***NOT FOR PUBLICATION**

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

GLAXOSMITHKLINE PLC, et al Plaintiffs, v. HIKMA PHARMACEUTICAL CO., LTD. et al Defendants.	:	Civil Action No. 12-1965 (FLW) **OPINION**

This matter comes before the Court upon a Complaint brought by Plaintiffs GlaxoSmithKline PLC *et al* ("Plaintiffs" or "GSK") against Defendants Hikma Pharmaceutical Co., Ltd. *et al* ("Defendants" or "Hikma") for patent infringement in violation of Title 35 of the United States Code. In response, Hikma has filed a counterclaim against GSK for declaratory judgment that the patent-in-suit is invalid and that Hikma does not infringe the patent at issue.

Defendants are alleged to infringe United States Patent No. 5,214,052 ("the '052 patent"), which relates to a pharmaceutical composition of the drug "Argatroban," which is both its consumer name and the name of the active ingredient, also known as argipidine or arginineamides, and a method for dissolving the same. Argatroban is used to control abnormal blood clotting during surgical procedures. Plaintiffs originally sought to preliminarily enjoin Defendants from introducing a generic version of the drug after GSK learned, indirectly, that Defendants, through their agent, Exela, filed a New Drug Application ("NDA") for approval to market a generic version of Argatroban prior to the expiration of the '052 patent. Because of the relatively few issues and the urgency of the matter, the parties agreed that an expedited trial

would be a more efficient method to resolve the dispute rather than by a preliminary injunction hearing. There are two issues before the Court: (1) whether propylene glycol is a "saccharide" as understood by the '052 patent; and (2) whether the '052 patent is enabled under 35 U.S.C. § 112.

The Court conducted a four-day bench trial with numerous experts testifying as to the issues of infringement and enablement.[1] GSK's singular theory of infringement is straightforward. There is no dispute that the claims of the '052 patent require the presence of a saccharide. There is no dispute that Hikma uses propylene glycol in its formulation of Argatroban. The question is whether propylene glycol is a saccharide as that term is used in the '052 patent. Both parties agree that saccharide is defined by the '052 patent, but disagree on how to apply that definition. GSK relies on expert testimony regarding how a monosaccharide can be reduced to propylene glycol and several academic sources, including prominently, the IUPAC Rules for naming compounds, to argue that propylene glycol is a saccharide or its derivative; Hikma relies on the treatment of propylene glycol in the patent specification as an alcohol, supposed disclaimers by the patentees in the file history that propylene glycol is not a saccharide, expert testimony that propylene glycol cannot be reduced from a saccharide as that term is used in the patent, and extrinsic evidence to support its theory. Alternatively, Hikma

[1] The parties stipulated to the qualifications of all the expert witnesses.

Three experts testified for the Plaintiffs: Dr. Ronald Sacher, Dr. Stephen Byrn, and Dr. Karl Hale. The Court accepted Dr. Sacher as an expert of hematology, heparin-induced thrombocytopenia, and the treatment of HIT. 7/102/2012 Sacher Trial Tr. at 46-47. The Court accepted Dr. Byrn as an expert in organic chemistry, medicinal chemistry, formulation science, and solubility. 7/10/2012 Byrn Trial Tr. at 62. The Court accepted Dr. Hale as an expert in saccharide and carbohydrate chemistry. 7/11/2012 Hale Trial Tr. at 52.

Two experts testified for Defendants: Dr. Jacquelyn Gervay-Hague and Dr. Samuel Yalkowsky. The Court accepted Dr. Gervay-Hague as an expert in the field or organic chemistry and carbohydrate chemistry. 7/12/2012 Gervay-Hague Trial Tr. at 8-9. The Court accepted Dr. Yalkowsky as an expert in the areas of drug formulation, pharmaceutical sciences, and drug solubility. 7/12/2012 Yalkowsky Trial Tr. a 124.

argues that the ’052 patent is not enabled because it does not teach a person of ordinary skill in the art (“POSITA”) to use the invention without undue experimentation and relies upon expert testimony for support. GSK relies on expert testimony to argue the patent is enabled.

After consideration of all the evidence, the Court finds that Defendants do not infringe the ’052 patent, either literally or under the doctrine of equivalents, because propylene glycol is not a saccharide. Further, the Court finds that the ’052 patent is enabled and therefore is not invalid.

I. OVERVIEW

a. Parties

GSK is the exclusive sublicensee of the ’052 patent. Kevin LaWall Decl., ¶ 13 (attached to GSK Opening Brief (Dkt. No. 7-1). The GSK Plaintiffs are a number of entities, including GlaxoSmithKline plc, GlaxoSmithKline LLC, Glaxo Group Limited, and SmithKline Beecham Limited (collectively “the GSK Entities”). In addition, Pfizer, Inc. and Encysive Pharmaceuticals, Inc. (collectively “Pfizer”) are also named plaintiffs. Pfizer neither joins nor opposes GSK’s requested relief. GSK Opening Brief at 1, n.1. Finally, Mitsubishi Chemical Corporation and Mitsubishi Tanabe Pharma Corporation (collectively “Mitsubishi”), were joined as involuntary plaintiffs. First Amended Complaint, Dkt. No. 49. The face of the patent shows it was assigned by the inventors to Mitsubishi. It was ultimately licensed to Pfizer and then sublicensed to the GSK Entities. LaWall Decl., ¶ 13.

Defendants Hikma Pharmaceutical Co., Ltd. and West-Ward Pharmaceutical Corp. filed a NDA on March 18, 2011. PTX-065.[2] Hikma sent its Paragraph IV Notice to Mitsubishi, Encysive, and Pfizer on June 3, 2011. DTX-060; 7/11/2012 Koneru Trial Tr. at 178. That letter

[2] PTX refers to “Plaintiffs’ Trial Exhibit.” DTX refers to “Defendants’ Trial Exhibit.”

set forth the basis for Hikma's assertion that its product was non-infringing: "Hikma's proposed argatroban product does not infringe the '052 patent, either literally or under the doctrine of equivalents, because it does not contain a saccharide…Propylene glycol is used instead of a saccharide in Hikma's formulation, but no worker of ordinary skill would ever consider propylene glycol a 'sugar' or 'saccharide.'" DTX-060 at GSK_PI 000799. None of the parties receiving the Paragraph IV Notice objected or filed suit. The NDA was given final approval by the Food and Drug Administration ("FDA") on January 5, 2012. DTX-077. GSK claims it did not learn of Hikma's intention to market a generic Argatroban product until January 19, 2012. Thomas D. Smith Decl., ¶¶ 7-8 (attached to GSK Opening Brief (Dkt. No. 7-7). Defendants plan to begin marketing and distributing the generic product within the calendar year.

b. Procedural History

GSK filed its initial Complaint on March 30, 2012, and moved for a preliminary injunction on April 3, 2012. The Court set an expedited briefing schedule to hear the motion on May 14, 2012, but Plaintiff represented that it believed an expedited bench trial would be the more efficient use of the parties' and the Court's resources in order to resolve the issues with some finality. See GSK Reply at 20 ("[T]here appears to be little need for the Court to decide this issue in a preliminary injunction context. Pursuant to Fed. R. Civ. P. 65(a)(2) the Court may (and GSK believes should) consolidate the proceeding with an expedited trial on the merits…."). The Court held a telephone conference with the parties on May 14, 2012, at which time they agreed to an expedited bench trial, after which the Court said it would endeavor to deliver its opinion no more than several weeks after the end of trial. During this time, Plaintiffs filed an Amended Complaint that added several GSK entities and added Mitsubishi as an Involuntary Plaintiff. Dkt. No. 49. Defendants answered on May 23, 2012, and filed counterclaims against

Plaintiffs seeking a declaratory judgment of invalidity and of noninfringement. Dkt. No. 63. Plaintiffs answered the counterclaims on June 21, 2012. Dkt. No. 75.

The parties stipulated to the issues to be decided at trial and the Court entered that stipulation on June 14, 2012. Dkt. No. 74 ("Stipulation"). In particular, the parties agreed:

> The issues for trial shall be limited to: (a) whether or not the Proposed Hikma Product infringes one or more claims of the '052 Patent, and (b) with respect to patent validity, whether or not the '052 Patent meets the requirements of 35 U.S.C. § 112

Stipulation, ¶ 1.[3] The Court conducted a four-day bench trial commencing on July 10, 2012, and heard evidence along with opening statements and closing arguments by counsel. In order to expedite the schedule, the Court did not require the parties to submit written proposed findings of facts or conclusions of law, and said it would consider the parties' closing arguments in lieu of post-trial briefing, in addition to relying on the preliminary injunction briefing that had been completed in May.[4]

The '052 patent has been the subject of prior litigation. In September 2007, the patent-owner, Mitsubishi, brought suit against Barr Laboratories, Inc. ("Barr"), in the Southern District of New York. Mitsubishi Chem. Corp. v. Barr Labs., Inc., Case No. 07-cv-11614, (S.D.N.Y. 2007). Barr filed an Abbreviated New Drug Application ("ANDA") and Mitsubishi brought suit to enjoin Barr from marketing and selling a generic Argatroban injection. Barr made no non-

[3] The parties also agreed that no party would offer evidence at trial regarding "the eBay factors for injunctive relief" because they stipulated as to the appropriate relief should either Plaintiffs or Defendants prevail. Stipulation, ¶ 6.

[4] The Court compliments counsel for both parties on how well-prepared they were for trial considering the extremely expedited fashion in which this matter proceeded. Counsel were able to bring this case from Complaint to closing arguments in a matter of a few months, streamlining the issues, managing discovery, and presenting their witnesses and evidence very effectively. The Court appreciates counsels' willingness to operate in such an expedited fashion and their ability to conduct themselves with such competence and professionalism under demanding conditions. Counsel are a credit to the profession.

infringement arguments, but argued that the patent was invalid, making a number of anticipation and obviousness arguments under 35 U.S.C. §§ 102 and 103, as well as an enablement argument under 35 U.S.C. § 112. Id. at 389. After a bench trial, the court found that the '052 patent was valid and infringed, and enjoined the approval of Barr's ANDA and its making, using, or selling the generic Argatroban product. Mitsubishi Chem. Corp. v. Barr Labs., Inc., 718 F. Supp. 2d 382, 445 (S.D.N.Y. 2010) ("Mitsubishi Litigation"). The district court focused on construing the phrase "pharmaceutical composition for injection." Id. at 411. Barr appealed to the Federal Circuit, which affirmed the district court. Mitsubishi Chem. Corp. v. Barr Labs., Inc., 435 Fed. Appx. 927 (Fed. Cir. 2011).

II. FINDINGS OF FACT

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

a. The '052 Patent

The '052 patent issued on May 25, 1993, and the term of the patent was extended under 35 U.S.C. § 156 from May 25, 2010, until June 30, 2014. '052 patent, PTX-001 at GSK_PI 00003. The priority date of the patent is July 28, 1987, which relates back to a foreign priority date from the Japanese Application No. 62-188484. Id. The '052 patent has two independent and two dependent claims. Claim 1 is a method claim directed towards "dissolving an arginineamide [Argatroban]…and/or its salt in a solvent system containing ethanol, water, and a saccharide." '052 Patent, Claim 1, PTX-001. Claim 3 is the other independent claim and is similar to claim 1 but is directed towards "a pharmaceutical for injection" rather than a method. Id. at Claim 3. Claim 2 depends on claim 1 and limits the saccharide to at least one of the following: "sorbitol, glucose, glycerin and sucrose." Id. at Claim 2. Claim 4 is identical but

depends on claim 3 instead. Id. at Claim 4. Plaintiffs argue that Defendants infringe claims 1, 2, and 4 under the doctrine of equivalents and infringe claim 3 literally or under the doctrine of equivalents.

b. Background of the Patent

The patent is directed towards a pharmaceutical solution for the drug Argatroban. The inventors did not invent the drug itself; Argatroban was well known in the art before the '052 patent. 07/10/2012 Byrn Trial Tr. at 63. Argatroban is an anticoagulant used to prevent or treat abnormal clot formation in hospitalized patients that suffer from either heparin-induced thrombocytopenia or thrombosis (HIT or HITT). 07/10/2012 Sacher Trial Tr. at 43-45. These conditions are side effects of treatment with heparin, which is an anticoagulant drug used to prevent blood clots during medical procedures such as kidney dialysis or bypass surgery. Id. Heparin can cause patients to develop HIT or HITT, which causes abnormal blood clotting. Id. Argatroban is used to treat such conditions and allows doctors to use heparin with patients who would otherwise experience abnormal blood clotting. Id. at 54-57. The object of the invention is to provide a means to dissolve Argatroban in a solution that allows for a high concentration of the drug while preventing it from precipitating out:

> Arginineamides [Argatroban] are known to have anti-thrombotic activities and are expected to be used as anti-thrombotic agents (please refer to Japanese Patent No. 1382377). However, it is very difficult to obtain a solution containing any of [*sic*] arginineamides at high concentration due to poor solubility in water and therefore any of these compounds is 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 [*sic*] containing them at high concentration.

