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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

GLAXOSMITHKLINE PLC, *et al.*,	:	
	:	**CIVIL CASE NO.**
Plaintiffs,	:	**3:12-CV-01965-FLW-DEA**
	:	
MITSUBISHI CHEMICAL CORP. and MITSUBISHI TANABE PHARMA CORP.,	:	
	:	
Involuntary Plaintiffs,	:	
	:	**REDACTED VERSION**
vs.	:	
	:	
HIKMA PHARMACEUTICAL CO., LTD., *et al.*,	:	
	:	
Defendants.	:	
	:	

PLAINTIFF GLAXOSMITHKLINE, PLC'S OPENING BRIEF IN SUPPORT OF ITS MOTION FOR PRELIMINARY INJUNCTION

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I. PRELIMINARY STATEMENT

Plaintiff GlaxoSmithKline plc ("GSK") moves for an order preliminarily enjoining defendants Hikma Pharmaceuticals Co. Ltd., a Jordanian company, and its U.S. affiliate, West-Ward Pharmaceutical Corp. ("West-Ward"), (collectively "Hikma") from making, using, selling, offering for sale, or importing their generic copy of GSK's Argatroban Injection that infringes U.S. Patent No. 5,214,052 ("the '052 Patent").[1] GSK is the exclusive sublicensee of the '052 Patent in the United States, with the exclusive right to manufacture and sell Argatroban Injection[2] using the patented formulation and method of the '052 Patent. (Decl. of Kevin LaWall in Support of GSK's Mot. for Preliminary Injunction ("LaWall"), ¶ 13.)

Hikma distributes generic drugs in the United States through its sister company, West-Ward.[3] *See* http://www.hikma.com/en/about-hikma/our-business.aspx. On January 5, 2012, Hikma received final approval from the FDA to sell a generic version of GSK's Argatroban Injection in the United States. (LaWall, Ex. 2.) Defendants' generic product has also received an AP rating,

[1] The '052 Patent was assigned to Mitsubishi Chemical Corporation, and ultimately licensed to Encysive (now Pfizer), which in turn sublicensed the patent to GSK. (LaWall, ¶ 13.) While Pfizer, Inc. and Encysive Pharmaceutical Corp. are, along with GSK, plaintiffs in this action, this motion is filed on behalf of GSK alone; Pfizer and Encysive, however, do not oppose GSK's requested relief.

[2] Argatroban does not have a brand name – rather, the active ingredient is itself called argatroban. For ease of reference, GSK refers to its product as Argatroban Injection.

[3] Upon information and belief, Hikma and West-Ward are both wholly-owned subsidiaries of Hikma Pharmaceutical PLC, a holding company based in the UK.

meaning that the FDA has deemed the generic product to be bioequivalent to and freely ***substitutable for*** GSK's Argatroban Injection. (*Id.* ¶ 27.) Hikma's argatroban product is the first generic version of Argatroban Injection to receive this rating from the FDA. (*Id.*) Thus, GSK believes that Defendants are planning on launching their generic copy of Argatroban Injection imminently. (*Id.* ¶ 23.)

The Court should enjoin Defendants from making, using, selling, offering to sell, and importing their infringing generic copy of GSK's Argatroban Injection pending trial on the merits because each element required for a preliminary injunction is satisfied:

First, GSK has established an overwhelming likelihood of success on the merits of its infringement claim. Hikma's generic copy of GSK's Argatroban Injection literally infringes claims 1 and 3 of the '052 Patent, which describes and claims, *inter alia*, an injectable pharmaceutical composition comprising argatroban, ethanol, water and a saccharide, and a method for dissolving argatroban in a solvent containing ethanol, water, and a saccharide to arrive at such a composition. (Expert Decl. of Stephen R. Byrn, Ph.D. ("Byrn") ¶ 1.) The combination of these ingredients, and in particular, the use of ethanol and a saccharide, greatly increases the solubility of argatroban in water. (Cmpt., Ex. A, col. 4:20-27.) [redacted]

[redacted]

