UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

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MITSUBISHI CHEMICAL CORP., ET AL.,

Plaintiffs,

07 Civ. 11614 (JGK)

- against -

FINDINGS OF FACT AND CONCLUSIONS OF LAW

BARR LABORATORIES, INC., ET AL.,

Defendants.

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JOHN G. KOELTL, District Judge:

**INTRODUCTION**

This patent infringement action presents a challenge to the validity of a patent covering the formulation of Argatroban Injection, a lifesaving drug for the treatment of heparin-induced thrombocytopenia ("HIT"). Patients who develop HIT after receiving the well-known blood thinner heparin may suffer a cascade of blood clots, amputations, and death if left untreated. Prior to the Food and Drug Administration's ("FDA") approval of Argatroban Injection in 2000, doctors had few options for HIT patients other than to cease heparin and hope that clotting did not occur.

Generic drug manufacturers Barr Laboratories, Inc. and Pliva-Hrvatska d.o.o., a wholly owned subsidiary of Barr Laboratories, Inc., (collectively "the defendants" or "Barr") now seek to market a generic copy of the FDA-approved product known as Argatroban Injection pursuant to Abbreviated New Drug Application ("ANDA") No. 79-238, which was filed by Barr Laboratories, Inc., as agent for Pliva. Mitsubishi Chemical Corporation ("MCC"), Mitsubishi Tanabe Pharma Corporation, Encysive Pharmaceuticals Inc., SmithKline Beechman PLC, SmithKline Beecham Corporation, doing business as GlaxoSmithKline, and Glaxo Group Limited (collectively "the plaintiffs" or "Mitsubishi") have brought the current action

against Barr. MCC is the assignee of United States Patent No. 5,214,052, entitled "Method of Dissolving Arginineamides and Pharmaceutical Compositions Containing Them" ("the '052 patent"). Encysive is the holder of the approved New Drug Application ("NDA") for Argatroban Injection.

Argatroban (also known as argipidine), the active ingredient in Argatroban Injection, was known years before the development of a marketable formulation. The argatroban molecule, however, is poorly soluble in water alone, and pharmaceutical formulators tried for years without success to develop an injectible argatroban product at a concentration sufficient to treat effectively severely ill patients who were under fluid restrictions. The problem of determining an acceptable formulation of an injectible argatroban product remained unresolved until Mitsubishi employees discovered that a co-solvent system comprising ethanol, water, and sorbitol would greatly enhance the solubility of argatroban. Dr. Timothy Kogan, who had attempted to develop a high-concentration argatroban product for 7 years, found this result extremely surprising.

The '052 patent claims a method for dissolving argabtroban in ethanol, water, and a saccharide, and a pharmaceutical composition for injection comprising argatroban along with

ethanol, water, and a saccaride. The plaintiff's Argatroban Injection product is covered by the '052 patent.

The '052 patent was issued on May 25, 1993 and expires on June 30, 2014 as a result of a patent term extension pursuant to 35 U.S.C. § 156. Barr filed ANDA No. 79-238 with the FDA pursuant to the Hatch-Waxman Act, 21 U.S.C. § 355(j), seeking to market a generic copy of Argatroban Injection prior to the expiration of the '052 patent.

On December 26, 2007, the plaintiffs filed this suit under the Hatch-Waxman Act, alleging that Barr's making, using, selling, or importing its proposed argatroban product would infringe, induce infringement of, or contribute to the infringement of the '052 patent. All parties in this case have stipulated that Barr's argatroban product described in ANDA No. 79-238 is either a direct infringement of claims 1-4 of the '052 patent pursuant to 35 U.S.C. § 271(a) or an indirect infringement of the '052 patent claims 1-4 pursuant to 35 U.S.C. § 271(b) or (c), unless the '052 patent is found to be invalid.

Barr alleges that claims 1-4 of the '052 patent are invalid because they are anticipated pursuant to 35 U.S.C. § 102 or obvious under 35 U.S.C. § 103. The '052 patent was issued as a continuation of a patent application that the plaintiffs represent without opposition was filed on July 28, 1988. Thus, for purposes of analyzing the prior art that could disqualify

the patent for anticipation or obviousness, the Court should look to prior art that existed one year before that date, namely before July 28, 1987.

Barr's anticipation defense rests entirely on one prior art reference, an article written by Mitsubishi employee Toshihiro Yamamoto and his co-authors publishing the results of a preclinical study of the effect of argatroban on rats. See Toshihiro Yamamoto, et al., Effect of Argipidine (MD-805) on Cerebral Microcirculation After Cerebral Ischemic Rats, 14 (Supp. 5) Japanese Pharmacology & Therapeutics 25 (1986). During the study, the investigators compared the blood flow after induced stroke in the brains of rats that had received an intraperitoneal injection of a highly acidic argipidine solution with the blood flow in the brain of rats after stroke that had not received such an injection. In one sentence, whose translation is hotly disputed by the parties, Yamamoto states that a solution was prepared containing argipidine, ethanol, sorbitol, water, and hydrochloric acid. Barr alleges that, under its various translations, this sentence discloses the '052 patent's invention. Mitsubishi offers a competing translation, and disputes Barr's contention that the Yamamoto article would enable one skilled in the art to create the '052 invention.

Barr also argues that the claims of the '052 patent would have been obvious to one skilled in the art in 1987, based upon

references in the literature other than the Yamamoto article. Mitsubishi responds that the invention was not obvious, and that the commercial success of Argatroban Injection, long felt need, the failure of others to discover the invention, and other objective factors point to nonobviousness.

The Court conducted a non-jury trial from January 26, 2010 through February 10, 2010. The Court makes now the following findings of fact and reaches the following conclusions of law.

**LEGAL BACKGROUND AND FINDINGS OF FACT**

1. To the extent that any of the findings of fact below is a conclusion of law, it is hereby adopted as a conclusion of law.

2. This case arises under the patent laws of the United States and the Drug Price Competition and Patent Term Restoration Act of 1984, Publ. L. No. 98-417, 98 Stat. 1585, as amended ("the Hatch-Waxman Act"). The defendants filed an ANDA with the FDA, seeking to market a generic copy of the plaintiffs' FDA-approved product known as Argatroban Injection. The defendants concede that their proposed generic product is covered by and would infringe all four claims of the '052 patent. Having conceded infringement, the defendants bear the burden of proving, by clear and convincing evidence, that the

'052 patent is invalid. Whether the defendants have met their burden is the only issue before this Court.

## I. Jurisdiction

3. The Court has subject matter jurisdiction over this case pursuant to 28 U.S.C. §§ 1331 and 1338(a). (Joint Pre-Trial Order ("JPTO") ¶ 2.)

## II. Relevant Statutory and Regulatory Provisions

4. To market a drug in interstate commerce, a drug manufacturer must obtain approval from the United States Food and Drug Administration ("FDA") through the submission of an NDA. The NDA includes the results of extensive testing to determine that a drug product is both safe and effective. 21 U.S.C. § 355(b).

5. The filing of an NDA represents an enormous expenditure of time, money, and human resources, particularly when the drug product is a pioneering one, requiring years of research involving animal and human studies, including clinical trials.

6. The pharmaceutical at issue here, marketed under the name Argatroban Injection, is just such a pioneering drug product. Its active ingredient is argatroban.

7. As discussed below, Argatroban Injection is used for the prophylaxis or treatment of thrombosis in patients with HIT, and for use in patients with or at risk for HIT undergoing percutaneous coronary intervention ("PCI").

8. An ANDA permits an applicant seeking approval of a generic version of a pioneering drug to avoid the costly and time-consuming studies required for the pioneer to demonstrate safety and effectiveness. Instead, the ANDA filer may avoid those requirements through the ANDA process, so long as the ANDA filer is able to establish that its generic version of the drug is "bioequivalent" to the drug for which approval has already been obtained. 21 U.S.C. § 355(j).

**III. The Presumption of Validity and the Standard of Proof**

9. By express Congressional declaration, patents are presumed valid. Each patent claim is independently presumed valid. 35 U.S.C. § 282.

10. The burden of proving invalidity rests on the patent challenger, who must do so by clear and convincing

evidence. Id.; Schumer v. Lab. Computer Sys., Inc., 308 F.3d 1304, 1315 (Fed. Cir. 2002).

11. "The 'clear and convincing' standard of proof of facts is an intermediate standard which lies somewhere between 'beyond a reasonable doubt' and a 'preponderance of the evidence'" and has been described as "evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" Buildex Inc. v. Kason Indus., Inc., 849 F.2d 1461, 1463 (Fed. Cir. 1988) (alteration in original) (internal quotation marks omitted).

12. The burden is "constant" and "remains throughout the suit on the challenger" and "does not shift at any time to the patent owner." TP Labs., Inc. v. Prof'l Positioners, Inc., 724 F.2d 965, 971 (Fed. Cir. 1984).[1]

[1] If a patent challenger alleges invalidity based upon the prior art which the PTO considered during prosecution of the patent, that challenger has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have expertise in interpreting the references, to be familiar from their work with the level of skill in the art, and whose duty it is to issue only valid patents. Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co., 204 F.3d 1360, 1367 (Fed. Cir. 2000) (quoting Am. Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1359 (Fed. Cir. 1984)). Mitsubishi is not entitled to this added deference because it failed to disclose most of the relevant prior art during the patent prosecution, including the Yamamoto (DX 10), Matsui (DX 83A), Krause and Cross (DX 18), Sorby 1963 (DX 23), Sorby 1965 (DX 25), and Martin (DX 22, DX 79) references. However, the defendants have not asserted any misconduct as a basis for invalidity of the '052 patent and the allegations do not affect the result. While the defendants need not overcome any additional burden that would apply if the PTO had considered these prior art references, particularly the Yamamoto article that is central to this case, the defendants retain the

**IV. The Parties**

13. Mitsubishi Chemical Corporation ("MCC") is a Japanese corporation having its corporate headquarters and principal place of business in Tokyo, Japan. (JPTO ¶ 17.) MCC is engaged in the business of employing the science of chemistry to create, develop, and improve products.

14. Mitsubishi Tanabe Pharma Corporation ("MTPC") is a Japanese corporation having its corporate headquarters and principal place of business in Osaka, Japan. (JPTO ¶ 18.) MTPC is a pharmaceutical company engaged in the business of the development, manufacture, and marketing of a broad spectrum of pharmaceutical products. (MCC and MTPC will sometimes be referred to collectively as "Mitsubishi.")

15. Encysive Pharmaceuticals Inc. ("Encysive"), formerly known as Texas Biotechnology Corporation ("TBC"), is a Delaware corporation having its corporate headquarters and principal place of business in New York, New York. (JPTO ¶ 19.) Encysive is also the holder of the approved NDA for Argatroban Injection. (Pls.' Ex. ("PX") 31; PX 116; PX 119.)

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burden of proving the alleged invalidity of the patent by clear and convincing evidence.

16. Glaxo Group Limited ("GGL") is a company organized and existing under the laws of England and Wales having its registered office in Greenford, England. (JPTO ¶ 20.)

17. SmithKline Beecham plc c/k/a SmithKline Beecham Limited ("SKB Ltd.") is a company organized and existing under the laws of England and Wales having its registered office in Brentford, England. (JPTO ¶ 21.)

18. SmithKline Beecham Corporation c/k/a GSK LLC ("GSK LLC") is a Pennsylvania corporation having a principal place of business at One Franklin Plaza, Philadelphia, Pennsylvania. (JPTO ¶ 22.) GSK LLC sells Argatroban Injection in the United States pursuant to the FDA's approval of NDA No. 20-883 on June 30, 2000.

19. Defendant Barr Laboratories, Inc. ("Barr") is a Delaware corporation with corporate headquarters in Pomona, New York. (JPTO ¶ 23.) Barr is in the business of manufacturing and marketing generic pharmaceuticals. On or about December 23, 2008, Barr was acquired by Teva Pharmaceuticals Industries Ltd. (JPTO ¶ 25.)

20. Defendant Pliva-Hrvatska d.o.o. ("Pliva") is a European generic pharmaceutical company with a principal place of business in Zagreb, Croatia. Pliva is a wholly-owned subsidiary of Defendant Barr. (JPTO ¶ 24.)

21. The patent at issue in this suit is United States Patent No. 5,214,052, entitled "Method for Dissolving Argininеamides and Pharmaceutical Compositions Containing Them," which was issued on May 25, 1993, to inventors Kunihiko Ofuchi and Tatsuo Nomura, and assigned to the plaintiff MCC (then known as Mitsubishi Kasei Corporation). (Defs.' Ex. ("DX") 1; JPTO ¶ 37.)

22. MCC is the assignee of record of the '052 patent, which expires on June 30, 2014, as a result of a patent term extension MCC received pursuant to 35 U.S.C. § 156. (JPTO ¶¶ 37-38.)

23. Barr filed ANDA No. 79-238 with the FDA under 21 U.S.C. § 355(j), seeking approval to market generic Argatroban Injection prior to the expiration of the '052 patent. (JPTO ¶ 32.)

24. On December 26, 2007, the plaintiffs filed a complaint in this Court, alleging that the defendants' making, using, selling, or importing its proposed argatroban product under ANDA No. 79-238 would infringe, induce infringement of, or contribute to the infringement of the '052 patent.

25. The plaintiffs filed the First Amended Complaint on February 21, 2008 and the Second Amended Complaint on March 25, 2008 alleging that the defendants' making, using, selling, and importing its proposed argatroban product under

ANDA No. 79-238 would infringe, induce infringement, or contribute to the infringement of the '052 patent.

26. On April 24, 2009 the parties stipulated that the commercial manufacture, use, importation, sale, or offer for sale within the United States of the pharmaceutical product described in ANDA No. 79-238 would be a direct infringement under 35 U.S.C. § 271(a) or an indirect infringement under 35 U.S.C. § 271(b) or (c) of claims 1-4 of the '052 patent, provided that such claims are not found to be invalid. (JPTO ¶ 3.)

27. Therefore, the only issue before the Court is the defendants' allegation that claims 1-4 of the '052 patent are invalid. (JPTO ¶ 4).

## V. Background of the '052 Patent

28. The '052 patent sought to solve the following problem, as stated in the patent specification:

> Arginineamides are known to have anti-thrombotic activities and are expected to be used as anti-thrombotic agents . . . . However, it is very difficult to obtain a solution containing any of [the] arginineamides at high concentration due to poor solubility in water and therefore any of these compounds [are] not suitable for applying as the injection containing it at high concentration.

> An object of the invention is to provide a method for improving the solubilities of arginineamides so as to apply as the injections containing them at high concentration.

(DX 1 at Col. 1, ll. 17-28.) In the terminology of the '052 patent, "high concentration" means a broad range of concentrations above the solubility of the arginineamide in water. (DX 1 at Col. 4, ll. 22-27.)

29. The claims of the '052 patent are directed to improvements in solubility of argatroban.[2] Argatroban was discovered by at least 1979, and was patented under United States Patent No. 4,258,192 ("the '192 patent") in 1981. (DX 51.) Although argatroban was considered to have promise as an inhibitor of thrombosis, that promise never came to fruition in the United States during the term of the '192 patent, which expired in 1995. Despite the fact that MCC licensed the argatroban compound to Genentech for pharmaceutical development in 1987 (DX 100), it was not until the technology of the '052 patent permitted the preparation of high concentration pharmaceutical compositions of argatroban for injection that a commercially viable product, namely Argatroban Injection, was approved by the FDA in 2000. (JPTO ¶ 28.)

[2] The chemical name for argatroban, which is an arginineamide, is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate. (DX 568 at 1.)

30. Because argatroban is poorly water-soluble, the concentration of argatroban that could be given to patients prior to the discovery of the '052 technology was severely limited. The maximum solubility of argatroban in water is about 1.0 mg/mL. Therefore the actual concentration of a pharmaceutical composition of argatroban in a water-based system would be substantially less than 1.0 mg/mL if that compound is to remain stable in solution and not precipitate before it gets to the patient. (See generally Tr. 267:24-268:25.) Prior to the invention of the '052 technology, both MCC and Daiichi Pharma were trying to make a high concentration argatroban solution. (Tr. 1314:12–24.)

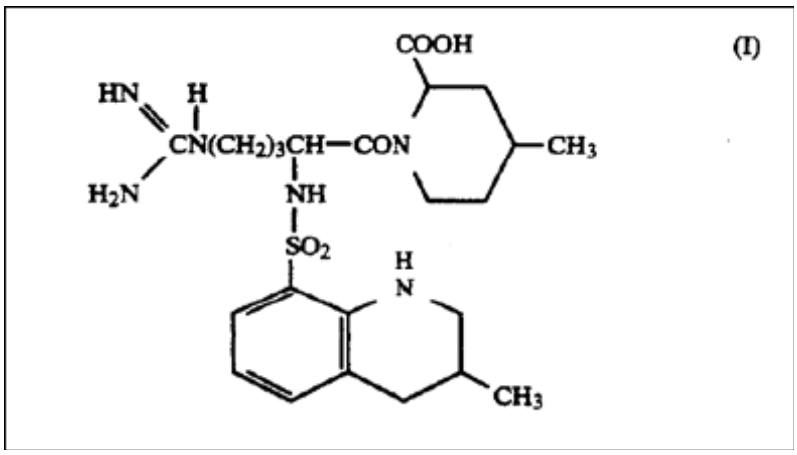
31. Surprisingly, the inventors of the '052 patent found that when argatroban was dissolved in combinations of ethanol, water, and sorbitol (or other saccharide), its solubility increased substantially over its solubility in water alone or in mixtures of water with sorbitol. (Compare DX 1, Figs. 3 & 4, with DX 1, Fig. 2.) This result was directly contrary to the expectations of those skilled in the art. Barr's expert Dr. Thomas E. Needham, retired professor of pharmaceutics from the University of Rhode Island College of Pharmacy, admitted that argatroban is the only exception to the general principle that the solubility of zwitterions, molecules with both a positive and negative charge, is reduced by the

introduction of ethanol. (Tr. 54:14-18, 219:7–220:11; see also PX 252.)

32. Moreover, as Dr. Needham acknowledged, the introduction of a material that was less polar than water, or lacking a plus and minus part of the molecule, such as sorbitol or ethanol, would be expected to lower the solubility of a zwitterion such as argatroban, and Figures 1 and 2 of the '052 patent confirmed that expectation. (DX 1, Figs. 1 & 2; Tr. 66:12-15, 294:1–296:6.) Therefore the fact that the addition of ethanol and sorbitol (or other saccharide) drastically increased the solubility of argatroban in the aqueous mixture was contrary to the expectations of those skilled in the art.

33. The '052 patent has four claims: claims 1 and 2 claim a method of dissolving argatroban; claims 3 and 4 claim a pharmaceutical composition for injection containing argatroban. The invalidity of all four claims is at issue in this case. Indeed, because it is undisputed that the defendants' product infringes all four claims of the '052 patent, the defendants must establish by clear and convincing evidence that each of the four claims in the '052 patent is invalid.

34. Claim 1 of the '052 patent claims: "A method for dissolving an argininеamide comprising: dissolving $N_2$-arylsulfonyl-L-argininamide represented by formula (I):



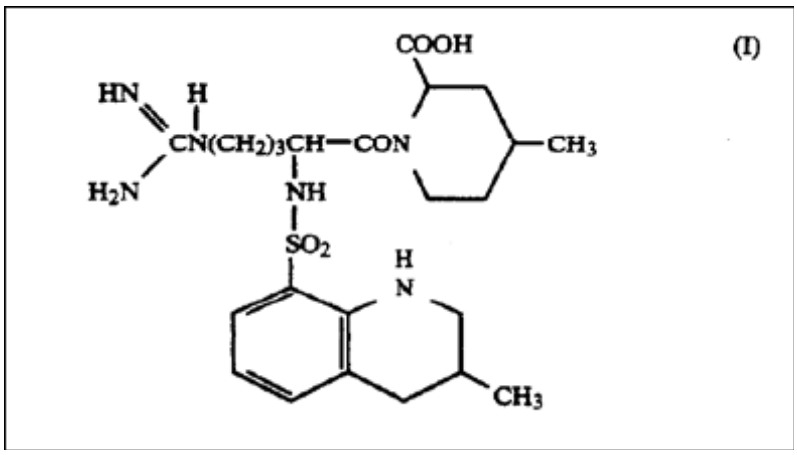

and/or its salt in a solvent containing ethanol, water and a saccharide." (DX 1 at Col. 6, ll. 23-39.)

35. The parties agree that the compound represented by formula (I) in the claim is known by the names "argipidine" and "argatroban." Accordingly, claim 1 may be restated as:

> Claim 1: A method for dissolving an argininеamide, comprising: dissolving [argatroban] and/or its salt in a solvent containing ethanol, water and a saccharide.

36. Claim 2 is dependent on claim 1, and adds the limitation that "the saccahride is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose." (DX 1 at Col. 6, ll. 41-44.)

37. Claim 3 of the '052 patent recites: "A pharmaceutical composition for injection, comprising: $N_2$-arylsulfonyl-L-argininamide represented by formula (I):




and/or its salt together with ethanol, water and a saccharide." (DX 1 at Col. 6, ll. 45-53.)

38. As noted, the parties agree that the compound represented by formula (I) is known by the names "argipidine" and "argatroban."

39. Accordingly, claim 3 can be restated as:

> Claim 3: A pharmaceutical composition for injection, comprising: [argatroban] and/or its salt together with ethanol, water and a saccharide.

40. Claim 4 is dependent on claim 3, and adds the limitation that "the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose." (DX 1 at Col. 4, ll. 4-7.)

41. The saccharide used in the Argatroban Injection product is sorbitol. (DX 568 at 1.)

**A. The '052 Patent Technology Permits Injection of Argatroban With Less Fluid Volume**

42. Argatroban Injection is supplied at the "high concentration" of 100 mg/mL. The benefits from that aspect of the invention are described below.