'052 Patent, Background of the Invention, col. 1:17-28; PTX-001. Because the molecule is poorly soluble in water it is not a viable treatment unless it can be dissolved at high

concentrations. 07/10/2012 Byrn Trial Tr. at 63. The inventors discovered that using a three-solvent system—one comprised of water, ethanol, and a saccharide—improved Argatroban's solubility dramatically, making it an effective injectible medicine. Id. at 63-64. Any of these solvents, either by itself or in combination with just one other solvent, were not as effective as the combination of all three solvents. Id. As discussed below in the context of the file history, the patentees stated this to be the case in order to overcome prior art rejections when they canceled all claims not relating to the three-solvent system. See, e.g., Ofuchi Declaration at 4, PTX-002 at GSK_PI 002214.

A person of ordinary skill in the art would be one of the following: (1) someone with a Ph.D. in formulation or related areas like physical chemistry, medicinal chemistry, or pharmaceuticals with at least a year of pharmaceutical formulation experience; (2) someone with a Master's degree in one of these fields, and at least two years of pharmaceutical formulation experience; or (3) someone with an undergraduate degree in one of these fields, and at least three five years pharmaceutical formulation experience. 7/10/2012 Byrn Trial Tr. at 64-65; 7/11/2012 Hale Trial Tr. at 52; 7/12/2012 Gervay-Hague Trial Tr. at 10.

c. The Accused Product

Defendants' accused product ("Accused Product" or "Hikma Product") was developed by Exela Pharma Sciences ("Exela"). 7/11/2012 Koneru Trial Tr. at 135. Exela's President and CEO, Dr. Phanesh Koneru, testified at trial. Exela was Hikma's agent before the FDA when it filed a NDA on Hikma's behalf. Exela filed an NDA on behalf of Defendants rather than an ANDA because it did not consider the Accused Product to be chemically equivalent to Plaintiffs' Product. Id. at 154. [redacted] Id. at 155. Exela was aware of the '052 patent and worked to design around it by trying to develop a

solution that either did not have a saccharide or ethanol. 7/11/2012 Koneru Trial Tr. at 136-137, 169. Exela began work on its Argatroban product in 2006. Id. at 137. Before designing the Accused Product or beginning testing, Exela's President and CEO reviewed the '052 patent and the file history. To find an adequate solution, Exela conducted over 90 experiments. Id. at 139.

As part of the NDA, Exela disclosed the ingredients of its Argatroban solution and explained that its "proposed drug product has the same active ingredient, dosage form, strength, route of administration, and conditions of use" as Plaintiff's product. Hikma New Drug Application, Module 1 at 8, PTX-065 H 000016; Hikma New Drug Application, Module 3 at 13, DTX-013 at H 000171. But the Hikma Product has a different solubilizing agent (propylene glycol) than Plaintiff's product, which contains D-Sorbitol. PTX-065 at 8 ("In Exela's formulation, propylene glycol replaces D-sorbitol as the solubilizing agent."). The Accused Product is comprised of Argatroban (100 mg/mL), dehydrated alcohol (320 mg/mL) (another name for ethanol), propylene glycol (520 mg/mL), and water. PTX-100 at EXCELA 001765. Plaintiff's Argatroban product is comprised of Argatroban (100 mg/mL), dehydrated alcohol (333.3 mg/mL), D-Sorbitol (250 mg/mL), and water. Id.; 7/10/2012 Byrn Trial Tr. at 68-71. Therefore, Hikma's Product indisputably meets all the claim limitations of Claim 3 except potentially whether it contains a saccharide.

At trial, Exela's CEO, Dr. Koneru, described the production process for the Accused Product. 7/11/2012 Koneru Trial Tr. at 158-162. The following production steps are relevant for the purposes of this matter. [redacted]

[redacted]

[redacted]

[redacted]

Defendants' process cannot literally infringe claim 1 of the patent because that claims a method where all three co-solvents (water, ethanol, and a saccharide) are used to dissolve the drug initially as opposed to Hikma's Product where [redacted]

d. Background Technology

At issue in this matter is how to classify saccharides and propylene glycol and what, if any, link there is between them. A saccharide is generally defined as a carbohydrate.[5] The patent defines the claimed saccharides as follows:

> If necessary, any saccharides can be admixed with the solvent of alcohol and water in the invention. As the saccharides used in the invention, monosaccharides, oligosaccharides, polysaccharides, and their reduced derivatives (for example sugar alcohol) which are soluble in water are mentioned.

'052 patent, col. 3:59-64, PTX-001. This is how the parties agreed saccharide should be construed. 7/10/2012 Byrn Trial Tr. at 73; 7/11/2012 Hale Trial Tr. at 54. Defendants' Expert, Dr. Gervay-Hague agreed that this was the definition the patent applied to the term saccharide but did not agree that —apart from the patent—a person of ordinary skill in the art would generally understand a saccharide to include its reduced derivative. 7/12/2012 Gervay-Hague Trial Tr. at 16-17. I agree with the parties and find that the patent defines saccharides as: "monosaccharides, oligosaccharides, polysaccharides, and their reduced derivatives (for example sugar alcohol) which are soluble in water." '052 patent, col. 3:60-63, PTX-001.

Whether a compound is a monosaccharide, oligosaccharide, or polysaccharides depends on the repetition of a particular chemical structure. A monosaccharide is defined as being a "polyhydroxy carbonyl compound." 7/12/2012 Gervay-Hague Trial Tr. at 18. It has one saccharide structure, while an oligosaccharide has a relatively small numbers of such structures, and a polysaccharide has many such structures. IUPAC 1969 Rules at 3984-3985, PTX-022 at GSK_PI 000035-36; 7/20/2012 Byrn Trial Tr. at 79. A monosaccharide is also known commonly as a simple sugar and has a molecular structure of $C_n(H_2O)_n$. Id.

[5] There is a dispute whether all carbohydrates are saccharides, but there is no dispute that all saccharides are carbohydrates. 7/12/2012 Gervay-Hague Trial Tr. at 43.

The patent defines the following compounds as saccharides: glucose, fructose, maltose, saccharose, and D-sorbitol (or sorbitol). '052 patent, col. 3:64-67, PTX-001. Glucose and fructose are monosaccharides; maltose and saccharose are oligosaccharides; and D-Sorbitol is a sugar alcohol and is achieved from a single reduction of a saccharide. 7/12/2012 Gervay-Hague Trial Tr. at 32. In addition, the patent claims glycerin as a saccharide. '052 patent, claims 2 and 4, PTX-001. Glycerin is also a sugar alcohol and is achieved through a single reduction of a monosaccharide. 7/12/2012 Gervay-Hague Trial Tr. at 32. All of the saccharides discussed by the patentees in the file history are also monosaccharides, oligosaccharides, polysaccharides, or are derived from a single reduction of one of these compounds. Id. at 33-34.

Propylene glycol is an alcohol that is commonly derived from propylene oxide. Gervay-Hague Decl., ¶ 34, attached to Hikma Opp. Brief (Dkt. No. 50-1). While it is not propane itself, it is conventionally known as related to propane and petroleum products. 7/10/2012 Byrn Trial Tr. at 100; 7/12/2012 Gervay-Hague Trial Tr. at 26. Its molecular formula is $C_3H_8O_2$. Propylene glycol does not have a carbonyl group. And because it is a dihydric alcohol, it has two hydroxyl groups. Alcohols containing only two hydroxyl groups are commonly called glycols. 7/12/2012 Gervay-Hague Trial Tr. at 46; DTX-005 at 642.

The patent discusses propylene glycol as an alcohol solvent to be used in the invention: "In the method for dissolving an arginineamide according to the invention, the arginineamide and/or its salt is dissolved in the solvent of alcohol and water. As the alcohols used in the invention…dihydric alcohols such as ethylene glycol, propylene glycol and the like…Methanol, ethanol, propylene glycol and polyethylene glycol are preferable. Ethanol is particularly preferable." '052 patent, col. 3:42-51, PTX-001. One of skill in the art would understand that

propylene glycol is discussed by the patent as an alcohol and not a saccharide. 7/12/2012 Gervay-Hague Trial Tr. at 28.

e. Prior Litigation

The '052 patent was previously at issue in the Mitsubishi Litigation. There it was found to be valid over various prior art references, enabled, and infringed by a product unrelated to this litigation. None of the same prior art arguments are being made here. In fact, Defendants do not raise any prior art arguments. The enablement argument being made here is different than the enablement argument made in the Mitsubishi Litigation.

A number of claim terms were discussed in the Mitsubishi Litigation, but only one is relevant for my purposes, and that is the district court's discussion of saccharide:

> The plaintiffs contend that saccharide should be construed to mean "monosaccharides, oligosaccharides, polysaccharides and their reduced derivatives (for example sugar alcohol) 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.

Mitsubishi Chem., 718 F. Supp. 2d at 409. Neither saccharides nor propylene glycol were at issue during the Mitsubishi Litigation. The defendant, Barr, did not oppose Mitsubishi's infringement arguments, but relied entirely on its invalidity claim. Id. at 389.

In addition, the district court made several findings regarding the background of the invention which are instructive here. These are: (1) "Drug formulation is a difficult and frequently unpredictable science;" (2) it takes a significant amount of "time and effort to develop a formulation of a drug compound that is suitable for use in patients;" and (3) the solubility of a given compound to be administered via intravenous injection is often very difficult to predict. Id. at 400. Although these arguments were made in the context of an obviousness analysis, they

are also relevant to an enabling analysis. In addition, I find that significant experimentation is routine in the pharmaceutical industry regarding solubilizing solutions in large part because of these factors.

f. File History

The ’052 patent had an involved file history. The claims were rejected multiple times by the examiner and the claims were amended during the prosecution history. Initially, 26 claims were filed. Those claims were rejected as being obvious. ’052 File History, PTX-002 at GSK_PI 2172-73. The applicants amended their application by canceling the original claims and adding the four claims now at issue. In particular, the patentees canceled all claims not relating to the three co-solvent solution. The applicants submitted a declaration by one of the inventors, Kunihiko Ofuchi. Ofuchi Declaration, PTX-002 at GSK_PI 2209-13. In that declaration, Mr. Ofuchi explained that Argatroban was dissolved in water, alcohol, and a saccharide and no mixture had near the efficacy as water, alcohol, and a saccharide. In particular, he said: “As [is] clear from the above results, the solubility of argipidine in water is very low and its solubility hardly increases by adding any saccharide into water. The solubility of argipidine in an alcohol is also very low. While, the solubility of argipidine remarkably increases by using our solvent (an aqueous solution containing saccharide + an alcohol).” Id. at GSK_PI 002212. The applicants redrafted the claims directed to the three co-solvent solution, although substantively they remained largely identical to the claims that were originally filed. Glycerin was added as a saccharide to dependent claims 2 and 4.

Despite the patentees’ efforts, the examiner rejected the amended claims as obvious over the prior art. Two pieces of prior art were discussed during the prosecution history and are relevant to this case. First is a section from a text Formulation of Veterinary Dosage Forms, by

Jack Blodinger ("Blodinger"). PTX-031. Second is U.S. Patent Number 2,854,380 ("Jensen"). DTX-010. Blodinger discusses "parenteral dosage" (i.e. injectible drugs) for animals. Blodinger at 153, PTX-031 at GSK_PI 000756. Nevertheless, the reference notes that "[i]n general the preparation of parental forms of drugs for animals is the same as for humans. Indeed many of the products used for humans are given to animals without any modification." Id. The examiner said that the secondary references, including Blodinger, "teach the use of alcohol in conjunction with water to increase the solubility of pharmaceuticals." '052 Patent File History, PTX-002 at GSK_PI 002173; GSK_PI 002246. Blodinger discloses that "the solubility of the drug in water may be improved by the addition of cosolvents such as alcohol, propylene glycol, polyethylene glycol, dimethylacetamide, dimethylsulfoxide, or dimethylformamide." Blodinger at 154, PTX-031 at GSK_PI 000756.

In response, the patentee noted that the Blodinger reference discloses the use of propylene glycol, but did not disclose the use of a saccharide to increase the solubility of a solution. The patentees made several statements regarding Blodinger throughout the file history. In the April 12, 1991 response to the January 14, 1991 Office Action, the patentees said:

> The Blodinger reference only discloses that the solubility of a drug in water can be improved by the addition of a cosolvent such as alcohol, propylene glycol, polyethylene glycol, dimethylacetamide, dimenthlsulfoxide, or dimethylformamide. However, Applicants do not contend [*sic*] the fact that it is known that the presence of alcohol in an aqueous medium may enhance or increase the solubility of a drug compound in water…However, whatever level of enhanced or increased solubilization is achieved by a water-alcohol combination for the claimed arginineamide compound of the present invention, such enhanced solubilization certainly would not suggest the results demonstrated at the bottom of page 3 of the Ofuchi Declaration for the solubilization of the claimed arginineamide compound in an aqueous medium containing ethanol and, in this case, sorbitol as a saccharide.

'052 Patent File History, PTX-002 at GSK_PI 002254-2255. After the examiner again rejected the patent as obvious over the prior art, including Blodinger (Id. at GSK_PI 002263), the patentees responded on October 30, 1991, by stating:

> Applicants submit that Blodinger does not lead one of skill in the art to the present invention, since this reference only discloses that the solubility of some drugs in water can be improved by the addition of such cosolvents as an alcohol, propylene glycol, polyethylene glycol, and the like. Such a teaching, however, does not suggest to one of skill in the art a solvent system which quite substantially increases the solubility of the compound Argipidine in an aqueous based medium. Certainly there is no reference to a saccharide on the part of Blodinger, and such a solubility enhancing effect exhibited in the present invention is not shown or suggested by Blodinger.