Hikma's sole non-infringement argument is wrong: propylene glycol ***is*** a saccharide ***as defined by the '052 Patent***. The '052 Patent defines the term "saccharide" as including "monosaccharides, oligosaccharides, polysaccharides ***and their reduced derivatives (for example sugaralcohol) which are soluble in water***." (Cmpt., Ex. A, col. 3:61-64 (emphasis added).) As set forth in the accompanying declaration of Dr. Steven Byrn, propylene glycol is a water-soluble, reduced derivative of various compounds that are considered monosaccharides or oligosaccharides, and therefore meets the specification's definition. (Byrn ¶ 70.) Propylene glycol is *also* a sugar alcohol. (*Id.* ¶¶ 75-76.) Accordingly, propylene glycol literally meets the saccharide element of the claims. (*Id.* ¶¶ 75-76.) Alternatively, propylene glycol is equivalent to a saccharide, and therefore satisfies this limitation of the claims under the doctrine of equivalents. (*Id.* ¶¶ 77-79.) Accordingly, Hikma's attempt to avoid infringement of the '052 Patent fails.

Further, Hikma cannot raise a substantial question of invalidity with respect to the '052 Patent. The validity of the '052 Patent has already withstood a rigorous challenge by another generic company in an earlier infringement suit. *See Mitsubishi Chem. Corp. v. Barr Labs., Inc.*, 718 F. Supp. 2d 382, 413-45 (S.D.N.Y. 2010), *aff'd*, 435 F. App'x 927 (Fed. Cir. 2011). [redacted]

[redacted]. As a consequence, GSK is likely to succeed on the merits of its infringement claim.

Second, the harm GSK will suffer as a result of Hikma's decision to launch its generic version of GSK's Argatroban Injection, both significant and irreparable, is not readily quantifiable. Here, GSK's strong showing of likelihood of success on the merits of its infringement claim – and the past success on the merits in a previous case – is strong evidence of irreparable harm. Even apart from that, irreparable harm to GSK is firmly established by the immediate, adverse impact upon GSK's Argatroban Injection sales, revenue, and market share resulting from Hikma's infringing generic copy saturating the market, as well as the devastating and immeasurable effect that loss of sales will have upon GSK's overall business operations, reputation, and customer goodwill.

Third, the balance of hardships overwhelmingly favors granting a preliminary injunction against Hikma. In contrast to the immediate, substantial,

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[4] Under 21 C.F.R. 314.52(a), the ANDA applicant must provide notification of the substance of its paragraph certification to the patent holder. That notification must contain, among other things:

> A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant shall include in the detailed statement: (i) For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed. (ii) For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.

21 C.F.R. 314.52(c)(6).

and irreversible harm GSK will experience, there would be no cognizable harm to Hikma in granting this motion. Defendants have a legal obligation not to infringe the '052 Patent and thus have no basis to complain about an order preventing them from doing so. Any "harm" Hikma may suffer thereafter is at its own risk and of its own making.

Fourth, the relief requested benefits the public, whose interest in honoring patent rights and encouraging innovation in the development of newer, safer, and more effective drugs is well established. More specifically, Defendants' introduction of their generic argatroban injection may hinder GSK's development and launch of new and important critical care products, the success of which depends on the relationships that GSK has developed over the years with hospital healthcare providers, and which may be prematurely terminated if Hikma is permitted to launch its generic copy of GSK's Argatroban Injection.

For these reasons, as more fully developed below, this Court should grant a preliminary injunction preventing Hikma's launch of its infringing generic version of GSK's Argatroban Injection during the pendency of this lawsuit.

II. STATEMENT OF THE FACTS

A. GSK and Argatroban Injection

GSK is a worldwide corporation, developing and commercializing pharmaceutical products that address a variety of medical needs, including asthma, anti-virals, mental health, diabetes, cardiovascular and digestive conditions, metastatic cancers, and infectious diseases. (LaWall ¶ 5.) GSK's Respiratory,

Neuroscience, and Medical Center ("RNMC") Division sells and actively promotes to U.S. hospitals several of GSK's FDA-approved products, including its Argatroban Injection. (*Id.* ¶ 6.) The RNMC division is also developing additional valuable treatments for use in the hospital setting, [redacted] (*Id.*) Of the 2,270 employees in the GSK's RNMC division, 350 are sales representatives calling on hospitals, health system pharmacy departments, and treating physicians. (*Id.* ¶ 7.)