43. More important to the patients, however, is the fact that the '052 patent technology allows argatroban to be injected into the patient at the high concentration of 1.0 mg/mL, twice the concentration of Novastan, a prior Japanese 0.5 mg/mL formulation where the solvent was water containing a small amount of sorbitol as a tonicity modifier. (DX 376.) This allows the physician using argatroban to manage the fluid load on the patient much more effectively than could be the case with aqueous argatroban at a 0.5 mg/mL concentration.

44. In determining whether and how to launch argatroban as a product, both Dr. John Plachetka, the head of clinical development programs at TBC from 1993 to 1995, and Dr. Richard Dixon, head of research at TBC from 1990 through 2008, focused on the importance of the clinical benefit obtained by using a higher concentration to minimize fluid load on the patient. (PX 199 at 29:21-23; see, e.g., PX 12). Dr. Plachetka pointed out his deep interest in the '052 technology: "this formulation could help us overcome some of our potential

problems with volume issues in the clinic." (PX 12). Dr. Plachetka explained that this meant that their issues involved the volume load on the patient. (PX 200 at 210:22-211:15.) Dr. Plachetka pointed out to TBC President David McWilliams that the more concentrated formula using the '052 technology "will allow us to reduce the volume load given to patients versus the old formulation by at least one-half . . . ." (PX 9 at GNE-ARG 624; see PX 200 at 212:1-15, 214:18–216-21, 218:24–221:21 (Dr. Plachetka's deposition); see also PX 199 at 59:2–59:11, 74:23–75:18, 96:16–97:14, 114:13–115:7 (Dr. Dixon's deposition).)

45. The importance of fluid volume control in HIT patients is typical of the importance of fluid volume control in a variety of different indications. The benefits of the high concentration formulation are clinically significant in the treatment of HIT patients. (Tr. 827:12-17.) If a 0.5 mg/mL formulation were available in the United States along with the Argatroban Injection 1.0 mg/mL formulation, clinicians would not prescribe the 0.5 mg/mL formulation. (Tr. 828:3-14.) Even Dr. Charles Eby, the defendants' medical expert and associate professor at the Washington University School of Medicine in St. Louis, testified to the superiority of the high concentration formulation of Argatroban Injection, conceding that "if you have got the choice of having a drug that's in a smaller volume and it makes no difference about the activity or the performance of

that drug, sure, take it." (Tr. 479:20-23; see also Tr. 352:9-10, 479:10-14, 834:11-19, 399:19-24, 441:9-15.)

46. A significant number of HIT patients are subject to fluid restrictions. Dr. Lewis, a principal investigator on the clinical trials that led to the approval of Argatroban Injection in the United States and an expert for the plaintiffs, testified that "the heart failure patients, the renal failure patients, the dialysis patients all are very obvious groups that require fluid restrictions. The pulmonary patients are another obvious group. And, you know, if I were to put a number, certainly that's over half the patients." (Tr. 834:14-19.) Dr. Eby conceded that there are at least some HIT patients requiring careful fluid management, who therefore benefit from the high concentration of Argatroban Injection. (See Tr. 441:12-15 ("It's like an iceberg. There's a tip of the iceberg of patients who are indeed – where fluid management is critical. I think we're arguing over the size of the iceberg and how much of it's above the water.")

47. As Dr. Lewis testified: "The '052 patent and the [claimed] formulation provides a huge advantage to these patients. We're able to deliver the compound through a pharmaceutical agent and an amount of fluid that our patients can tolerate and we can affect the outcome of that horrific

course of disease." (Tr. 760:4-8; see also Tr. 826:12–828:6, 837:7–840:13.)

48. The ability to use small amounts of ethanol and sorbitol to hold 1.0 mg/mL of argatroban in solution as a pharmaceutical composition for injection, contrary to the expectation of those skilled in the art, is a great boon to patients, and a great advantage over the 0.5 mg/mL product.

**B. The Ability to Supply Argatroban in 2.5 ml 100 mg/mL Vials Provides Substantial Advantages**

49. Other significant advantages achieved by use of the high concentration Argatroban Injection include the benefits of storage, dilution, and other benefits appreciated by pharmacists. For example, prior to discovery of the availability of the '052 technology, TBC was faced with the choice of using a 0.5 mg/mL solution comprising 10 mg in 20 mL ampoules. These were highly impractical. For the indications under consideration at TBC when it licensed argatroban, a "typical patient might require 2,000 milliliters of fluid in a day of the [a]rgatroban solution, and that would require breaking a hundred of these glass amp[o]ules, filtering the contents, [and] putting it into an IV bag under sterile conditions, which would be quite difficult to do for most

hospitals." (PX 200 at 48:18–23; see also PX 200 at 50:17–51:6.) Dr. Sophia Pasedis, an expert pharmacist with over twenty years of experience as a hospital pharmacy director, testified that breaking the 20 ml/0.5 mg/mL ampules of argatroban to administer a day's dosage for an average-sized patient would be "an immense burden" on a hospital pharmacy. (Tr. 1331:16-19, 1345:8.) Dr. Plachetka testified at his deposition: "Well, that was a nonstarter from day one. I mean, that was commercially a killer. That product in 20 milliliter amp[o]ules for any of the indications that Texas considered would be a nonstarter." (PX 200 at 70:19–22; see also PX 200 at 49:16–51:6.)

50. TBC's other alternative was to fill 500 mL glass bottles with 0.5 mg/mL argatroban solution. (Cf. Tr. 654:7-9 (0.5 mg/mL argatroban solution was available in 500 mL glass bottles).) However, the larger glass bottles also had very significant drawbacks in terms of higher storage and shipping costs, as compared to the 2.5 mL vials in which Argatroban Injection is supplied. (See PX 200 at 68:17-69:3.)

51. When the members of TBC found out about the fact that the '052 technology allowed the provision of 250 mg of argatroban in only a 2.5 mL container, "it was almost beyond belief . . . . It was startling and completely unexpected from

[Dr. Plachetcka's] perspective." (PX 200 at 62:6-10; see also PX 200 at 74:7-12.)

52. The '052 technology made it possible to make highly concentrated, highly stable solutions of argatroban, which meant that the Argatroban Injection could be packaged and stored at very high concentrations and very low volumes, and simply diluted to the desired dosage just prior to being injected into the patient. (DX 1 at Col.4, ll. 42-51.) The benefits of that aspect of the invention are significant, to patients, physicians, pharmacists, hospitals and to the manufacturer of Argatroban Injection. Argatroban Injection can be provided at a concentration of 100 mg/mL in a 2.5 mL vial, which can be simply and accurately diluted with the diluent of choice (e.g., dextrose solution, saline or Ringers solution) by putting it into a 250 mL IV bag, and filling the bag with diluent. The ability to supply it in a small vial avoids the costs of large bottles, shipping charges, the necessity of breaking multitudes of ampoules, and is not a burden on space in hospital pharmacies, where space is at a premium. (Tr. 1334:10-13, 1338:23-1345:8.) It also relieves pharmacists from having to use lengthy filtration steps to remove any glass shards that would come from the required breaking of the ampoules. (Tr. 1340:22-1342:19.)

53. This increase in solubility of argatroban in ethanol and a saccharide was surprising to everyone, including the defendants' expert Dr. Needham. (Tr. 311:3-5.)

### C. Clinical Background Relevant to the '052 Patent

#### 1. HIT

54. Argatroban Injection is an anticoagulant indicated for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia, and for use in patients with or at risk for heparin-induced thrombocytopenia undergoing PCI. (DX 568 at 10.)

55. According to Dr. Lewis, heparin is "one of the most commonly prescribed drugs in the hospital setting at this point in time, and has been for decades." (Tr. 758:3-5.) As acknowledged by Dr. Eby, heparin is administered to many hospitalized patients because many of them are at risk of forming blood clots, for example, patients who have sustained serious trauma, either accidentally or postoperatively, are at high risk for forming blood clots, especially in the veins in their legs. (Tr. 371:7-14.) In a significant number of patients treated with heparin, however, it triggers an immune

response called HIT, which, paradoxically, promotes blood clotting. (Tr. 758:2-11.)

56. Any patient exposed to heparin is at risk for developing HIT. (Tr. 372:13-14.) HIT is considered to be the most potent hypercoagulable state in medicine, and is one of the most serious and potentially catastrophic blood-related complications of drug therapy. (Tr. 758:11-13, 758:24-759:4.) The blood clots associated with HIT can occur anywhere in the body, leading to the possibility of stroke, heart attack, and death of the affected portion of the bowel, and clots can also occur in the adrenal glands, kidneys and limbs. (Tr. 774:4-22.) HIT is the most serious disease process that Dr. Lewis has encountered in his years of clinical experience. (Tr. 774:24-775:1.)

57. The marked increase in clotting activity caused by HIT results in clinically relevant blood clots in approximately 50% of untreated HIT patients. (Tr. 773:2-9.) About 10-50% of untreated HIT patients require amputation (Tr. 773:21-774:1) and about 30% die. (Tr. 773:15-17.)

58. HIT patients typically have multiple medical or system failures that result from HIT and underlying disease. (Tr. 827:12-16.) It is not unusual for these patients to require intravenous medications for one or more of the following: support of blood pressure, treatment for a failing

heart, or antibiotics for concomitant medical problems. (Tr. 790:12-791:2.) Each of these therapies adds fluid volume to the patient's daily requirement in a situation where clinicians are trying to restrict fluid intake. (See Tr. 790:12-791:2.) Dr. Eby acknowledged that if a patient is on fluid restriction, the only way to implement this is by restricting the fluids administered to the patient. (Tr. 487:22-25.) As explained by Dr. Lewis, in such patients it is recommended that fluids be restricted to 1500 to 2000 mL per day, depending on the patient's size and condition. (Tr. 762:22-24.) "That includes all fluids, whether it be intravenous or oral intake," and "that can be very challenging." (Tr. 762:24-763:1.) Fluid load was a significant concern in the development and commercialization of Argatroban Injection. (PX 9; PX 13; PX 199 at 74-75, 97; PX 200 at 210-16, 219-21.)

59. According to Dr. Plachetka, HIT presented a "very significant unmet medical need." (PX 200 at 18-19, 41; see also PX 50 at 1839.)

60. In the early 1990s, the primary treatment for HIT was limited to discontinuation of heparin. This was not a successful strategy, because many patients require anticoagulation for underlying medical conditions, and approximately 40-50% of untreated HIT patients suffered a thrombotic event after heparin was discontinued. (Tr. 776:1-

777:12 (discussing PX 50 at 1839).) At that time, the only treatment for a HIT patient with a thrombosis (known as heparin-induced thrombocytopenia with thrombosis syndrome, or "HITTS") was "surgical removal of the clot with an attempt to rapidly anticoagulate the patient with an oral drug, which usually failed." (PX 200 at 41:14-17.) "The choices a physician had when this occurred were extremely dire . . . a good physician, could try and extract a clot and hope that it wouldn't reoccur. But more [often] than not, it resulted in amputation and then slowly spun down to death." (PX 200 at 43:3-9.)

61. Other anticoagulant therapies available at the time, including warfarin, ancrod, low-molecular weight heparin, danaproid, and lepirudin, had disadvantages and were generally unsuccessful. (PX 50 at 1839; see generally Tr. 775-785.) For example, physicians treating HIT patients were so "very desperate" that, ancrod, an unapproved drug derived from pit viper venom (of which the entire United States supply was locked in a single refrigerator in Connecticut), was used through the FDA's compassionate use mechanism. (Tr. 781:3-4; see generally Tr. 779-81.)

62. In a 1996 meeting with TBC representatives, Stephen Fredd, M.D., Director of FDA's Division of Gastrointestinal and Coagulation Drug Products, characterized HIT and HITTS patients "as a class of subjects with a life-

threatening condition for which there is no available therapy." (PX 199 at 262:10-19 (discussing PX 23 at ENCY 10511); see PX 42 at ENCY 246682.) According to Dr. Lewis, "there was no existing therapy and . . . this was a catastrophic problem . . . ." (Tr. 804:19-20.) Argatroban Injection "satisfied a very long-felt need and did a very nice job of satisfying that need." (Tr. 787:1-2.)

63. The patient population receiving Argatroban Injection for HIT is generally a population of very sick people who, beyond suffering from HIT, present with one or more indications giving rise to their need for heparin anticoagulation in the first place, including cardiac-related diagnoses, cardiac surgery, cardiac interventional procedure(s), other surgery, or prevention or treatment of deep vein thrombosis. (Tr. 827:12-14.) Additionally, because many patients receiving Argatroban Injection have other serious problems such as cardiovascular surgery, congestive heart failure, or kidney impairment, they require restriction of fluid loads. (Tr. 793:3-9.) In fact, there is a correlation between the conditions that require a higher dose of Argatroban Injection and those that require fluid restrictions due to the large background of heparin treatment by the time these patients develop HIT. (Tr. 851:9-19.) By the time such patients develop HIT, they have likely lost some cardiac function and, as a

consequence, are in advanced stages of heart failure or decline in kidney function or pulmonary function. (Tr. 851:19-24.) Accordingly, the HIT subgroup is an extremely sick group of patients. (Tr. 851:24-852:1.)

**2. Treatment of HIT**

64. Two direct thrombin inhibitors ("DTIs") are presently approved for use in the United States for treating HIT, namely, Argatroban Injection (first approved in 2000) and Refludan® (first approved in 1998). (Tr. 375:15-19, 376:11-16, 382:5-6.)

65. As its FDA-approved label shows, Argatroban Injection is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT and HITTS, and as an anticoagulant in patients with or at risk for HIT or HITTS undergoing PCI. (Tr. 376:11-16; DX 568 at 10.)

66. Refludan® (lepirudin) is indicated for anticoagulation in patients with HIT and associated thromboembolic disease in order to prevent further thromboembolic complications. (DX 482.) Refludan® does not have approval for use with HIT patients undergoing PCI. (DX 482 at 2; Tr. 848:10-11.)

67. Angiomax® (bivalirudin) is a DTI approved in 2000 for use in the United States in patients with or at risk for HIT who are undergoing PCI, but Angiomax® is not approved for use for treating HIT in other patients. (DX 603 at B-ARG-112873.)

68. Dr. Lewis testified that Argatroban Injection has clear clinical advantages over Refludan®, including reduced fluid administration. (Tr. 829:13-18 (discussing DX 758).) Barr's expert Dr. Eby testified that the clinical advantages of Argatroban Injection over Refludan® are due to the active ingredient argatroban, but also acknowledged that reduced fluid load is an advantage for Argatroban Injection. (Compare Tr. 384:7-15, with Tr. 384:2-4, and 386: 18-19. See generally Tr. 383-86.) The high concentration at which Argatroban Injection can be administered to HIT patients results in a clinically significant two-thirds reduction in infusion volume as compared to Refludan®.[3] (Tr. 828:15-829:18 (discussing DX 758); see also Tr. 386:18-19 (Dr. Eby noting that "fluid volume would favor argatroban [over Refludan®]").)

69. Unlike Argatroban Injection, Refludan® and Angiomax® are immunogenic compounds, and carry the risk of a secondary anaphylactic response. (Tr. 785:3-10, Tr. 383:15-23.) Argatroban Injection also carries a lower (and shorter) risk of

[3] A hypothetical 100 kg patient at the starting dose listed in the FDA-approved labeling for Argatroban Injection and Refludan®, respectively, would receive 620 mL less fluid with Argatroban Injection than with Refludan® over a twenty-four hour period. (See Tr. 828:15-829:18; DX 758.)

bleeding compared to Refludan® because the anticoagulant effect of Argatroban Injection has a much shorter half-life. (Tr. 383:24-384:1.) Argatroban is preferable in renally-impaired patients. (Tr. 860:2-11; see generally Tr. 383:3-384:1 (discussing DX 758).)

70. Argatroban Injection quickly became the most frequently prescribed treatment for HIT, even though Refludan® was on the market as a treatment for HIT prior to approval of Argatroban Injection. (Tr. 663:8-21.)

71. Argatroban Injection, prescribed in terms of mcg/kg/min (micrograms of drug per kilogram of patient weight per minute) at the approved concentration of 1.0 mg/mL would require double the obligatory infusion volume if administered at a 0.5 mg/mL concentration. (Tr. 822:11-823:9 (discussing PX 175).)

72. "The recommended initial dose of Argatroban for adult patients without hepatic impairment is 2 mcg/kg/min, administered as a continuous infusion." (DX 568 at 19; see Tr. 378:10-12 (discussing DX 568).) Dosing requirements can, however, vary substantially both with the underlying medical condition and with concomitant medical therapies. (See Tr. 825:5 (noting that "[e]ach patient is different.").) In cases of severe liver disease, Argatroban Injection may be started at a lower dose, while medical HIT patients on circulatory assist

devices may require dosing "in the range of at least 10 and oftentimes 25 mics per kilo per minute" on a 24-hour basis. (Tr. 821:5-13, 824:12-826:10; see also PX 175.)

73. Angioplasty patients are maintained on even higher doses of Argatroban Injection and require a 250-350 mcg/kg bolus and maintenance infusions of 25-30 mcg/kg/min. (See generally Tr. 814:3-817:10.) Angioplasty procedures in HIT patients can last up to seven hours. (Tr. 817:15-18.) HIT patients undergoing a PCI procedure usually do not just stop receiving Argatroban Injection after the PCI procedure is completed; they continue in their treatment with Argatroban Injection at their resumed regular dose for HIT treatment "until the HIT process is controlled." (Tr. 820:8, see generally Tr. 817:11-820:8.)

74. Dr. Lewis summarized the treatment of HIT with Argatroban Injection as follows: "The '052 patent and the [claimed] formulation provides a huge advantage to these patients. We're able to deliver the compound through a pharmaceutical agent and an amount of fluid that our patients can tolerate and we can affect the outcome of that horrific course of disease." (Tr. 760:4-8.)

**D. Background on Pharmaceutical Development and Formulation in the Prior Art Period**

75. Both the plaintiffs' drug formulation expert, Dr. Stephen Byrn, and the defendants' drug formulation expert, Dr. Thomas Needham, agreed in large part on the propositions set forth in this section.

76. Drug formulation is a difficult and frequently unpredictable science. "The bottom line is," Dr. Needham testified, "you have to do the work, meaning go to the lab and do empirical testing of the solubility of the compound." (Tr. 212:19-23.)

77. It takes months, and often years, of time and effort to develop a formulation of a drug compound that is suitable for use in patients. As Dr. Needham testified, "[i]t's always a struggle to get a formulation that's stable, efficacious, and nontoxic." (Tr. 269:7-8.)

78. The solubility of a given compound to be administered via intravenous injection is often very difficult to predict. (Tr. 212:12-213:3.)

79. In addition to solubility, the pH of the solution to be administered via intravenous injection is extremely important. The pH of human blood is approximately 7.4. (PX 107 at 155; Tr. 1131:16-1132:1.) It is important that injectables

be as compatible with blood as possible, including with respect to pH. (PX 107 at 155; Tr. 255:3-8.) As Dr. Needham testified, "what you want to do when you have an injectable solution is, you want it to be as compatible with the body fluids in the cells as you can have it." (Tr. 103:9-11.) As a consequence, a solution designed for injection should not be below pH 3.0 nor above pH 10.5. (PX 107 at 155; Tr. 1130:4-1132:12.)

80. Tonicity is also an important consideration for an injectable formulation. (Tr. 103:8-18.) Tonicity is a measure of a solution's ability to exert osmotic pressure on a cell membrane. (Tr. 103:8-18, 1229:2-4, 1229:14-16.) Tonicity is affected by the nature of solute particles in an aqueous solution: in particular, whether they can cross the cell membrane freely or not. (Tr. 1408:14-1409:25.) An "isotonic" solution has the same tonicity as human blood. (Tr. 1228:13-19.) If an injection of improper tonicity is administered to a patient, blood cells can either burst or shrink to death. (Tr. 1229:5-23.)

81. The stability of an injectable is also extremely important to the formulator. (Tr. 267:22-23.) The stability of a given drug will vary depending upon the solution in which the drug is dissolved. (Tr. 268:19-21.) Additionally, the stability profile of a drug at different pHs is important to know when developing a formulation of that drug. (Tr. 268:22-25.)

Dr. Needham took the position at his deposition that a composition prepared by Iida by dissolving argatroban in acid and then neutralizing it to a pH of 7 "required a good bit more work" because 4 mg/mL of aqueous argatroban at a pH of 7 would be unstable and would be expected to form a precipitate. (PX 174 at 140; see also Tr. 272:6-273:17.) As of 1987 or before there was no stability profile available for argatroban. (Tr. 269:1-3.)

82. An injectable must also be safe, i.e., non-toxic, to administer to patients. This is why a person of ordinary skill in the art would always want to make a dosage form "as simple as possible" and "as compatible with the body fluids in the cells as you can have it." (Tr. 65:7-8, 103:9-11.)

**E. Development of Argatroban Injection**

**1. The Surprising Nature of the Discoveries Claimed in the '052 Patent**

83. Scientists who have worked with argatroban agree that the molecule has "rather unusual solubility characteristics." (PX 22 at ENCY 262046.)

84. Despite many attempts, Mitsubishi and Daiichi Pharma failed to develop an acceptable high concentration

injectable formulation until Mitsubishi ultimately invented the ethanol-water-sorbitol formulation covered by the '052 patent. Even in the late 1980s and 1990s, Genentech, TBC and others, not knowing of the '052 technology, tried and failed to develop an injectable argatroban pharmaceutical composition with improved solubility. (See infra.)

