and sodium salicylate that are uncoated or coated with hydroxypropyl methylcellulose. *Id.*, ¶¶[0080]-[0082] (Examples 2-3). The uncoated and coated pellets were combined with chitosan and mannitol and used to fill hard gelatin capsules. *Id.*, ¶¶[0084]-[0085] (Examples 5-6). A comparative tablet composition was prepared by directly compressing a chitosan/mannitol blend (*id.*,

¶[0075] (Example 1)), and a comparative capsule composition was prepared by mixing chitosan, succinic acid, and sodium salicylate, which was used to fill hard gelatin capsules (*id.*, ¶[0083] (Example 4)).

The dissolution rates of chitosan from the dosage forms of Examples 4-6 were measured at pH 7.4 and pH 5.6 using standard procedures, and the results for chitosan dissolution are shown in Figures 1 and 3. *Id.*, ¶[0076]-[0079], [0086]-[0089].





Leane discloses that the chitosan tablets of Example 1 “disintegrated almost immediately,” but negligible amounts of chitosan were assayed in the pH 7.4 dissolution media, indicating that the chitosan was released rapidly from the tablets but did not dissolve. *Id.*, ¶¶[0076]-[0079]. Further, Leane teaches that chitosan more rapidly dissolved from capsules in which the acid was incorporated as coated or uncoated pellets (Examples 5 and 6), compared with capsules comprising acid in the form of a powder (Example 4). *Id.* ¶¶ [0088]-[0089]. Further, while capsules with coated or uncoated acid pellets showed similar chitosan dissolution rate at pH 7.4, capsules with coated acid pellets showed faster chitosan dissolution at pH 5.6. *Id.* at Figures 1 and 3.

C. U.S. Patent Publication No. 2004/0109890 (“Sugimoto”)

Sugimoto was published on June 10, 2004, and is prior art to the ’729 patent under 35 U.S.C. § 102(b) (pre-AIA). Sugimoto was not cited as prior art during prosecution of the ’729 patent.

Sugimoto discloses orally disintegrating tablet (“ODT”) formulations for use with drugs that are “hardly water-soluble under neutral or alkaline conditions and being highly water-soluble under acidic conditions yet presenting unpleasant taste” that contain the drug with a water-soluble acid, either of which, or both, are prepared as granules coated with a water-soluble coating agent that is insoluble in alcohol. Ex. 1010, Abstract, ¶¶[0001], [0008]-[0009], [0077]-[0084]. Sugimoto discloses that the compositions can be used with any drug that is hardly water-soluble under neutral or alkaline conditions and is highly water-soluble under acidic conditions but with unpleasant taste, which can include drugs having a solubility in water of ≤ 0.1 mg/mL at 25 °C and $\text{pH} \geq 7$ and a solubility in water of ≥ 1 mg/mL at $\text{pH} \leq 2$ at 25° C. *Id.*, ¶[0031]. The ODTs can be administered without unpleasant taste in the oral cavity, while providing release and absorption of the drug in the digestive tract. *Id.*, ¶[0013].

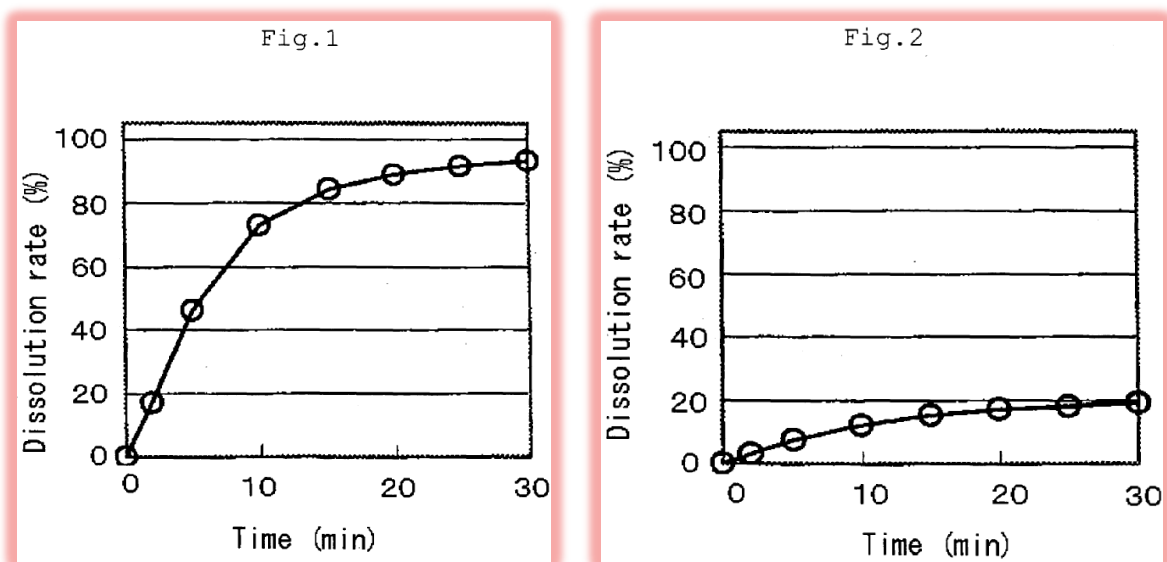
Sugimoto teaches organic acids are preferred, with fumaric, tartaric, succinic, malic, ascorbic, and aspartic acids as examples. *Id.*, ¶[0026] The acid increases “the solubility of the medicinal substance especially when administered to a subject who

is suffering from anacidity or wishes to use the preparation immediately after eating.” *Id.*, ¶[0024]. The water-soluble coating(s) on the drug and/or water-soluble acid prevent contact of the drug with the acid throughout the manufacturing process as well as in the oral cavity after administration, while enabling rapid dissolution of the drug in the digestive tract. *Id.*, ¶¶[0024]-[0025]. Suitable water-soluble coating agents include cellulose derivatives such as hydroxypropyl methylcellulose and methylcellulose, polysaccharides, polyalkylene oxides, and peptide derivatives. *Id.*, ¶[0029].

Sugimoto’s exemplary embodiments include preparing a mixture of drug-containing granules and coated organic acid-containing granules. *See, e.g., id.*, ¶¶[0131]-[0133] (Example 1). Specifically, in Example 1, a drug is granulated with mannitol and polyvinylpyrrolidone to provide drug-containing granules. *See id.*, ¶[0131]. Fumaric acid is first wet granulated with a 6% w/w aqueous solution of hydroxypropyl methylcellulose in a fluidized bed granulator, and the granules are coated with a mixture of hydroxypropyl methylcellulose, talc, ethanol, and water. *Id.*, ¶[0132]. The drug- and coated acid-containing granules are mixed with aspartame (*id.*, ¶[0133]), and the mixture is then combined with a mixture of crystalline cellulose and magnesium stearate and compressed. *Id.*, ¶¶[0133]-[0135]. Similar ODT dosage forms containing drug and coated acid granules are described in Examples 2-4. *Id.*, ¶¶[0136]-[0152].