GSK's Argatroban Injection is a lifesaving anticoagulant used for the prevention or treatment of thrombosis (abnormal clot formation) in hospitalized patients with a condition known as heparin-induced thrombocytopenia (HIT) and thrombosis (HITT), and those with or at risk for HIT/HITT while undergoing certain surgical procedures. (LaWall ¶ 8; Decl. of Dr. Ronald A. Sacher in Support of GSK's Mot. for Preliminary Injunction ("Sacher") ¶ 35.)

HIT and HITT are side effects of treatment with heparin, an intravenous anticoagulant drug used in many hospitalized patients to prevent the formation of blood clots for a variety of conditions and in procedures such as bypass surgery and kidney dialysis. (LaWall ¶ 8; Sacher ¶ 23.) It is estimated that 12 million individuals – or one third of hospitalized patients, most of whom are critically ill and/or elderly – receive heparin treatment within a given year. (Sacher ¶ 24.) Heparin treatment can paradoxically cause thrombocytopenia, a condition that actually ***raises*** the risk of abnormal clotting. (Sacher ¶ 25.) Patients who develop HIT after receiving heparin may suffer a cascade of blood clots, resulting in

amputations and possibly death if left untreated. (LaWall ¶ 8; Sacher ¶ 27.)

Prior to the FDA's approval of GSK's Argatroban Injection on June 30, 2000, doctors had few options for HIT patients other than to cease heparin and hope that clotting did not occur. (Sacher ¶¶ 31-33.) As of January 2012, GSK's Argatroban Injection had approximately 80% of the market in the U.S. for the treatment of HIT.[5] (LaWall ¶ 17; Decl. of Dr. Christopher A. Vellturo in Support of GSK's Mot. for Preliminary Injunction ("Vellturo") ¶ 15.) In addition to GSK's Argatroban Injection, there are two "ready-to-use" ("RTU") argatroban products approved for use by the FDA, one manufactured by The Medicines Company ("TMC"),[6] the other by Sandoz, Inc.[7] Neither of these products is currently readily available due to quality or supply issues.[8] (LaWall ¶ 15; Vellturo ¶¶ 24-30.)

Healthcare providers overwhelmingly prefer GSK's Argatroban Injection over the non-argatroban products for treatment of HIT. (LaWall ¶¶ 17-18; Sacher

[5] The other non-argatroban HIT therapies are Refludan, an rDNA biomolecule approved by the FDA in 1998, and Angiomax, approved on November 30, 2005. (LaWall ¶ 9; Sacher, ¶ 33.)

[6] TMC's RTU product was approved by the FDA on June 29, 2011 and launched in September 2011. (Vellturo ¶ 28.)

[7] Sandoz's RTU product was approved by the FDA on May 9, 2011 and launched later that same month. (Vellturo ¶ 25.)

[8] In December 2011, TMC's supplier issued a voluntary recall of the TMC product "due to a potential for visible particulates" which presents "a risk of embolization/infarction to organs with potential organ complications." (Vellturo ¶ 30.) As a result, all of TMC's argatroban product was immediately quarantined. There has been no indication of when this quality issue would be resolved and when the product would re-enter the market. (*Id.*) In February 2012, Sandoz announced it would have temporary supply disruptions due to remediation efforts at its plant in response to a November 2011 FDA Warning Letter. This disruption essentially removed the RTU from the market as of December 2011. (*Id.* ¶ 27.)

¶ 38.) Among other reasons, GSK's Argatroban Injection is safer for use in renally impaired patients, *e.g.*, in patients undergoing dialysis, than Refludan or Angiomax. (Sacher ¶ 34.) In addition, GSK's Argatroban Injection has broader indications than either Refludan or Angiomax, and therefore is suitable for use in a greater variety of patients. (Sacher ¶ 38.) GSK's Argatroban Injection also has the flexibility to be used in different diluents, and thereby appropriate for patients who are receiving multiple prescribed fluids, while avoiding any negative interactions. (*Id.*) Further, its high concentration allows GSK's Argatroban Injection to be administered in a lesser total volume of fluid, an important safety consideration because many patients requiring treatment for HIT/HITT suffer from adverse medical conditions requiring strict fluid volume control. (*Id.*)