85. Ethanol, water, and sorbitol, individually, can hardly dissolve argatroban (water and sorbitol to only about 1.0 mg/mL, and ethanol to only about 4 mg/mL). Mitsubishi researchers eventually made the surprising discovery that adding sorbitol to ethanol-water mixtures yielded improved argatroban solubilities, some approaching 300 mg/mL, despite the fact that simply adding sorbitol to water generally decreased the solubility of argatroban in the mixture. (DX 1, Figs. 1-3.) The defendants' expert Dr. Needham admitted at trial that these results were "surprising and unexpected," and that it is unusual to achieve an increase in solubility of 300-fold, or even 100-fold. (Tr. 310:19-311:11.)

86. Mitsubishi researchers also discovered that similarly high solubilities of argatroban could be achieved in mixtures of ethanol, water, and certain saccharides other than sorbitol, including glucose, glycerin and sucrose. (DX 1, Fig. 4.)

87. The ‘052 patent, which discloses these results, was duly issued by the United States Patent and Trademark Office (“PTO”) on May 25, 1993. (DX 1.)

**2. Concurrent and Subsequent Failures of Others**

88. In the late 1980s and early 1990s, Mitsubishi sought out partners to help develop and market an approved argatroban injectable for use in both Europe and the United States. As of that time, the maximum concentration argatroban solution was a 0.5 mg/mL formulation. (PX 8 at M 52330; PX 200 at 155-56.)

89. In the United States, Mitsubishi initially licensed its rights in argatroban to Genentech, Inc.; it was Genentech that filed the first Investigational New Drug Application (“IND”) for argatroban with the FDA. (DX 100; DX 111; DX 705.)

90. Genentech later sublicensed its development rights in the United States to TBC. (DX 146.)

91. In 1997, TBC began collaborating on argatroban with SmithKline Beecham (later GlaxoSmithKline, or “GSK”). (DX 308.)

92. All of Mitsubishi’s collaborators were intensely interested in developing a high concentration formulation of

argatroban as a needed step in the development of argatroban as an approvable drug. For example, Genentech was looking into high concentration formulations of argatroban at least as early as 1992. (See PX 22 at ENCY 262047, 262060-64.) TBC, on the very day it signed its license agreement in 1993, made a presentation in which it noted the need to develop a high concentration formulation of argatroban. (See PX 19 at M 52153.)

93. Genentech experimented with dozens of formulations of argatroban. (PX 22 at ENCY 262047, 262060-64.) Yet all of those turned out to be either toxic, unstable, or only achieved argatroban solubilities of approximately 100 fold less than those disclosed in the '052 patent. (PX 22 at ENCY 262047, 262060-64.) As a result of these toxicity concerns, Genentech reported that it had "dropped [its] efforts to increase the solubility of Argatroban." (PX 22 at ENCY 262060.)

94. TBC, in conjunction with researchers at the University of Iowa, also conducted extensive solubility studies of argatroban, using many different solvent systems. High solubilities of argatroban were only achieved in solutions that were not pharmaceutically acceptable for injection. (PX 22 at ENCY 262046-47, ENCY 262065-66.) When TBC learned that Mitsubishi had developed a high concentration formulation, it

switched its development efforts to that formulation. (See, e.g., PX 8; PX 9; PX 12; PX 13.)

95. Timothy P. Kogan, Ph.D., then head of TBC's chemistry department, ultimately concluded that "I am absolutely confident that it is not possible to formulate [argatroban] at 100 mg/mL outside the claims of US 5,214,052" using generally-recognized-as-safe ("GRAS") ingredients for intravenous injection. (PX 22 at ENCY 262047; see PX 199 at 254-57.) Dr. Kogan offered: "If anyone at SKB would like to investigate this further, I have bulk [argatroban] available, and that person can either come here to try, or we can transfer material to SKB for investigation." (PX 22 at ENCY 262047.)

96. That all of this effort met with no success is evidence of the uniqueness of the ethanol-water-sorbitol formulation and the '052 patent. In short, as Dr. Kogan, the TBC (and former Genentech) researcher who was familiar with much of these data and failed efforts reported, the degree of solubility achieved by the water-ethanol-sorbitol formulation developed by Mitsubishi was an "extremely surprising result!" (PX 22 at ENCY 262047, Tr. 316:9-14.)

97. In 2000, upon receiving FDA approval, TBC and GSK began selling the 100 mg/mL Argatroban Injection that is still on the market today, using Mitsubishi's patented ethanol-water-sorbitol formulation. (Tr. 663:4-5.)

**F. The '052 Patent Claims**

98. As explained above, the '052 patent has four claims, each of which is asserted in this case. The claims, with argatroban substituted for its recited structure, read as follows:

1. A method for dissolving an arginineamide, comprising: dissolving argatroban and/or its salt in a solvent containing ethanol, water and a saccharide.
2. The method according to claim 1, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.
3. A pharmaceutical composition for injection, comprising: argatroban and/or its salt together with ethanol, water and a saccharide.
4. The composition according to claim 3, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.

(DX 1 at Col. 6, ll. 23-67.)

99. With respect to both anticipation and obviousness arguments in this case, the parties agree that the prior art consists of information in the public domain prior to July 28, 1987, the filing date of the '052 patent Japanese priority application.

## VI. The Prior Art

### A. Ordinary Skill in the Art

100. The parties agree that a person of ordinary skill in the art relevant to the '052 patent is a person who, at the time of the invention, had (1) a Ph.D. in a field related to pharmaceutical formulation and processing (such as physical chemistry, medicinal chemistry, or pharmaceutics) and at least one year of experience in the area of pharmaceutical formulation, (2) a similar master's degree and at least two to three years experience in pharmaceutical formulation, or (3) a similar undergraduate degree and at least five years of experience in pharmaceutical formulation. (Tr. 61:15-25, 1075:23-1076:9; see also DX 700.)

101. The plaintiffs' expert, Dr. Stephen R. Byrn, is personally familiar, through extensive experience, with the science and practice of pharmaceutical formulation, the relevant scope and content of the prior art, and the capabilities of a person of ordinary skill in the art.

102. Dr. Byrn currently holds the title of Charles B. Jordan Professor of Medicinal Chemistry at Purdue University. He is an elected member of the United States Pharmacopia

Revision Committee, its Council of Experts, and its Dissolution Subcommittee. He has extensive knowledge of, and experience in, pharmaceutical formulation, chemistry, and solubility. (Tr. 1069:1-1075:15; see generally PX 100 (Dr. Byrn's curriculum vitae).)

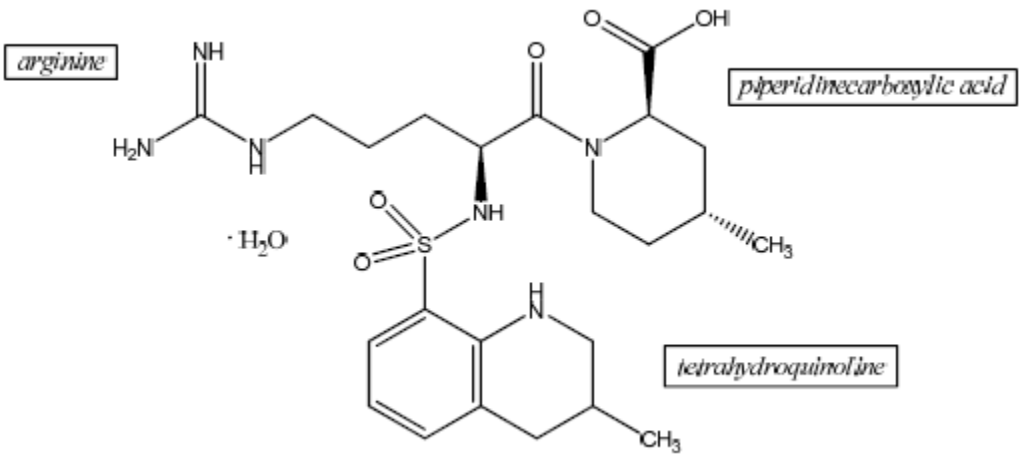
103. Dr. Byrn is qualified to express expert opinions on organic chemistry, medicinal chemistry, formulation science, and solubility. (Tr. 1075:16-22.)

104. As noted above, the defendants' expert, Dr. Thomas E. Needham, is a retired professor of pharmaceutics from the Rhode Island College of Medicine. He is also qualified as an expert witness to offer opinions with respect to the relevant prior art for the '052 patent.

**B. Relevance of the Chemical Structure of Argatroban**

105. The chemical structure of argatroban was known by at least March 24, 1981, the issue date of the '192 patent, which claimed a variety of $N_2$-arylsulfonyl-L-arginineamides, including argatroban. (DX 51.)

106. The argatroban molecule is composed of three distinct chemical moieties, as depicted in the structure below:




(Tr. 1080:20-1081:42.)

107. A person of ordinary skill in the art at the relevant time would have noticed that one portion of the argatroban molecule is derived from the amino acid arginine, which has a three-carbon chain ending in a guanidino group that will be positively charged at physiological pH. (Tr. 1081:3-7, 1082:12-14.)

108. A person of ordinary skill in the art would have noticed that another portion of the argatroban molecule is derived from a piperidine carboxylic acid (specifically, a 4-methyl-2-piperidine carboxylic acid), and expected it to have a negative charge at physiological pH. (Tr. 1081:13-19, 1082:12-16.)

109. A person of ordinary skill in the art would have known that the third portion of the argatroban molecule contains

an arylsulfonyl group (or more specifically, a tetrahydroquinolinesulfonyl group). (Tr. 1081:21-24.)

110. A zwitterion is an internally dissociated molecule with both positive and negative charges. (PX 252). Zwitterions are also referred to synonymously as "emphoteric electrolytes," "ampholytes," and "dipolar ions." (Tr. 222:12-25, 223:11-17; see also PX 103 at 241-42.) Argatroban, containing a functional group with a positive charge and a functional group with a negative charge, is a zwitterion. (Tr. 1080:6-11; see also PX 103 at 241-42.) Argatroban was readily recognizable as a zwitterions to a person of ordinary skill in the art in 1987. (Tr. 216:10-14; see also Tr. 1078:25-1079:4.)

111. The Court credits Dr. Byrn's testimony that if a person of ordinary skill were to have focused on any structural feature of argatroban, it would have been its zwitterionic character, and its zwitterionic character would have guided the formulator's approach to addressing argatroban's poor aqueous solubility. (Tr. 1078:17-24, 1079:15-21.)

112. The evidence establishes that, based on argatroban's structure and zwitterionic character, a person of ordinary skill in the art as of 1987 or before could not have predicted argatroban's solubility in any particular solvent or solvent mixtures. But such a person would have had the following general expectations about argatroban's solubility:

(1) acid would increase its aqueous solubility, (2) ethanol would decrease its aqueous solubility, and (3) saccharides (including sorbitol) would decrease its aqueous solubility.

113. One property that was known to be shared by all zwitterions is that their solubility increases at both ends of the acid/base (pH) spectrum, regardless of their baseline solubility. (PX 105 at 1511, Fig. 1; PX 111 at 566, Fig. 2; Tr. 216:19-217:3.) This property results in a "u"-shaped solubility curve when a zwitterion's solubility is measured as a function of pH. (Tr. 216:10-217:13, 1084:3-5.) Accordingly, it was known that adjusting the pH of a zwitterion such as argatroban toward acidity or basicity would increase its solubility. (Tr. 217:23-218:3.)

114. The acidic portion of the zwitterion becomes protonated (deionized) in a low pH (highly acidic) solution, yielding a species with a lone positive charge, which increases aqueous solubility. (Tr. 1084:17-1085:6.)

115. Conversely, in a high pH (highly basic) solution, the basic portion of the zwitterion becomes deprotonated (deionized), yielding a species with a lone negative charge, and increasing aqueous solubility. (Tr. 1086:7-21.)

116. Several prior art references, including Kumada (DX 97 at 4-5) and Matsui (DX 83A at 1) confirmed that argatroban behaved exactly as a zwitterion should, namely, that

its solubility was significantly enhanced under acidic conditions. (Tr. 218:4-13.) Dr. Needham also testified that in a prior art article by Iida, acid was used to dissolve argatroban. (Tr. 218:14-16.)

117. As early as 1936, Cohn reported that the aqueous solubility of all naturally occurring alpha amino acids, which are zwitterions, decreases upon addition of ethanol. (PX 103 at 248; Tr. 225:19-24, 1091:12-20.)

118. In a 1971 paper, Dr. Needham confirmed this trend regarding zwitterionic amino acid solubility, stating that "all alcoholic solvents decreased the solubility of the amino acids to a point considerably below that of water alone." (PX 111 at 566; Tr. 1096-23-1097:3.) This is consistent with the expectation of a person of ordinary skill in the art as to what adding ethanol to water would do to the solubility of a zwitterion. (Tr. 1097:4-8.) Dr. Needham acknowledged that as of 1987 ethanol was known to reduce the solubility of zwitterions generally (whether or not they were amino acids). (Tr. 219:15-25.) There is no teaching in the prior art that this expectation was not applicable to zwitterions like argatroban. (Tr. 1091:25-1092:5.) Accordingly, a person of ordinary skill in the art in 1987 would have expected that ethanol would depress the solubility of argatroban in water. (Tr. 1092:5-7.)

119. In rebuttal, Dr. Needham offered a new carbon count theory that the Cohn article and his own 1971 article, which he admitted "does show that the solubility [of amino acids] is less in ethanol," only applies to amino acids with less than 8 side-chain $CH_2$ groups. (Tr. 1386:25-1388:1; PX 103 at 248 n.3.) As Dr. Needham admitted, however, that was because the molecule was getting less polar as the $CH_2$ groups were added. (Tr. 1387:10-20.) Dr. Byrn and Dr. Needham agreed that argatroban, a zwitterion, is polar. (Tr. 294:15-16, 1099:6-9, 1099:17-20.)

120. In any event, Dr. Needham's "$CH_2$" count theory does not show that ethanol was a known solvent for a zwitterions prior to the '052 patent. Indeed, Dr. Needham conceded in his direct testimony that Cohn would have indicated that using ethanol on a molecule like argatroban "wasn't the best approach." (Tr. 323:9-10.) The basis of the new theory is that an exception exists to the general rule that ethanol reduces the aqueous solubility of alpha amino acids for alpha amino acids with more than eight $CH_2$ groups. (Tr. 1382:21-1383:11.) However, Dr. Needham never testified as to exactly how many $CH_2$ groups argatroban has that might relate in some way to this issue. (See Tr. 1384:24-1385:9 (Dr. Needhman noting that there were "five, six groups right here," and referring to some non-$CH_2$ groups).) Moreover, on numerous occasions, Dr. Needham freely

admitted that the entire subject of the Cohn article – and in particular that article's statement about ethanol's effect on solubility – is outside his area of expertise, and that he is not competent to express to the Court an opinion about it. (Tr. 225:19-226:15, 1417:5-11.)

121. Dr. Needham's new theory is also inconsistent with his own prior publications. For example, Table 1 of his 1971 article demonstrates that across the board, for all the amino acids studied, their solubility (measured in moles) in ethanol was uniformly poor (between 0.002 and 0.004) and uniformly far below water (between 0.172 and 2.9) regardless of either the number of $CH_2$ groups in those amino acids or whether their baseline solubility in water was high or low. (PX 111 at 1, Table 1; Tr. 1422:5-1424:13.)

122. Dr. Byrn and Dr. Needham agreed that there is prior art showing that the general principle that ethanol reduces aqueous solubility of zwitterions applies to zwitterions regardless of whether the zwitterion is an amino acid. (Tr. 227:5-229:16, 1091:21-1093:23.)

123. For example, a 1969 paper by Hou showed that ampicillin and its derivatives exhibit reduced solubility in ethanol-water systems over water alone. (PX 105 at 1511, Fig. 2; Tr. 1092:16-1093:13.) Ampicillin is a zwitterion of similar structure to argatroban. (Tr. 1094:11-17.) Indeed, Dr. Byrn

and Dr. Needham agreed that the chemical structure of the molecules described in the Hou article (ampicillin and Wy-4508) are the closest in chemical structure to argatroban over any of the other specific compounds that were the subject of testimony at trial, including the amino acids, phenobarbital, Cedilanid-D, and DHE-45. (Tr. 227:5-229:5, 1094:7-1095:15, 1417:21-1418:25.) Ampicillin is not structurally similar to the amino acids, and yet Hou concluded that, on account of its zwitterionic nature, ampicillin's solubility behavior bears a "close relation" to that of the amino acids. (PX 105 at 1514.) Dr. Needham acknowledged that ampicillin and its derivatives are non-amino acid zwitterions that exhibit the classic U-shaped solubility curve along the pH scale, as well as decreased solubility in ethanol. (Tr. 228:5-18, 229:3-5.)

124. Like argatroban, ampicillin and Wy-4508 are (1) zwitterions, (2) not amino acids, (3) have their solubility enhanced in acid, and (4) have their solubility decreased in ethanol. (Tr. 227:5-229:5, 1094:7-1095:15, 1417:21-1418:25; see also PX 105.)

125. It is clear that the consistent teaching of the prior art, including the prior art closest to argatroban (both in terms of structure and solubility characteristics) is that ethanol would be expected to reduce the aqueous solubility of argatroban. (Tr. 1098:10-16.)

126. Dr. Needham conceded that argabtroban is the only exception he knows to this general principle – accepted for nearly a century – and he conceded that prior to issuance of the '052 patent in suit it was unknown that argatroban did not follow this general rule. (Tr. 219:1-220:18, 1425:17-1426:18.)

127. The defendants have identified no prior art to refute the fact that the addition of ethanol decreased the solubility of zwitterions or, more specifically, the solubility of the zwitterion argatroban (Tr. 1098:10-16), nor have the defendants identified any prior art to refute the overall conclusion that zwitterions show reduced solubility in ethanol-water systems over water alone.

128. Argatroban is a polar molecule. Both Dr. Byrn and Dr. Needham agree that as of 1987 and before, the expectation of the person of ordinary skill in the art would have been that solvents of relatively greater polarity would be better able to dissolve polar molecules than solvents of relatively lesser polarity. (Tr. 294:1-16, 1100:2-5.) However, ethanol, saccharides generally, and sorbitol in particular, are less polar than water. (See e.g., DX 3 at B-ARG-7088.) Therefore, the expectation of the person of ordinary skill in 1987 and before would be that the introduction of ethanol or saccharides (including sorbitol) into water would reduce the solubility of argatroban below its solubility in water alone.

(Tr. 1100:2-1102:5.) As of 1987 and before, there was nothing in the prior art which would have indicated that this general rule did not apply to argatroban.

## VII. Claim Construction

129. The parties do not have any material dispute as to the claim construction of the words of the claims, with one notable exception. The parties do not agree on the proper construction in claim 3 of "pharmaceutical composition for injection."

### A. The Law Governing Claim Construction

130. Claim construction is matter of law for the Court to decide. Markman v. Westview Instruments, Inc., 517 U.S. 370, 390-91 (1996).

131. "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1115 (Fed. Cir. 2004)). The Supreme Court has made clear that the claims are "of primary importance, in the

effort to ascertain precisely what it is that is patented." Merrill v. Yeomans, 94 U.S. 568, 570 (1876). Indeed, the Supreme Court has explained that "[b]ecause the patentee is required to define precisely what his invention is . . . it is unjust to the public, as well as an evasion of the law, to construe it in a manner different from the plain import of its terms." Phillips, 415 F.3d at 1312 (citing White v. Dunbar, 119 U.S. 47, 52 (1886)) (internal quotation marks omitted).

132. Judicial redrafting of claims to preserve validity is impermissible. As the Supreme Court warned over a century ago:

> [W]e know of no principle of law which would authorize us to read into a claim an element which is not present, for the purpose of making out a case of novelty or infringement. The difficulty is that, if we once begin to include elements not mentioned in the claim, in order to limit such claim, and avoid a defense of anticipation, we should never know where to stop.

McCarty v. Lehigh Val. R. Co., 160 U.S. 110, 116 (1895); see also Phillips, 415 F.3d at 1312.

**1. Claims Are To Be Given Their Ordinary Meaning**

133. In interpreting a claim, courts look first to intrinsic evidence in the patent itself, including the claims,

the specifications, and the prosecution history. See Dow Chem. Co. v. Sumitomo Chem. Co., 257 F.3d 1364, 1372 (Fed. Cir. 2001).

134. The "claims themselves provide substantial guidance as to the meaning of particular claim terms." Phillips, 415 F.3d at 1314. The Court of Appeals for the Federal Circuit has "frequently stated that the words of a claim are generally given their ordinary and customary meaning." Id. at 1312 (quotation marks omitted). "[M]oreover, . . . the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e. as of the effective filing date of the patent application." Id. at 1313.

135. The Court should read the claim terms both in the context of the particular claim and in the context of the entire patent, including the specification. Id.

136. A review of the specification may show that a claim term should not be given its ordinary meaning, and that the patentee has instead acted as his own lexicographer. Id. at 1316. "When a patentee acts as his own lexicographer in redefining the meaning of particular claim terms away from their ordinary meaning, he must clearly express that intent in the written description." Merck & Co. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1370 (Fed. Cir. 2005); see also Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc., 214 F.3d 1302, 1307 (Fed

Cir. 2000) ("Absent an express intent to impart a novel meaning, claim terms take on their ordinary meaning.").

**2. Limitations From the Specification Should Not Be Read Into the Claims**

137. The purposes of the specification are "to teach and enable those of skill in the art to make and use the invention and to provide a best mode for doing so." Phillips, 415 F.3d at 1323. Limitations from the specification should not be read into the claims. Id.

138. While the specification may describe specific embodiments of the invention, the claims should not be confined to those embodiments. Id.; see also Novartis Pharm. Corp. v. Apotex Corp., No. 02 Civ. 8917, 2006 WL 626058, at *5 (S.D.N.Y. Mar. 13, 2006) (holding that factors set forth in patent specification relevant to claim meaning "were included as part of the specification's teaching function and are not limits on the claimed invention.").