Id. at GSK_PI 002273-2274. The Blodinger reference does disclose the use of saccharides, but in a section unrelated to the section cited by the examiner. The examiner cited pages Blodinger pages 152-155 (GSK_PI 002174), which were the photocopied pages he included in the file history (GSK_PI 002182-2184). Within those pages the only full section is "Section D. Parenteral Dosage Forms." This section is what the examiner relied upon and is what the patentee responded to during the course of the prosecution history. What Blodinger said in other sections is immaterial in the context of what the patentees and the patent examiner were discussing.

The examiner also rejected the application as obvious over Jensen, which disclosed the use of an aqueous solution for reserpine that included propylene glycol and sorbitol. In particular, Jensen described its solution as follows: "The use of sorbitol in the vehicle increases chemical stability and therapeutic effect…Both propylene glycol and ethanol act as solvents for the reserpine which is practically insoluble in aqueous media and not only contribute to chemical stability of the reserpine but also bring about a more rapid onset of physiological effect." Jensen,

col. 1:59-col. 2:4, DTX-010. The patentees made several statements about Jensen. In the April 12, 1991 response to the January 14, 1991 Office Action, the patentees said:

> Applicants submit that the Jensen '380 reference, is irrelevant to the present invention…since Jensen discloses a therapeutic composition in which reserpine is dissolved in aqueous solution containing propylene glycol and sorbitol. The facts are that propylene glycol is not ethanol, and reserpine certainly is not the claimed arginineamide compound of the present invention. Certainly, it is impossible for the Jensen et al reference to provide any teaching or suggestion to one of skill in the art that the specific combination of ethanol and a saccharide such as sorbitol would markedly improve the solubility of the claimed arginineamide compound of the present invention in an aqueous medium.

PTX-002 at GSK_PI 002253. After a subsequent rejection, the patentees said in their October 30, 1991 response to the June 13, 1991 Office Action:

> It is appropriate here to consider Jensen et al…since it describes a therapeutic composition comprising reserpine in an aqueous solvent system of ethanol, propylene glycol, and sorbitol. Although the Jensen et al reference discloses a composition which contains a saccharide, i.e., sorbitol, nevertheless, as disclosed at column 1, lines 59-60 of the reference, sorbitol is only used as a vehicle which increases chemical stability and the therapeutic effect of the disclosed composition. There is absolutely no teaching or suggestion in the reference that sorbitol is employed to increase the solubility of reserpine in the liquid medium employed. Accordingly, one of skill in the art would not be led by Jensen to employ a saccharide as a solubility enhancing agent for a therapeutic compound.
>
> In light of the fact that the above discussed references do not show a saccharide in a solubility enhancing role and in view of the fact that none of the other references show or suggest the use of a saccharide in a therapeutic composition, it is clear that a very important aspect of the invention, as demonstrated by the comparative evidence of record in this case, is not shown or suggested by the prior art.

Id. at GSK_PI 002271-2272. Jensen focused on increasing the chemical stability and not the solubility of the solution. But it did state, explicitly, that the solubility was affected by adding propylene glycol and ethanol. An object of the invention was "to provide a fluid dosage form of reserpine." Jensen, col. 1:36-37, DTX-010. Similarly, the patentees here described Jensen as teaching "the likes of propylene glycol and ethanol" as "an alcohol solvent," also referring to it

as a solvent agent. Therefore, the Court finds that examiner and the patentees discussed Jensen in the context of disclosing the use of propylene glycol as an alcohol solvent to be used with reserpine.

g. Propylene Glycol Is Not a Monosaccharide, Oligosaccharide, or Polysaccharide

Saccharide and propylene glycol are not identical, interchangeable elements. 7/12/2012 Gervay-Hague Trial Tr. at 18, 21. Their molecular structures are different, they each have different properties, and they are used for different purposes. Id. at 21-24. Generally, propylene glycol is not considered by one of skill in the art to be a saccharide. Id. at 12. There is no dispute that propylene glycol is not a monosaccharide, an oligosaccharide, or a polysaccharide. 7/11/2012 Byrn Trial Tr. at 16-17. In particular propylene glycol is not a monosaccharide because it does not have a carbonyl group. Id. at 22. Besides having a carbonyl group, a monosaccharide needs to be polyhydric, meaning it has multiple hydroxy groups. Id. at 20-21. Plaintiffs argue that poly means "two or more" and relies on

> Polyhydric alcohols are those containing two or more OH groups; dihydric alcohols are often called "glycols." The class name polyol includes both polyhydric alcohols and polyhydric phenols, as do the class names diol, triol, etc.

Nomenclature of Organic Compounds at 153, PTX-110. Defendants point to other literature that says polyhydric means "A compound containing more than 2 hydroxyl groups." 7/12/2012 Gervay-Hague Trial Tr. at 20; Grant & Hackh's Chemical Dictionary at 462, DTX-058. Dr. Gervay-Hague agreed that her understanding is that poly means "many" and refers to it often meaning more than ten, but it generally depends on the context of how the term is being used. 07/12/2012 Gervay-Hague Trial Tr. at 84. But whether the scientific literature or a person having skill in the art generally would understand polyhydric to mean "two or more" or "more than two" is secondary to the intrinsic evidence itself. The patent refers to dihydric alcohols and

polyhydric alcohols separately. '052 patent, col. 3:42-46, PTX-001. Clearly, the patentee intended to differentiate between the two groups. Propylene glycol cannot be an oligosaccharide or polysaccharide for the same reasons.

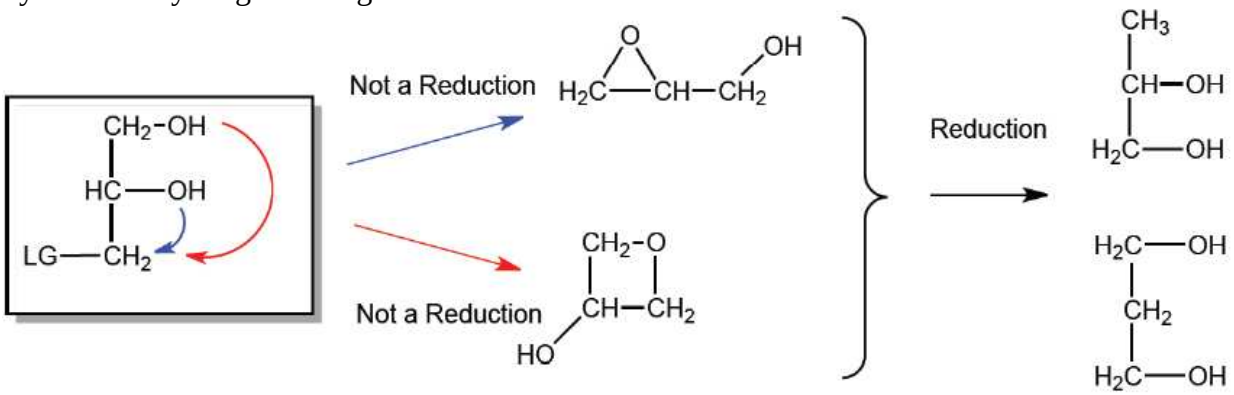
h. Propylene Glycol Can Be Derived From a Saccharide Using a Two-Step Reduction Process

Plaintiffs' expert, Dr. Stephen Byrn, testified that it is possible, through the use of two reduction reactions, to convert a monosaccharide into propylene glycol. Defendants' expert, Dr. Gervay-Hague, largely agreed with the overall contours of Dr. Byrn's analysis, but added substantial detail to it.[6] At trial, the parties' experts agreed that for purposes of the'052 patent a reduction reaction is one that decreases the oxygen content of a compound or increases its hydrogen content. Byrn Trial Tr., 7/20/2012 at 83-84; T.W. Solomons Fundamentals of Organic Chemistry at 613, PTX-025 at GSK-PI 000100. In other words, it removes oxygen or adds hydrogen. Each type of reduction is described as a separate reduction by the parties' experts and the scientific literature.

Dr. Byrn testified that one can derive propylene glycol from a saccharide using glyceraldehyde as the starting material. Glyceraldehyde is a monosaccharide and it is also an aldose. Byrn Trial Tr., 7/20/2012 at 81-82. Glycerin is a reduced derivative of a glyceraldehyde and therefore is a saccharide within the meaning of the '052 patent; it is also described as an alditol. Id. at 86-88, 98. A sugar alcohol is also an alditol and is defined by the patent as a reduced derivative of a saccharide. 7/11/2012 Byrn Trial Tr. at 16. Propylene glycol itself is not an alditol. Id. at 17. One can go from glyceraldehyde to glycerin by adding an hydrogen atom, which is a common, relatively simple reduction reaction. 7/10/2012 Byrn Trial Tr. at 91;

[6] Dr. Gervay-Hague has only been an expert witness once before; she devotes the majority of her time to her research and academic pursuits. The Court found Dr. Gervay-Hague to be not only preeminent in her field, but immensely credible and helpful as an expert witness.

7/12/2012 Gervay-Hague Trial Tr. at 23, 25. Next, it is possible to reduce glycerin to create propylene glycol. But to do this, one needs to perform intermediary steps that do not involve reactions. 7/12/2012 Gervay-Hague Trial Tr. at 24. To perform the second reaction, one needs to activate the oxygen so that it will attempt to break the carbon bond. Id. To do this, it must first be converted, which does not involve a reduction, then after the oxygen has been removed, a reducing agent can be added to transform the molecule. Id. The second reaction was illustrated by Dr. Gervay-Hague during trial:



Gervay-Hague Demonstrative Ex. at 37. This second reduction step is far more difficult and unpredictable than the first. 7/11/2012 Byrn Trial Tr. at 27-28; 7/12/2012 Gervay-Hague Trial Tr. at 26. Moreover, it creates additional elements that are neither glycerin nor propylene glycol and there is no guarantee that propylene glycol will result from this reaction. 7/12/2012 Gervay-Hague Trial Tr. at 25-26. Therefore, to go from a monosaccharide to propylene glycol requires, at a minimum, two reduction reactions—one involving the addition of hydrogen and the other involving the removal of oxygen. The second reduction reaction is more difficult than the first and more unpredictable. In addition, there may be other compounds created as byproducts. It is not common for propylene glycol to be derived in this way; it is more traditionally a derivative of petroleum products. Id. Extrinsic evidence also supports the finding that propylene glycol is not commonly considered a derivative of glycerin. The Collins treatise lists "Glycerol

derivatives," but it does not list propylene glycol among them. P.M. Collins, Carbohydrates at 707-708, DTX-076 at 51-52; 7/11/2012 Byrn Trial Tr. at 24-25.

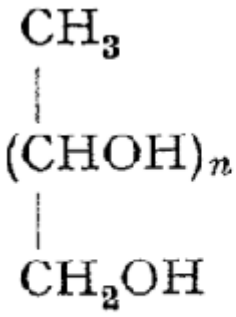
i. Scientific Labeling of Propylene Glycol and Saccharides

The International Union of Pure and Applied Chemistry (IUPAC) Commission on the Nomenclature of Organic Chemistry Tentative Rules for Carbohydrate Nomenclature from 1969 ("IUPAC 1969 Rules") are instructive for naming carbohydrate and saccharide compounds. PTX-022. The IUPAC 1969 Rules are intended as a supplement to the IUPAC 1965 Rules and are only "intended to govern those aspects of the nomenclature of carbohydrates not covered by those rules." IUPAC 1969 Rules at 3983-3984, PTX-022 at GSK_PI 000034-35; 7/11/2012 Byrn Trial Tr. at 21. The 1965 Rules list propylene glycol as an alcohol. IUPAC 1965 Rules at 74-75, DTX-017 at H 002484-2485; 7/11/2012 Byrn Trial Tr. at 21; 7/11/2012 Hale Trial Tr. at 75. The IUPAC 1969 Rules define a monosaccharide as an aldose (IUPAC 1969 Rules at 3985, PTX-022 at GSK_PI 000036) and also define "deoxyalditol" as an aldose derivative. Id. at 3995 (GSK_PI 000046) ("The name of an aldose derivative having a terminal CH_3 and CH_2OH group is derived from that of the appropriate alditol (Rule Carb-2) by use of the prefix 'deoxy'").[7]

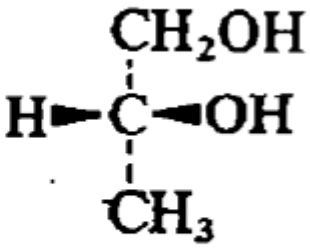
Plaintiffs argue that another name for propylene glycol is "deoxyalditol." The IUPAC 1969 Rules define "deoxyalditol" as follows: "The name of an aldose derivative having a terminal CH3 and CH2OH group is derived from that of the appropriate alditol." 1969 IUPAC Rules at 3995, PTX-022 at GSK_PI 000046. Dr. Hale's opinion that propylene glycol is the

[7] Plaintiffs also rely on the IUPAC 1996 Rules. PTX-023. The priority date for the patent, however, was July 1987. Therefore, the IUPAC 1996 Rules were published well after the priority date. While Plaintiffs' expert, Dr. Byrn, testified that there is no inconsistency between the earlier rules and the 1996 Rules, this convinces the Court that the 1996 Rules are unnecessary. 7/10/2012 Trial Tr. at 77. If there is no material difference, and indeed the Court can find none other than perhaps clearer language being used in the 1996 Rules, the 1965 and 1969 Rules should suffice for all of Plaintiffs' purposes.

same as deoxyalditol is based, in part, on Rodd's Chemistry of Carbon Compounds. PTX-046. That text contains a description of deoxyalditols and a general representation of their chemical composition. He argued that this composition is the same as propylene glycol when $n = 1$.