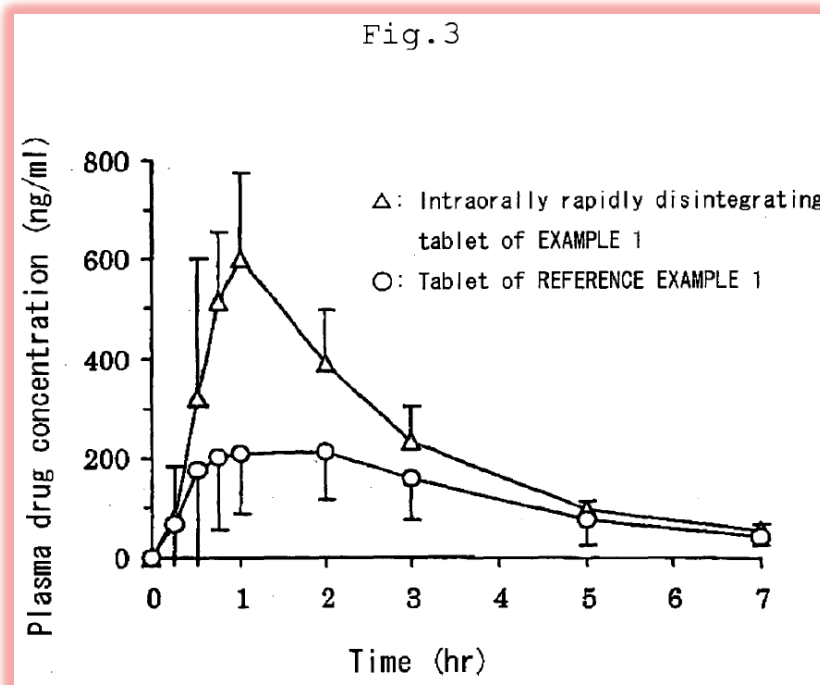
Sugimoto also discloses the preparation of comparative reference compositions in which the acid-containing granules are not coated (*id.*, ¶¶[0158]-[0160] (Reference Examples 3-4)), as well as ODTs that contain no acid-containing particles (*id.*, ¶¶[0161]-[0163] (Reference Examples 5-6)).

Dissolution testing of the ODTs of Example 1 and Reference Example 6 are provided in Figures 1 and 2, respectively, and show “a high dissolution rate in a short time” for the Example 1 ODTs, and “very poor dissolution profile” for Reference Example 6 ODTs. *Id.*, ¶¶[0178]-[0182].



The *in vivo* bioavailability provided by the ODTs of Example 1 and Reference Example 6 was measured in dogs and the results provided in Figure 3 show that ODTs of Example 1 “presented high blood drug concentration within a short time and showed high bioavailability,” while the ODTs of Reference Example 6 “could present only very low blood drug concentration and failed to show sufficient

bioavailability.” *Id.*, ¶¶[0183]-[0186].¹



VIII. DETAILED EXPLANATION OF GROUNDS (37 C.F.R. § 42.104(B)(4))

A. Motivation to Combine the Prior Art

Brauns and Leane (Ground 1) and Brauns and Sugimoto (Ground 2) render claims 1-18 obvious because when combined, they teach each and every element of the claims.

Brauns discloses dabigatran etexilate mesylate dosage forms having suitable dissolution, bioavailability, and stability. In particular, Brauns disclosed a layered

¹ Figure 3’s legend includes a typo. A POSA would have understood that the “Tablet of REFERENCE EXAMPLE 1” should instead read “Tablet of REFERENCE EXAMPLE 6.” Ex. 1005, ¶180, FN.149.

pellet structure with an insulating layer that spatially separated the organic acid core from the dabigatran etexilate layer before the preparation is taken, thus increasing the stability of the finished drug product, while allowing the organic acid to go into solution after the preparation has been taken to produce an acid environment in the stomach in which dabigatran etexilate can dissolve, independent of the stomach pH. Ex. 1005, ¶¶184-187.

A POSA would have been motivated to design a dabigatran etexilate oral dosage form that retained the advantageous properties of Brauns' preparation but differed structurally from its layered pellets, for example, to design around Brauns' pending claims that had been allowed by the PTO at that time. Ex. 1005, ¶188; Ex. 1008, pp. 55, 127, 173. Further, a POSA would have been motivated to look for alternative ways of spatially separating the tartaric acid from dabigatran etexilate to Brauns' multilayered pellet structure because, in practice, it was known to be difficult to prepare an intact insulating layer, which was required for storage stability and durability of the finished product. Ex. 1005, ¶190; Ex. 1022, p. 5.

The prior art clearly taught such an alternative. Indeed, preparing distinct particles (e.g., pellets) was known as a "convenient way" to separate chemically incompatible substances that needed to be delivered in a single dose. Ex. 1005, ¶191. Thus, a POSA would have been motivated to prepare a composition comprising two distinct particles of dabigatran etexilate and tartaric acid so that this organic acid

would be spatially separated from the chemically incompatible dabigatran etexilate before administration but could improve the dissolution of dabigatran etexilate after administration. *Id.*, ¶192.

The prior art also taught successful applications of the two-particle system. In particular, each of Leane and Sugimoto discloses that solid oral dosage forms containing an organic acid in separate coated particles improved the solubility of a pH-dependent material while controlling when, or the rate by which, the material encounters the organic acid. Ex. 1005, ¶¶193-196. Specifically, Leane teaches using organic acid particles to improve the dissolution of chitosan, a substance that is soluble only in acidic pH levels, over the pH range found in intestine (5 to excess of 7.5) while controlling the rate of the organic acid dissolution, which was important for rapid chitosan dissolution. Ex. 1005, ¶194. And, a POSA would have recognized that one of Leane's preferred embodiments was a capsule formulation containing coated organic acid particles separated from chitosan that provided faster chitosan dissolution compared to capsules where organic acid was not separated from chitosan. Ex. 1005, ¶195; Ex. 1009, ¶¶[0085]-[0089] (Examples 6-7). Sugimoto similarly teaches solid oral dosage forms containing coated organic acid granules (i.e., particles) and granules containing a drug having pH-dependent solubility kept the drug separated from the acid until the composition reached the stomach and improved the dissolution of the drug independent of the stomach pH, after the drug

reached the stomach. Ex. 1005, ¶196; Ex. 1010, ¶¶[0131]-[0135], [0178]-[0182].

A POSA would have readily combined Brauns with either Leane or Sugimoto to arrive at claims 1-18 of the '729 patent, because Brauns, Leane, and Sugimoto are each attempting to solve the same problem of improving dissolution in the digestive tract of a material having pH-dependent solubility while controlling the timing or the rate at which the acid comes into contact with the material. Ex. 1005, ¶¶187, 193-194, 196.