139. While claims are to be interpreted in light of the specification, limitations, objectives and examples from the specification cannot be read into the claims. Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 904-05 (Fed. Cir. 2004); Procter & Gamble Co. v. Nabisco Brands, Inc., 711 F. Supp. 759,

765 (D. Del. 1989). Rather, "the decision maker must consider the specification as one factor in claim interpretation and should not be confused with adding an extraneous limitation appearing in the specification, which is improper." Procter & Gamble Co., 711 F. Supp. at 765 (internal citation and quotation marks omitted); see also Iovate Health Scis., Inc. v. Bio-Engineered Supplements & Nutrition, Inc., 586 F.3d 1376, 1382 (Fed. Cir. 2009) (declining to read efficacy limitations into claims for method of administering nutritional supplement, which did "not require any further measurement or determination of any result achieved by administering the claimed composition."). "Absent a clear disavowal or contrary definition in the specification or the prosecution history," the claim is to be given its full ordinary meaning. Home Diagnostics, Inc. v. LifeScan, Inc., 381 F.3d 1352, 1358 (Fed. Cir. 2004).

**3. The Role of Prosecution History and Extrinsic Evidence**

140. When intrinsic evidence is insufficient, courts may look to extrinsic evidence such as expert testimony, articles, and inventor testimony. Dow Chem., 257 F.3d at 1373. However, extrinsic evidence is generally "less reliable than the patent and its prosecution history." Phillips, 415 F.3d at

1318. Among the types of extrinsic evidence that can be consulted, "judges are free to consult dictionaries and technical treatises at any time in order to better understand the underlying technology . . . [and] when construing claim terms, so long as the dictionary definition does not contradict . . . the patent documents." Id. at 1322-23 (internal citation omitted).

141. A court "should also consider the patent's prosecution history, if it is in evidence." Id. at 1317 (internal quotation marks omitted). Because the prosecution history, however, "represents an ongoing negotiation between the PTO and the applicant," it is generally less useful for claim construction purposes than the specification. Id.

142. Expert testimony may also be considered. However, expert testimony is "generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." Id. at 1318. Moreover, expert testimony must be rejected when it "is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history." Id. (internal quotation marks omitted).

143. The parties have agreed upon the construction of almost all claim terms. The parties have identified other terms that need to be construed, but in most cases the difference

between the constructions proposed by the parties is not material and the construction of those claim terms is not relevant to the issues in this case. The primary dispute between the parties as to claim construction concerns the claim term "pharmaceutical composition for injection" as used in claim 3. The parties agree that all remaining terms should be given their ordinary meaning.

**B. The Construction of Claim Terms**

144. Arginineamide. The parties agree that the claim term "arginineamide" shall be construed as "[a] group of compounds having the general formula (I) as shown in Col. 1, ll. 35-40 of the '052 patent, including compounds corresponding to formula (I) of claims 1 and 3 of the '052 patent."

145. $N^2$-arylsulfonyl-L-argininamide represented by formula (I). The parties agree that this claim term should be construed to mean "any compound corresponding to formula (I) as shown in claims 1 and 3 of the '052 Patent." More specifically, the parties agree that this claim term refers to "argatroban," which has also been referred to as "argipidine" (See DX 1 at Col. 4, ll. 66-68) and by the designation MD-805. (Tr. 348:23-349:1; Pl.'s Supplemental Resp. to Req. for Admis. No. 5; see also Tr. 72:24; DX 705.)

146. Solvent. Barr contends that the term "solvent" should be given its ordinary meaning as "a liquid capable of dissolving another material to form a solution." This is supported by the specification. (See, e.g., DX 1, Examples 1-3 at Col. 4, l. 65-Col. 5, l. 45.) The plaintiffs contend that a solvent as used in claim 1 should be construed as "a substance (including a combination of substances) that acts to dissolve another substance to form a solution." There is no material difference between these proposed constructions that is relevant to any issue in dispute.

147. Saccharide. The plaintiffs contend that saccharide should be construed to mean "monosaccharides, oligosaccharides, polysaccharides and their reduced derivatives (for example sugaralcohol) which are soluble in water." Barr contends that the proposed construction should also include "any mixtures thereof." (See DX 1 at Col. 3, ll. 67-68 (noting that "[a] mixture of these saccharides may be used.").) There is no material difference between these proposed constructions that is relevant to any issue in dispute.

148. Comprising and Containing. Claim 1 describes a "method for dissolving an arginineamide, comprising: dissolving [argatroban] and/or its salt in a solvent containing ethanol, water and a saccharide." Claim 3 states "[a] pharmaceutical

composition for injection, comprising: [argatroban] together with ethanol, water and a saccharide."

149. The terms "comprising" and "containing" are terms of art in patent law with well-defined meanings.

150. According to the Manual of Patent Examining Procedure ("MPEP"), the term "comprising" is "inclusive or open-ended and does not exclude additional, unrecited elements or method steps." MPEP § 2111.03 (8th Ed., rev. 7 2008). "The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps." Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1368 (Fed. Cir. 2003). Comprising "simply means that the device may contain elements in addition to those explicitly mentioned in the claim." In re Skvorecz, 580 F.3d 1262, 1267 (Fed. Cir. 2009).

151. "Containing" is also an open-ended term, synonymous with "comprising," "including," and "characterized by." Mars, Inc. v. H.J. Heinz Co., 377 F.3d 1369, 1376 (Fed. Cir. 2004) (citing MPEP, § 2111.03 (8th ed., rev. 1 2003)).

152. Therefore, claim 1 does not exclude the use of additional steps or elements. Claim 3 also uses the term "comprising." Therefore, the pharmaceutical composition of claim 3 may contain elements in addition to those explicitly mentioned in the claim.

**C. The Proper Construction of "Pharmaceutical Composition For Injection"**

153. Claims 3 and 4 of the '052 patent claim a "pharmaceutical composition for injection." (DX 1 at Col. 6, ll. 45-67.)

154. Claim 3 is a composition of matter claim. It claims a "pharmaceutical composition." A "composition" is a term of art that means a mixture of two or more substances. Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980); PIN/NIP, Inc. v. Platte Chem. Co., 304 F.3d 1235, 1244 (Fed. Cir. 2002). The dictionary defines "pharmaceutical" as a "medicinal drug." Webster's New International Dictionary 1694 (3d ed. 1993); see Novartis Pharm. Corp. v. Eon Labs Mfg., Inc., 363 F.3d 1306, 1310 (Fed. Cir. 2004).

155. The plaintiffs have consistently defined this claim term to mean "[a] composition that is suitable for treating medical conditions of patients by injection." (Docket No. 61, Ex. A.)

156. The defendants, however, have changed their proposed definition. In their initial proposed claim construction, the defendants proposed the following definition: "Medicinal drug product in a state suitable for injection."

(Docket No. 61, Ex. A.) The definition the defendants initially proposed is almost identical to that adopted in a 2008 case in which Barr's corporate parent, Teva, was involved: "'A pharmaceutical composition' means a medicinal drug product in a state suitable for administration to a patient." See Takeda Pharm. Co. v. Teva Pharm. USA Inc., 542 F. Supp. 2d 342, 348 (D. Del. 2008), aff'd, 298 F. App'x 969 (Fed. Cir. 2008); see also Abbott Labs. v. Sandoz, Inc., 529 F. Supp. 2d. 893, 903 (N.D. Ill. 2007) ("The term 'pharmaceutical composition' means an aggregated product formed from two or more substances for use as a drug in medical treatment."). The defendants' original definition omitted part of that definition, namely, "administration to a patient," but conceded that a "medicinal drug product" was required as part of the claim. The defendants' definition was supported by the opinion of their expert, Dr. Needham, who opined that a "pharmaceutical composition" means a "medicinal product." (Tr. 286:9-25, 287:1-8.)

157. It became clear at Dr. Needham's deposition that the material described in the Yamamoto article, and which the defendants relied on for their claim of anticipation, was not a "medicinal drug product." Dr. Needham conceded that the material was not being used as a "medicine" to "treat" any indication (Tr. 282:22-289:9); that the material could not be

given intravenously at the very low pH of 1.5 to 1.7 (Tr. 281:12-283:4; PX 174); and that the material was not a "medicinal product" but merely something which, with a lot of work and testing, might eventually be adapted to become a product some day (Tr. 286:4-287:8; see also PX 260.)

158. At trial, Dr. Needham responded to the uncomfortable fact that his claim construction did not cover the material in the Yamamoto article by changing his claim construction. At trial, Dr. Needham testified that "a pharmaceutical composition for injection" means "a medicinal drug composition that can be administered by injection." (Tr. 107:8-14, 287:9-12.) However, Dr. Needham also explained that, in this context, medicinal means that "the compound has the potential of being therapeutically active in the body." (Tr. 108:11-13.) He also explained that a "medicinal drug" is a compound "that has the potential to elicit a therapeutic effect when it's given to a person." (Tr. 109:6-12.)

159. The defendants now propose the following definition of "pharmaceutical composition for injection": "medicinal drug composition that can be administered by injection." (Tr. 107:8-15; DX 718.) The defendants' current construction suggests an effort to move further away from the implication that a "pharmaceutical composition for injection" must be a stage in the development of a product suitable for

treating a clinical indication, despite Dr. Needham's agreement that "medicinal" requires that the compound have the potential to elicit a therapeutic effect. (Tr. 109:6-12.) Indeed, in their proposed findings, the defendants argue that the "pharmaceutical composition" is simply the mixture of the medicinal drug argatroban with alcohol, water, and a saccharide. (Defs.' Proposed Finding 133.) The defendants read out any requirement that the "pharmaceutical composition" itself be a medicinal drug product. Under the defendants' claim construction, a plainly toxic composition, such as a cleaning fluid or a pesticide, would be a "pharmaceutical composition" so long as it contained a constituent that could be characterized as a medicinal drug. That is an unreasonable interpretation of "pharmaceutical composition" that is contrary to the import of the specification, the dictionary definition, and the cases that have interpreted the term.

160. The plaintiffs argue that a "pharmaceutical composition for injection" must be an injection that is suitable for treating medical conditions of patients, and that the claim terms impart a notion of safety and efficacy. The defendants object that "pharmaceutical composition for injection" need not be a product that is readily amenable to injection in patients for treatment of illness, or a drug that could be approved by the FDA for use in humans. The plaintiffs' proposed

construction blurs the distinction between the PTO issuing the '052 patent and the FDA's approval of the NDA for Argatroban Injection. Cf. Novo Nordisk A/S v. Eli Lilly & Co., No. 98 Civ. 643, 1999 WL 1094213, at *12 (D. Del. Nov. 18, 1999) (rejecting reliance in claim construction on definition of "drug" in Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(g)(1) because "the FDA, not the Patent and Trademark Office, is responsible for determining whether drugs are safe and effective and because drugs not approved by the FDA are still patentable."). The defendants are correct that importing a requirement of safety and efficacy into claim 3 would go beyond the patent claims and specification. However, the fact that the patent does not require that the pharmaceutical composition be in a state to be approved by the FDA does not mean that the claim does not describe a composition that is suitable for treating medical conditions.

161. The defendants are correct that there is no limitation in the claim or the specification that limits the "pharmaceutical composition" to a medical product for the treatment of humans, as opposed to mammals, including animals. While there is nothing in the specification that suggests a use of the "pharmaceutical composition" for the treatment of animals, there is nothing that precludes it. See Amgen Inc. v. Hoechst Marion Roussel, Inc., 457 F.3d 1293, 1300 (Fed. Cir.

2006); In re Brana, 51 F.3d 1560, 1564 (Fed. Cir. 1995); In re Krimmel, 292 F.2d 948, 953 (C.C.P.A. 1961). Thus, the Court will not include the plaintiffs' suggested limitation of the claim that the composition is suitable for t reating medical conditions "of patients," which implies human patients. However, the inclusion of possible animal subjects does not change the result in this case because, as discussed below, it is plain that the composition at issue in Yamamoto was not used to treat animals and there is no evidence that it could be used to treat animals.

162. However, the defendants' proposal that claim 3 merely describes a composition effectively reads out the "medicinal" requirement of the term "pharmaceutical composition." While the defendants' new definition nominally includes the term "medicinal," their argument goes too far by arguing that any combination of argatroban, water, ethanol, and a saccharide, along with any other substance, no matter how harmful, is sufficient to meet the claim terms. Courts have interpreted the claim term "pharmaceutical composition" to incorporate a requirement that the composition be a medicinal drug or be used for treating medical conditions, even if the composition is not required to meet the standards for FDA approval. See Takeda Pharm., 542 F. Supp. at 348; Abbott Labs., 529 F. Supp. 2d at 903 (defining "pharmaceutical composition" as

"an aggregated product formed from two or more substances for use as a drug in medical treatment"); Ortho-McNeil Pharm., Inc. v. Kali Labs., Inc., 482 F. Supp. 2d 478, 499 (D.N.J. 2007), aff'd in part and vacated in part on other grounds, 344 F. App'x 595 (Fed. Cir. 2009) (defining "pharmaceutical composition" as "a medicinal preparation comprising an intimate admixture, prepared outside the body, generally in the form of a dosage unit, such as a tablet or capsule"). In defining another patent term in a claim containing the phrase "pharmaceutical injection," the Court of Appeals for the Federal Circuit noted that the dictionary defines "pharmaceutical" as "medicinal drug." Novartis Pharm., 363 F.3d at 1310. If there is no minimal requirement that a composition meeting claim 3 must have some medicinal aspect or must pertain to treatment of a clinical indication, then any liquid could qualify as a "pharmaceutical composition for injection" so long as it would be possible to inject the liquid into a human or animal, no matter how harmful the results. But plainly there are liquid compositions that could not be considered medicinal merely because they are injected into an organism.

163. Moreover, the patent specification supports the plaintiffs' contention that a "pharmaceutical composition for injection" must be a medical drug or be used for treating medical conditions. The patent background refers to the known

anti-thrombotic properties and poor solubility of argatroban, strongly suggesting that the invention is aimed at obtaining a solution that can be used to exploit argatroban's anti-thrombotic properties. (DX 1 at Col. 1, ll. 17-24; see also DX at 1 Col. 4, ll. 33-36 ("The pharmaceutical compositions of the invention are useful for treating thrombosis. Accordingly, the pharmaceutical compositions can be used as the anti-thrombotic agents.").) Plainly, this is a medical or clinical application. Moreover, examples 4 and 6 in the patent explain how the solution can be used for dialysis, and example 5 explains how the solution can be used for drip infusion. These are plainly uses for the treatment of medical conditions.

164. The Court therefore finds that a "pharmaceutical composition for injection" is a composition that is suitable for treating medical conditions by injection.

## VIII. Anticipation

165. The defendants contend that each of claims 1 through 4 of the '052 patent are invalid pursuant to 35 U.S.C. § 102(b) as anticipated by the Yamamoto article.

**A. The Law of Anticipation**

166. 35 U.S.C. § 102(b) provides that a person shall be entitled to a patent unless "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." An anticipating prior art reference may be foreign. See, e.g., Mazzari v. Rogan, 323 F.3d 1000, 1005-06 (Fed. Cir. 2003).

167. Whether a reference anticipates the invention is measured by comparing the reference to the claims. See Hewlett-Packard Co. v. Mustek Sys., Inc., 340 F.3d 1314, 1324 (Fed. Cir. 2003) (rejecting argument that additional limitations should be read into method claims to avoid anticipation by the prior art).

168. As the Court of Appeals for the Federal Circuit has said, "it is axiomatic that that which would literally infringe if later anticipates if earlier." Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001). In other words, if the embodiment disclosed in the prior art reference would infringe the claim, then it anticipates it.

169. In order for an invention to be anticipated by a prior art reference under 35 U.S.C. § 102, each and every element of the claimed invention must be disclosed, either

expressly or inherently, within the four corners of that single prior art reference. See Finisar Corp. v. DirecTV Group, Inc., 523 F.3d 1323, 1334 (Fed. Cir. 2008), cert. denied, 129 S. Ct. 754 (2008); SRI Int'l, Inc. v. Internet Sec. Sys., Inc., 511 F.3d 1186, 1192 (Fed. Cir. 2008); Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003); Transclean Corp. v. Bridgewood Servs., Inc., 290 F.3d 1364, 1370 (Fed. Cir. 2002); Celeritas Techs., Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1360 (Fed. Cir. 1998). For a reference to anticipate, "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed. Cir. 1991), overruled on other grounds by, Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1293 (Fed. Cir. 2009), cert. denied, 130 S. Ct. 1052 (2010).

170. A prior art reference may anticipate without expressly disclosing each feature of the claimed invention, if it is shown that the "missing characteristic is necessarily present, or inherent, in the single anticipating reference." Schering Corp., 339 F.3d at 1377. "[I]f the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999).

171. Claim 1 claims a "method for dissolving [argatroban] in a solvent containing ethanol, water and a saccharide." (DX 1 at Col. 6, ll. 23-40.)[4] Claim 2 provides that the saccharide is from a group consisting of sorbitol, glucose, glycerin, and sucrose. Claim 3 claims a composition of matter, a "pharmaceutical composition for injection comprising [argatroban] together with ethanol, water and a saccharide."[5] (DX 1 at Col. 6, ll. 45-63.) Claim 4 further defines the saccharide in the same way that claim 2 does.

172. A method patent may recite as claim elements one or more steps required to practice or carry out the claimed method. Where a method claim has multiple steps, a prior art reference must show either expressly or inherently all the claimed steps of the method in order to be anticipatory. See Gen. Elec. Co. v. Sonosite, Inc., 568 F. Supp. 2d 983, 1006 (W.D. Wisc. 2008), appeal dismissed, No. 2008-1567, 2009 WL 6084615 (Fed. Cir. Nov. 10, 2009) (finding a method claim reciting multiple steps anticipated by prior art patent which

[4]As a matter of law, this type of claim is considered to be a "process" or method claim. See 35 U.S.C. § 101. A process is patentable if "it transforms a particular article into a different state or thing." In re Bilski, 545 F.3d 943, 954 (Fed. Cir. 2008) (en banc), cert. granted, 129 S. Ct. 2735 (2009).

[5]"[C]omposition of matter has been construed consistent with its common usage to include all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids." Diamond, 447 U.S. at 308 (alteration in original) (internal quotation marks omitted).

disclosed "precisely the method disclosed in the asserted claims").

173. Alternatively, a method claim may recite claim elements consisting of one step. In that case, the prior art reference only need disclose, either expressly or inherently, that single step to be anticipatory. See Iovate Health Sciences, 586 F.3d at 1382-83 (finding single-step claim for method of administering nutritional supplement anticipated) An anticipatory reference need not disclose more detail than the patent has in its claims. See In re Gleave, 560 F.3d 1331, 1336 (Fed. Cir. 2009) ("Certainly where the claims themselves do not require a particular activity, we have no call to require something more from the anticipating reference.").

174. Anticipation requires that the disclosures in the prior art reference be sufficient to enable one skilled in the art to carry out the claimed invention. See Transclean, 290 F.3d at 1370 (citing In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985)); see also In re Gleave, 560 F.3d at 1335 (finding that enabling reference must contain sufficient information such "that a person of ordinary skill would know how to use—in other words, to practice or carry out—the method in light of the reference"). A reference is enabling if a person of skill in the art "could have combined the publication's description of the invention with his own knowledge to make the claimed

invention." In re Donohue, 766 F.2d at 533; see also Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research, 346 F.3d 1051, 1054-55 (Fed. Cir. 2003) (en banc) (anticipation requires that the reference "must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation").

175. The issue is simply whether the prior art reference "is enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention." Impax Labs., Inc. v. Aventis Pharms. Inc., 468 F.3d 1366, 1383 (Fed. Cir. 2006). The requirement is satisfied by showing that one of ordinary skill in the art would know how to make the relevant composition. See In re Gleave, 560 F.3d at 1336.

176. In order to be enabling, and thus anticipatory, the disclosures must provide a "reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Elan Pharmaceuticals, 346 F.3d at 1055 (quoting In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)).

177. A prior art reference "so obscure in its terminology that two conflicting theories may be deduced therefrom and supported by equally plausible arguments is too indefinite to be utilized as an anticipation." Lever Bros. Co. v. Procter & Gamble Mfg. Co., 139 F.2d 633, 641 (4th Cir. 1943)

(quoting Cimiotti Unhairing Co. v. Comstock Unhairing Co., 115 F. 524, 524 (C.C.S.D.N.Y. 1902)).

178. An ambiguous prior art reference is not anticipatory. See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 364 F. Supp. 2d 820, 901 (S.D. Ind. 2005) (citing In re Brink, 419 F.2d 914, 918 (C.C.P.A. 1970)), aff'd, 471 F.3d 1369 (Fed. Cir. 2006); In re Turlay, 304 F.2d 893, 899 (C.C.P.A. 1962) ("It is well established that an anticipation rejection cannot be predicated on an ambiguous reference."); In re Hughes, 345 F.2d 184, 188 (C.C.P.A. 1965) ("[A]n ambiguous reference . . . will not support an anticipation rejection.").

179. A finding of anticipation "is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations." Scripps Clinic, 927 F.2d at 1576. "If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not § 102 anticipation, but § 103 obviousness." Id. at 1577.

**B. Yamamoto**

180. The defendants have identified only one allegedly anticipating prior art reference in this case—the Yamamoto article. (DX 7.)

181. There is no dispute that the Yamamoto Article was published in the Japanese-language journal Japanese Pharmacology & Therapeutics in December 1986 and is thus a "printed publication" within the meaning of Section 102(b). It has been admitted by Mitsubishi that the Yamamoto Article was published more than one year prior to the earliest U.S. application date of the '052 patent. (Tr. 349:22-350:22, Pl.'s Resp. to Am. Req. for Admis. No. 11.) Therefore, the Yamamoto Article is prior art to the '052 patent.