Deoxyalditol



Propylene Glycol

Rodd's Chemistry of Organic Compounds at 58, PTX-046 GSK_PI 021588; P.M. Collins, Carbohydrates at 423, PTX-026. The IUPAC 1969 Rules do not control the nomenclature of propylene glycol because propylene glycol is included in the 1965 Rules. A review of the scientific literature reveals that propylene glycol is known as 1,2-propanediol. This is consistent with the IUPAC Rules. DTX-076 at 423; T.W. Solomons Fundamentals of Organic Chemistry at 613, DTX-005-05 ("Alcohols containing two hydroxyl groups are commonly called glycols. In the IUPAC system they are named as diols."); 7/11/2012 Byrn Trial Tr. at 22-25. Propylene glycol is not generally known as a deoxyalditol. 7/12/2012 Gervay-Hague Trial Tr. at 40-41.

There is conflicting evidence regarding whether all carbohydrates should be considered saccharides. See n. 5, supra. Because the resolution of this issue is not necessary for the disposition of this case, I do not need to find whether or not all carbohydrates are saccharides.

III. CONCLUSIONS OF LAW

a. Claim Construction

Claims define the scope of the inventor's right to exclude. Phillips v. AWH Corp., 415

F.3d 1303, 1312 (Fed. Cir. 2005). Claim construction determines the correct claim scope, and is a determination exclusively for the court as a matter of law. Markman v. Westview Instruments, Inc., 52 F.3d 967, 978-79 (Fed. Cir. 1995) (en banc). Indeed, the court can only interpret claims, and "can neither broaden nor narrow claims to give the patentee something different than what it has set forth" in the specification. E.I. Du Pont de Nemours v. Phillips Petroleum Co., 849 F.2d 1430, 1433 (Fed. Cir. 1988).

This interpretive analysis begins with the language of the claims, which is to be read and understood as it would be by a person of ordinary skill in the art. Dow Chem. Co. v. Sumitomo Chem. Co., 257 F.3d 1364, 1372 (Fed. Cir. 2001); see also Markman, 52 F.3d at 986 ("The focus [in construing disputed terms in claim language] is on the objective test of what one of ordinary skill in the art at the time of invention would have understood the terms to mean"); Phillips, 415 F.3d at 1312-13. In construing the claims, the court may examine both intrinsic evidence (e.g., the patent, its claims, the specification, and prosecution history) and extrinsic evidence (e.g., expert reports, testimony, and anything else). Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309 (Fed. Cir. 1999). Courts first look to intrinsic evidence when interpreting disputed terms. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). Generally, words in patent claims are given their "ordinary and accustomed meaning as understood by one of ordinary skill in the art" at the priority date of the patent application. Dow Chem., 257 F.3d at 1372; K-2 Corp. v. Salomon S.A., 191 F.3d 1356, 1362 (Fed. Cir. 1999). The claims must be construed objectively in the context of both the particular claim and the entire patent because "the claims themselves provide substantial guidance as to the meaning of particular claim terms," and claim terms are normally used consistently throughout the patent. Phillips, 415 F.3d at 1313-14.

Moreover, courts are instructed to look to the specification, which is a written description of the invention. "[C]laims 'must be read in view of the specification, of which they are a part.'" Id. at 1315 (quoting Markman, 52 F.3d at 979). Indeed, the specification is perhaps "the single best guide to the meaning of a claim term" due to its statutory requirements of being in "full, clear, concise, and exact terms." Id. at 1316; see 35 U.S.C. §112. "The specification acts as a dictionary when it expressly" or implicitly defines terms used in the claims. Markman, 52 F.3d at 979. Thus, it effectively limits the scope of the claim. On Demand Mach. Corp. v. Ingram Industries, Inc., 442 F.3d 1331, 1340 (Fed. Cir. 2006). Due to its nature, "the specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive." Id. (quoting Vitronics Corp., 90 F.3d at 1582).

Extrinsic evidence includes all evidence external to the patent and prosecution history, i.e., expert and inventor testimonies, dictionaries, and learned treaties. Markman, 52 F.3d at 980. It is considered supplemental to the intrinsic evidence when ambiguities remain. See Vitronics, 90 F.3d at 1583; Johnson Worldwide Assocs. v. Zebco Corp., 175 F.3d 985, 989 (Fed. Cir. 1999). Yet extrinsic evidence cannot be used to vary or contradict claim terms when their meanings are discernible from intrinsic evidence. C. R. Bird, Inc. v. U.S. Surgical Corp., 388 F.3d 858, 862 (Fed. Cir. 2004).

The only claim term relevant to this dispute is "saccharide." The parties have agreed that the '052 patent specification expressly defines the claimed saccharides as: "monosaccharides, oligosaccharides, polysaccharides, and their reduced derivatives (for example sugar alcohol) which are soluble in water." '052 patent, col. 3:60-63, PTX-001. I have found this to be the definition of saccharide for purposes of this patent. Because the Court finds that propylene glycol is not a monosaccharide, oligosaccharide, or polysaccharide (which I refer to as the base

saccharide compounds), the remaining question is whether it can be considered a "reduced derivative" of one of these base saccharide compounds. The parties have framed the argument as whether "reduced derivatives" allows for "doubly-reduced" derivate compounds or "directly-reduced" derivative compounds.

I start with the intrinsic evidence. In particular, the plain meaning of the definition is that a saccharide is either (1) one of the listed base compounds or (2) the reduced derivate of those base compounds. Therefore, this suggests that any compound must be directly related to the base compounds. Further, the definition lists "sugar alcohol" as an example of a reduced derivative. Sugar alcohol is not one of the base compounds, but is achieved through one reduction of a monosaccharide. All other saccharide compounds listed in the patent specification or the file history are either one of the base compounds or are derived from one a single reduction reaction of the base compounds. 7/12/2012 Gervay-Hague Trial Tr. at 32-34. For example, claims two and four list several specific saccharides that may be used. Each of these is a monosaccharide, oligosaccharide, or a polysaccharide (sorbitol, glucose, and sucrose) or a direct result from a single reduction reaction of a base saccharide (glycerin). Id. The patentee does not list any compounds as a saccharide that cannot be directly reduced from a monosaccharide, oligosaccharide, or a polysaccharide. Id. at 31 ("No. There are no double derivatives included in the examples, the claims, or the Ofuchi declaration.").

Dr. Byrn opined that there is no requirement in the patent for a "direct reduction." 7/10/2012 Byrn Trial Tr. at 130-131. He based his opinion on his experience and several learned treatises. I find the extrinsic evidence is inconclusive and ambiguous. Dr. Byrn stated that "in Solomons there is no requirement in the field of chemistry that it be a one-step reduction, and I don't see a requirement in the IUPAC rules that it be a one-step reduction." Id. Solomons refers

to Fundamentals of Organic Chemistry by T.W. Graham Solomons. PTX-025. It is a well-regarded chemistry text that is routinely used by first-year organic chemistry students. 7/10/2012 Byrn Trial Tr. at 83. The IUPAC Rules are discussed above, and specifically Dr. Byrn was referring to the 1969 and the 1996 IUPAC Rules. PTX-022; PTX-023. The Court finds these are authoritative sources, but they do not address the issue at hand. These sources treat reduction reactions separately based on whether hydrogen is being added or oxygen is being removed and do not address whether a compound can be called a "reduced derivative" even if multiple reductions have taken place. Moreover, this approach of starting with the extrinsic evidence or relying on it exclusively is inappropriate. What the extrinsic evidence *does not say* is far less persuasive than what the intrinsic evidence *does say*.

What I find most troubling is how expansive Plaintiffs' interpretation can potentially be. Following GSK's argument to its natural conclusion—that is to allow multiple reduced derivative reactions—could bring nearly limitless compounds within the definition of saccharide. A reduced derivative is not, by definition, the same as a reduced derivative of a reduced derivative. One changes the chemical structure with each reduction and one achieves an entirely different molecule. 7/10/2012 Byrn Trial Tr. at 83. Compounds even with slight molecular structures can behave in very different ways and have very different properties. Id. at 86-88. If one is allowed to repeatedly use the reduction process, then one can conceivably produce a vast array of chemicals that are not saccharides, but would be classified as such under Plaintiffs' interpretation. This would improperly expand the patent's scope. Plaintiffs' own expert, Dr. Hale, perhaps described it best when he explained at his deposition that if you evaluate saccharides in such a way, "you're limited by your own imagination." 7/11/2012 Hale Trial Tr. at 124. Indeed, I find the analogy used by Dr. Gervay-Hague at trial apt. She explained

Plaintiffs' application of the saccharide definition as expanding the boundaries of a city to include the space around it. If this is allowed to repeat—meaning one continues to add the space around what has just been added—then the city has no boundary, it simply becomes everything. 7/12/2012 Gervay-Hague Trial Tr. at 12, 17. ("Well, it's as if the patent is defining a confined space. For example, a city and with the expanded definition by GSK, it opens up to essentially the universe."). Such a result is obviously incorrect. The patentees did not intend, nor can they be allowed, to claim almost all compounds as saccharides.

Dr. Byrn recognized that there must be a stopping point to the number of reduced derivate reactions that are allowed, because in his words if you allow an infinite amount of reductions "everything would be a saccharide." Byrn Trial Tr., 7/20/2012 at 96. He proposed that the stopping point would be that only a compound considered to be a "deoxyalditol" could be a saccharide—so any alditol (or sugar alcohol) that has had an oxygen removed by a further reduction—fits within this definition. Id. He based this opinion, largely, on the IUPAC Rules. Id. at 100 ("I'm not going beyond that generally because there isn't much deoxyalditol in the IUPAC. That's the end of it. We stop right here. We can't keep reducing forever."). Dr. Byrn's opinion is conclusory. Nothing from the patent suggests that a reduced derivative should be limited to an alditol that has had an oxygen element removed nor is there anything in the IUPAC Rules specifically supporting his opinion. Instead, the patent specification lists sugar alcohol as an example of a reduced derivative; sugar alcohol is an alditol. To suggest that one can be allowed to take one more, and only one more, reduction exemplifies the speculative nature of Plaintiffs' position. There appears to be no principled reason to stop at two reductions, other than that it conveniently encompasses propylene glycol, and other than Dr. Byrn's observation

that one has to stop somewhere. That stopping point should be determined by the intrinsic evidence and the patent itself, not conjecture based on ambiguous extrinsic evidence.

By way of further example, I note the parties' discussion of propylene glycol and its relationship to propane. Dr. Byrn testified at trial that he did not believe propane is a saccharide for purposes of the '052 patent and he based his opinion on the fact that propane was not in the 1969 or the 1996 IUPAC Rules:

> Q. If you look at the IUPAC rules in 1969 or 1996, are you going to find anything about propane in there?
>
> A. No.
>
> Q. Does that absence of propane affect your opinion that propylene glycol is a saccharide?
>
> A. Yes, it does.
>
> Q. How?
>
> A. Well, because by the absence of propane, it tells me you cannot go that far. It can't be considered a saccharide.
>
> Q. In 1987, would a person of ordinary skill in the art come to that same conclusion in your opinion?
>
> A. Yes.
>
> Q. Why?
>
> A. Well, because the rules, classification rules are out there, and these reactions and descriptions are in Solomons, and the analysis would be straightforward to reach that conclusion.

7/10/2012 Byrn Trial Tr. at 100-101. This same analysis should apply with equal weight then to propylene glycol, which is not referenced directly in either the 1969 or 1996 IUPAC Rules. If "you cannot go that far" to say that propane is a saccharide then you cannot go that far to say that propylene glycol is a saccharide. This example illustrates what is so troubling with Plaintiffs'

analysis. Why should the Court limit the definition of saccharide based on what are in certain editions of the IUPAC Rules or based on whether a compound is a derivative of an alditol or sugar alcohol? Nothing in the patent, the specification, the claims, or the file history suggests any link between the patent's definition of saccharide and the IUPAC rules or any other piece of extrinsic evidence.

I find, as a matter of law, that the definition of saccharide set forth in the patent should be read to include the three enumerated base saccharide compounds (a monosaccharide, an oligosaccharide, or a polysaccharide) or a compound that is derived through a single reduction of the base saccharide compounds. This is the most logical conclusion based upon the patent itself rather than construing what the extrinsic evidence does not say.

b. Infringement

Plaintiffs bear the burden of showing that Defendants infringe the '052 patent by a preponderance of the evidence. Mannesmann Demag Corp. v. Engineered Metal Prods. Co. Inc., 793 F.2d 1279, 1282 (Fed. Cir. 1986). To prove infringement of a patent claim to a method, Plaintiffs must prove that every step in the method is performed by the accused process, either literally or under the doctrine of equivalents. Canton Bio-Medical, Inc. v. Integrated Liner Techs., Inc., 216 F.3d 1367, 1370 (Fed. Cir. 2000). The absence of any one limitation of a claim in the accused process precludes a finding of literal infringement of that claim. Kahn v. GMC, 135 F.3d 1472, 1477 (Fed. Cir. 1998).