And, a POSA would have had a reasonable expectation of success in combining Brauns with Leane or Sugimoto, because each reference teaches similar solutions (incorporating an organic acid in the drug preparation while spatially separating the organic acid from the compound with pH dependent solubility and acid incompatibility until the drug preparation reaches the intended site of dissolution) with a similar and predictable outcome (increased dissolution of the compound with pH dependent solubility when the drug product reached its desired site of action while avoiding contact between the acid and the compound with pH dependent solubility before the drug product reached its desired site of action). *Id.*

B. Ground 1: Claims 1-18 are Obvious Over Brauns in view of Leane

1. Independent Claim 1

a) Element 1.1: “A composition comprising: a mixture of at least two distinct types of particles”

Leane discloses “a composition comprising a mixture of two distinct types of

particles.” Ex. 1009, ¶¶[0038]-[0040], [0059]; Ex. 1005, ¶¶199-201. For example, Leane discloses that a “drug compound can be formed into agglomerates with chitosan or a derivative thereof or a salt of chitosan or salt of a derivative of chitosan, which are then mixed with the organic acid, which may be in the form of agglomerates.” Ex. 1009, ¶[0059]; Ex. 1005, ¶200. Leane defines the term “agglomerate” as “an association of particles,” such as “individual particles of acid engineered to a specific size.” Ex. 1009, ¶[0039]. Leane further explains that acid agglomerates “may be in the form of a granule, pellet, tablet or acid particle engineered to a specific size,” (*id.*, ¶[0042]) and exemplifies “pellets” containing an acid. *E.g., id.*, ¶¶[0080]-[0082]. Thus, the term “agglomerates” in Leane falls within the scope of the term “particles,” as this term should be construed. *Supra* Section IV.A.

b) Element 1.2: “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”

Brauns discloses particles (pellets) that contain dabigatran etexilate mesylate, which is a pharmaceutically acceptable salt of dabigatran etexilate. Ex. 1007, ¶¶[0003], [0050]-[0053]; Ex. 1005, ¶202.

c) Element 1.3: “wherein the first type of particles is free from organic acids and inorganic acids; and”

Element 1.3 is obvious over Brauns in view of Leane, the latter of which

discloses that a “drug compound can be formed into agglomerates with chitosan or a derivative thereof or a salt of chitosan or salt of a derivative of chitosan, which are then mixed with the organic acid, which may be in the form of agglomerates.” Ex. 1009, ¶¶[0059]; Ex. 1005, ¶¶203-205. Thus, Leane discloses an embodiment in which the drug compound and chitosan (the material having pH-dependent solubility) are in a separate particle (agglomerate) from the organic acid that is present to improve chitosan’s dissolution. Ex. 1005, ¶204. Further, dabigatran etexilate was known to be prone to chemical degradation and polymorphic form transformation in acidic environment. *Supra* Section V.A.1. Thus, a POSA would have used Leane’s teachings to prepare dabigatran etexilate particles free from organic acids and inorganic acids.

- d) Element 1.4: “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.”**

Brauns discloses particles or pellets that contain tartaric acid (a pharmaceutically acceptable organic acid), which are coated with a protective coating layer. Ex. 1007, ¶¶[0039]-[0049]; Ex. 1005, ¶¶206-209. The protective coating layer prevents contact between the acid and the acid sensitive drug substance (dabigatran etexilate) until after the composition is administered, thus increasing the “durability of the finished product” before the drug is taken, (*id.*, ¶[0013]) while

allowing the organic acid to create an acidic microclimate to dissolve the active substance after the drug is taken. Ex. 1007, ¶¶[0011], [0013]; Ex. 1005, ¶206. Leane similarly discloses particles (agglomerates) of a pharmaceutically acceptable organic acid (i.e., succinic acid), which are coated with a protective coating layer. *See* Ex. 1009, ¶¶[0080]-[0082]. Leane teaches coating the acid agglomerates advantageously improves chitosan dissolution by preventing contact between the acid and chitosan until after administration and further controlling the rate at which the acid comes into contact with chitosan. *Id.*, ¶[0044]; Ex. 1005, ¶¶210-211.

Element 1.4's requirement that "the second type of particles ... is free from dabigatran etexilate" is rendered obvious by Leane, which discloses coated acid-containing agglomerates that are free from chitosan (i.e., the pH-dependent material that the acid is present to solubilize). Ex. 1009, ¶¶[0080]-[0082]; Ex. 1005, ¶¶212-213. Leane also discloses that a "drug compound can be formed into agglomerates with chitosan [], which are then mixed with the organic acid, which may be in the form of agglomerates." Ex. 1009, ¶[0059]; *see also id.*, ¶[0058] (describing a composition comprising drug compound agglomerates and organic acid agglomerates). Thus, Leane discloses organic acid particles that are free from the drug compound and/or chitosan. Further, dabigatran etexilate was known to be prone to chemical degradation and polymorphic form transformation in acidic environment. *Supra* Section V.A.1. Thus, a POSA would have used Leane's

teachings to prepare organic acid particles free from dabigatran etexilate.

Accordingly, the combination of Brauns and Leane renders claim 1 obvious.

2. Independent Claims 11 and 16, and Dependent Claims 2, 10, and 14

The only differences between independent claim 1 and independent claims 11 and 16 is in the preambles and first limitations. Specifically, whereas claim 1 requires “[a] composition comprising: a mixture of at least two distinct types of particles,” claim 11 requires “[a] composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient,” and claim 16 requires “[a] capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient.” The subsequent limitations of claims 11 and 16 are identical to those of claim 1 and are obvious for the same reasons as discussed in the previous section.

Claims 11 and 16, which require a composition consisting of two distinct types of particles and at least one pharmaceutically acceptable excipient, are obvious over Brauns in view of Leane. First, Leane discloses an embodiment consisting of two distinct types of particles in which chitosan (the material having pH-dependent solubility) and the drug substance are present in the first particles and an organic acid is present in the second particles. Ex. 1009, ¶[0059]; Ex. 1005, ¶217. Leane also

teaches that the disclosed compositions may also contain at least one pharmaceutically acceptable excipient, such as a diluent, disintegrant, surfactant, lubricant, etc., “generally used in solid pharmaceutical preparations and well known to those skilled in the art.” Ex. 1009, ¶[0062]. Ex. 1005, ¶218. Further, as discussed above, it was also well-known that a pharmaceutically acceptable excipient, such as a separating agent, glidant, lubricant, and diluent/filler, can be added to particles in order to prepare a finished dosage form, such as a capsule. *Supra* Section V.A.2.

With respect to claim 16, both Brauns and Leane disclose capsule dosage forms that contain pellets. Ex. 1007, ¶¶[0054], [0072]; Ex. 1009, ¶¶[0084]-[0085]. Therefore, it would be obvious to formulate the composition of claim 1 in a capsule. Ex. 1005, ¶¶220-221.

Claim 2, which depends from claim 1 and requires that the composition further comprises “at least one pharmaceutically acceptable excipient,” is invalid as obvious for the same reasons as claims 11 and 16.