**1. The Yamamoto Translations**

182. In this case, the Court first must resolve a preliminary issue concerning the proper translation of the Yamamoto Article. Barr contends that the Yamamoto Article anticipates the '052 patent because the article sets forth each limitation of each claim of the '052 patent. The plaintiffs dispute this. Each of the parties have submitted their own translations of the Yamamoto Article. In order to determine whether the Yamamoto Article is anticipatory prior art, the Court must first decide which of the different translations is an accurate translation.

183. The Yamamoto Article, while written in Japanese, includes in English the title and an abstract of the article, as follows:

Effect of Argipidine (MD-805) on Cerebral Microcirculation After Cerebral Ischemia in Rats

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**Abstract**

The effect of argipidine (MD-805) on the cerebral microcirculation was studied with the so called “no-reflow-phenomenon” generated by blood recirculation after the cerebral ischemia produced by 4-vessel occlusion in rats as reported by Pulsinelli et al. No-perfusion region was detected by the infusion of India ink and no-perfusion area (NPA) was measured for 10 colonal [sic] sections of the stained brain. Argipidine reduced no-perfusion area with 5.8 ± 2.1% NPA at 5 mg/kg i.p. and 6.3 ± 1.2% NPA at 10 mg/kg i.p. as compared with 14.6 ± 0.7% NPA of the control group. Tissue culture urokinase at 48000 and 96000 U/kg i.v. did not reduce NPA.

Argipidine is considered to improve the cerebral microcirculation by the inhibition of platelet aggregation by its potent thrombin inhibitory effect, since electronmicroscopical observation of the the [sic] no-perfusion area of the brain showed that the platelet aggregates occluded the micro vessels.

(DX 7 at 25.)

184. While the parties have each submitted their own translations of the Yamamoto Article, the testimony at trial

related to the proper translation of a specific sentence. In Japanese, this sentence reads:

2 薬物投与方法

7.5% D-sorbitol-4% ethanol 中に塩酸酸性下（pH 1.5～1.7）で溶解した argipidine 溶液を 1 ml/kg の用量で総頸動脈閉塞 15 分前に腹腔内投与した。対照群には溶媒を投与した。‥

(DX 7 at 26.)

185. The disputed sentence is located in Part 2 of the Test Materials and Methods section in Yamamoto (entitled "Drug Administration Method"), a brief section discussing how argatroban was administered to test animals used in their experiments. (DX 7.) The sentence provides only a cursory description of the argatroban solution that was administered to the laboratory rats.

**i. The Hartmann Translation**

186. Barr relies on a translation of the Yamamoto Article prepared by Gregor Hartmann. (DX 10B, the "Hartmann translation.")[6] Mr. Hartmann translated the sentence in dispute as follows:

2. Drug Administration Method

[6] DX 10B is a corrected version of Mr. Hartmann's translation dated Jan. 23, 2010, which incorporates certain corrections dated Jan. 21, 2010 (DX 10A; see Tr. 572:7-22.)

> A solution of argipidine dissolved in 7.5% D-sorbitol-4% ethanol with hydrochloric-acid acidity (pH 1.5~1.7) was administered intraperitoneally at a dose of 1 ml/kg 15 minutes prior to occlusion of the common carotid arteries.

(DX 10B at 3.)

187. Mr. Hartmann admits, however, that his original translation of the Yamamoto article contained numerous errors. (Tr. 577:5-11.) While Mr. Hartmann characterizes the errors as "minor," they are numerous and some of them substantially alter the meaning of the sentences in which they appear; for example, "five minutes before restarting blood flow" was changed to "the chest was opened five minutes after restarting blood flow." (Tr. 578:23-584:3.) In at least one example of such "minor errors," Mr. Hartmann acknowledged that his original translation did not make scientific sense. (Tr. 580:11-581:10, 599:13-18.) Mr. Hartmann also did not consult with a native speaker of Japanese in preparing his translation. (Tr. 578:10-13.)

188. Mr. Hartmann's translation does not properly translate the Yamamoto sentence. "中に" does not have an exact equivalent in English. The term "中" or "chu" by itself means "inside" or "in the middle." (Tr. 993:1-6.) The expression "中に" (chu ni), found in "7.5% D-sorbitol-4% ethanol 中に," can be translated in English as "in," but in Japanese the phrase

strongly conveys the meaning of “within,” “into,” or “throughout,” depending on context. (Tr. 994:9-13, 1012:20-23.)

189. Mr. Hartmann’s translation, in which he considers “7.5% D-sorbitol-4% ethanol 中に” to be an adjectival phrase, is grammatically incorrect. His translation violates a basic rule of Japanese grammar because “chu ni” cannot modify a noun phrase. (Tr. 992:16-19.)

190. Mr. Hartmann also admitted that after having read the translation by Martin Cross, the expert translation expert for the plaintiffs, he went back to check his own translation, and changed certain portions of it after deciding that Mr. Cross’s was the “preferable translation.” (Tr. 582:12-16.). Mr. Hartmann acknowledged that Mr. Cross’s translation of this text was superior to his own at various points. (Tr. 601:3-6.) With regard to errors in his original translation of a different sentence in the relevant portion of the article, Mr. Hartmann admitted “I was not quite there. I should have researched it more.” (Tr. 601:7-12.)

191. Mr. Cross opined that the Hartmann translations, original and corrected, are not accurate or reliable. (Tr. 970:8-16, 971:1-5, 972:3-8.) Mr. Cross found more than 50 errors in the Hartmann translation. (Tr. 971:11-18, 972:3-8.)

192. In view of the multitude of substantive errors that changed the meaning of the original source text and lack of

proper translation skill and judgment, Mr. Hartmann's translation lacks sufficient credibility and reliability.

**ii. The Aschmann Translation**

193. Barr also relies on the expert testimony of Charles Aschmann in support of its position that the Hartmann translation is correct. Mr. Aschmann testified that, in his opinion, the Hartmann translation is an accurate translation of the original Japanese and that the Cross translation is not. (Tr. 511:16-25.) The Aschmann translation reads:

> A dose of 1ml/kg of a solution where argipidine was dissolved in 7.5% D-sorbitol-4% ethanol under hydrochloric acid acidity (pH of 1.5 to 1.7) was administered intraperitoneally 15 minutes before occlusion of the common carotid arteries.

(DX 802.)

194. Mr. Aschmann's translation is not accurate. (Tr. 970:3-7.) When pressed to identify the location of the character in the original Japanese source text corresponding to the word "where" in his translation, for example, Mr. Aschmann admitted that the word "where," as used in the common parlance of English language, is not in the Japanese source text. (Tr. 549:11-13.) The defendants' other expert translator Mr. Hartmann also acknowledged that there is no "where" in the

original Japanese source text to support Mr. Aschmann's translation. (Tr. 608:2-4.)

**iii. The FDA Translation**

195. A translation of the Yamamoto Article was also produced from the files of the plaintiffs Mitsubishi and Encysive. This translation was provided by TBC, Encysive's predecessor, to the FDA (the "FDA translation") as part of its New Drug Application for argatroban. (See DX 5 at ENCY 68343, ENCY 68599-619 (NDA excerpt).) In the FDA translation, the disputed sentence reads:

> 2. Drug Administration
>
> Argatroban solution which was obtained by dissolving argatroban in 7.5% D-sorbitol-4% ethanol-hydrochloric acid (pH 1.5 to 1.7) was administered intraperitoneally in a dose of 1 ml/kg 15 min before the clamping of the common carotid arteries, and the controls were given the vehicle.

(DX 5 at 6.) Barr relies on the FDA translation in further support of its argument that the Hartmann translation, not the Cross translation, of this sentence should be accepted.

196. The FDA translation is an inaccurate translation of the Yamamoto sentence.[7] (Tr. 973:4-7, 974:1-5.) For example, the original Japanese sentence has no Japanese text which says

[7] In fact, however, the defendants did not introduce expert testimony sufficient to support an invalidity defense based on the FDA translation.

"which was obtained" (Tr. 1001:8-9) or "the controls were given the vehicle" (Tr. 1001:24-25). That version also has two references to argatroban in the single sentence having two different roles when it is clear that argatroban is not even mentioned in the Japanese text and the word argipidene appears only once. (Tr. 1001:10-13.) The FDA translation also fails to mention "under" or "acidity," and fails to convey the same meaning as the original Japanese source text. (Tr. 1001:16-18.)

**iv. The Cross Translation**

197. The plaintiffs rely on a translation of the Yamamoto Article prepared by Martin Cross (DX 11, the "Cross translation.") Mr. Cross translated this sentence as follows:

> 2. Drug Administration Method
>
> In 7.5% D-sorbitol-4% ethanol, an argipidine solution dissolved under hydrochloric acid acidity (pH 1.5 to 1.7) was intraperitoneally administered at a dosage of 1 ml/kg, 15 minutes before common carotid artery occlusion.

(DX 11 at 26.)

198. Tatsuo Nomura, a named inventor on the '052 patent, and who is both a scientist and native speaker of Japanese, testified that the disputed sentence in Yamamoto should properly be understood to mean: "in hydrochloric acid the argipidine was dissolved, and after that it's been put into

D-sorbitol and ethanol." (Tr. 1327:25-1328:2.) This is consistent with the translation of Yamamoto proffered by Martin Cross, as well as the scientific interpretation offered by Dr. Byrn. While the defendants are correct that Nomura is not an expert in injectable formulations, his testimony is credible given his experience as a native Japanese speaker and one of the inventors of the '052 patent.

199. Mr. Cross explained that he used the word "under" to translate the Japanese term KA DE because that term in Japanese is a single semantic unit and means "under." (Tr. 1004:8-9, 1016:23-1017:1.) That is, the argatroban in the Yamamoto article was "dissolved under hydrochloric acid acidity." (DX 11 at 26.) That is also consistent with Dr. Byrn's scientific understanding.

200. According to the original Yamamoto article and Cross translation, the language "In 7.5% D-sorbitol-4% ethanol" refers to how the argipidine solution was administered, not how it was dissolved. (Tr. 977:1-5.) The language "7.5% D-sorbitol-4% ethanol" is an adverbial phrase modifying the predicate of the sentence, which is "administered." (Tr. 985:15-986:5.) This translation is in accordance with standard Japanese sentence structure. (Tr. 986:4-5.)

201. In Yamamoto, "argipidine solution" is a compound noun that should not be split in translation. (Tr. 983:14-25.) It was not split in the Cross translation.

202. The Court finds that the Cross translation is the only reliable Yamamoto translation in evidence.

**v. The Yamamoto Reference**

203. Yamamoto was a preclinical pharmacology paper. (Tr. 1102:19-21.) As the defendants' expert Dr. Eby testified "preclinical" means "before clinical," i.e., it has nothing to do with patients and encompasses "anything leading up to beginning to do research, investigation with patients." (Tr. 490:9-10.)

204. The Yamamoto reference describes experiments designed to investigate what effect the argatroban molecule might have on cerebral ischemia in rats. Specifically, the experiments described in the Yamamoto article consisted of administering the argatroban compound to the rats approximately fifteen minutes prior to inducement of cerebral ischemia (a stroke) via occlusion of blood flow in the carotid arteries. Then, approximately thirty minutes later, blood flow to the rats' brains was restarted. Shortly after restarting blood flow, the rats were decapitated and their brains studied. (See

DX 11.) The purpose of the study was to see what effect the argatroban molecule had on the rats' brains. The study was not to study or monitor the rats who received argatroban; it was to see what the effect was on the rat brains by administering the argatroban molecule and killing the rats to analyze the effect the argatroban had. (Tr. 1103:9-24.)

205. Both Dr. Byrn and Dr. Needham agree that Yamamoto was not focused on argatroban's solubility or on treating the rats. (Tr. 1102:19-21, 243:20-23.) It assessed the pharmacological activity of the argatroban molecule. It neither assesses the solubility of argatroban, nor studies the methods by which argatroban might be dissolved. Yamamoto records, in passing, how argatroban was administered; it does not disclose the methods or steps by which any formulations of argatroban were prepared. (Tr. 244:9-10, 492:5-8, 1102:23-24, 1403:25-1404:9.) As Dr. Byrn explained, preclinical pharmacologists are interested merely in getting the drug into the animal; they are not experts in formulation and are not interested in formulation. (Tr. 1104:24-1105:1.) The rats were sacrificed soon after receiving the drug. (Tr. 1102:25.)

**2. Yamamoto Did Not Anticipate Claims 1 and 2 of the '052 Patent**

206. Yamamoto does not anticipate claims 1 and 2 of the '052 patent unless Yamamoto discloses a method of dissolving argatroban in ethanol, water, and a saccharide and enables one skilled in the art to make the invention.

**i. Yamamoto Did Not Disclose the Patented Method for Dissolving Argatroban in Ethanol, Water, and a Saccharide**

207. Claim 1 of the '052 patent claims a "method" for dissolving argatroban. That method requires that the dissolution occur "in a solvent containing ethanol, water, and a saccharide." (DX 1 at Col. 6, ll. 39-40.) Claim 2 defines the saccharide to include sorbitol.

208. By the express terms of Claims 1 and 2, the solvent – i.e., the thing that dissolves the argatroban – must contain all three components of ethanol, water, and a saccharide. If the solvent does not contain all three of these components, then it does not fit within the scope of Claim 1 or 2. Thus, if a reference discloses argatroban dissolved in something other than a solvent containing all three of ethanol,

water, and a saccharide, it cannot anticipate the '052 patent. See Scripps Clinic, 927 F.2d at 1576 ("There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention."); see also Finisar, 523 F.3d at 1336. With respect to Claims 1 and 2, then, what is important is the method by which the argatroban was actually dissolved, not whether additional materials were subsequently added after the argatroban was already dissolved.

209. The Yamamoto reference states that the argatroban used in the experiment described in the reference was dissolved under hydrochloric acid acidity. This is consistent with the Cross translation of Yamamoto. A person of ordinary skill in the art at the relevant time, given how such solutions are normally prepared and the level of skill in the art at the relevant time, would have understood the Yamamoto reference to mean that the argatroban was dissolved in acid. (Tr. 1088:16-18, 1108:2-7, 22-1109:6; see also PX 257.)

210. Dissolution of argatroban in hydrochloric acid is consistent with the understanding of one of ordinary skill in the art that argatroban is a zwitterion, that zwitterions show markedly enhanced solubility at low pH, that the pH of 1.5 to 1.7 disclosed in Yamamoto is an extremely low pH, and that there would be no reason to use such a low pH in an argatroban

formulation if not for solubility purposes. (See supra; Tr. 1078:25-1079:3, 1079:15-21, 1119:16-21). It is also consistent with the fact that one of ordinary skill in the art would have expected that both ethanol and sorbitol would depress the solubility of argatroban, such that they would not be understood to be part of the solvent. (Tr. 1104:13-1108:7; see also PX 256.)

211. Dr. Needham's original interpretation of Yamamoto posited that argatroban was dissolved in a 7.5% D-sorbitol/4% ethanol solution, and then "some amount" of hydrochloric acid was added to "adjust pH" to 1.5 to 1.7. (Tr. 248:15-22.) However, as Dr. Needham admitted at his deposition and again at trial, it would not have been possible to obtain the concentrations in Yamamoto using his first theory. (Tr. 249:12-253:18; PX 258.)

212. When his first interpretation was shown to be scientifically implausible, Dr. Needham later proposed a second theory as to what Yamamoto discloses, namely, that the hydrochloric acid is what dissolved the argatroban. Under this new theory, the water, sorbitol, ethanol and argatroban would have only yielded "a suspension" with some of the argatroban dissolved, and then the hydrochloric acid was added to completely dissolve the argatroban. (Tr. 246:10-15, 330:18-331:16; PX 258.) This new theory requires nine steps to produce

the Yamamoto solution even though Yamamoto does not discuss multiple steps. (Tr. 1120:9-1121:21.)

213. Dr. Needham admitted that he could think of no reason to add hydrochloric acid to pH 1.5 to 1.7 prior to administration of the argatroban solution into rats other than for the purpose of aiding the dissolution of the argatroban. (Tr. 255:21-25, 246:10-15.)

214. As Dr. Byrn testified, it is customary in scientific literature for authors to state if the material involves making a suspension, but there is no reference to a suspension in Yamamoto. (Tr. 1120:21-1121:12.)

215. Claims 1 and 2 require that the solvent that dissolves argatroban contain all three components – ethanol, water and a saccharide – at the time the solvent dissolves the argatroban. In plain usage, this can only refer to complete dissolution, not a suspension. Dr. Needham's definition of "solvent" – namely, "a liquid capable of dissolving another material to form a solution" – does not refer to a suspension. (Tr. 95:9-11; DX 712.)

216. The fact that Dr. Needham admitted that his first theory was scientifically invalid detracts from his credibility. The fact that Yamamoto does not disclose any of the nine separate steps needed for his second theory also detracts from his credibility. (Tr. 244:25-245:6, 1121:19-21; PX 258.)

217. Dr. Needham also testified at trial that he had no idea how a person of ordinary skill in the art might have interpreted the phrase "under hydrochloric acid acidity," even though that phrase exists not just in the translation by Mr. Cross, but also in the translation by the defendants' expert, Mr. Aschmann. (Tr. 232:4-233:23; DX 802.) Yet to say that the argatroban was dissolved "under hydrochloric acid acidity" is consistent with a person of ordinary skill in the art's expectation that a zwitterion like argatroban would be dissolved in high acidity.

218. The Court credits the testimony of Mr. Nomura, Mr. Cross and Dr. Byrn that Yamamoto indicated that hydrochloric acid dissolved the argatroban, with ethanol and sorbitol added after the argatroban was already dissolved. (Tr. 1327:25–1328:2, 1088:16-18, 1108:22-1109:15; DX 11 at M 4503; see also PX 257.)

219. Finally, even if Dr. Needham's latest theory is given any weight, it would not render Yamamoto anticipating because, even under his revised theory Yamamoto does not complete dissolution of argatroban in water, ethanol, and sorbitol; the hydrochloric acid is necessary to achieve dissolution. (Tr. 245:25-246:15.) Yamamoto also does not disclose the nine steps described in Dr. Needham's new theory. (Tr. 1120:9-1121:21.)

220. The defendants' attempt to connect the '052 patent to Yamamoto is misplaced. Example 4 of the '052 patent describes dissolving argatroban by the patented method of dissolution with ethanol, water, and sorbitol. (DX 1 at Col. 5, ll. 48-54.) In other words, no acid was necessary to dissolve the argatroban. Then, that dissolved solution can be used for dialysis, after diluting it with acidic solution containing D-sorbitol. (DX 1 at Col. 5, ll. 55-57.) The solutions used in Yamamoto, as admitted by Dr. Needham, required acid in order to dissolve the argatroban. Moreover, the solutions used in the Yamamoto article were not for dialysis, but for study of rat brains. (Tr. 1102:23-24.) Dr. Needham admitted that using hydrochloric acid to bring a solution to a pH of 1.5 to 1.7 is not how the skilled artisan would expect to prepare a solution for dialysis. (Tr. 101:2-5.)[8]

[8] Dr. Needham's assertion that an internal Mitsubishi formulation of argatroban is "the same essential formulation" as what was used by the Yamamoto researchers is inappropriate. (Tr. 124:21; DX 82 at B-ARG-112657.) That internal formulation, even if it were the same, is non-public information and does not constitute prior art, and cannot form any part of an anticipation or obviousness analysis. (Tr. 1122:21-25.) See Cordis Corp. v. Boston Scientific Corp., 561 F.3d 1319, 1333-34 (Fed. Cir. 2009), cert. denied, 130 S. Ct. 748 (2009). What the Yamamoto article discloses must be assessed based on the disclosures in the article as understood by a person skilled in the art at the time and without reference to non-public documents that were not part of the prior art.

**ii. Yamamoto Was Not Enabling**

221. For Yamamoto to anticipate claims 1 and 2 would also require the disclosure in Yamamoto be sufficient to enable one skilled in the art to carry out the claimed invention. See, e.g., Transclean, 290 F.3d at 1370. In order to be enabling, the disclosure must provide a "reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Elan Pharms., 346 F.3d at 1055.

222. The single-sentence disclosure in Yamamoto would have confirmed the skilled artisan's expectation that a zwitterionic compound like argatroban would be readily soluble under acidic conditions. If anything, a formulator would have been guided by Yamamoto to dissolve argatroban by using hydrochloric acid. The small quantities of ethanol and sorbitol referenced in Yamamoto would have provided no reasonable guidance to the formulator, particularly in light of (a) the known tendency of acidic solvents to dissolve zwitterions, (b) the fact that sorbitol was not generally known at the time as a solubility enhancer, and (c) the fact that ethanol was known at the time to reduce the solubility of zwitterions.

223. Dr. Needham testified that Yamamoto would enable a formulator to make the disclosed solution, but his testimony on this point is not credible. Dr. Needham changed his original

theory, indicating that it was not immediately clear to him what process Yamamoto would direct a formulator to follow. Moreover, the theory Dr. Needham testified to at trial consisted of nine separate steps, none of which are explicitly disclosed in the single sentence of Yamamoto.[9] It is the defendants who bear the burden of proving by clear and convincing evidence that Yamamoto would enable one skilled in the art to produce the invention, and Dr. Needham's testimony does not meet this burden.

224. Thus, the single-sentence disclosure in Yamamoto would not have been sufficient to enable one of ordinary skill in the art to carry out the invention described in Claims 1 or 2 of the '052 patent.

225. The defendants have failed to prove by clear and convincing evidence that Yamamoto anticipated Claim 1 of the '052 patent.