Specifically, for literal infringement, the accused product or process must "contain each limitation of the claim exactly" and there cannot be "any deviation from the claim." Litton Sys. v. Honeywell, 140 F.3d 1449, 1454 (Fed. Cir. 1998); see also Telemac Cellular Corp. v. Topp Telecom, Inc., 247 F.3d 1316, 1330 (Fed. Cir. 2001). If each limitation is not satisfied exactly,

infringement may still be found under the doctrine of equivalents, but only if the difference between any claim limitation not literally present and the corresponding element in the accused device or process is "insubstantial." Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 39-40 (1997); Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1139, 1351 (Fed. Cir. 2003). An accused device may infringe under the doctrine of equivalents only if it possesses all of the limitations of the relevant claim either literally or equivalently. See Warner-Jenkinson Co., 520 U.S. at 40-41.

Thus, a determination of infringement requires a two-step analysis. "First, the court determines the scope and meaning of the patent claims asserted.... [Second,] the properly construed claims are compared to the allegedly infringing device." Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1454 (Fed.Cir.1998) (en banc) (citations omitted). Step one, claim construction, is an issue of law. Markman v. Westview Instruments, Inc., 52 F.3d 967, 970-71 (Fed. Cir.1995) (en banc), aff'd, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Step two, comparison of the claim to the accused device, requires a determination that every claim limitation or its equivalent be found in the accused device. See Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 29 (1997).

There are four claims, two independent and two dependent, in the '052 patent. Plaintiffs contend that Defendants literally infringe claim 3 and infringe the other claims under the doctrine of equivalents. Claim 1 is an independent, method claim for dissolving Argatroban or its salt in a solvent containing (1) ethanol, (2) water, and (3) a saccharide. Claim 3 is identical except it is directed towards a composition for injection. Claim 2 depends on claim 1 and limits the saccharide to at least one of the following: sorbitol, glucose, glycerin, and sucrose. Claim 4 is identical but depends on claim 3.

Defendant admits its accused product meets all the claim limitations save one: its solution uses propylene glycol instead of a saccharide. 7/11/2012 Koneru Trial Tr. at 168; Hikma Paragraph IV Letter at 6, DTX-060 at GSK_PI 000799. Thus, the battle is joined on this one, narrow issue: is propylene glycol a saccharide. If the two are either literally identical or equivalent to one another, then Defendants infringe; if they are not the same, then Defendants do not infringe.

a. Literal Infringement

Plaintiffs argue that only claim 3 is literally infringed. 7/11/2012 Byrn Trial Tr. 31. The Court has accepted the parties' agreement that the patent defines the term saccharides as "monosaccharides, oligosaccharides, polysaccharides, and their reduced derivatives (for example sugar alcohol) which are soluble in water." '052 patent, col. 3:59-64, PTX-001. The Court has also found that to be a reduced derivative of one of the base saccharide compounds, the compound in question must result from a single reduction reaction of the base saccharide compound.

Looking first to patent itself, it treats propylene glycol as an alcohol and not a saccharide. 7/10/2012 Byrn Trial Tr. at 212-213. In particular, it says: "In the method for dissolving an arginineamide according to the invention, the arginineamide and/or its salt is dissolved in the solvent of alcohol and water. As the alcohols used in the invention…dihydric alcohols such as ethylene glycol, propylene glycol and the like…Methanol, ethanol, propylene glycol and polyethylene glycol are preferable." '052 Patent, col. 3:42-50, PTX-001. The patent never states the propylene glycol is a saccharide. 7/11/2012 Byrn Trial Tr. at 6. Further, the original claims treated propylene glycol exclusively as an alcohol. PTX-002 at GSK_PI 002119-2120 (original claims 4 and 17). Plaintiffs argue that this intrinsic evidence has little weight because glycerin is

referred to as both an alcohol and a saccharide. 7/11/2012 Hale Trial Tr. at 74. Defendants rejoin and say that this shows the patentees knew how to describe a solvent that might not be conventionally thought of as a saccharide, such as glycerin, if they desired. 7/12/2012 Gervay-Hague Trial Tr. at 28-29. While Plaintiffs are correct that the patent is silent as to whether propylene glycol is a saccharide, that does not militate against the logic of Defendants' argument. The patentees could have listed propylene glycol as both an alcohol and a saccharide if they intended to claim propylene glycol, which is not generally considered a saccharide, and they knew how to describe a compound as both an alcohol and a saccharide if they so choose. Indeed, after the patentees canceled their original claims, they included glycerin within the list of claimed saccharides for claims 2 and 4.

Plaintiffs argue that aside from propylene glycol's treatment as an alcohol, nothing in the specification or the claims explicitly says that propylene glycol is not a saccharide. Yet the file history is also replete with statements showing that at the time of prosecution, the patentees did not consider propylene glycol to be a saccharide. Plaintiffs argue that the statements made in the file history do not rise to the level of a clear and unambiguous waiver. Those points, however, go to whether the prosecution history estops Plaintiffs from positing their doctrine of equivalents claims. As such, these arguments will be discussed in more detail within that context. Nevertheless, the file history is still instructive in determining whether propylene glycol was considered to be within the literal scope of the claim. After the patent examiner rejected the application over Jensen—which disclosed the use of propylene glycol, sorbitol, and ethanol—the patentees noted that "the Jensen et al reference discloses a composition which ***contains a saccharide, i.e., sorbitol***….one of skill in the art ***would not be led by Jensen to employ a saccharide***…the above discussed references ***do not show a saccharide***." PTX-002 at GSK_PI

002271-2272. The patentee said the only saccharide disclosed in Jensen was sorbitol. The term "i.e." is shorthand for the Latin phrase *id est* meaning "that is." It is meant to specify or to add clarity to a statement. See Eaton Corp. v. ZF Meritor LLC, No. 03-74844, 2007 U.S. Dist. LEXIS 74183, at *11 (E.D. Mich. Oct. 4, 2007). This should not be confused with the term "e.g.," which is shorthand for the phrase *exempli gratia* meaning "for example." Substituting English for Latin then, the patentees said that Jensen discloses a solution that contains a "saccharide, that is sorbitol." If sorbitol was the only saccharide disclosed in Jensen, then the patentees did not consider propylene glycol a saccharide at the time of the application. Moreover, the patentee considered propylene glycol to be an alcohol only: "The facts are that propylene glycol is not ethanol, and reserpine certainly is not the claimed arginineamide compound of the present invention." PTX-002 at GSK_PI 002253. By comparing propylene glycol only to ethanol, the claimed alcohol compound, and not a saccharide, the patentees signaled that they believed propylene glycol to only be an alcohol.

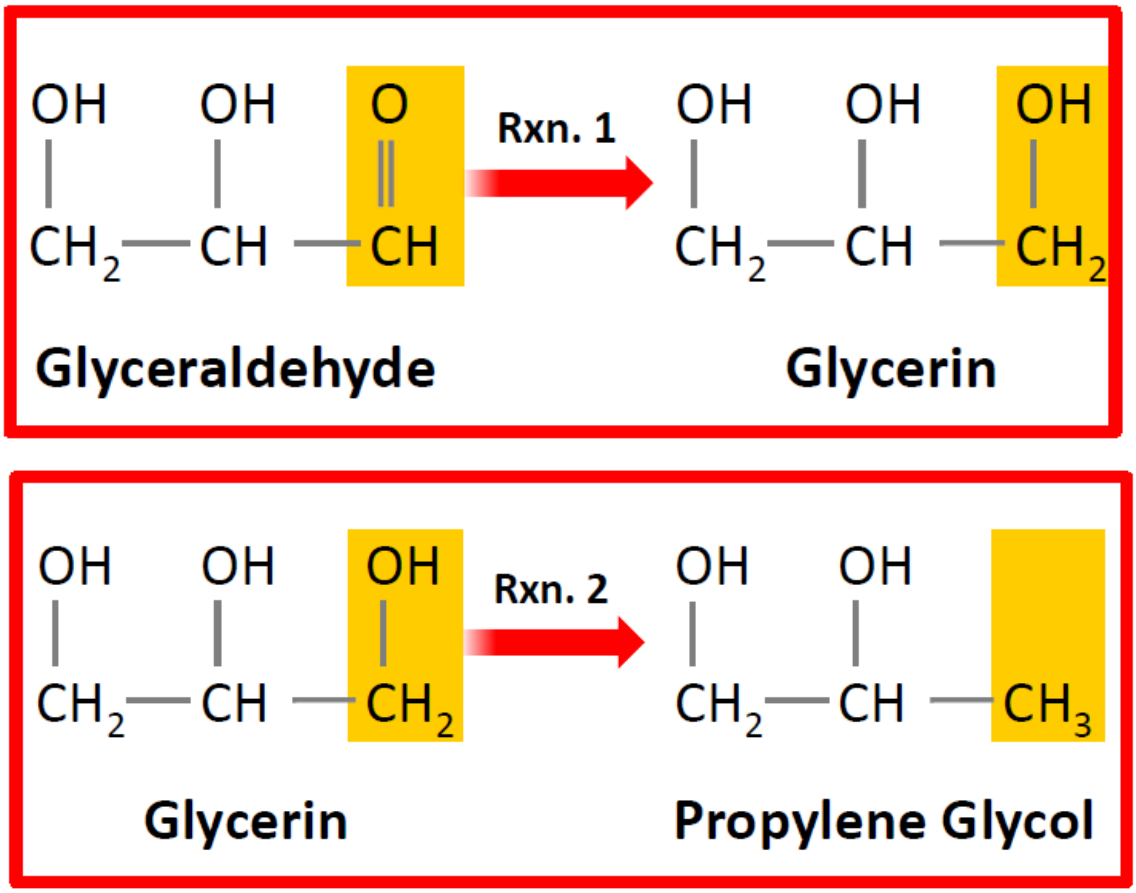
The Blodinger reference also disclosed the use of propylene glycol with other excipients. Again, the patentees noted the reference disclosed the use of propylene glycol, but referred to it as part of the alcohol solution and said that "Certainly there is no reference to a saccharide on the part of Blodinger." PTX-002 at GSK_PI 002273. In an earlier response, the applicants explained that Blodinger only disclosed alcohol co-solvents, including propylene glycol, but that this did not show how a more effective solution could be achieved by adding a saccharide: "However, whatever level of enhanced or increased solubilization is achieved by a water-alcohol combination [shown in Blodinger]…such enhanced solubilization certainly would not suggest the results demonstrated at the bottom of page 3 of the Ofuchi Declaration for the solubilization of the claimed arginineamide compound in an aqueous medium containing ethanol and, in this

case, sorbitol as a saccharide." Id. at GSK_PI 002254-2255. Based on the intrinsic evidence, therefore, it is clear that at the time of filing, the applicants did not consider propylene glycol to be a saccharide.

Although this strongly buttresses Defendants' argument, it does not foreclose the issue. It is not clear that the statements, in and of themselves, would amount to a disclaimer of claim scope. I recognize that in some instances the patent or the file history "may reveal an intentional disclaimer, or disavowal, of claim scope by the inventor." Ventana Medical Systems, Inc. v. Biogenex Laboratories, Inc., 473 F.3d 1173, 1181 (Fed. Cir. 2006) (quoting Phillips, 415 F.3d at 1316) (internal citations omitted). Yet such disclaimers are rare and will only be found when the disavowal is "clear." Thorner v. Sony Comp. Entm't Am. LLC, 669 F.3d 1362 (Fed. Cir. 2012) ("Mere criticism of a particular embodiment encompassed in the plain meaning of a claim term is not sufficient to rise to the level of clear disavowal."). This is a related, but separate issue than prosecution history estoppel, which applies to a doctrine of equivalents analysis.