Claims 10 and 14 depend from claims 2 and 11, respectively, and require that “the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.” As discussed above, Leane teaches that the disclosed compositions may contain at least one pharmaceutically acceptable excipient, such as a diluent, disintegrant, surfactant, lubricant, etc., “generally used in solid

pharmaceutical preparations and well known to those skilled in the art.” Ex. 1009, ¶[0062]. Ex. 1005, ¶224. Further, it was well within the knowledge of a POSA to combine pellet compositions with a diluent, glidant, or lubricant. *Supra* Section V.A.2.

Accordingly, the combination of Brauns in view of Leane renders obvious each limitation of claims 2, 10, 11, 14, and 16.

3. Dependent Claims 3, 5, 12, 15, and 17

Claims 3 and 12 depend from claims 1 and 11, respectively, and require that the compositions contain “from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.” And claims 5, 15, and 17 depend from claims 1, 14, and 16, respectively, and require that the compositions contain “from 50 mg to 200 mg of dabigatran etexilate mesylate.” Brauns discloses that “the active substance [i.e., dabigatran etexilate] content is 5% to 60%, preferably 10% to 50% of the pharmaceutical composition.” Ex. 1007, ¶[0014]. Brauns also discloses composition that the “preferred salt” of dabigatran etexilate is “the mesylate (methanesulphonate)” and dabigatran etexilate mesylate is present in Brauns’ exemplary embodiments in amounts of 57.7 mg and 115.3 mg. *Id.*, ¶¶[0039], [0055] (Examples 1-2). A POSA would have found it obvious to use dabigatran etexilate mesylate in the amounts disclosed by Brauns, which overlap with the claimed

amounts,² in a two-pellet composition as disclosed by Leane. Ex. 1005, ¶¶228-231.

Accordingly, the combination of Brauns in view of Leane renders obvious each limitation of claims 3, 5, 12, 15, and 17.

4. Dependent Claim 4

Claim 4 depends from claim 1 and requires that the composition comprises “from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.” Brauns discloses that the organic acid is present in a concentration of “between 20 and 90%, preferably between 20 and 80% in the finished pellet (i.e., in the pharmaceutical composition).” Ex. 1007, ¶[0012]. And Braun’s exemplary embodiments disclose pellet compositions that contain 61.3% and 38.5% by weight of tartaric acid. *See id.*, ¶¶[0039], [0055] (Examples 1-2); Ex. 1005, ¶233. Leane discloses that “[t]he amount of acid is chosen in order to provide rapid dissolution of the chitosan present in the composition. The weight ratio of acid:chitosan ... in the composition of the invention is preferably in the range 10: 1 to 1: 1, more preferably in the range 8: 1 to 1: 1 and most preferably in the range 6: 1 to 1: 1.” Ex.

² The overlapping disclosures “establish[] a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). Thus, the burden would shift to the patentee to show that the overlapping range would not have been obvious by showing: the prior art teaches away from the claimed range; the claimed range produces new and unexpected results; the claimed range is critical to the alleged invention; and/or that a “process parameter . . . was not recognized as ‘result-effective.’” *See, e.g., Genentech Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341 (Fed. Cir. 2020). The petitioners are not aware of any such evidence.

1009, ¶[0049]. Leane’s exemplary embodiments disclose a capsule containing an organic acid in the form of coated pellets where the organic acid is 45% w/w of the composition prior to coating and ~40% after coating. *See id.*, ¶¶[0080]-[0082], [0085] (Examples 2, 3, and 6); Ex. 1005, ¶234. Thus, both Brauns and Leane teach compositions comprising the organic acid at wt% that overlap with the amount required by claim 4.³

Accordingly, the combination of Brauns in view of Leane renders obvious each limitation of claim 4.

5. Dependent Claims 6-9

Claim 6 depends from claim 2 and is directed to “[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 7 depends from claim 6, and specifies that “the first type of particles are prepared by granulation.” Claim 8 depends from claim 7, and specifies additional process steps. Claim 9 requires a process that is the same in all respects to claim 8 except for step iv. Thus, claims 6-9 are product-by-process claims.

It is well-settled that a product-by-process claim is invalid if a product made

³ *See supra*, FN. 1.

by the recited process is anticipated by or obvious from prior art products, even if those prior art products are made by different processes. *Cf. Cochrane v. BASF*, 111 U.S. 293, 311 (1884) (assessing the invalidity of an old product recited in a product-by-process claim in terms of patentability); *Atl. Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 841 (Fed. Cir. 1992) (explaining that, in *BASF*, the validity rule “focused on the product with less regard for the process limits”); *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369-70 (Fed. Cir. 2009) (“In determining validity of a product-by-process claim, the focus is on the product and not on the process of making it.”). For the same reasons explained above, the product recited in claim 2 prepared by the process of claims 6-9 is invalid as obvious over the combination of Brauns and Leane. Therefore, the product-by-process claims 6-9 are also invalid as obvious over the combination of Brauns and Leane.

Alternatively, claims 6-9 are invalid as obvious in view of Brauns and Leane. First, as discussed above, a POSA would have found it obvious to mix the two types of particles with at least one pharmaceutically acceptable excipient, as required by claim 6. *Supra* Section VIII.B.2.

Claim 7 depends from claim 6 and further provides a step “wherein the first type of particles are prepared by granulation.” Leane discloses, the agglomerates can be in the form of a granule, pellet, tablet, or particle prepared a wide range of methods including wet or dry granulation or fluid bed granulation. Ex. 1009,

¶[0042]. Leane also discloses embodiments in which the drug compound and chitosan are formed into agglomerates, which are then mixed with acid agglomerates. *Id.*, ¶[0059]. Thus, a POSA would have found it obvious to prepare particles containing dabigatran etexilate by granulation as required in claim 7. Ex. 1005, ¶240.

Claim 8 depends from claim 7 and specifies additional process steps. In steps i)-ii), dabigatran etexilate is first blended with at least one pharmaceutically acceptable excipient and then the blend of step i) is granulated with a binder solution to form granulates of dabigatran etexilate. And in steps iii)-iv), at least one organic acid is first blended with at least one pharmaceutically acceptable excipient and then the blend of step iii) is granulated with a binder solution to form organic acid-containing granules.

As discussed above, Leane discloses that agglomerates can be in the form of a granule, pellet, tablet, or particle prepared a wide range of methods including wet or dry granulation or fluid bed granulation. Ex. 1009, ¶[0042]. Leane also discloses the use of wet granulation to form acid-containing agglomerates in which a binder is mixed with an organic acid and drug and then water is added to form a granulate. *Id.*, ¶[0080]. Further, it was well-known in the pharmaceutical arts that a binder can be added to the granulation fluid. *Supra* Section V.A.2. Leane also discloses that a “drug compound can be formed into agglomerates with chitosan [], which are then

mixed with the organic acid, which may be in the form of agglomerates.” Ex. 1009, ¶[0059]; Ex. 1005, ¶245. Thus, a POSA would have found it obvious in view of Brauns and Leane to use a granulation method to form granules of dabigatran etexilate and a binder and/or granules of an organic acid and a binder. Ex. 1005, ¶¶242-246.