[9] The defendants' argument that the '052 patent itself does not enable one skilled in the art to carry out the invention is incorrect. The specification of a valid patent must enable one skilled in the art to make and use the invention. See 35 U.S.C. § 112. Dr. Byrn testified that examples 4 and 5 of the '052 patent enable one skilled in the art to follow a series of steps to make and use the disclosed invention. (Tr. 1240:14-1241:24, 1244:21-1246:18; see also DX 1 at Col. 5, l.46-Col. 6, l.2.) Examples 4 and 5 of the specification detail quantities of each ingredient, the order in which the ingredients are mixed, and at what points heating and stirring should be used, as well as stating that the resulting solution may be used for either dialysis or drip infusion after appropriate dilution. (DX 1 at Col. 5, l.45-Col. 6, l.2.) While the standard for enablement under § 112 is higher than the level of enablement required to show anticipation under § 102, it is not the case that Yamamoto enables one of skill in the art to make the invention. See Verizon Servs. Corp. v. Cox Fibernet Virginia, Inc., 602 F.3d 1325, 1337 (Fed. Cir. 2010) (stating anticipation argument under § 102 does not require the utility or efficacy requirement of § 112). The Yamamoto article simply states what formula was injected into the rats, but does not discuss any of the nine steps described by Dr. Needham.

226. The defendants have failed to prove by clear and convincing evidence that Yamamoto anticipated Claim 2 of the '052 patent.

### 3. Yamamoto Did Not Anticipate Claims 3 and 4 of the '052 Patent

227. Yamamoto does not anticipate claims 3 and 4 unless Yamamoto discloses a pharmaceutical composition for injection comprising argatroban, water, ethanol, and a saccharide, and, for purposes of claim 4, the saccharide must be one of a group including sorbitol. As explained above, a "pharmaceutical composition for injection" is a composition that is suitable for treating medical conditions by injection.

#### i. Yamamoto Did Not Disclose a Pharmaceutical Composition for Injection Comprising Argatroban, Water, Ethanol, and a Saccharide

228. The experimental material used in Yamamoto is not a "pharmaceutical composition for injection" under this Court's claim construction—namely, a composition that is suitable for treating medical conditions by injection. According to Dr. Needham's own testimony, Yamamoto disclosed a solution that was

administered to laboratory rats at a pH of 1.5 to 1.7, prior to their being sacrificed. (Tr. 98:7-8.) This is an extremely low pH (Tr. 276:9-14), which is not acceptable for use in a medicine, and would not have been considered to be a pharmaceutical composition for injection as required by the claims of the '052 patent. (Tr. 1128:20-24.) Nor was the material intended to be a pharmaceutical composition because the rats were to be sacrificed as part of the experiment.

229. At the time of the invention, the generally acceptable pH range for parenterals was from about 3.0 to 10.5. (PX 107 at 155; Tr. 1130:4-7, 1131:5-15.)

230. The pH 1.5 to 1.7 in Yamamoto is something that a person of ordinary skill would not normally use for injection because, as Dr. Needham admitted, "it is rendering it less and less compatible with blood." (Tr. 255:14-20.) A parenteral administered at a pH below 3.0 can cause extreme pain and phlebitis, in addition to tissue damage. (Tr. 1132:8-10.) Because the pH scale is logarithmic, a solution at pH 1.5 (as in Yamamoto) is approximately thirty times more acidic than a solution at pH 3.0. (Tr. 276:15-18, 1132:16-21, 1135:6-14.)

231. If the Yamamoto material were diluted thirty fold, this would have reduced the concentration of argipidine by thirty-fold as well. (Tr. 1135:15-19.) The necessary dilution would have decreased the concentration of the Yamamoto material,

at its highest concentration, from 10 mg/mL to 0.33 mg/mL. (Tr. 1135:23-1136:7.) That would defeat the purpose of selecting a 10 mg/mL concentration, and the fact that Yamamoto reported results for 10 mg/mL, 5 mg/mL and 2.5 mg/mL shows that he did not dilute it. (The 5 mg/mL and 2.5 mg/mL concentrations used in Yamamoto would have been similarly reduced to 0.167 mg/mL and 0.08 mg/mL, respectively, by a thirty-fold dilution.) These diluted concentrations, however, are well below any effective dose. (Tr. 1135:9-15.) The defendants introduced no evidence demonstrating that the material in Yamamoto was in fact diluted to an acceptable pH, nor did they introduce evidence indicating how that would have been done, or that the argatroban would stay in solution after neutralization.

232. It is not surprising that the investigators in Yamamoto used such an unacceptably low pH, because they had no intention of "treating" the rats, or of giving them argatroban in the form of a "medicine." To the contrary, they knew that the rats were going to be sacrificed shortly after the argatroban test agent was administered. (Tr. 283:5-284:9, 282:22-283:4, 1403:25-1404:9, 492:5-10.) The pH at which the argatroban solution was administered to the rats in Yamamoto was not important. (Tr. 285:21-23.)

233. Based on pH, stability, and toxicity considerations, a person of ordinary skill in the art would have

known that one could not take the composition allegedly disclosed in Yamamoto and administer it for the treatment of any medical condition. (Tr. 1141:14-20; PX 107 at 155.)

234. Moreover, the defendants identified no intravenous drugs actually administered within the pH range referenced in the Yamamoto article. It was known in the art, for example, that the drug Flagyl could not be administered at its listed pH of 0.5-2.0, but rather had to be diluted and neutralized prior to administration. (Tr. 280:11-281:11; PX 172 at 1671 (stating "Flagyl I.V. cannot be given by direct intravenous injection (I.V. bolus) because of the low pH (0.5 to 2.0) of the reconstituted product. FLAGYL I.V. MUST BE FURTHER DILUTED AND NEUTRALIZED FOR I.V. INFUSION.") (emphasis in original).)

235. Dr. Needham also confirmed that the Yamamoto solution is approximately five times more acidic than even the most acidic drug product identified by the defendants (glycopyrrolate). (Tr. 278:1-5.)

**ii. Yamamoto Did Not Enable Claims 3 and 4 of the '052 Patent**

236. Testing for the safety and efficacy of a new compound is initially conducted on laboratory animals. There is

a long path – involving extensive experimentation and failure – between basic preclinical research through experiments on rats and a pharmaceutically acceptable product.

237. Two of the defendants' experts – Dr. Needham and Dr. Eby – testified that Yamamoto does not teach or describe the steps that one of ordinary skill in the art would need to follow in order to make the Yamamoto material a pharmaceutical composition suitable for injection. (Tr. 244:25-245:6, 493:10-14.)

238. Yamamoto provides no guidance as to how to proceed to develop a pharmaceutical composition for injection, and therefore is not enabling.

239. The defendants have failed to prove by clear and convincing evidence that Yamamoto anticipated Claim 3 of the '052 patent. (Tr. 1076:16-20.)

240. The defendants have failed to prove by clear and convincing evidence that Yamamoto anticipated Claim 4 of the '052 patent. (Tr. 1076:16-20.)

241. Therefore, the defendants have not met their burden of establishing by clear and convincing evidence that Yamamoto anticipated the '052 patent.

## IX. Obviousness

242. The defendants contend that each of claims 1 through 4 of the '052 patent are invalid pursuant to 35 U.S.C. § 103(a) as obvious.

### A. The Law of Obviousness

243. 35 U.S.C. § 103(a) ("§ 103") provides that:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

244. The Supreme Court has instructed that, in "determining whether the subject matter of a patent claim is obvious," what matters "is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 419 (2007). Obviousness is a conclusion of law based on underlying findings of fact. In re Kubin, 561 F.3d 1351, 1355 (Fed. Cir. 2009). The obviousness determination is based on factual determinations including the following: (1) the scope and content of the prior

art, (2) the differences between the prior art and the claims at issue, (3) the level of skill in the art, and (4) where relevant, objective evidence of nonobviousness, that is, the secondary considerations. KSR, 550 U.S. at 406; Graham v. John Deere Co., 383 U.S. 1, 17 (1966); see also Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535-39, 1541 (Fed. Cir. 1983).

245. The first three obviousness factors comprise the so-called prima facie case. Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1350 (Fed. Cir. 2000). The Supreme Court has directed courts to reject a "rigid approach" with respect to the prima facie case in favor of "an expansive and flexible approach," using common sense when assessing whether an invention would have been obvious to a person of ordinary skill in the art. KSR, 550 U.S. at 415-16.

246. As the Federal Circuit has held:

> If all the elements of an invention are found in a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

Velander v. Garner, 348 F.3d 1359, 1363 (Fed. Cir. 2003) (internal citation omitted); see also PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007).

247. The obviousness analysis requires an examination of the subject matter as a whole to ascertain if the claimed invention would have been obvious at the time the invention was made, that is, based on the "state of the art that existed at the time" the invention was made. Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1051 (Fed. Cir. 1988) (quoting Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138 (Fed. Cir. 1985)).

248. For the combination of two or more prior art elements to have been obvious to the skilled artisan, there must have been a reason at the time of the invention, in the prior art or otherwise, that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting KSR, 550 U.S. at 418). "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." In re Wesslau, 353 F.2d 238, 241 (C.C.P.A. 1965).

249. Courts assessing questions of obviousness must be extremely cautious of "distortion caused by hindsight bias" and of "arguments reliant upon ex post reasoning." KSR, 550 U.S. at

421; see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008) ("In retrospect, [the inventor's] pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted."). A proper obviousness analysis thus requires the recognition that the prior art, not hindsight knowledge of a patentee's success, must motivate a person skilled in the art to do what the patentee has done. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citing In re Rouffet, 149 F.3d 1350, 1357-58 (Fed. Cir. 1998)); Grain Processing Corp. v. Am. Maize-Prods. Co., 840 F.2d 902, 907 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'") (quoting Orthopedic Equip. Co. v. United States, 702 F.2d 1005, 1012 (Fed. Cir. 1983)).

250. Indeed, where the prior art "teaches away" from the claimed invention rather than motivating a person of ordinary skill in the art to do what the patentee has done, the claimed invention is nonobvious. In re Hedges, 783 F.2d 1038, 1041 (Fed. Cir. 1986); W.L. Gore & Assocs. v. Garlock, Inc., 721

F.2d 1540, 1552-53 (Fed. Cir. 1983). A reference "teaches away" if one skilled in the art, upon reading the reference, "would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

251. The Supreme Court has instructed that

> When there is a design need or market pressure to solve a problem and there is a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421. On the other hand, the Court of Appeals for the Federal Circuit has rejected a claim of obviousness when there are many, unpredictable solutions to a potential problem. Takeda, 492 F.3d at 1359 (citing KSR, 550 U.S. at 420.)

252. What a reference teaches, and whether it teaches toward or away from the claimed invention, is a question of fact addressed to a "person of ordinary skill in the art." In re Bell, 991 F.2d 781, 783-84 (Fed. Cir. 1993). The parties agreed on the definition of a person skilled in the art relevant to the '052 patent. (See supra ¶ 100.) Both the plaintiffs' expert,

Dr. Byrn, and the defendants' expert, Dr. Needham, were skilled in the art relevant to the '052 patent. However, Dr. Needham's opinions with respect to obviousness were impermissibly characterized by a hindsight search for nonobviousness rather than an objective view of the prior art.

253. The assessment of obviousness also requires examination of secondary objective evidence of nonobviousness. Such objective evidence, when present, must be considered and includes the extent of commercial success of the patented invention, unexpected properties of the invention compared to the prior art, whether the invention satisfies a long-felt need, whether others have failed to find a solution to the problem plaguing the art, and any copying of the invention by others. Graham, 383 U.S. at 17-18; see also Stratoflex, 713 F.2d at 1538-41.

254. Objective evidence is "often . . . the most probative and cogent evidence in the record." Stratoflex, 713 F.2d at 1538. "It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." Id. at 1538-39; see also Ruiz v. A.B. Chance Co., 234 F.3d 654, 667 (Fed. Cir. 2000).

255. "That each element in a claimed invention is old or unpatentable does not determine the nonobviousness of the claimed invention as a whole." Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 959 (Fed. Cir. 1986). "There is no basis in the law . . . for treating combinations of old elements differently in determining patentability." Id. (quoting Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1556 (Fed. Cir. 1985)) (alteration in original). "Casting an invention as 'a combination of old elements' leads improperly to an analysis of the claimed invention by the parts, not by the whole . . . . The critical inquiry is whether 'there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" Custom Accessories, 807 F.2d at 959 (quoting Fromson, 755 F.2d at 1556).

**1. The Defendants' Burden of Proof**

256. The defendants have the burden of proof with respect to obviousness. Once the patent challenger's prima facie case has been established, the burden shifts to the patentee to come forward with rebuttal evidence showing facts supporting nonobviousness. See WMS Gaming Inc. v. Int'l Game Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999). The party

asserting invalidity, however, always retains the burden of persuasion on the issue of obviousness until a final judgment is rendered. Each fact forming the factual foundation upon which the court bases its ultimate conclusion regarding the obviousness of the claimed subject matter as a whole must be established by clear and convincing evidence. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 291-92 (Fed. Cir. 1985) (internal citations omitted); see also Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1376, 1380 (Fed. Cir. 1986) (objective evidence must be considered before a conclusion on obviousness is reached and is not merely "icing on the cake").

257. The weight to which the objective evidence is entitled depends on its nature and its relationship to the merits of the invention. In re GPAC Inc., 57 F.3d 1573, 1580 (Fed. Cir. 1995); Ashland Oil, 776 F.2d at 306 n.42. For example, "[f]or objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." GPAC, 57 F.3d at 1580. "The term 'nexus' is often used, in this context, to designate a legally and factually sufficient connection between the proven success and the patented invention, such that the objective evidence should be considered in the determination of nonobviousness. The burden of proof as to this connection or

nexus resides with the patentee." Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1392 (Fed. Cir. 1988); Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1130 (Fed. Cir. 2000) ("[I]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus.").

**B. The Defendants' Prima Facie Case**

258. The defendants contend that several pieces of prior art rendered formulations of argatroban including ethanol, water and a saccharide (particularly sorbitol), as claimed in the '052 patent, obvious prior to the issuance of the patent. To determine whether the invention was obvious at the time the patent was issued, the Court applies an expansive and flexible approach, looking to the scope and context of the prior art compared to the claims at issue, and taking into account whether there was a reason at the time that would have prompted one skilled in the art to make the claimed composition or carry out the claimed process. The Court also considers whether one skilled in the art would have had a reasonable expectation of success in carrying out the invention. See KSR, 550 U.S. at 415-22; Takeda, 492 F.3d at 1356-57; Velander, 348 F.3d at 1363.

### 1. The Prior Art Provided No Basis for One Skilled in the Art to Create the Invention

259. The defendants do not rely on Yamamoto in support of their obviousness argument. Instead, the defendants rely on various prior art references that discuss argatroban, and prior art references that discuss solubility of zwitterions or amino acids in general.

#### i. Prior Art References Involving Argatroban

260. Kumada (DX 97): Kumada was a paper describing the potential effect of argatroban on cerebral infarction in rats. Kumada referenced a 50 mg/mL suspension of argatroban in water that was then dissolved by addition of concentrated hydrochloric acid. (Tr. 196:16-25.) Both Drs. Needham and Byrn testified that it was the addition of concentrated hydrochloric acid that dissolved the argatroban in Kumada. (Tr. 197:9-15, 1087:18-21.) This use of hydrochloric acid to dissolve argatroban is consistent with the expectation of one of ordinary skill in the art in 1987 or before that argatroban would exhibit enhanced solubility in acid. (Tr. 1088:4-9.)

261. Kumada is consistent with what was known regarding the solubility of zwitterions like argatroban in acid. (Tr. 1088:4-9, 1079:15-21.)

262. Matsui (DX 083A): Matsui described the use of argatroban for hemodialysis. Matsui referenced argatroban dissolved in an "acidic" or "low pH" ethanol solution. (DX 83A at B-ARG-112712-13.) Matsui does not mention water, sorbitol, or any other saccharide. Dr. Needham admitted at trial that acid was used in Matsui to dissolve the argatroban, a fact consistent with argatroban's zwitterionic nature. (Tr. 218:4-10.) Dr. Needham provided no scientific reason to indicate why a person of ordinary skill at the time would have thought that it was the ethanol (the amount of which was never disclosed in Matsui) that was responsible for dissolving the argatroban. (Tr. 1420:6-8, 1420:23-1421:1.)

263. European Patent '746 ("EP '746") (DX 466): EP '746 did not disclose any particular solutions of argatroban. It only disclosed the possibility that argatroban might be used for parenteral administration in the form of a sterile solution containing "sufficient saline or glucose to make the solution isotonic." (DX 466 at 17, ll. 21-22.)

264. '192 Patent (DX 51): Example 4 of the '192 patent referenced argatroban in water, glucose, and an unspecified "buffer system." (DX 51 at Col. 9, l. 48–Col. 10,

l. 8.) In view of the low solubility of argatroban at neutral pH, the example gives little information as to what undisclosed buffer system at what undisclosed concentration would be required to make the proposed dissolution take place, if at all. The '192 patent also states that argatroban may be administered with "pharmaceutically acceptable carriers" but does not explain which carriers, or identify any such "carriers" that can be used as solvents. (DX 51 at Col. 6, l. 1.)

265. As Dr. Needham acknowledged, the '192 patent says nothing about why glucose is used in Example 4. (Tr. 266:7-9.) The presence of glucose in the '192 patent is consistent with EP '746 and with the use of glucose for tonicity purposes. (Tr. 265:21-266:5.)

266. Use of glucose as a tonicity modifier is also consistent with the position taken by the applicant, and accepted by the examiner, during the prosecution of the '052 patent. (DX 3 at B-ARG-7214.)

**ii. One Skilled in the Art Would Not Have Been Motivated to Pursue the '052 Invention in View of the Prior Art Regarding Argatroban**

267. The primary category of prior art cited by the defendants consists of references which disclose the argatroban

compound but are not focused on argatroban's solubility or any particular methods of formulating argatroban (hereinafter, "argatroban references"). In fact, to the extent these references disclose anything about argatroban's solubility properties, they merely confirm that its solubility improves dramatically under acidic conditions. This is exactly what would have been expected by a person of ordinary skill in the art at the relevant time, because zwitterions like argatroban were known to show dramatic solubility improvements under acidic conditions. Furthermore, to the extent these references disclose anything about the use of sorbitol or other saccharides in conjunction with argatroban, they confirm that such additives are frequently used as tonicity modifiers, not as solvents. To the extent these references disclose anything about the use of ethanol in conjunction with argatroban, they do not suggest that ethanol is being used as a solvent.

268. Two of the argatroban references are Japanese papers describing the use of argatroban in biological experiments when dissolved under acidic conditions. Kumada described a suspension of argatroban in water (50 mg/ml) that was then solubilized by addition of concentrated hydrochloric acid. Matsui involved a "low pH" or "acidic" solution of argatroban. Kumada and Matsui both involve argatroban dissolved in an acidic medium, which is exactly what a person of ordinary

skill in the art would have expected in light of argatroban's known properties as a zwitterion. Far from rendering the ethanol-water-sorbitol combination claimed in the '052 patent obvious to a person of ordinary skill in the art, the Kumada and Matsui references would instead have taught away, providing strong motivation to use the known successful method of dissolving argatroban through the use of acid – specifically, hydrochloric acid. They provide no reason or motivation to do anything else.

269. The other two argatroban references cited by the defendants – the '192 patent and EP '746 – are compound patents, and do not discuss or disclose how to dissolve argatroban. EP '746, for example, does not even reference any particular solutions of argatroban. It merely notes the possibility that argatroban might be used for parenteral administration in the form of a sterile solution containing "sufficient saline or glucose to make the solution isotonic." The '192 patent is similar to EP '746 in that it references argatroban in a glucose solution of approximately 5%.

270. Both EP '746 and the '192 patent are missing at least a critical element, ethanol, of Claims 1-4 of the '052 patent. (Tr. 1263:16-21; DX 466.) The absence of ethanol in these references is consistent with the teaching that ethanol was known to decrease the solubility of zwitterions. (Tr.

219:18-25.) As even Dr. Needham acknowledged, the expectation in the prior art was that solubility of zwitterions is reduced by the addition of ethanol. (Tr. 229:6-15.) A person of ordinary skill in the art in 1987 would have expected that ethanol would decrease the solubility of argatroban, and thus would not have had reason or motivation to add it to water based on the disclosures in the '192 and EP '746 patents. (Tr. 1092:5-7.)

271. The disclosures in both the '192 patent and EP '746 are consistent with the common use of a small amount of glucose in injection solutions for tonicity purposes.

272. One of ordinary skill in the art would have known that ethanol decreased the solubility of those zwitterions in which it had been studied. (PX 103 at 248; PX 105 at 1511, Fig. 2; PX 111 at 566; Tr. 219:18-25, 1091:21-24.) Indeed, this general knowledge would have given the skilled artisan reason not to employ ethanol in the dissolution of argatroban, and so provides significant evidence that the '052 patent would not have been obvious to one of ordinary skill in the art from these references. In fact, Dr. Needham specifically testified that argatroban is the only zwitterion he is aware of having the distinct property of increased solubility in ethanol. (Tr. 220:1-11.)

273. Dr. Needham admitted that there was no information in the prior art regarding argatroban's solubility in ethanol, water, and any saccharide. (Tr. 214:10-215:1.) As Dr. Byrn testified, it was not known that ethanol or combinations of ethanol, water, and a saccharide would dissolve argatroban. (Tr. 1106:7-15, 1157:16-21.)

274. Therefore, in 1987 or before, these argatroban references would not have motivated one skilled in the art to dissolve argatroban in water, ethanol, and a saccharide. (Tr. 1077:2-1078:11.)

275. The defendants have not demonstrated that the prior art references regarding argatroban would clearly and convincingly have motivated a person of ordinary skill in the art to dissolve argatroban in an ethanol-water-saccharide solvent. To the contrary, the argatroban references teach away from the '052 patent because they suggest that argatroban can be dissolved under acidic conditions (as expected given argatroban's zwitterionic character) and that a saccharide might be used to adjust the tonicity of the final solution (as expected given the common use of saccharides like glucose and sorbitol as tonicity modifiers, but not as solvents).