Providers and hospitals also prefer GSK's Argatroban Injection because, along with the drug itself, GSK provides important educational support services. HIT is difficult to diagnose because it can be asymptomatic until abnormal clotting develops. (LaWall ¶ 8; Sacher ¶ 28.) Furthermore, proper dosing of argatroban, like other anticoagulant drugs, is critically important: too much, and the patient's blood will no longer clot, which can lead to potentially fatal hemorrhaging; too little, and the patient remains at high risk for thrombosis, causing severe complications or death. (LaWall ¶¶ 8, 10; Sacher ¶ 27.) In light of these challenges in diagnosing and treating HIT, GSK, through its sales representatives and independent experts, undertakes a wide variety of educational outreach efforts in order to increase doctors' and nurses' awareness of HIT, its diagnosis, and

treatment. (LaWall ¶ 20; Sacher ¶¶ 42-48.)

In addition to educational outreach, GSK sales and marketing personnel spend significant amounts of time and energy responding to questions or concerns expressed by clinicians. (LaWall ¶ 21.) GSK also works to ensure that it is maintaining a high level of production in order to alleviate consumer concern over availability, a serious and well-founded concern as of late. (*Id.* ¶ 22.) Moreover, GSK expends significant funds to develop novel business strategies, such as the launch of a "private label" argatroban drug in conjunction with the group purchasing organization NovaPlus. This program alone accounts for [redacted] of argatroban sales. (*Id.* ¶ 21; Vellturo ¶ 19.)

B. The Patented Technology of GSK's Argatroban Injection

The compound argatroban and its anticoagulant effect were known for years before the development of a marketable formulation for the treatment of HIT. The argatroban molecule is poorly soluble in water, frustrating for years the companies trying to develop an injectable product at a concentration sufficient to treat severely ill patients under fluid restrictions. (Byrn ¶ 48; Cmpt., Ex. A, col. 1:17-24.) In the early 1990s, the inventors of the '052 Patent discovered that a co-solvent system comprising ethanol, water, and a saccharide greatly enhanced argatroban's solubility. (Cmpt., Ex. A, col. 4:20-27.)

GSK is the exclusive U.S. sublicensee of the '052 Patent, entitled "Method for Dissolving Arginineamides and Pharmaceutical Compositions Containing Them." The '052 Patent contains four claims:

1. A method for dissolving an arginineamide, comprising: dissolving N2-arylsulfonyl-L-argininamide[9] . . . and/or its salt in a solvent containing ethanol, water and a saccharide.
2. The method according to claim 1, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.
3. A pharmaceutical composition for injection, comprising: argatroban and/or its sale together with ethanol, water and a saccharide.
4. The composition according to claim 3, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.

(*Id.*, col. 6:24-67.)

The '052 Patent specification expressly defines "saccharides as used in the invention" to mean "monosaccharides, oligosaccharides, polysaccharides and their reduced derivatives (for example sugaralcohol) which are soluble in water." (*Id.*, col. 3:61-64.)

C. Infringement Litigation Against Barr

In September 2007, Barr Laboratories, Inc. ("Barr") filed ANDA No. 79-238 with the FDA pursuant to 21 U.S.C. § 355(j), seeking to market a generic copy of GSK's Argatroban Injection. *See Mitsubishi*, 718 F. Supp. at 389. Mitsubishi, Encysive, and GSK filed suit for patent infringement in December 2007, alleging that Barr's generic argatroban injection product would infringe the four claims of the '052 Patent. *Id.* Barr conceded infringement, but asserted that the '052 Patent was invalid on anticipation or obviousness grounds. *Id.* at 389-90. On June 16, 2010, Judge Koeltl of the Southern District of New York issued a fifty-seven page

[9] N_2-arylsulfonyl-L-argininamide is also known as argatroban. (Byrn ¶ 65.)

opinion finding that Barr had failed to prove invalidity of any of the claims of the '052 Patent. *Id.* at 444-45. On August 2, 2011, the Federal Circuit affirmed Judge Koeltl's decision. *Mitsubishi Chem. Corp. v. Barr Labs., Inc.*, 435 F. App'x 927, 936 (Fed. Cir. 2011).