Step v) of claim 8 requires “coating the organic acid granules with a protective coating layer.” Brauns discloses that organic acid cores are coated with an “insulating layer, which separates the acid core from the layer containing the active substance.” Ex. 1007, ¶[0010]. Leane also discloses coating the organic acid-containing pellets with a water-soluble polymer layer. Ex. 1009, ¶¶[0044]-[0047], [0081]-[0082]. The coating of pellets is also routinely done in the pharmaceutical arts, for example, to modify dissolution properties, control drug release rates, or for taste-masking. *Supra* Section V.a.2. Thus, a POSA would have found it obvious in view of Brauns and Leane to apply a protective coating layer to the organic acid-containing pellets. Ex. 1005, ¶¶247-251.

Step vi) of claim 8 requires “blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules.” Leane teaches blending the coated acid granules with other ingredients before weighing them into hard gelatin capsules. Ex. 1009, ¶[0084]. As discussed above, Leane also discloses that a “drug compound can be formed into agglomerates with chitosan [],

which are then mixed with the organic acid, which may be in the form of agglomerates.” Ex. 1009, ¶[0059]; Ex. 1005, ¶253. Thus, a POSA would have found it obvious to blend the two types of granules to form a mixture. Ex. 1005, ¶¶252-254.

Step vii) of claim 8 requires “optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient.” And step viii) of claim 8 requires “adding a lubricant to the blend of step (vii).” Leane teaches that the disclosed compositions may contain at least one pharmaceutically acceptable excipient, such as a diluent, disintegrant, surfactant, lubricant, etc., “generally used in solid pharmaceutical preparations and well known to those skilled in the art.” Ex. 1009, ¶[0062]. Ex. 1005, ¶256. As discussed above, it was well within the background knowledge of a POSA to combine pellet compositions with a diluent, glidant, and/or lubricant. *Supra* Section V.A.2. Thus, a POSA would have found it obvious to add at least one pharmaceutically acceptable excipient, and in particular, a lubricant to the blend of granules. Ex. 1005, ¶¶255-258.

Step ix) of claim 8 requires “filling the lubricated mixture of step (viii) into suitable hard capsules.” Both Brauns and Leane disclose dosage forms of hard capsules. Ex. 1007, ¶¶[0021], [0054], [0072]; Ex. 1009, ¶¶[0061], [0084]-[0085]. The use of hard capsules for pelleted compositions was also well-known in the

pharmaceutical arts. *Supra* Section V.A.2. Thus, a POSA would have found it obvious to use the pellet compositions to fill a hard capsule. Ex. 1005, ¶¶259-262. Thus, claim 8 is invalid as obvious over Brauns in view of Leane.

Claim 9 requires a process that is the same in all respects to claim 8 except that step iv) of claim 9 requires “extruding and spheronizing the blend of step (iii) to form organic acid pellets.” Further, extrusion and spheronization was one of the most popular methods for preparing pellets in the pharmaceutical arts. *Supra* Section V.A.2. Further, Leane discloses extrusion and spheronization of a wet granulate to form acid-containing agglomerates. Ex. 1009, ¶[0080]. Thus, a POSA would have found it obvious in view of Brauns and Leane to use extrusion and spheronization to form granules of an organic acid and a binder. Ex. 1005, ¶¶264-268.

Accordingly, the combination of Brauns in view of Leane renders obvious each limitation of claims 6-9.

6. Dependent Claims 13 and 18

Claims 13 and 18 depend from claims 11 and 16, respectively, and further require that “the first type of particles comprise at least one pharmaceutically acceptable excipient.” As noted above, the first type of particles contain dabigatran etexilate, and a POSA would have found it obvious to prepare pellets that contain an active pharmaceutical ingredient such as dabigatran etexilate in combination with a pharmaceutically acceptable excipient such as a binder or diluent. Ex. 1005, ¶¶270-

273. For example, Brauns discloses the formation of a dabigatran etexilate layer that contains a binder. Ex. 1007, ¶¶[0019], [0050]-[0051], [0066]-[0068]. Leane also discloses that the agglomerate compositions “may also contain other pharmaceutically acceptable ingredients” such as diluents and binders. Ex. 1009, ¶[0062]. The use of binders to prepare drug-containing pellets was also well known in the pharmaceutical arts. *Supra* Section V.A.2.

Accordingly, the combination of Brauns in view of Leane renders obvious each limitation of claims 13 and 18.

C. Ground 2: Claims 1-18 are Obvious Over Brauns in View of Sugimoto

1. Independent Claim 1

a) Element 1.1: “A composition comprising: a mixture of at least two distinct types of particles”

Sugimoto discloses “a composition comprising a mixture of two distinct types of particles.” Ex. 1010, ¶¶[0024], [0078], [0084]; Ex. 1005, ¶¶295-297. For example, Sugimoto discloses preparing uncoated granules comprising a drug substance (Ex. 1010, ¶¶[0024], [0078]) and coated granules comprising an acid (*id.*, ¶[0084]) and further exemplifies mixtures of coated drug-containing granules and coated organic acid-containing granules. *See, e.g., id.*, ¶¶[0131]-[0133] (Example 1); *see also id.* ¶¶[0136]-[0150] (Examples 2-5). Thus, Sugimoto discloses “particles” recited in the ’729 patent claims, as this term should be construed. *See supra* Section

IV.A.

- b) **Element 1.2: “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”**

Brauns discloses particles or pellets that contain dabigatran etexilate mesylate, which is a pharmaceutically acceptable salt of dabigatran etexilate. Ex. 1007, ¶¶[0003], [0050]-[0053]; Ex. 1005, ¶298. Further, Sugimoto discloses a composition having two types of particles, wherein the first particles contain a drug that is “hardly water-soluble under neutral or alkaline conditions and being highly water-soluble under acidic conditions yet presenting unpleasant taste under acidic conditions.” Ex. 1010, ¶¶[0013], [0131]; Ex. 1005, ¶299.

- c) **Element 1.3: “wherein the first type of particles is free from organic acids and inorganic acids; and”**

Element 1.3 is obvious over Brauns in view of Sugimoto, the latter of which discloses both the preparation of drug-containing granules that are free from any acids and that the drug and acid should be kept separated from one another to avoid contact between the drug and the acid until the composition reaches the stomach. Ex. 1010, ¶¶[0013], [0024], [0131]; Ex. 1005, ¶¶300-302. Further, dabigatran etexilate was known to be prone to chemical degradation and polymorphic form transformation in an acidic environment. *Supra* Section V.A.1. Thus, a POSA would have used Sugimoto’s teachings to prepare dabigatran etexilate particles free from

organic acids and inorganic acids.