**iii. Prior Art References Not Involving Argatroban**

276. The defendants also rely on several pieces of prior art that supply relevant information generally with respect to co-solvents.

277. Martin (DX 79): Martin is focused on nonelectrolytes and undissociated molecules, not zwitterions. (Tr. 224:3-8; see also PX 254.) Even if there were any expectation that ethanol might be useful for dissolving nonelectrolytes, argatroban is drastically different from nonelectrolytes. (Tr. 1148:1-6, 1150:23-1151:3.)

278. Krause (DX 18): Krause concerns the solubility of phenobarbital in ethanol-glycerin and ethanol-water-glycerin mixtures. Phenobarbital, however, is a markedly different molecule from argatroban. (Tr. 1149:22-24.) Dr. Byrn and Dr. Needham agree that phenobarbital is not a zwitterion like argatroban, does not share any other structural features with argatroban, and does not have similar biological activity. (Tr. 297:6-14, 1149:7-24, 1148:1-6; see also PX 255.) Phenobarbital contains no carboxylic acid, amine or sulfonamide groups. (Tr. 1149:7-24.) To a person of ordinary skill in the art, phenobarbital would not have been a pertinent reference compound for argatroban. In fact, Dr. Needham admitted that he could not

identify a single compound, other than phenobarbital itself, to which Krause would apply. (Tr. 341:19-346:6.) The only reason he relies on Krause or Martin is "[b]y the time you get down to this level of not being successful" you will try any possibility. (Tr. 343:15-21; PX 174 at 105:23-106:13.) Further, Dr. Needham testified that the person of skill in the art would have tried and failed in various other approaches before considering Martin or Krause. (Tr. 345:16-346:6; PX 174 at 105:23-106:13.)

279. The only connection between argatroban and phenobarbital is that both are poorly water soluble. (Tr. 296:13-297:25.) However, the highest solubility that Krause demonstrated for phenobarbital was a two solvent system, glycerin and ethanol, without water. (Tr. 299:1-7.) The highest solubility in the examples disclosed by Krause always involved only two solvents. (Tr. 299:8-11.) One of ordinary skill in the art, upon reading Krause, would not know whether a combination of three solvents would increase or decrease the solubility of argatroban because Krause did not provide any teaching in this respect. (Tr. 299:18-300:3.)

280. Sorby (DX 23, DX 25): The defendants rely on a single clause in Sorby stating that ethanol-water-saccharide systems are "common pharmaceutical solvent systems." (Tr. 152:13, 154:14.) However, various version of the Physician's

Desk Reference ("PDR") of drugs in the United States market showed only two out of two thousand drugs employed ethanol and a saccharide for any reason (Tr. 302:12-22) and none of them employed ethanol-water-sorbitol. (See Tr. 293:6-25.) The suggestion that these solvent systems are "common" is incorrect.

281. Wang (DX 45): Wang disclosed many commonly available solvents and solubilizers. Dr. Needham provided no reason for why ethanol-water-sorbitol (or even ethanol-water-saccharide) should be selected from this long list in the case of argatroban.

282. 1981 PDR (DX 46): The defendants also suggest that proof of the "commonness" of the ethanol-water-saccharide solvent system is found in the 1981 version of the PDR. The PDR is a treatise listing all FDA-approved pharmaceutical products, including injections. The 1981 PDR lists approximately two thousand different pharmaceutical products approved for use by the FDA. (Tr. 293:16-20; see also PX 106 (Foreword to 1981 PDR).) As explained in more detail below, there are only two listed drugs that used ethanol and a saccharide and these would not lead one skilled in the art to use ethanol and a saccharide as a solvent system for argatroban.

283. Dr. Needham acknowledged that the Sorby articles and other work done in the 1960s to try and come up with a predictive mechanism for co-solvents failed. (Tr. 213:4-10.)

One still has to go and try co-solvents in the lab. (Tr. 213:11-135.)

284. At the time of the invention, there were at least 50 "common" pharmaceutical solvents and solubilizers to choose from. The number of three solvent combinations (such as the one in the '052 patent) is about 19,600. The number of experiments required to test those combinations at differing relative ratios and pHs is in the millions. (Tr. 1152:15-1156:15; see also PX 269.)

**iv. One Skilled in the Art Would Not Have Been Motivated to Pursue the '052 Invention in View of the Other Prior Art**

285. None of these references concern argatroban, molecules similar to argatroban, or even zwitterions generally. Therefore, none provide any particular reason why a person of ordinary skill in the art would consider them useful in solving the problem of argatroban's solubility.

286. A person of ordinary skill in the art could not have predicted whether the solubility of any given compound would be increased or decreased by the use of co-solvents but, rather, such solubilities need to be empirically determined through multiple studies of the drug's solubility in water, the

drug's solubility at different pHs, and the drug's solubility in different co-solvents. (Tr. 65:7-66:3, 212:12-213:3.)

287. At the time of the invention, very little, if anything, was known in the prior art about argatroban's solubility properties other than that it would display a u-shaped solubility curve as a function of pH. (Tr. 214:7-216:198.) Nothing was known about its solubility in saccharides or ethanol. (Tr. 214:14-215:1.)

288. From 2,000 drugs in the 1981 PDR, Dr. Needham found two drugs containing water, ethanol, and glycerine with poorly water soluble active ingredients, namely, Cedilanid-D (deslanoside) and DHE 45 (dihydroergotamine mesylate). (Tr. 302:12-22, 306:20-307:3.) However, Dr. Needham admitted that both Cedilanid-D and DHE 45 are very dissimilar in structure from argatroban. Neither molecule is a zwitterion; neither molecule shares any other structural similarity with argatroban, and neither molecule has similar pharmacology to argatroban. (Tr. 304:23-305:13; see also PX 255.) Without the benefit of hindsight, there would have been no reason for a formulator to have considered the Cedilanid-D or DHE-45 formulations for insight into the solubility of argatroban. (Tr. 1150:23-1151:15.) With so many solvent possibilities to choose from, it is important that the defendants supply a "reason that would have prompted a person of ordinary skill in the relevant field

to combine the elements in the way the claimed new invention does." Takeda, 492 F.3d at 1356-57 (quoting KSR, 550 U.S. at 418). Yet Dr. Needham provided no coherent reason why, in the case of argatroban, ethanol-water-sorbitol (or even ethanol-water-saccharide) would have been selected from the long list of solvent possibilities.

289. Moreover, nothing in the PDR entries for Cedilanid D and DHE-45 indicate what role is played by the ethanol or the glycerin listed in the formulations for those compounds. (Tr. 303:3-6, 305:18-22.) Even if a person of ordinary skill in the art looked at the 1981 PDR listings for either Cedilanid-D or DHE-45 in relation to argatroban, it would not have been obvious that it was the tripartite combination of ethanol, water and glycerin that was responsible for the drug's dissolution (and not citric acid or sodium phosphate in the case of Cedilanid-D, or methanesulfonic acid/sodium hydroxide in the case of DHE-45).

290. Pharmaceutical companies work very hard to put together formulations and are protective of their know-how. Thus, in the Physician's Desk Reference, the companies do not disclose to the reader what the function of each ingredient in a formulation is, nor are they required to do so. (Tr. 308:10-25, 1109:25-1110:3.) Dr. Byrn explained that this makes sense for

various reasons, including the fact that most manufacturers want to keep this information confidential. (Tr. 1110:7-15.)

291. It is hindsight for Dr. Needham to suggest that the ethanol and glycerin listed in conjunction with the Cedilanid-D and DHE 45 injections would have been known to be acting as "solvents." (Tr. 303:3-6, 305:18-22.) Dr. Needham did not look through the 1981 PDR – and its thousands of listed pharmaceuticals – in any systematic way. This suggests that he selected them simply because he believed they supported his theory. Dr. Needham admitted that in the case of Pantopon, ethanol and glycerin (a saccharide) are listed in conjunction with a drug that is explicitly stated to be water soluble, and therefore the ethanol and glycerin would not be solvents in Pantopon. (PX 173; Tr. 307:4-308:14.)

292. Dr. Needham acknowledged that there is no teaching or mention for the use of ethanol or sorbitol as solvents in injectables in the Handbook of Pharmaceutical Excipients from 1986 ("the Handbook"). (DX 95; DX 94; Tr. 291:24-25, 293:3-5.) The Handbook provides information regarding the applications of excipients in pharmaceutical formulations (Tr. 291:1-4) but fails to list ethanol or sorbitol as solvents for injectables. (Tr. 291:17-25; 293:3-5; DX 94; DX 95.)

293. Dr. Needham admitted that a person of ordinary skill in the art who was interested in making a pharmaceutical composition for injection would generally minimize the amount of alcohol in the injection, because "alcohol-based injections can cause pain, irritation, and tissue damage." (Tr. 1137:23-1138:4.) Dr. Byrn agreed. (Tr. 1138:7-1139:3.) It was known in the art at the time of the invention that ethanol was not common in injectable formulations. (Tr. 1137:15-17; PX 104 at B-ARG-8150.)

294. There was no motivation for a person of ordinary skill in the art to add ethanol to an argatroban solution in the first place. (Tr. 1140:17-21.) As Dr. Byrn testified, it was not known that ethanol or combinations of ethanol, water, and a saccharide would dissolve argatroban. (Tr. 1106:7-15, 1157:16-21.) Instead, ethanol was expected to decrease the solubility of argatroban, as it does for other zwitterions. (Tr. 1092:5-7.) Sorbitol, being less polar than water, would also have been expected to reduce argatroban's aqueous solubility. (Tr. 1100:2-1102:5.) Zwitterions were known to exhibit reduced solubility in co-solvents that are less polar than water, such as ethanol or saccharides (including sorbitol). (Tr. 294:1-16, 296:3-6; PX 103 at 248; PX 105, at Fig. 2; PX 111 at 566.)

295. A person of ordinary skill in the art would have no reason or motivation to try an ethanol-water-sorbitol mixture as a solvent system for argatroban.

296. Dr. Needham conceded that a person of ordinary skill in the art would have had "no idea" which solubility techniques might be successful in the case of a poorly water soluble drug like argatroban. (Tr. 299:24-25, 322:7-8.) Indeed, even today, "our scientific understanding of exactly what happens with co-solvent systems is less than perfect, so a lot of times you try a lot of different things . . . ." (Tr. 323:6-9.)

297. The defendants' argument – based on the solubility of structurally dissimilar compounds – is analogous to one that was made and rejected in In re Brimonidine Patent Litig., 666 F. Supp. 2d 429 (D. Del. 2009). There, the defendants pointed to the solubilizing properties of carboxymethylcellulose, a polyanionic solubility component, to suggest that it would have been obvious to use carboxymethylcellulose as a solubilizer for brimonidine (the active component of the drug at issue in the case). Id. at 442. However, the court found that none of the compounds whose solubility was aided by carboxymethylcellulose were "even in the same drug class as brimonidine," and thus the court found no persuasive reason why a person of ordinary skill in the art

"would have expected [carboxymethylcellulose] to increase the solubility of brimonidine." Id. at 443.

298. There would have been no motivation for a person of ordinary skill in the art to add ethanol to an argatroban solution in the first place. As early as 1936, it was reported that the aqueous solubility of all naturally occurring amino acids (all of which are zwitterions) decreases upon addition of ethanol. (PX 103 at 248.) In a 1971 paper, Dr. Needham himself confirmed this trend regarding zwitterionic amino acids in ethanol-water systems. (PX 111 at 566; Tr. 219:18-20.) And a 1969 paper showed that several non-amino acid zwitterions of similar size to argatroban (ampicillin and its derivatives) showed reduced solubility in ethanol-water systems over water alone. (PX 105 at 1511; Tr. 219:21-25.) This is a classic example of "teaching away." In re Gurley, 27 F.3d at 553. As of today, argatroban is the only zwitterions that exhibits increased solubility in ethanol and this was not known prior to the issuance of the '052 patent. (Tr. 220:1-13.)

299. The defendants have not demonstrated by clear and convincing evidence that the prior art regarding the many solvents that could be used to formulate solutions for injection would have motivated a person of ordinary skill in the art to dissolve argatroban in the water-ethanol-saccharide solvent of

the ‘052 patented invention or formulate a pharmaceutical composition comprising such components.

**2. A Person Skilled in the Art Would Have Had No Reasonable Expectation of Success Prior to the Issuance of the ‘052 Patent**

300. A person of ordinary skill in the art would have had no reasonable expectation that the addition of ethanol and a saccharide would have increased the solubility of argatroban. Instead, a person of skill in the art would have expected ethanol and saccharides to depress the solubility of argatroban.

**i. The Claimed Inventions of the ‘052 Patent Would Not Have Been Obvious in View of the Prior Art in 1987**

301. Dr. Needham admitted that a person of ordinary skill in the art at the time of the invention who was interested in making a pharmaceutical composition for injection would have known that alcohol-based injections can cause pain, irritation, and tissue damage. Given the known problems with using ethanol in solutions for injection, and given the known propensity for ethanol to decrease the solubility of zwitterions, there would

have been no "reasonable expectation of success" in adding ethanol to an argatroban solution. See Velander, 348 F.3d at 1363.

302. Dr. Byrn testified credibly that claims 1-4 in the '052 patent were not obvious to a person of ordinary skill in the art in 1987, or before, that a person of ordinary skill in the art would have had no reason or motivation to dissolve argatroban in a solvent containing water, ethanol, and a saccharide or to formulate a pharmaceutical composition for injection using those ingredients, and would not have had a reasonable expectation of success that the person could make that solution or formulate that pharmaceutical composition. (Tr. 1077:2-25, 1078:1-10.)

303. The defendants have failed to prove by clear and convincing evidence that Claim 1 of the '052 patent was obvious.

304. The defendants have failed to prove by clear and convincing evidence that Claim 2 of the '052 patent was obvious.

305. The defendants have failed to prove by clear and convincing evidence that Claim 3 of the '052 patent was obvious.

306. The defendants have failed to prove by clear and convincing evidence that Claim 4 of the '052 patent was obvious.

**C. Secondary Considerations**

307. Moreover, the plaintiffs have presented sufficient objective evidence of nonobviousness to prove that the claims in the ‘052 patent were not obvious in 1987 or before.

308. The objective evidence of nonobviousness or secondary considerations includes but is not limited to the commercial success of the patented invention, unexpected properties of the invention compared to the prior art, whether the invention satisfies a long-felt need, whether others have failed to find a solution to the problem, and copying of the invention. Graham, 383 U.S. at 17-18; Stratoflex, 713 F.2d at 1538-41.

**1. Commercial Success**

309. Under 35 U.S.C. § 282, a patent is presumed valid and the burden is on the challenger to show by clear and convincing evidence the facts leading to a conclusion of invalidity for the claims at issue. Am. Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1360 (Fed. Cir. 1984); see also Rockwell Int’l Corp. v. United States, 147 F.3d 1358, 1364 (Fed. Cir. 1998) (“Throughout the obviousness determination, a

patent retains its statutory presumption of validity, see 35 U.S.C. § 282, and the movant retains the burden to show the invalidity of the claims by clear and convincing evidence as to underlying facts.").

310. Commercial success is a key secondary consideration that must be considered in an obviousness inquiry. See Stratoflex, 713 F.2d at 1538 ("[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not."). The Court of Appeals for the Federal Circuit has consistently reaffirmed the importance of the commercial success inquiry. See Süd-Chemie, Inc. v. Multisorb Techs., Inc., 554 F.3d 1001, 1008 (Fed. Cir. 2009) ("As we have repeatedly emphasized, evidence relating to secondary considerations 'constitutes independent evidence of nonobviousness' and can be quite instructive in the obviousness inquiry.").

311. Commercial success of an invention is significant evidence that the invention would not have been obvious and it should be given great weight. See Goodyear Tire & Rubber Co. v. Ray-O-Vac Co., 321 U.S. 275, 279, (1944); Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573-74 (Fed. Cir. 1996); Demaco, 851 F.2d at 1391 (citing Graham, 383 U.S. at 35-36). Commercial success of an invention is "objective evidence

of how the patented device is viewed in the marketplace, by those directly interested in the product." Demaco, 851 F.2d at 1391.

312. "For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." GPAC, 57 F.3d at 1580. A nexus is "a legally and factually sufficient connection between the proven success and the patented invention, such that the objective evidence should be considered in the determination of nonobviousness." Demaco, 851 F.2d at 1392.

313. The patentee bears the initial burden of coming forward with evidence sufficient to constitute a prima facie case of the requisite nexus. See id. There is a presumption of nexus when a patentee can demonstrate "significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 417 F. Supp. 2d 341, 371 (S.D.N.Y. 2006), aff'd, 492 F.3d 1350 (Fed. Cir. 2007) (citation and internal quotation omitted). However, a nexus is presumed only if the marketed product "embodies the claimed features" and "is coextensive with them." Brown & Williamson, 229 F.3d at 1130. A successful product is "coextensive" with the patented invention when it is commensurate in scope with the patented

invention, as opposed to when the patented invention is "only a component of a commercially successful machine or process." Demaco, 851 F.2d at 1392. The law does not require the patentee to prove such a relationship is the sole basis of the commercial success. Ecolochem, Inc. v. S. Ca. Edison Co., 227 F.3d 1361, 1378 (Fed. Cir. 2000) (finding nexus where commercial success could be attributed to the patented invention in addition to non-patented factor); see also Demaco, 851 F.2d at 1394 ("A patentee is not required to prove as part of its prima facie case that the commercial success of the patented invention is not due to factors other than the patented invention.").

314. Once the patentee makes the requisite prima facie showing of nexus, the burden shifts to the alleged infringer to rebut the presumption of commercial success by proving that the success was due to extraneous factors such as advertising or superior workmanship. Demaco; 851 F.2d at 1393.

**i. Argatroban Injection Has Significant Sales**

315. Argatroban Injection is a successful product in terms of its sales, sales growth and market share. Argatroban Injection's net sales in the United States have grown from $10.8 million in 2001, the first full year after its launch, to $107.4 million in 2007, equal to a compound annual growth rate of 47%.

(Tr. 1280:10-11; PX 270; PX 271.) Through the month of May in 2008, the annualized U.S. net sales were $128.2 million, demonstrating continued growth of approximately 20% compared to 2007. (Tr. 1279:25-1280:2, 11-18; PX 270; PX 271.)

316. Argatroban Injection has competed successfully against the other DTIs, Refludan® and Angiomax®, and Argatroban Injection's sales in the HIT market greatly exceed those of both Refludan® and Angiomax®. (Tr. 632:21-633:5.) The defendants' economic expert Dr. Sumanth Addanki acknowledged that Argatroban Injection has overtaken Refludan's ® sales since the FDA approval of Argatroban Injection in 2000 despite Refludan's ® earlier market entry date. (Tr. 663:4-11.) As of 2008, Argatroban Injection had an 80% market share of the non-PCI HIT market while only the remaining 20% went to Refludan®. (Tr. 1281:20-25, 1297:15-20.) Angiomax's® market share in the non-PCI HIT market is de minimus. (Tr. 635:9-15.)

### ii. **Argatroban Injection Embodies the Invention of the '052 Patent**

317. Argatroban Injection is on the market because of the patented invention. The claimed invention is not a part that can be separated out from the remainder of the product. The formulation is an inextricable and essential part of what

doctors are prescribing. The formulation is not a segregable component, such as a particular type of O-ring seal integrated into a drill bit bearing. The product itself would not exist without the claimed invention, and therefore there is a nexus between the commercial success of Argatroban Injection and the patented invention.

318. Argatroban Injection embodies the claimed invention. The ‘052 patent claims, among other things, a pharmaceutical composition comprising argatroban together with ethanol, water, and a saccharide, as well as a method of dissolving argatroban. The formulation that results from practicing the claimed invention comprises four elements: argatroban, ethanol, water and a saccharide. Every claim in the patent requires each element, and each element is linked to the invention as a whole.

319. The defendants argue that, because argatroban itself is no longer patented, Argatroban Injection is not coextensive with the patented invention. Without any of the individual components of Argatroban Injection (argatroban, ethanol, water and a saccharide) there is no dissolution of the compound and no embodiments of the ‘052 patent can exist. Similarly, the Argatroban Injection cannot exist if any of those elements (argatroban, ethanol, water and a saccharide) is missing. It is the formulation as a whole that is both the

patented invention and the successful commercial product, Argatroban Injection.

320. The defendants contend that it is the unpatented argatroban in Argatroban Injection that is responsible for its commercial success. This case demonstrates why the law provides a presumption of a nexus after it has been shown that the product embodies the claimed features and is coextensive with them. Demaco, 851 F.2d at 1394 ("A requirement for proof of the negative of all imaginable contributing factors would be unfairly burdensome, and contrary to the ordinary rules of evidence."). Otherwise, a proponent of commercial success could be forced to disprove a negative. (Tr. 665:9-13.) Moreover, it is not necessary for the plaintiffs to prove that the success of Argatroban Injection is unrelated to its constituent parts, including the argatroban molecule. "It is not necessary . . . that the patented invention be solely responsible for the commercial success, in order for this factor to be given weight appropriate to the evidence, along with other pertinent factors." Cont'l Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1273 (Fed. Cir. 1991) (citing Demaco, 851 F.2d at 1392-94).