Nevertheless, even putting patentees' treatment of propylene glycol solely as an alcohol aside, Plaintiffs have not shown by a preponderance of the evidence that propylene glycol is a saccharide under the patent's definition. The only question for the Court is whether propylene glycol is a "reduced derivative" of a saccharide. The Court has found that one may convert a monosaccharide to propylene glycol through a reaction that involves two reductions. In particular, it is possible to start with a monosaccharide (glyceraldehyde) and reduce it to glycerin, which is also called an alditol or sugar alcohol. Glycerin is within the definition of saccharide as used by the '052 patent as are alditols and sugar alcohols. One may then reduce glycerin further to propylene glycol. This is not the common way one would derive propylene

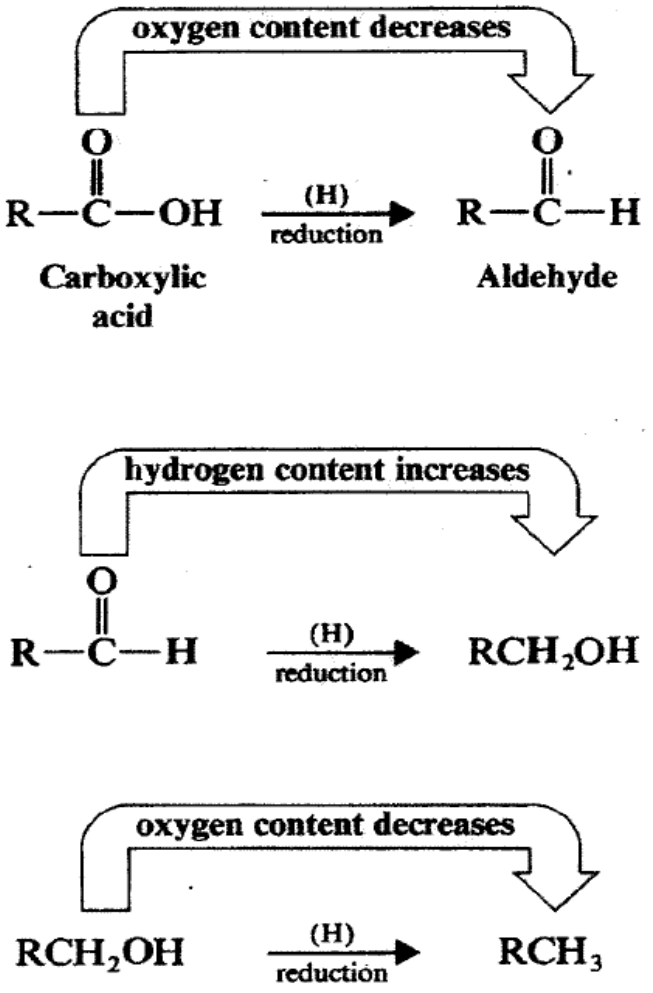
glycol. Important for purposes here, however, is that there are undoubtedly two reactions involved in this process, as Plaintiffs showed at trial:



Byrn Demonstrative Ex. at 12-13, PDX-3; 7/10/2012 Byrn Trial Tr. at 89-93.[8] Further, the literature that Dr. Byrn and Dr. Hale relied upon to discuss these reactions also clearly treat these types of reductions as separate processes. For example, Solomons generally discusses these types of reduction reactions as distinct processes: "Reduction of an organic molecule usually corresponds to increasing its hydrogen content or to decreasing its oxygen content. For example, converting a carboxylic acid to an aldehyde ***is a reduction*** because the oxygen content is decreased. Converting an aldehyde to an alcohol ***is also a reduction***. Converting an alcohol to

[8] Dr. Byrn explained at trial that these demonstrative exhibits only provide an abstract illustration of the process. 7/10/2012 Byrn Trial Tr. at 93 (explaining the reductions "can be complex and involve some intermediate [steps]").

an alkane ***is also a reduction***." T.W. Solomons Fundamentals of Organic Chemistry at 613, PTX-025 at GSK_PI 000100. The text illustrates these reactions separately as well:



Id. Because two separate and distinct reduction reactions are required under Plaintiffs' analysis, propylene glycol is not a compound that is derived through a direct, single reduction of one of the base saccharide compounds listed in the patent.

This conclusion is bolstered by the difficulty of the second reaction, the fact that it will not produce propylene glycol in all instances, and that it produces other unrelated compounds. This was stressed by Dr. Gervay-Hague, but recognized by Dr. Byrn as well:

Q. What you show as reaction 1 is a pretty mild reduction reaction. Correct?

A. I think I could generally agree with that.

Q. But you are putting on two extra hydrogens. Right?

A. Correct.

Q. When we go to that second reaction to go from glycerin to propylene glycol, you have to lose the oxygen by breaking a carbon oxygen bond. Right?

A. Correct.

Q. That's harder to do chemically than step 1, which is converting the glyceraldehyde into glycerin.

Right?

A. Correct. I think generally taking oxygen out is harder.

Q. In fact, it's probably a lot easier to add the two hydrogen atoms than it is to break that carbon oxygen bond. Right?

A. I think that's generally correct.

Q. What you've got is reaction 2; you just don't know how that would work. Right?

A. There are several different possible mechanisms, and I don't think it's being completely worked out, correct.

Q. You don't really know how it would work. Right?

A. You don't really know.

7/11/2012 Byrn Trial Tr. at 27-28. This reduction therefore is not only additional to the first, but it is difficult and unpredictable. Considering all of these factors, I find that any link between a base saccharide compound and propylene glycol is simply too attenuated to fall within the patent's definition of saccharide.

Irrespective of the number of reactions, Plaintiffs offered evidence that propylene glycol can be considered a derivative of a saccharide based on the extrinsic evidence. Although they

admitted that no reference directly links or equates propylene glycol with a saccharide (7/11/2012 Byrn Trial Tr. at 6), they rely on a number of definitions from the 1969 and 1996 IUPAC Rules and other texts to argue that propylene glycol could also be considered a deoxyalditol, which could also be considered a carbohydrate, which could also be considered a saccharide. 7/11/2012 Hale Trial Tr. at 62-63. The 1969 IUPAC Rules define "deoxyalditol" as follows: "The name of an aldose derivative having a terminal CH3 and CH2OH group is derived from that of the appropriate alditol." 1969 IUPAC Rules at 3995, PTX-022 at GSK_PI 000046. Dr. Hale based his opinion that propylene glycol is the same as deoxyalditol, in part, on Rodd's Chemistry of Carbon Compounds. PTX-046. That text contains a description of deoxyalditols and a general representation of the chemical composition in which the CHOH group is repeated *n* times. The text neither defines the variable *n* nor gives any limits to it. Dr. Hale opined that this composition is the same as propylene glycol when $n = 1$.

Dr. Byrn and Dr. Hale also opined that propylene glycol should therefore be considered a carbohydrate, which they believed to be equivalent to a saccharide. 7/11/2012 Hale Trial Tr. at 64-65 (relying on Jaroslav Stanek, Monosaccharides, PTX-045); 7/10/2012 Byrn Trial Tr. at 102-104. The primary basis for Dr. Byrn's opinion was a definition of carbohydrates from the 1996 IUPAC Rules:

> The generic term 'carbohydrate' includes monosaccharides, oligosaccharides and polysaccharides as well as substances derived from monosaccharides by reduction of the carbonyl group (alditols), by oxidation of one or more terminal groups to carboxylic acids, or by replacement of one or more hydroxy group(s) by a hydrogen atom, an amino group, a thiol group or similar heteroatomic groups. It also includes derivates of these compounds.

IUPAC 1996 Rules at 1924, PTX-023 GSK_PI 006045; 7/10/2012 Byrn Trial Tr. at 110. Dr. Hale also relied on the fact that propylene glycol is listed in the Collins text, which is titled "Carbohydrates" although he admitted on cross-examination that other compounds are included

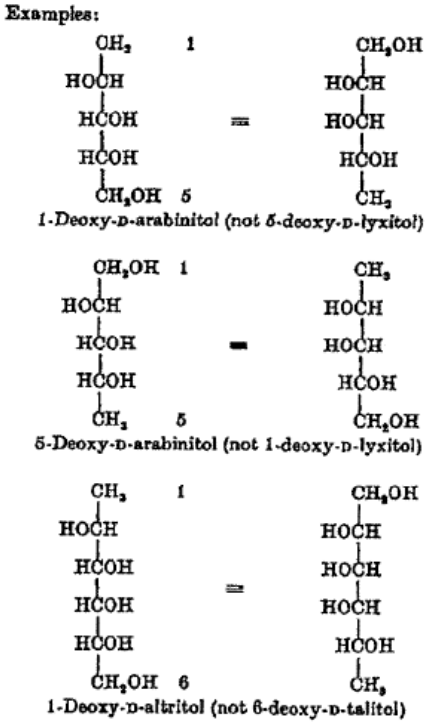
in the book besides carbohydrates. 7/11/2012 Hale Trial Tr. at 102-104. Other academic sources suggest that a saccharide is a type, albeit the most common type, of carbohydrate. Pigman & Horton, Carbohydrates at 3, DTX-057 at GSK_PI 021504; see also 7/11/2012 Hale Trial Tr. at 112-113; 7/12/2012 Gervay-Hague Trial Tr. at 42-43, 59 (opining that saccharide and carbohydrate were not interchangeable, but later admitting that they often are treated as such).

Plaintiffs' logic then can be summed up as follows: propylene glycol is a deoxyalditol; a deoxyalditol is a derivative of an alditol (sugar alcohol); therefore, a deoxyalditol is a carbohydrate and because all carbohydrates are saccharides then deoxyalditol is a saccharide; and because propylene glycol is a deoxyalditol, propylene glycol is also a saccharide. 7/10/2012 Byrn Trial Tr. at 110-111; 7/11/2012 Hale Trial Tr. at 62-69. This logic, much like the chain of multiple reactions and steps to go from a saccharide to propylene glycol, is too attenuated to be persuasive. First, it is not clear whether propylene glycol is in fact a deoxyalditol nor is it clear that all carbohydrates, as understood by the '052 patent, are saccharides. What is clear is that the patent claims saccharides and does not mention carbohydrates and that propylene glycol is not a monosaccharide, oligosaccharide, a polysaccharide, or a compound that can be derived from a direct reduction of one of these compounds.

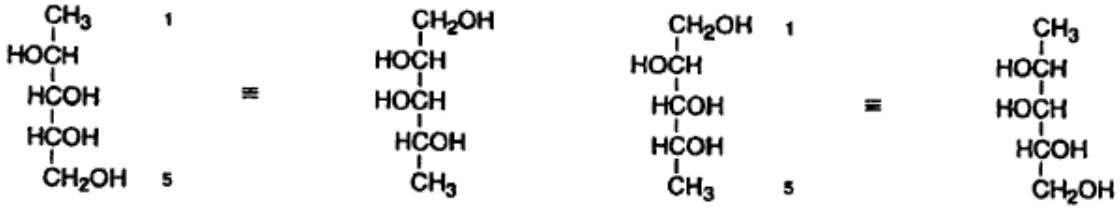
Whether or not all saccharides are carbohydrates or vice versa is unavailing for Plaintiffs' argument. Deoxyalditol is discussed as an "aldose derivative" and as an "alditol derivative." Dr. Hale gave this explanation: "[1-deoxyalditol] is derived from an aldose derivative." 7/11/2012 Hale Trial Tr. at 63. Again, there is the same double-derivative issue, but now it is between an alditol and deoxyalditol, which are essentially different names for the same compounds that were discussed above. Deoxyalditol could be a derivative of glycerin, which is a derivative of glyceraldehyde. This raises the same issues regarding Plaintiffs' argument of the two reduction

conversion of glyceraldehyde to propylene glycol. See, e.g., 7/10/2012 Byrn Trial Tr. at 104. Because one must go from an aldose (which is a saccharide) to an alditol (such as glycerin, which is a reduced derivative of a saccharide and therefore within the claims of the patent) to a deoxyalditol, there is no direct link between a saccharide and a deoxyalditol for purposes of the '052 patent. 7/12/2012 Gervay-Hague Trial Tr. at 42.

Further, I found Dr. Gervay-Hague's testimony persuasive that in all the scientific literature referring to deoxyalditol, none of the references discuss the propylene glycol molecule. 7/12/2012 Gervay-Hague Trial Tr. at 40-41. She argues this is because deoxyalditol must always have at least three hydroxyl groups, while propylene glycol will by definition have only two because it is a glycol and dihydric. Id. at 79. Plaintiffs stressed at trial that Dr. Gervay-Hague had no support for her assertion besides her own expertise and experience. First, Dr. Gervay-Hague's expertise and experience speak for themselves; she is a Fellow of the American Chemical Society and even Plaintiffs' counsel acknowledged her impeccable credentials. 7/11/2012 Hale Trial Tr. at 99; 7/12/2012 Gervay-Hague Trial Tr. at 85-86. Furthermore, consistent with Dr. Gervay-Hague's opinion, in all examples that Plaintiffs showed of a complete deoxyalditol molecule, there were at least three hydroxyl groups:



1969 IUPAC Rules at 3995, PTX-022 at GSK_PI 000046.



1996 IUPAC Rules at 1946, PTX-023 at GSK_PI 006067. Dr. Hale also noted the deoxyalditol molecule he discussed in Rodd's was in a chapter named "Penta-, Hexa-, and Higher Polyhydric Alcohols." 7/11/2012 Hale Trial Tr. at 61 (discussing Rodd's Chemistry of Carbon Compounds at 55-57, PTX-046 at GSK_PI 021585-587). Therefore, propylene glycol, which all parties agree is a dihydric alcohol, would not be included within that chapter that concerns molecules that had five, six, or more hydroxyl groups. This same chapter lists examples of deoxyalditols in two tables (Tables 7 and 8), but propylene glycol does not appear in these tables.

Rather, the scientific literature overwhelmingly refers to propylene glycol either as propylene glycol or as 1,2-propanediol. 7/12/2012 Gervay-Hague Trial Tr. at 40-41. And whether it is called propylene glycol or 1,2–propanediol, the literature classifies the molecule as an alcohol.[9] Therefore, I cannot find that propylene glycol is equivalent to deoxyalditol. Even if it were, I do not find that deoxyalditol would necessarily fall within the definition of saccharide as used by the patent because it too involves a double-reduction derivative reaction to be obtained from a base saccharide compound.