- d) **Element 1.4: “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.”**

Brauns discloses particles or pellets that contain tartaric acid (a pharmaceutically acceptable organic acid), which are coated with a protective coating layer. Ex. 1007, ¶¶[0039]-[0049]; Ex. 1005, ¶¶303-306. The protective coating layer prevents contact between the acid and the drug substance until after the composition is administered, thus increasing the “durability of the finished product” before the drug is taken, (*id.*, ¶[0013]) while allowing the organic acid to create an acidic microclimate to dissolve the active substance after the drug is taken and reaches the stomach. Ex. 1007, ¶¶[0011], [0013]; Ex. 1005, ¶303. Sugimoto similarly discloses granules of a pharmaceutically acceptable organic acid (i.e., fumaric acid), which are coated with a protective coating layer that prevents contact between the acidic pH soluble drug substance and the acid until the composition reaches the stomach. Ex. 1010, ¶¶[0024]-[0025], [0132]; Ex. 1005, ¶¶307-310.

Element 1.4’s requirement that “the second type of particles ... is free from dabigatran etexilate” is rendered obvious by Sugimoto, which discloses coated acid-containing agglomerates that are free from a drug having pH-dependent solubility. Ex. 1010, ¶¶[0013], [0024], [0132]; Ex. 1005, ¶311. Further, dabigatran etexilate

was known to be prone to chemical degradation and polymorphic form transformation in acidic environment. *Supra* Section V.A.1. Thus, a POSA would have used Sugimoto's teachings to prepare organic acid particles free from dabigatran etexilate.

Accordingly, the combination of Brauns in view of Sugimoto renders obvious each limitation of claim 1.

2. Independent Claims 11 and 16, and Dependent Claims 2, 10, and 14

The only differences between independent claim 1 and independent claims 11 and 16 is in the preambles and first limitations. Specifically, whereas claim 1 requires "[a] composition comprising: a mixture of at least two distinct types of particles," claim 11 requires "[a] composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient," and claim 16 requires "[a] capsule containing a pharmaceutical composition consisting of a mixture of two distinct types of particles and at least one pharmaceutically acceptable excipient." The subsequent limitations of claims 11 and 16 are identical to those of claim 1, and are obvious for the same reasons as discussed in the previous section.

Claims 11 and 16, which require a composition consisting of two distinct types of particles and at least one pharmaceutically acceptable excipient are obvious

over Brauns in view of Sugimoto. First, Sugimoto discloses an embodiment consisting of two distinct types of particles in which a drug having pH-dependent solubility similar to dabigatran etexilate is in the first particles and an organic acid is present in the second particles. Ex. 1010, ¶¶[0013], [0024], [0131]-[0132]; Ex. 1005, ¶¶315-317. Sugimoto also teaches that the disclosed compositions contain at least one pharmaceutically acceptable excipient, such as a binding agent. Ex. 1010, ¶[0024]. It was also well-known that a pharmaceutically acceptable excipient can be added to particles in order to prepare a finished dosage form, such as a capsule. *Supra* Section V.A.2.

With respect to claim 16, Brauns discloses capsule dosage forms that contain pellets. Ex. 1007, ¶¶[0054], [0072]. Therefore, it would have been obvious to use the composition of claim 1 in a capsule. Ex. 1005, ¶319.

Claim 2, which depends from claim 1 and requires that the composition further comprises “at least one pharmaceutically acceptable excipient,” is invalid as obvious for the same reasons as claims 11 and 16.

Claims 10 and 14 depend from claims 2 and 11, respectively, and require that “the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, diluents, surfactants, glidants, lubricants, and combinations thereof.” Sugimoto discloses using binders when preparing granules. Ex. 1010, ¶[0081]; *see also id.*; ¶[0024] (disclosing binding agent); Ex. 1005, ¶323.

As discussed above, it was well within the background knowledge of a POSA to combine pellet compositions with a binder, diluent, glidant, or lubricant. *Supra* Section V.A.2.

Accordingly, the combination of Brauns in view of Sugimoto renders obvious each limitation of claims 2, 10, 11, 14 and 16.

3. Dependent Claims 3, 5, 12, 15, and 17

Claims 3 and 12 depend from claims 1 and 11, respectively, and require that the compositions contain “from 0.01 wt % to 90 wt % of dabigatran etexilate, as dabigatran etexilate mesylate.” And claims 5, 15, and 17 depend from claims 1, 14, and 16, respectively, and require that the compositions contain “from 50 mg to 200 mg of dabigatran etexilate mesylate.” Brauns discloses that “the active substance [i.e., dabigatran etexilate] content is 5 to 60%, preferably 10 to 50% of the pharmaceutical composition.” Ex. 1007, ¶[0014]. Brauns also discloses composition that the “preferred salt” of dabigatran etexilate is “the mesylate (methanesulphonate)” and dabigatran etexilate mesylate is present in Brauns’ exemplary embodiments in amounts of 57.7 mg and 115.3 mg. Ex. 1007, ¶¶[0014], [0039], [0055] (Examples 1-2). A POSA would have found it obvious to use dabigatran etexilate mesylate in the amounts disclosed by Brauns, which overlap

with the claimed amounts,⁴ in a two-pellet composition as disclosed by Sugimoto. Ex. 1005, ¶¶326-330.

Accordingly, the combination of Brauns in view of Sugimoto renders obvious each limitation of claims 3, 5, 12, 15, and 17.

4. Dependent Claim 4

Claim 4 depends from claim 1 and requires that the composition comprises “from 2 wt % to 95 wt % of the at least one pharmaceutically acceptable organic acid.” Brauns discloses that the organic acid is present in a concentration of “between 20 and 90%, preferably between 20 and 80% in the finished pellet (i.e., in the pharmaceutical composition).” Ex. 1007, ¶[0012]. And Brauns’ exemplary embodiments disclose pellet compositions that contain 61.3% and 38.5% by weight of tartaric acid. Ex. 1007, ¶¶[0039], [0055] (Examples 1-2); Ex. 1005, ¶332. Further, Sugimoto discloses a composition in which the organic acid in the form of coated pellets is 6.7% w/w. Ex. 1010, ¶¶[0131]-[0133] (Example 1); Ex. 1005, ¶333. Thus, both Brauns and Sugimoto teach compositions comprising the organic acid at wt% that overlap with the claimed amount⁵ required by claim 4.

Accordingly, the combination of Brauns in view of Sugimoto renders obvious each limitation of claim 4.

⁴ See *supra*, FN. 1.

⁵ See *supra*, FN. 1.

5. Dependent Claims 6-9

Claim 6 depends from claim 2, is directed to “[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 7 depends from claim 6, and specifies that “the first type of particles are prepared by granulation.” Claim 8 depends from claim 7, and specifies additional process steps. Claim 9 requires a process that is the same in all respects to claim 8 except for step iv. Thus, claims 6-9 are product-by-process claims. For the same reasons discussed above in Section VIII.B.5, these claims are invalid as obvious over Brauns and Sugimoto.

Alternatively, claims 6-9 are invalid as obvious in view of Brauns and Sugimoto. First, as discussed above, a POSA would have found it obvious to mix the two types of particles with at least one pharmaceutically acceptable excipient, as required by claim 6. *Supra* Section VIII.BC.2.