321. The evidence in this case demonstrates that there is a nexus between the commercial success of Argatroban Injection and the inventions of the '052 patent. The inventions

claimed in the '052 patent enable Argatroban Injection to be administered at the high concentration of 1.0 mg/mL, thereby minimizing fluid loads on patients when compared to lower concentration formulations in different solvent systems. (Tr. 827:1-12, 1282:9-14.) There is no evidence that a lower concentration would be a successful product in the United States. As Dr. Lewis explained, the high concentration is highly valued by physicians prescribing Argatroban Injection. (Tr. 827:7-17.) Dr. Gregory K. Bell, the plaintiffs' economic expert, explained that is a significant factor in evaluating commercial success. (Tr. 1284:2-10.) Additionally, the '052 patent enables Argatroban Injection to be manufactured, transported and stored at a concentration of 100 mg/mL. (Tr. 1282:18-20.) As a result, Argatroban Injection conserves space in hospital pharmacies, allows better product management with respect to waste, allows the product to be diluted to different strengths, and allows for the use of different diluents. (Tr. 1282:18-24.) It also eliminates the need for time consuming manipulations of ampoules and the associated risks of glass shards. (Tr. 1341:1-1343:23, 1347:8-14; PX 200 at 47:23-48:23, 49:12-50:1.) The decrease in fluid volume to be administered to patients and the logistical benefits of the high concentration formulation are reasons the ARG 911 clinical trials were changed to use the high concentration formula. (Tr. 810:3-17.)

322. A low 0.5 mg/mL concentration argatroban formulation existed in Japan prior to the approval of Argatroban Injection in the United States. This Japanese formulation does not infringe the '052 patent. (Tr. 199:13-18.)

323. The trial evidence shows that the ability to administer Argatroban Injection at the 1.0 mg/mL concentration provides a clinical advantage over both the non-patented 0.5 mg/ml argatroban formulation and Refludan® and has contributed to the success of Argatroban Injection's acceptance by physicians. (Tr. 760:4-8.) The relative amount of fluid required to administer the Japanese 0.5 mg/mL formulation is double that required to administer the patented 1.0 mg/mL Argatroban Injection. (Tr. 398:24-399:4, 761:22-762:5.) According to the recommended dosing in the FDA-approved package inserts, it also takes more fluid to administer Refludan® (the most direct competitor of Argatroban Injection in terms of approved indications) over 24 hours than to deliver Argatroban Injection. (Tr. 384:2-4.) Dr. Eby acknowledged that fluid volume is an advantage of Argatroban Injection over Refludan®, although Dr. Eby is of the opinion that fluid load is an advantage for either concentration of argatroban over Refludan®. (Tr. 384:2-6.)

324. The clinical profile of Argatroban Injection encompasses, among other things, the way the product is used, the types of patients in whom it is used, the reasons physicians

use it, and the ease of use from the pharmacy's perspective. (Tr. 1282:20-1283:7, 1300:12-16.) This clinical profile is enabled by the '052 patent and the evidence established that it is the one of the primary reasons for the product's acceptance in the United States market. (Tr. 1282:6-1283:7.)

325. Dr. Eby could think of no reason not to take advantage of a drug that ultimately reduces the total amount of fluid that the patient receives. (Tr. 479:15-18.) In fact, Dr. Eby testified that if a 2.0 mg/mL formulation were available, he would prefer that formulation. (Tr. 479:12.) As Dr. Lewis testified, if the 0.5 mg/mL formulation was available in the United States he would not prescribe it, and neither would clinicians in general. (Tr. 828:3-11.) This testimony shows that the commercial success of Argatroban Injection is intertwined with the higher concentration formulation enabled by the '052 patent and is not dependent solely on the argatroban molecule. Indeed it is clear that if another manufacturer attempted to market a 0.5 mg/mL formulation of argatroban in the United States, Argatroban Injection would prevail over that product because clinicians would prefer the higher concentration.

326. There is no evidence that the low-concentration non-patented solution of argatroban would achieve substantially the same level of sales as the high-concentration Argatroban

Injection. The low dose Japanese product is used with a very different patient population that requires different dosage levels. (Tr. 671:3-12.)

327. The defendants' expert Dr. Addanki acknowledged that the Japanese recommended dose for the treatment of HIT is approximately one third the recommended dose in the United States. (Tr. 671:3-14.) A clinical trial in Japan using the United States dosage of argatroban caused serious bleeding problems in a number of patients. (PX 96; Tr. 672:21-674:23.)

328. Moreover, the low concentration formulation has not been used in or been established as safe and effective in clinical treatment in the United States. Dr. Addanki admitted that he has seen no evidence that the Japanese formulation would have been approved for treatment of HIT in the United States. (Tr. 676:10-13.) Additionally, Dr. Addanki could not provide any opinion of his own as to whether the Japanese formulation could be safely used in the patient population in the United States. (Tr. 676:14-17.)

329. The defendants have not presented any evidence to show that doctors would prescribe the 0.5 mg/mL formulation in the same circumstances in which they prescribed the 1.0 mg/mL formulation of Argatroban Injection. On the contrary, the evidence demonstrates that there is a clear clinical advantage

to the higher concentration 1.0 mg/mL formulation of Argatroban Injection over both the 0.5 mg/mL formulation and Refludan®.

330. Until the invention of the '052 patent and the approval of the formulation that embodies that invention, there was no approved formulation for administration to patients in the United States. Dr. Addanki acknowledged that at any time between the expiration of the '192 patent and the 2000 FDA approval of Argatroban Injection, pharmaceutical companies were free to develop a whole host of formulations related to argatroban. (Tr. 690:22-691:1.) However, no FDA-approved product came to market during that period. (Tr. 691:7-9.)

331. Moreover, the five-year new chemical entity exclusivity for Argatroban Injection expired on June 30, 2005. Therefore, there has been no patent or regulatory impediment to anyone making a 0.5 mg/mL argatroban product in the United States which does not infringe the '052 patent. (Tr. 1284:11-14.) If another pharmaceutical manufacturer believed that a low-concentration argatroban product would be a success in the marketplace, then it could have launched a low-concentration product. (Tr. 1285:4-11.)

332. No pharmaceutical manufacturer has attempted to introduce a low-concentration or non-infringing 0.5 mg/mL argatroban product. Both SciDose LLC/Eagle Pharmaceuticals,

Inc. and Baxter International, Inc. have been trying to develop their own allegedly non-infringing formulations of argatroban to be administered at a concentration of 1.0 mg/mL, and not 0.5 mg/ml. (PX 29 at GSK375980, GSK375982-GSK375983; Tr. 705:3-16, 1286:9-1287:4.) That no pharmaceutical manufacturer has pursued a non-infringing lower concentration formulation reveals the widespread belief in the value of a high-concentration product, and tends to show that the commercial success of Argatroban Injection is due to the high concentration enabled by the '052 patent rather than simply the active ingredient. The active ingredient argatroban could have been produced in a 0.5 mg/mL concentration even prior to the issuance of the '052 patent, without the need to conduct extensive testing to discover a method for creating a higher concentration.

333. As Dr. Bell explained, the difference in value between the 1.0 mg/mL high concentration Argatroban Injection enabled by the '052 patent and a potential 0.5 mg/mL low concentration product is "probably fairly substantial, because nobody has chosen to launch a [0].5 [mg/Ml] concentration." (Tr. 1300:21-1301:6.) Dr. Bell testified that the absence of an attempt by the defendants or other generic pharmaceutical manufacturers to launch a 0.5 mg/mL concentration of argatroban, demonstrates an inextricable link between the practice of the

'052 patent and the commercial success of Argatroban Injection in the United States. (Tr. 1285:11-1286:1.)

334. The defendants suggest that because the 1.0 mg/mL concentration enabled by the '052 patent is not a focus of GSK's marketing efforts, there is no nexus. (Tr. 1295:9-12.) However, the 1.0 mg/mL concentration of Argatroban Injection is evident on the labeling of the product and the package insert. (Tr. 1295:14-15.) Moreover, there is no 0.5 mg/mL product available against which GSK could have marketed the patented formulation to indicate that Argatroban Injection is more concentrated and does a better job managing fluid load. (Tr. 1295:17-25.)

**iii. The Plaintiffs Are Entitled to a Presumption of Nexus Between the Commercial Success of Argatroban Injection and the '052 Patent**

335. The defendants do not dispute the commercial success of Argatroban Injection. (Tr. 661:14-662:15.) Because the plaintiffs have shown that Argatroban Injection has significant sales and embodies the claimed invention, the plaintiffs are entitled to a presumption of a nexus between the commercial success of Argatroban Injection and the invention of the '052 patent. See Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d

714, 719 (Fed. Cir. 1991) ("[P]rima facie evidence of nexus is established if there was commercial success and if the invention disclosed in the patent was that which was commercially successful.").

336. Argatroban Injection enjoys commercial success, and it is entitled to the presumption of a nexus to the patented invention.

**iv. The Defendants Have Not Overcome the Presumption of Nexus**

337. Even without a presumption of nexus, the plaintiffs have demonstrated a legally and factually sufficient connection between the proven success of Argatroban Injection and the patented invention, including its superior clinical profile and reduced fluid load. See Demaco, 851 F.2d at 1392. Practical advantages like conserving storage space, reducing product waste, and diluent flexibility further demonstrate a nexus between the patented invention and the success of Argatroban Injection.

338. The defendants have failed to meet their burden of proving that the success of Argatroban Injection is due to any segregable unpatented product features or to extraneous factors such as advertising or marketing. Brown & Williamson,

229 F.3d at 1130 ("The presumed nexus cannot be rebutted with mere argument; evidence must be put forth."); Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 679 (Fed. Cir. 1988) (holding that the challenger failed to rebut the prima facie case of nexus where there was no evidence of extraneous factors, such as advertising or superior workmanship, to rebut the patentee's evidence of substantial commercial success and sales growth of the patented product).

339. The plaintiffs have established the nexus between the commercial success of Argatroban Injection and the claimed invention and this factor weighs in favor of the plaintiffs.

**2. Unexpected Results**

340. Unexpected superior properties from an invention support the conclusion that the invention was not obvious to one of ordinary skill in the art. As the Court of Appeals for the Federal Circuit has explained, "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (quoting In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995)).

341. In order for a showing of unexpected results to be probative of nonobviousness, such evidence must at least

establish that: (1) there is a difference between the results obtained and those of the closest prior art, and (2) the difference would not have been expected by one skilled in the art at the time of the invention. In re Freeman, 474 F.2d 1318, 1324 (C.C.P.A. 1973). "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991) (internal citation omitted).

342. Figures 3 and 4 of the '052 patent depict the high solubility of argatroban in ethanol-water-sorbitol and ethanol-water-saccharide solvents (including sorbitol, glucose, glycerin and glycerin). (DX 1 at Figs. 3-4.) These solubilities are in the hundreds of milligrams per milliliter, vastly in excess of the solubilities shown in Figures 1 and 2 for argatroban in water alone (approximately 1.0 mg/mL) or ethanol alone (approximately 4 mg/mL), or even for argatroban in water-sorbitol or water-ethanol binary mixtures (approximately 1.0 mg/mL and 30 mg/mL, respectively). (DX 1 at Figs. 1-2.) The fact that a mixture of these three components can greatly increase the solubility of argatroban is unexpected. This is especially true given the expectation that the addition of ethanol to water would reduce the solubility of a zwitterion. Dr. Needham conceded that the results displayed in Figures 3 and

4 of the ‘052 patent were surprising and unexpected. (Tr. 310:19-311:8.) Further, the defendants’ ANDA application reported that the addition of sorbitol to various mixtures of ethanol and water “significantly enhanc[ed]” the solubility of argatroban. (PX 44 at B-ARG-223.)

343. Dr. Timothy P. Kogan, a chemist for TBC, who previously worked at Genentech, who knew the work of both companies, and who studied the ethanol-water-saccharide formulations in comparison with alternative formulations, described the argatroban ethanol-water-sorbitol mixture claimed by the ‘052 patent as an “extremely surprising result.” (PX 22 at ENCY 262046-47; Tr. 316:9-14.) Dr. Needham agreed with this assessment. (Tr. 316:15-16.) As Dr. Byrn testified, the data in the ‘052 patent is “completely unbelievable.” (Tr. 1162:3-6.)

344. It is also surprising that even at low amounts of ethanol and sorbitol, the solubility of argatroban is greater than would have been expected by a person of ordinary skill in the art at the time of the invention. For example, Dr. Needham admitted that Figure 2 of the patent is consistent with the expectation that a non-polar molecule such as sorbitol would reduce the aqueous solubility of argatroban. (Tr. 295:21-296:6.) Unexpectedly, however, in conjunction with ethanol and

water, sorbitol greatly increases the solubility of argatroban in water.

345. The same is true with respect to ethanol. Dr. Needham admitted that argatroban is the only zwitterion he knows of whose solubility is increased upon addition of ethanol. (Tr. 220:1-18.) This is consistent with Dr. Byrn's testimony that any increase in argatroban's solubility over that in water alone would have been unexpected. (Tr. 1260:20-24.)

346. The defendants argue that these unexpected results are not commensurate in scope with the claims because they do not pertain throughout the solubility curve.[10] As Dr. Byrn explained, this is incorrect. Given what was known in the prior art, the expectation would have been that mixing ethanol and sorbitol with water would reduce the solubility of a polar zwitterion such as argatroban. (Tr. 1156:16-1158:5; PX 266.) The opposite is true. Solubility increases at every point along the solubility curve. The entire direction in which solubility moved (i.e., above that of water alone, rather than below it) was itself unexpected. Therefore, every result was unexpected. (Tr. 1158:6-1162:8; PX 265; PX 250.)

[10] Barr also makes a comparison to Kumada's 50 mg/mL solubility. That is an inappropriate comparison because Kumada was under acidic – not neutral – conditions. (Tr. 1158:6-1158:22.)

**3. Long-Felt Need**

347. Evidence of a long-felt but unresolved need in the industry for the solution offered by the patented invention supports a finding that the invention was not obvious at the time it was made. See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 884 (Fed. Cir. 1998).

348. "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." Texas Instruments, Inc. v. United States Int'l Trade Comm'n, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

349. There existed a long-felt need for a safe and effective treatment for HIT before Argatroban Injection became available. Dr. Lewis testified about the long-felt unmet need for a HIT therapy (Tr. 787:1-2) and the defendants' expert Dr. Addanki also recognized the lack of available treatments for HIT.

350. The previous alternatives for treating HIT proved unsuccessful in view of the fact that thrombotic event rates remained high in these patients together with the various disadvantages associated with these agents. (Tr. 778:10-785:18.) Dr. Eby acknowledged that he personally had observed a need within the medical community for new ways to treat HIT. (Tr. 450:1-5.)

351. The high concentration formulation Argatroban Injection satisfied the previously long-felt but unmet need in the HIT patient population for an effective treatment for HIT that would significantly reduce the infusion volume otherwise required during treatment, by allowing a clinically significant reduction in obligatory infusion volume during treatment. (Tr. 760:9-18, 787:1-2, 827:12-17; PX 23.)

352. In addition to patients who are subject to fluid restrictions, there is concern about the volume of infusion in all patients with HIT because of inflammation and concentration of HIT antibody at sites of injury in veins. Moreover, physicians worry about the integrity of veins whenever they violate or injure a vein by IV, surgery, or blunt bruising during surgery, any of which can provoke an immune response to the affected area. (Tr. 834:20-835:1.) As a consequence, the affected veins tend to be weaker and cannot hold fluid quite as well as compared to non-HIT patients. (Tr. 835:1-3.) Accordingly, all patients with HIT benefit from minimizing the volume of fluid being pushed through an already inflamed vein.

353. The flexibility in preparation afforded by the 1.0 mg/mL high concentration Argatroban Injection allows for better and customized patient care not possible with the prior-Japanese formulation. As Dr. Lewis stated, “I have no doubt

that argatroban satisfied a very long-felt need and did a very nice job of satisfying that need." (Tr. 787:1-2.)

354. The plaintiffs have shown long-felt need for the claimed invention.

4. **Failure of Others**

355. Evidence of failed attempts by others supports a finding that the patented invention was not obvious. Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 2000); Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1574-75 (Fed. Cir. 1992) (reasoning competitors' failure to develop the patented invention suggested nonobviousness); Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 21 F. Supp. 2d 366, 374 (S.D.N.Y. 1998), aff'd, 231 F.3d at 1339 (stating that the evidence showing that "the pharmaceutical industry at large was attempting to improve upon existing [anti-ulcer drugs] with only a small number of producers coming close to success" supports court's conclusion of nonobviousness).

356. Mitsubishi's collaborators believed for a long time that a high concentration injectable formulation of argatroban was needed for the various clinical indications that they were investigating. (See, e.g., PX 19; PX 21.) Several

well-regarded and experienced companies tried many different approaches to attain such a high concentration formulation without success. (PX 22 (recognizing that "extensive solubility studies have been conducted by Mitsubishi, Genentech, and Texas Biotechnology (by University of Iowa under contract)," and "[h]aving worked with [argatroban] for the past 7 years at both Genentech and Texas Biotechnology, I am absolutely confident that it is not possible to formulate an SVP at 100 mg/mL outside the claims of US 5,214,052 in a GRAS for iv excipient").) Where others failed, Mitsubishi succeeded, despite argatroban's "unusual solubility characteristics." (PX 22 at ENCY 262046.)

357. In the case of argatroban, all of Mitsubishi's collaborators in the United States and Europe were interested in the potential clinical utility and flexibility of Mitsubishi's ethanol-water-sorbitol high-concentration formulation (see, e.g., PX 19), and all of them invested considerable time and effort in the early 1990s researching alternative high-concentration formulations. None of these efforts met with success, however, which is evidence of the nonobviousness of the ethanol-water-sorbitol formulation and the '052 patent.

358. The evidence establishes the repeated failure of others. This is consistent with the difficulty inherent in dealing with the solubility of a complex zwitterion like argatroban. This factor supports a finding of nonobviousness.

**5. Copying**

359. The defendants' ANDA requests leave to copy Argatroban Injection. The plaintiffs argue that the fact that the defendants seek to copy Argatroban Injection establishes this nonobviousness factor, especially in view of the fact that the non-infringing low concentration formulation (0.5 mg/mL) of argatroban is well known and available, but the defendants chose not to copy that. However, copying bears little weight on its own as an objective indicator of non-obviousness in the context of generic drugs. The burdensome NDA procedures provides generic drug manufacturers with an incentive to copy an already approved drug, so that they can avail themselves of the less burdensome ANDA procedure of the Hatch-Waxman Act. See Purdue Pharma Prods. L.P. v. Par Pharm., Inc., 642 F. Supp. 2d 329, 373 (D. Del. 2009), aff'd, No. 2009-1553, 2010 WL 2203101 (Fed. Cir. Jun. 3, 2010).

360. In any event, nearly all the objective indicia of nonobviousness support the conclusion that the defendants have not shown by clear and convincing evidence that the claimed invention would have been obvious to one of ordinary skill in the art at the relevant time.

**6. Skepticism by Others**

361. Dr. Plachetka testified that after learning of Mitsubishi's high concentration formulation in 1994 that:

> Well, I asked Mitsubishi if it was a real deal. I don't recall specifically what actions I took, but I would have either called or written or telexed -- I don't think e-mail was available then -- and asked if this presentation was available and if it were possible to provide us some so we could put it through our own testing and see if it would be suitable for use in humans in the United States.
>
> * * *
>
> [T]he issue with Argatroban, as I recall, is that it is very insoluble in water. We had undertaken several attempts to create a different formulation involving a variety of conditions and hadn't been successful.
>
> So it was almost beyond belief that Mitsubishi could come up with a dosage form that produced this high a concentration of drug in only two cc's of fluid. It was startling and completely unexpected from my perspective.

(PX 200 at 61:14-24, 62:1-10; PX 200 at 74:7-12 ("But I would say on first learning about this, my initial reaction was one of disbelief that it actually, as I said, was the real deal, that it could be actually created in this context, because of the insolubility issue that was well known about Argatroban.").)

362. The plaintiffs' have demonstrated secondary considerations that are sufficient to support a finding of nonobviousness.

## CONCLUSIONS OF LAW

### I. Anticipation

#### A. Legal Standard for Anticipation Under 35 U.S.C. § 102

1. 35 U.S.C. § 102(b) states that a person shall be entitled to a patent unless "the invention was patented or described in a printed publication in this or a foreign country on in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States."

#### B. Claims 1-4 of the '052 Patent Are Not Anticipated by the Yamamoto Article

2. Claim 1 of the '052 patent is not anticipated by the Yamamoto Article.

3. Claim 2 of the '052 patent is not anticipated by the Yamamoto Article.

4. Claim 3 of the '052 patent is not anticipated by the Yamamoto Article.

5. Claim 4 of the '052 patent is not anticipated by the Yamamoto Article.

## II. Obviousness

### A. Legal Standard for Obviousness Under 35 U.S.C. § 103

6. 35 U.S.C. § 103(a) states that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

### B. Claims 1-4 of the '052 Patent Are Not Obvious in Light of the Prior Art

7. Claim 1 of the '052 patent would not have been obvious to one of ordinary skill in the art.

8. Claim 2 of the '052 patent would not have been obvious to one of ordinary skill in the art.

9. Claim 3 of the '052 patent would not have been obvious to one of ordinary skill in the art.

10. Claim 4 of the '052 patent would not have been obvious to one of ordinary skill in the art.

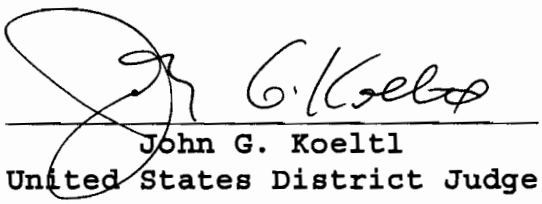
**CONCLUSION**

The Court finds the '052 patent valid and infringed, and enjoins the approval of the defendants' ANDA and the defendants' making, using, or selling the product which is the subject of their ANDA until after the expiration of the '052 patent.

The plaintiffs should submit a proposed judgment within 5 days. The defendants may submit a counter-judgment 2 days thereafter.

**SO ORDERED.**

**Dated: New York, New York**
**June 16, 2010**



**John G. Koeltl**
**United States District Judge**