Claim 3 of the '052 patent is not literally infringed by the Accused Product because propylene glycol is not a saccharide within the meaning of the patent.[10]

b. Infringement Under The Doctrine of Equivalents

Plaintiffs also argue that even if propylene glycol is not literally a saccharide for claim 3, it is equivalent. Further, they argue that Defendants' process is equivalent to claim 1 and that Defendants infringe claims 2 and 4 under the doctrine of equivalents because propylene glycol is equivalent to glycerin, one of the named saccharides. According to Plaintiffs' experts, propylene glycol performs the same function—to improve the solubility of the solution—as does a saccharide; it performs in the same manner by forming a co-solvent system with ethanol and

[9] Dr. Hale himself used the term 1,2 propanediol when referring to propylene glycol in an earlier academic paper. Hale et al., Morpolino-glucosides: new potential sweeteners derived from sucrose at 268, DTX-069-001. He also agreed that propanediol is the "most common usage in the literature." 7/11/2012 Hale Trial Tr. at 111.

[10] Defendants also rely on Dr. Byrn's statements made during the course of the Mitsubishi Litigation. After reviewing a catalog of solvents, he explained that there were two out of 2,000 systems that used water, ethanol, and a saccharide. Defendants point out that four other solutions (Dilantin, Valium, Lanoxin, Nembutal Sodium Solution) contained in that volume list propylene glycol, ethanol, and water. 7/11/2012 Byrn Trial Tr. at 14; DTX-008 at 2-4, DTX-063 at 2-4. Dr. Byrn testified that he reviewed that catalog by doing keyword searches of the specific saccharides enumerated in Claims 2 and 4. This leads to the conclusion that he reviewed the patent and did searches for solvents he believed were saccharides, yet he did not search for propylene glycol, because after reviewing the patent he did not consider it to be a saccharide.

water; and achieves the same result of a higher concentration of Argatroban than do other solvent alternatives.

The doctrine of equivalents broadens a patent claim to cover "those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." AquaTex Indus. v. Techniche Solutions, 419 F.3d 1374, 1382 (Fed. Cir. 2005) (quoting Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 733 (2002)). "An element of an accused product is equivalent to a claim limitation if the differences between the two are insubstantial, a question that turns on whether the element of the accused product performs substantially the same function in substantially the same way to obtain the same result as the claim limitation." Absolute Software, Inc. v. Stealth Signal, Inc., 659 F.3d 1121, 1139-40 (Fed. Cir. 2011).

i. Claim 3

Plaintiffs stressed at trial that the inventive step of the patent was using a three-solvent solution to enhance the solubility of Argatroban in water and that either the separate solvents or a combination of just two of them would not provide an adequate solution. 7/10/2012 Byrn Trial Tr. at 64-65. In support of this, Plaintiffs point to the Ofuchi Declaration in the file history, in which the patentees submitted reports that showed concentrations of Argatroban in differing solutions. An ethanol-water-saccharide solution had a rate of 300 mg/ml, which was 70 times better than the next best solution, ethanol alone. Dr. Byrn explained that the solubility of Defendants' propylene glycol solution is at least 100 mg/ml, which demonstrates the equivalence of the Accused Product to the patented-product, as the Accused Product also far exceeds any other solvent such as ethanol alone.

Dr. Gervay-Hague opined that there was no equivalence because, in part, [redacted] unlike Plaintiffs' invention. [redacted] A review of the evidence and testimony shows that using propylene glycol instead of a saccharide does not appear to produce substantially similar results.

A doctrine of equivalents analysis is often contingent on how abstract or detailed the inquiry. Plaintiffs would have me look broadly and find that Defendants replace propylene glycol for sorbitol in a solution that increases the solubility for Argatroban. Thus, Plaintiffs argue, they are similar. For support, Plaintiffs point to Defendants' NDA [redacted] Byrn Trial Tr., 7/20/2012 at Hikma New Drug Application, Module 1 at 25, PTX-065 at H 000033; Hikma New Drug Application, Module 2 at 17, PTX-066 at H 000135. There is no question that propylene glycol is meant to act as a solvent in lieu of sorbitol or a saccharide. The question is whether the two compounds are substantially the same or whether the differences between the two are trivial. Additionally, Plaintiffs point to Exela's statement in the NDA that [redacted] 7/11/2012 Koneru Trial Tr. at 202-203. Again, I do not find this elucidating on whether the differences between propylene glycol and saccharide are insubstantial. It is undisputed, and immaterial, that the Accused Product was meant as a pharmaceutical substitute for Plaintiffs' Product.

First, I note that the actual solution rates are quite different when propylene glycol is used instead of a saccharide. Defendants' product has 520 mg/ml of propylene glycol per dose while Plaintiff's Argatroban product has 250 mg/ml of D-Sorbitol, despite having the same amount of

active ingredient and similar amounts of ethanol. Hikma New Drug Application, Module 1 at 25, PTX-065 at H 000033. Additionally, the Accused Product contains a propylene glycol concentration of 1300 mg/vial as compared to Plaintiffs' Product that has a concentration of 750 mg/vial. Id. The two agents do not appear to operate in substantially the same way as it takes over twice as much propylene glycol to achieve the result of Plaintiffs' product with sorbitol and thus the Accused Product needs nearly twice as much concentration of propylene glycol as Plaintiff's Product does of D-Sorbitol.

This is consistent with Plaintiffs' experiments and reports regarding Argatroban in a solution of only water and alcohol, that it is not as effective as a solution involving saccharides, water, and alcohol. '052 patent, figs. 1-4, PTX-001. Indeed, none of the saccharides listed in the patent is nearly as effective on its own for improving solubility as is propylene glycol, further supporting a finding that they are not equivalent. For example, figure 2 in the patent shows the solubility of Argatroban in a water and saccharide at a very low rate of 1 mg/ml. Id. at fig 2, col. 5:10-23 ("As shown in FIG. 2, the solubility of argipidine in the aqueous sorbitol solution was low and it was the [*sic*] substantially same as the solubility of argipidine in water."). The Ofuchi Declaration, submitted during the prosecution history, lists a number of experiments where the patentees used only a saccharide-water solution and again the results barely reached above 1 mg/ml. Ofuchi Decl. at 2-3, PTX-002 at GSK_PI 002211-2212 ("As clear from the above results, the solubility of argipidine in water is very low and its solubility hardly increases by adding any saccharide into water."). Using a solution of propylene glycol (at room temperature) and water, Argatroban solubilizes to greater than 51 mg/ml.[11] Using propylene glycol instead of

[11] Dr. Koneru testified that Exela was able to develop a propylene glycol solution with higher solubility rates, closer to [redacted], at room temperature [redacted]. 7/11/2012 Koneru Trial Tr. at 149; DTX-051 at EXCELA 000061.

a saccharide produces significantly higher solubility rates with Argatroban. Dr. Byrn testified at trial as to how ineffective saccharide was for dissolving Argatroban by itself. 7/10/2012 Byrn Trial Tr. at 186.[12] No doubt, this is in part due to the fact that Argatroban reacts differently with different types of compounds. 7/12/2012 Dr. Yalkowsky Trial Tr. at 137-140. Therefore, I find that propylene glycol is not equivalent to a saccharide under the doctrine of equivalents because it does not perform in substantially the same way and does not product substantially the same result as using a saccharide.

Plaintiffs' position is further belied by the file history. A patentee, or its licensee, can be estopped from relying on the doctrine of equivalents when the patentee surrenders that same subject matter during the patent's prosecution by either amendment or argument. Pharmacia & Upjohn Co. v. Mylan Pharm., Inc., 170 F.3d 1373, 1376-77 (Fed. Cir. 1999). To apply, the narrowing amendment must have been made "for purposes of patentability" or the surrender by argument must have been made "clearly and unmistakably" to an examiner. Salazar v. Procter & Gamble Co., 414 F.3d 1342, 1344 (Fed. Cir. 2005). Nevertheless, the Court must bear in mind that it is "particularly important not to limit claim scope based on statements made during prosecution '[a]bsent a clear disavowal or contrary definition." Digital-Vending Services Intern., LLC v. University of Phoenix, Inc., 672 F.3d 1270, 1273 (Fed. Cir. 2012) (citing August Tech. Corp. v. Camtek, Ltd., 655 F.3d 1278, 1286 (Fed. Cir. 2011) (quoting Home Diagnostics, Inc. v. LifeScan, Inc., 381 F.3d 1352, 1358 (Fed. Cir. 2004)). The reason for such a stringent rule is "because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the

[12] Dr. Hale testified at some length about the similarities between the chemical structures of sorbitol, which all parties agree is a saccharide, and propylene glycol. 7/11/2012 Hale Trial Tr. at 89-94. But the experimental evidence of the patentees showed that sorbitol is not nearly as effective as a solution by itself as is propylene glycol. Sorbitol needs the addition of an alcohol as well as water to be effective whereas propylene glycol does not.

specification and thus is less useful for claim construction purposes." Id. (quoting Phillips, 415 F.3d at 1317).

Defendants make several arguments regarding the prosecution history. First, they point to the applicants canceling the original claims, which claimed a solution of water and alcohol, suggesting that this amendment was made for purposes of patentability and precludes a doctrine of equivalents analysis here because while there is a dispute whether propylene glycol is a saccharide, it is certainly an alcohol. In particular, patentees originally claimed a solution that had only alcohol and water; dependent on these claims, the applicants claimed a solution where the alcohol was "selected from methanol, ethanol, propylene glycol, and polyethylene glycol." PTX-002 at GSK_PI 002119 (original claim 4).[13] Therefore, Defendants argue that Plaintiffs cannot now reclaim what the patentee abandoned. I am not convinced this forecloses the entire doctrine of equivalence analysis as Defendants suggest. In particular, Defendants have not shown that their product would have been covered by the original claim because in addition to propylene glycol and water, there is the addition of ethanol. Further, the claims of the '052 patent were present in the original claims, albeit in slightly modified form. The saccharide element was never added to secure patentability or overcome prior art.

Nevertheless, as I have already noted, this does support the other intrinsic evidence that patentees considered propylene glycol only as an alcohol and not a saccharide. In addition to original claims 4 and14, original claims 9 and 22 list the same saccharides that are claimed in claims 2 and 4 with the exception of glycerin. In making their amendments the patentees clearly identified glycerin, which is also considered an alcohol, and included it as a saccharide. Patentees could have done the same with propylene glycol if they considered it to be a saccharide

[13] Original claim 17 has identical language but depends on original claim 14. PTX-002 at GSK_PI 002120.

or equivalent to a saccharide as apparently they did with glycerin. 7/11/2012 Hale Trial Tr. at 74 (recognizing that the patentees disclosed glycerin as being both a saccharide and an alcohol).

More troubling than the amendments are the statements that the applicants made in distinguishing prior art that discussed propylene glycol. The statements that the patentees made regarding Jensen are particularly enlightening. It is clear that the applicants did not consider propylene glycol to be a saccharide because if they had, then they likely could not have successfully overcome the examiner's obviousness objection.

Jensen disclosed a solution that contained water, propylene glycol, ethanol, and sorbitol. The primary difference is that it claimed a solution for reserpine rather than Argatroban and it said that sorbitol was used for chemical stability and propylene glycol and ethanol were needed to act as solvents as well as chemical stability. In distinguishing their invention from this disclosure, the applicants focused squarely on the fact that sorbitol was the only saccharide disclosed in Jensen and it was used for stability rather than solubility:

> It is appropriate here to consider Jensen et al…since it describes a therapeutic composition comprising reserpine in an aqueous solvent system of ethanol, propylene glycol, and sorbitol. Although the Jensen et al reference discloses a composition which ***contains a saccharide, i.e., sorbitol***, nevertheless, as disclosed at column 1, lines 59-60 of the reference, sorbitol is only used as a vehicle which increases chemical stability and the therapeutic effect of the disclosed composition. There is absolutely no teaching or suggestion in the reference that sorbitol is employed to increase the solubility of reserpine in the liquid medium employed. Accordingly, one of skill in the art ***would not be led by Jensen to employ a saccharide*** as a solubility enhancing agent for a therapeutic compound.
>
> In the light of the fact that the above discussed references ***do not show a saccharide in a solubility enhancing role*** and in view of the fact that none of the other references show or suggest the use of a saccharide in a therapeutic composition, it is clear that a very important aspect of the invention, as demonstrated by the comparative evidence of record in this case, is not shown or suggested by the prior art.

PTX-002 at GSK_PI 002271-2272 (emphasis added). Most damaging to Plaintiffs' argument now, is that Jensen specifically disclosed propylene glycol as a solvent for reserpine which is "practically insoluable in aqueous media." Jensen, col. 1:65-2:2, DTX-010. The applicants recognized this in the file history when they described Jensen as teaching "the likes of propylene glycol and ethanol" as "an alcohol solvent." Plaintiffs argue that a close read of Jensen does not teach using propylene glycol as a solvent. But this is how the examiner and the applicants understood the reference when they made their statements. 7/12/2012 Gervay-Hague Trial Tr. at 12, 15-17. Plaintiffs' expert, Dr. Hale, concurred with this analysis. 07/11/2012 Hale Trial Tr. at 120-121 ("Well [Jensen is] saying [propylene glycol] acts as a solvent for reserpine, so that means that propylene glycol and ethanol, both of them, act as solubilizing agents for reserpine.").[14] Within this context, patentees' arguments would have likely failed if they considered propylene glycol to be a saccharide. It would therefore have been incorrect for the patentees to represent, as they did, that the "discussed references do not show a saccharide in a solubility enhancing role" or that "one of skill in the art would not be led by Jensen to employ a saccharide as a solubility enhancing agent for a therapeutic compound." Moreover, the patentees clearly signaled that they considered sorbitol to be the only saccharide disclosed by the Jensen reference.