Claim 7 depends from claim 6 and further provides a step “wherein the first type of particles are prepared by granulation.” Sugimoto discloses the use of wet granulation methods to form the drug- and acid-containing granules. Ex. 1010, ¶¶[0131]-[0132], [0136], [0140], [0148]-[0149]. A POSA would have found it obvious to prepare particles containing dabigatran etexilate by granulation, as required in claim 7, for example using the method disclosed in Sugimoto. Ex. 1005,

¶339.

With respect to steps i)-iv) of claim 8 (discussed above in Section VIII.B.5), Sugimoto discloses the use of wet granulation methods to form the drug- and acid-containing granules. Ex. 1010, ¶¶[0131]-[0132], [0136], [0140], [0148]-[0149]. Further, Sugimoto discloses mixing the drug substance with a water-soluble saccharide, such as mannitol, before preparing granules comprising the drug substance, and discloses using a binder during the granulation process. *See* Ex. 1010 at ¶¶[0028], [0078], [0081], [0131]; Ex. 1005, ¶¶341-345. Further, incorporating binders into pellet formulations to bind powders and maintain the integrity of the pellets, and adding other pharmaceutically acceptable excipients, such as fillers or lubricants, before preparing pellets or granules, were well-known in the art. Ex. 1005, ¶¶346-347. Thus, a POSA would have found it obvious in view of Brauns and Sugimoto to use a wet granulation method to form granules of dabigatran etexilate and a binder and/or granules of an organic acid and a binder. *Id.*, ¶348.

Step v) of claim 8 requires “coating the organic acid granules with a protective coating layer.” Brauns discloses that organic acid cores are coated with an “insulating layer, which separates the acid core from the layer containing the active substance.” Ex. 1007, ¶[0010]. Sugimoto also discloses coating the organic acid-containing granules with a water-soluble polymer layer. Ex. 1010, ¶¶[0013], [0132], [0149]. The coating of pellets is also routinely done in the pharmaceutical arts, for

example, to modify dissolution properties or for taste-masking. *Supra* Section V.A.2. Thus, a POSA would have found it obvious in view of Brauns and Sugimoto to apply a protective coating layer to the organic acid-containing pellets. Ex. 1005, ¶¶349-353.

Step vi) of claim 8 requires “blending the granules of step (ii) with the coated granules of step (v) to form a mixture of at least two types of granules.” Sugimoto discloses blending drug- and acid-containing granules. Ex. 1010, ¶¶[0133], [0137], [0141], [0145], [0150]. Thus, a POSA would have found it obvious to blend the two types of granules to form a mixture. Ex. 1005, ¶¶354-355.

Step vii) of claim 8 requires “optionally blending the mixture of at least two types of granules of step (vi) with at least one pharmaceutically acceptable excipient.” And step viii) of claim 8 requires “adding a lubricant to the blend of step (vii).” Sugimoto discloses blending drug- and acid-containing granules with a pharmaceutically acceptable excipient, including a lubricant. Ex. 1010, ¶¶[0133]-[0134], [0137]-[0138], [0141]-[0142], [0145]-[0146]. Further, it was well within the background knowledge of a POSA to combine pellet compositions with a diluent, glidant, and/or lubricant. *Supra* Section V.A.2. A lubricant in particular was known to enhance the flow properties of granules and avoid sticking and agglomeration. *Id.* Thus, a POSA would have found it obvious to add at least one pharmaceutically acceptable excipient, and in particular, a lubricant to the blend of granules. Ex. 1005,

¶¶356-359.

Step ix) of claim 8 requires “filling the lubricated mixture of step (viii) into suitable hard capsules.” Brauns discloses dosage forms of hard capsules. *See* Ex. 1007, ¶¶[0021], [0054], [0072]. The use of hard capsules for pelleted compositions was also well-known in the pharmaceutical arts. *Supra* Section V.B.2. Thus, a POSA would have found it obvious to use the pellet compositions prepared by combining Brauns and Sugimoto to fill a hard capsule. Ex. 1005, ¶¶360-363. Thus, claim 8 is invalid as obvious over Brauns in view of Sugimoto.

Claim 9 requires a process that is the same in all respects to claim 8 except that step iv) of claim 9 requires “extruding and spheronizing the blend of step (iii) to form organic acid pellets.” Brauns discloses forming pellets by “extrusion/spheronization.” Ex. 1007, ¶¶[0012], [0017]. The formation of pellets by extrusion and spheronization was also well-known in the pharmaceutical arts. *Supra* Section V.A.2. Thus, a POSA would have found it obvious in view of Brauns and Sugimoto to use extrusion and spheronization to form granules of an organic acid and a binder. Ex. 1005, ¶¶365-369.

Accordingly, the combination of Brauns in view of Sugimoto renders obvious each limitation of claims 6-9.

6. Dependent Claims 13 and 18

Claims 13 and 18 depend from claims 11 and 16, respectively, and further

require that “the first type of particles comprise at least one pharmaceutically acceptable excipient.” As noted above, the first type of particles contain dabigatran etexilate, and a POSA would have found it obvious to prepare pellets that contain an active pharmaceutical ingredient such as dabigatran etexilate in combination with a pharmaceutically acceptable excipient such as a binder or diluent. Ex. 1005, ¶371. For example, Brauns discloses the formation of a dabigatran etexilate layer that contains a binder. Ex. 1007, ¶¶[0019], [0050]-[0051], [0066]-[0068]. Sugimoto also discloses drug substance-containing granules that include an excipient. Ex. 1010, ¶[0131]. The use of binders to prepare drug-containing pellets was also well-known in the pharmaceutical arts. *Supra* Section V.A.2.

Accordingly, the combination of Brauns in view of Sugimoto renders obvious each limitation of claims 13 and 18.

D. No Objective Indicia of Non-Obviousness

For the reasons discussed above a POSA would have been motivated to combine the prior art with a reasonable expectation of successfully preparing oral dosage forms of dabigatran etexilate mesylate according to claims 1-18 of the '729 patent. Indeed, the prior art discussed above discloses each and every limitation of claims 1-18.

As noted above, claims 1-18 were only allowed because the PTAB found that a POSA would not have had a reason to combine Brauns and Habib. *See* Ex. 1002

at 58, 82-88. However, unlike Habib, both Leane and Sugimoto are directed to pharmaceutical dosage forms in which an organic acid is used to assist with the dissolution of a material having pH-dependent solubility—in Leane, chitosan, and in Sugimoto, a weakly basic drug. Thus, claims 1-18 are *prima facie* obvious over Brauns in view of either Leane or Sugimoto.

During prosecution of the '729 patent, applicants submitted three declarations that purported to show unexpected results based on 1) stability due to coating of the acid-containing pellets (Ex. 1002, pp. 447-450, “Gandhi declaration”); 2) faster dissolution compared to Brauns (*id.*, pp. 442-445, “Tyebji declaration”); and 3) bioequivalence to Brauns (and Pradaxa[®]) despite a purportedly faster dissolution profile (*id.*, pp. 439-441, “Xu declaration”). None of these results are unexpected and certainly do not overcome the strong *prima facie* case of obviousness over the prior art. Ex. 1005, ¶¶274-286.

First, the Gandhi declaration describes the results of stability studies showing compositions comprising dabigatran etexilate particles and coated acid particles were more stable than compositions without said coating. Ex. 1002, pp. 447-450. However, the Gandhi declaration fails to compare the claimed composition with the closest prior art, i.e., Brauns, which discloses particles comprising *coated* acid core. It is well-established that “when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the

closest prior art.” *In re Theripion, Inc.*, 2023 WL 5125187, at *6 (Fed. Cir. Aug. 10, 2023) (quoting *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006)). Indeed, Bruns discloses that the coating was included “[t]o increase the durability of the finished product.” Ex. 1007, ¶[0013]. Thus, it would not have been surprising to observe compositions without coated acid particles were less stable than those with coated acid particles. Ex. 1005, ¶279. Further, both Leane and Sugimoto disclose acid-containing pellets having a protective coating that prevents contact with the material having pH-dependent solubility until after the composition has been administered. Ex. 1009, ¶¶[0038]-[0048], [0081]-[0082]; Ex. 1010, ¶¶[0013], [0024], [0029], [0131]-[0132]. Thus, the Gandhi declaration does not overcome the strong case of obviousness presented here. Ex. 1005, ¶¶275-279.

Second, the Tyebji declaration purports to demonstrate faster dissolution of the two-pellet compositions of the ’729 patent compared to the layered single-pellet compositions of Brauns. Ex. 1002, pp. 442-445. The dissolution data is provided in the following table:

Time (minutes)	% release	
	Formulation A (two types of particles/pellets)	Formulation B (one type of particles/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

Ex. 1001, 14:30–16:6; *see also* Ex. 1002, pp. 444-445. Notably, as the Examiner explained, the Tyebji declaration is insufficient to overcome the obviousness case at issue, because “the Formulation A and B cannot be properly compared to each other, as the ratio and amount of tartaric acid and active substance are not the same in [each].” Ex. 1002, pp. 398-400; *see also* Ex. 1005, ¶¶282-283 (concluding that any observed differences in the dissolution profiles for Formulations A vs. B cannot be properly attributed to the two-pellet vs. one-pellet structures of the formulations).

Notwithstanding the lack of comparability, the only time points at which Formulation A provides faster dissolution are at 10 and 15 minutes. By 20 minutes and at all following time points, the dissolution rates of the two dosage forms are similar. Ex. 1005, ¶285. However, there is nothing unexpected or surprising about these two different dosage forms having different dissolution rates at 10 and 15

minutes. *Id.*, ¶284. Further, the pellets in Formulation B include three layers separating the media from the tartaric acid core, whereas the coated acid particles in Formulation A only include one layer separating the tartaric acid from the media. Therefore, it would not have been surprising to observe it would take a few minutes longer for the tartaric acid in Formulation B to be released into the media compared to Formulation A. Given that tartaric acid was known to enhance dabigatran etexilate's solubility, the different dissolution rates at 10 and 15 minutes would not have been surprising or unexpected to a POSA. *Id.*, ¶286.

Third, the Xu declaration alleges that, in addition to exhibiting a faster dissolution rate, the claimed two-pellet composition shows the same bioavailability to the one-pellet composition of Brauns. As discussed above, the faster dissolution rate at 10 and 15 minutes would not have been unexpected to POSA. Further, based on the teachings of the relevant FDA Guidance, a POSA would have reasonably expected that bioavailability of a drug product is not limited by its dissolution if it undergoes 85% dissolution in 15-20 minutes under mild dissolution test conditions in 0.1N HCl, the same conditions used for measuring the dissolution of Formulations A and B. Ex. 1005, ¶¶291-292. As shown above, Formulations A and B reach approximately 85% dissolution by 20 minutes. Therefore, a POSA would have reasonably expected that the bioavailability of dabigatran etexilate would not be limited by its dissolution rate. Ex. 1005, ¶293. Thus, it would not have been

surprising or unexpected to observe that Formulations A and B showed the same bioavailability.

Further, during prosecution of the '729 patent much was made of a Brauns declaration submitted during Brauns' prosecution, which alleged that Brauns' dosage forms required the acid and drug to be included on the same pellets in order to create an acidic microenvironment to facilitate drug dissolution. Ex. 1002, pp. 173-184, 249-255, 299-303. However, post-filing date submissions in Brauns' prosecution history, which are not prior art to the '729 patent, are irrelevant to how a POSA would have viewed the teachings of Brauns. *See Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus.*, 145 F.3d 1303, 1313 (Fed. Cir. 1998) (affirming the district court's conclusion that a study performed after a patent's filing date was not relevant to determining whether the patent was obvious). Rather, as of the earliest priority date of the '729 patent, a POSA would have understood that Brauns had received a Notice of Allowance for the pending claims at that time, which required that the organic acid and dabigatran etexilate be present on a pellet with an optional separating agent. Ex. 1008, p. 127. Therefore, a POSA would have considered the information available at that time, which would have included a motivation to develop a dabigatran etexilate dosage form that retained the advantageous properties of the dosage form disclosed in Brauns (e.g., increased dabigatran etexilate bioavailability independent of the stomach pH and final product stability) while

designing around the claims of Brauns that had received a Notice of Allowability from the PTO. Ex. 1005, ¶¶187-189.

In sum, based on the prosecution history of the '729 patent and related patent applications, there are no objective indicia that overcome the obviousness of claims 1-18 in view of the prior art discussed herein.

IX. PTAB DISCRETION SHOULD NOT PRECLUDE INSTITUTION

Petitioners believe that discretionary denial is unwarranted, and yet, Petitioners intend to utilize the bifurcated briefing process contemplated by the March 26, 2025, Stewart Memorandum, Ex. 1024, to rebut contentions if offered by Patent Owner to the contrary. *See* <https://www.uspto.gov/about-us/events/learnaboutnew-interim-processes-relating-institution-aia-proceedings> (April 24, 2025); <https://uspto.cosocloud.com/p9xpz6s4jn75> (Video).

X. CONCLUSION

In sum, the challenged claims are unpatentable. Petitioners respectfully request that the Board grant this Petition for *inter partes* review and institute trial.

Respectfully submitted,

Date: June 6, 2025

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CERTIFICATE OF SERVICE

The undersigned certifies, in accordance with 37 C.F.R. §§ 42.6(e)(4) and 42.105, that service was made on the Patent Owner as detailed below:

Date of service: June 6, 2025

Manner of service: Priority Overnight Federal Express Mail

Documents served Petition for *Inter Partes* Review Under 35 U.S.C. § 312 and 37 C.F.R. § 42.104;
Petitioner's Exhibit List;
Exhibits 1001-1024; and
Power of Attorney

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