This if further buttressed by the fact that the applicants' argument to overcome Jensen is meritless if propylene glycol were a saccharide. At trial, Plaintiffs focused on the difference between solubility and stability in how the separate chemicals are used and that this was the

[14] Dr. Byrn opined that "Jensen says that reserpine is already soluble in water and ethanol." 7/20/2012 Byrn Trial Tr. at 177. Nothing in the patent says this. Even if it did, it is clear Jensen intended to improve the solubility of a reserpine solution by adding propylene glycol. As stated in Jensen, an object of the invention is "to provide a fluid dosage form of reserpine." Jensen, col. 1:36-37. Dr. Byrn was also impeached at trial with his deposition testimony where he agreed that the examiner was stating that propylene glycol was being used in Jensen to enhance the solubility of the solution. 7/20/2012 Byrn Trial Tr. at 194.

crucial distinguishing feature that the applicants relied on in overcoming the examiner's objection to Jensen. 7/20/2012 Byrn Trial Tr. at 174-181. Plaintiffs argue that applicants did not explicitly state that propylene glycol is not a saccharide and therefore there was no clear disavowal. But the applicants effectively did say that sorbitol was the only listed saccharide by the use of "i.e." when explaining that Jensen disclosed a saccharide, i.e. sorbitol. There were only four compounds listed in Jensen; it defies logic to believe that the applicants considered propylene glycol to be a potential saccharide but specified and discussed only sorbitol as the saccharide listed in Jensen. I find this to be a clear and unmistakable statement to a person of ordinary skill in the art that the patentees did not consider propylene glycol to be a saccharide. 7/12/2012 Gervay-Hague Trial Tr. at 16.

Applicants also distinguished the Blodinger reference, which disclosed the use of propylene glycol with other ingredients. They noted the reference disclosed the use of propylene glycol (again referring to propylene glycol as part of an alcohol solution), but did not consider it to be a possible saccharide:

> Blodinger does not lead one of skill in the art to the present invention, since this reference only discloses that the solubility of some drugs in water can be improved by the addition of such cosolvents as an alcohol, propylene glycol, polyethylene glycol, and the like. Such a teaching, however, does not suggest to one of skill in the art a solvent system which quite substantially increases the solubility of the compound Argipidine in an aqueous based medium. ***Certainly there is no reference to a saccharide on the part of Blodinger***, and such a solubility enhancing effect exhibited in the present invention is not shown or suggested by Blodinger.

PTX-002 at GSK_PI 002273 (emphasis added). By stating that Blodinger does not disclose the use of a saccharide, the patentees unmistakably did not consider propylene glycol as a saccharide or a trivial substitute. Plaintiffs argue that because saccharides are listed in a separate section of Blodinger that their statement to the examiner was incorrect and must be read in the context of

the entire reference. In particular, Plaintiffs contend that the thrust of applicants' argument was that none of the references disclosed a three co-solvent solution. Because saccharides are disclosed, albeit in a different section, Plaintiffs essentially ask the Court to ignore the plain language of the file history and replace it with something to the effect that Blodinger does not disclose a three co-solvent solution.[15] But the appropriate context is the section cited to and relied upon by the examiner, which I have found to be Section D. This section did not contain any mention of a saccharide. The patentees clearly were not considering anything beyond this when they explained that Blodinger did not disclose a saccharide. The patentees listed the compounds provided for in Blodinger, including propylene glycol, and said "certainly there is no reference to a saccharide on the part of Blodinger." I find that the statements clearly and unambiguously show that the patentees never considered propylene glycol to ever fall within the patent's definition of saccharide nor did they consider it to be a substitute for a saccharide. A person of skill in the art reviewing the file history would find that the patentees did not consider propylene glycol to be a saccharide. 7/12/2012 Gervay-Hague Trial Tr. at 14. Whether the patentees' statements invoke the doctrine of prosecution history estoppels is ultimately a finding I do not need to make because I have already found that the doctrine of equivalents does not apply by its own terms.

ii. Claim 1

Plaintiffs also argue that Defendants' process infringes claim 1 under the doctrine of equivalents. They do not argue literal infringement because the Accused Product [redacted] Plaintiffs' argument must fail because I have already found

[15] Plaintiffs also suggest because this section made a general reference to "suspensions" in Section D and because suspensions were discussed in the prior section, this supports their argument. I disagree.

that propylene glycol is not equivalent to saccharide. Also, I do not find that the two products are produced in substantially similar ways. Dr. Byrn testified that Defendants use propylene glycol to form a three solvent system just as Plaintiffs do. Byrn Trial Tr., 7/10/2012 at 125-126. But this is not correct. [redacted] which is unlike the patented claim of a method that combines three distinct elements—water, ethanol, and a saccharide—all being used in conjunction to improve the solubility of the solution at once. Id. at 141. In the patented process, all three elements are necessary for the invention to be effective. [redacted] During the prosecution, the patentees differentiated compounds based on whether they were used to solubilize or to stabilize the drug. Dr. Byrn also testified that the difference between stability and solubilization is "entirely different" and one "has nothing to do" with the other. Id. at 174 ("Q. That stabilization you are just talking about that's referenced in the Jensen patent, does that differ from the concept of solubility? A. Yes. It's entirely different. It's chemically stable. It has nothing to do with dissolving."). Therefore, Defendants do not use propylene glycol as an equivalent substitute for a saccharide, [redacted], and they produce their product not in an insubstantially different way.

iii. Claims 2 and 4

Plaintiffs also argue that Claims 2 and 4 would be infringed under the doctrine of

equivalents because propylene glycol is equivalent to glycerin. 7/10/2012 Byrn Trial Tr. at 135-136. This argument fails for the reasons addressed above. Because the Accused Product does not infringe the independent claim, it cannot infringe the dependent claim. In addition, I do not find that glycerin is equivalent to the propylene glycol for the purposes of the '052 patent. Dr. Byrn based his equivalence opinion, in part, on the fact that scientific literature says glycerin is generally substitutable for propylene glycol and glycerin can also be used as a solvent with Argatroban. 7/10/2012 Byrn Trial Tr. at 137 (citing Remington's Pharmaceutical Sciences at 244, PTX-002 at GSK_PI 002179). But using glycerin with Argatroban is significantly less effective than using propylene glycol with Argatroban. Dr. Byrn himself recognized this. 7/10/2012 Byrn Trial Tr. at 151 ("Argatroban was substantially more soluble in propylene glycol than in glycerin."). Propylene glycol, by itself, solubilizes Argatroban to at least a rate of 51 mg/ml, while glycerin solubilizes Argatroban to only a rate of approximately 6 mg/ml. Id. at 152. This could be in part due to the fact that propylene glycol is more hydrophobic than glycerin, which Plaintiffs' expert admitted. 7/11/2012 Byrn Trial Tr. at 34. While generally propylene glycol may be substituted for glycerin, it is clear that there are substantial differences between how these compounds interact with Argatroban. Therefore, I find that for this reason, in addition to the reasons stated above, glycerin is not equivalent to propylene glycol for purposes of the '052 patent.

Plaintiffs have not met their burden of proving by a preponderance of the evidence that the '052 patent is infringed, either literally or under the doctrine of equivalents, by the Accused Product.

c. Validity

Defendants make one argument regarding the validity of the '052 patent and that is that

the patent is not enabled. The issue appears to be framed that if the term saccharide is so expansive as to include compounds such as propylene glycol, then a person of skill in the art could not practice the patent without undue experimentation because so many elements would be available for one of skill in the art to use. 7/12/2012 Dr. Yalkowsky Trial Tr. at 147-150. Because I do not apply saccharide as expansively as Plaintiffs suggest, Defendants' enablement argument is significantly weakened.

A patent must enable one of skill in the art to make and use what is claimed. 35 U.S.C. § 112 ("The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same."). Although not readily discernible from the plain language of the statute, the Federal Circuit informs us that enablement is a requirement distinct from that of an adequate written description. Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010). A patent is enabled when one skilled in the art, having read the specification, can practice the invention without "undue experimentation." In re Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Routine or standard experimentation is not "undue." Id. The Wands Court set forth the following factors to consider when determining whether a disclosure requires undue experimentation: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Wands, 858 F.2d at 737. These factors are illustrative and a court need not specifically address each one. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1213 (Fed. Cir. 1991). Under 35 U.S.C.S. § 282, a

patent is presumed valid and the burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity. The Supreme Court recently affirmed that one who challenges the validity of a patent must satisfy the factual predicate for a holding that the patent is invalid with clear and convincing evidence. Microsoft Corp. v. i4i Ltd. P'ship, __ U.S. __, 131 S. Ct. 2238, 2251 (2011). Therefore, Defendants had a heavy burden at trial to prove the patent's invalidity.

First, the Court notes that the issue of whether the '052 patent is enabled has been discussed in detail by the Southern District of New York and the Federal Circuit. Both found the patent to be enabled, although they were considering different legal arguments.

> Finally, Barr argues that claims 3 and 4, as construed by the district court, would be invalid for lack of enablement. We disagree. Under the proper construction of "pharmaceutical composition," as set forth above, the claims are clearly enabled. The specification of the '052 patent discloses methods of preparing three sample solutions containing argatroban, ethanol, water, and a saccharide to be administered by injection. '052 patent, col. 5, line 47, to col. 6, line 15. The examples mention only those four components of the composition, in addition to a diluting solution that is "weak[ly] acidic." Id., col. 5, 11. 56-57; col. 6, 11. 14-15. The specification notes that the compositions "may contain stabilizer, buffer, preservative and the like which are acceptable for the injection . . . ." Id., col. 4, 11. 43-44. Because the specification provides straightforward guidance for preparation of the claimed pharmaceutical compositions, it enables claims 3 and 4.

Mitsubishi Chem. Corp. v. Barr Labs., Inc., 435 Fed. Appx. 927, 935 (Fed. Cir. 2011). The district court had addressed enablement more broadly

> 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.

Mitsubishi Chem. Corp. v. Barr Labs., Inc., 718 F. Supp. 2d 382, 423 (S.D.N.Y. 2010). At bottom, Defendants' argument is that the patent is not enabled because it would take a significant amount of experimentation to isolate the most effective solution. I am not convinced, however, that such experimentation would be "undue." When one needs to empirically determine a result, it does not necessarily involve undue experimentation. "Enablement is not precluded by the necessity for some experimentation such as routine screening." Wands, 858 F.2d at 737. Whether undue experimentation is required "is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." Alza, 603 F.3d at 940. Defendants' expert, Dr. Yalkowsky, had difficulty on cross-examination explaining some of the factual bases for his opinion. 7/12/2012 Dr. Yalkowsky Trial Tr. at 170-190. It was clear that he relied on the factual findings from the district court's opinion in the Mitsubishi Litigation as told to him by counsel, without Dr. Yalkowsky independently reviewing or considering the findings. These factual findings were made in the context of the court's obviousness analysis, not its enablement analysis. This is not to say that those factual findings do not also potentially weigh on an enablement analysis, but considering Defendant's high burden, this is insufficient to create the predicate factual basis necessary for a finding of invalidity. Rather, the predicate factual findings from the Mitsubishis Litigation support my finding that significant experimentation is not uncommon in the context of finding effective solutions in the pharmaceutical industry and for Argatroban, that the state of the art at the time was unpredictable, and that one of skill in the art would anticipate extensive experimentation and be prepared to conduct such experimentation. Defendants conducted nearly 100 experiments in their own trials to design around the '052 patent. 7/11/2012 Koneru Trial Tr. at 139.

Similar to the Federal Circuit's analysis, under the proper construction of "saccharide," the claims are clearly enabled. The specification of the '052 patent discloses methods of preparing sample solutions containing Argatroban, ethanol, water, and a saccharide to be administered by injection that give specific quantities and report the results. In addition, the patentees explain that in general "the mixed ration (by weight) of alcohol to water in the above solvent is generally .1 to 10, preferably .2 to 5, and most preferably .3 to 3" and the mixed ratio (by weight) of saccharide (if present) to water is generally .1 to 10, preferably .4 to 4, and most preferably .5 to 2." '052 patent, col. 3:56-58, col. 4:1-3, PTX-001. Moreover, the patent provides several examples of using Argatroban with a water-alcohol-saccharide solution. This provides sufficient guidance to enable one of skill in the art to practice the '052 patent.

Defendants have not met their burden of establishing that the'052 patent is not enabled and invalid.

IV. CONCLUSION

For the foregoing reasons, the Court finds that the '052 patent is not infringed and is not invalid.

Dated: July 31, 2012

/s/ Freda L. Wolfson
Honorable Freda L. Wolfson
United States District Judge