D. Hikma's Paragraph IV Notice

[redacted] GSK did not learn that Hikma had sought approval to market its generic product until approximately January 19, 2012. (*Id.* ¶¶ 7-8.) Further, GSK did not receive a copy of Hikma's Paragraph IV Notice until February 13, 2012, when Mitsubishi's counsel sent an electronic version. (*Id.* ¶ 9.) [redacted]

III. ARGUMENT

A party is entitled to a preliminary injunction if it establishes: (1) that it "is likely to succeed on the merits;" (2) that it "is likely to suffer irreparable harm in

the absence of preliminary relief;" (3) "that the balance of equities tips in its favor;" and (4) "that an injunction is in the public interest." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1049 (Fed. Cir. 2010) (citation omitted). "The purpose of a preliminary injunction is merely to ***preserve*** the relative positions of the parties until a trial on the merits can be held." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1344-45 (Fed. Cir. 2008) (emphasis added) (quoting *University of Tex. v. Camenisch*, 451 U.S. 390, 395 (1981)).[10]

First, to establish its entitlement to a preliminary injunction, a plaintiff must demonstrate that it will likely prove that defendant's product infringes and that it will likely withstand a challenge to validity and enforceability. *See Ortho McNeil Pharm., Inc. v. Barr Labs., Inc.*, No. 03-4678, 2009 WL 2182665, at *1-*2 (D.N.J. July 22, 2009); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1374 (Fed. Cir. 2006). This burden, however, must be considered "in light of the presumptions and burdens that will inhere at trial on the merits," *Sanofi-Synthelabo*, 470 F.3d at 1374, and as such, the court must not ignore the presumption of validity to which a patent is due. *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1148-49 (Fed. Cir. 2011); *Canon Computer Sys., Inc. v. Nu–Kote Int'l., Inc.*, 134 F.3d 1085, 1088 (Fed. Cir. 1998) ("[A] patent is presumed valid, and this presumption exists at every stage of the litigation.").

Second, a plaintiff must demonstrate that, without an injunction, it will

[10] The standard for a preliminary injunction in a patent case is controlled by Federal Circuit law. *Hybritech Inc. v. Abbott Labs., Inc.*, 849 F.2d 1446, 1451 (Fed. Cir. 1988).

suffer irreparable harm. Although establishment of a reasonable likelihood of success on the merits does not alone justify an injunction, this factor ***weighs strongly in favor*** of a finding of irreparable harm. *See Robert Bosch*, 659 F.3d at 1148-49 (finding that despite the *eBay* opinion, the fact that a patent is found to be valid and infringed is ***still an important consideration*** in the irreparable harm analysis (emphasis added)); *Acumed LLC v. Stryker Corp.*, 551 F.3d 1323, 1328 (Fed. Cir. 2008) (finding in a post-*eBay* decision that "[i]n view of that right [to exclude], infringement may cause a patentee irreparable harm not remediable by a reasonable royalty").

While irreparable harm can present in a variety of ways, the Federal Circuit has consistently affirmed the grant of preliminary injunctions where the plaintiff was likely to suffer significant "[p]rice erosion, loss of goodwill, damage to reputation, and loss of business opportunities." *See e.g., Celsis In Vitro, Inc. v. Cellzdirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012); *Abbott*, 544 F.3d at 1362; *Sanofi-Synthelabo*, 470 F.3d at 1382-83. In particular, where a generic company threatens to flood the market with infringing copies of a patented drug, these harms can be swift, irreversible, and impossible to sufficiently compensate with money damages. *See Albany Molecular Research, Inc. v. Dr. Reddy's Labs. Ltd.*, No. 09-4638, 2010 WL 2516465, at *10 (D.N.J. June 14, 2010) (collecting Federal Circuit cases affirming district court decisions equating with irreparable harm price erosion and losses in market position, revenue, goodwill, R&D support, and business opportunities); *AstraZeneca LP v. Apotex, Inc.*, 623 F. Supp. 2d 579, 608-

14 (D.N.J. 2009) (finding irreparable harm "in the form of irreversible loss of market share, permanent price erosion, . . . loss of capitalization, adverse impact on employees, reduction of research and development funds, loss of good will, and consumer confusion"), *aff'd*, 633 F.3d 1042 (Fed. Cir. 2010).

Third, with regard to the balance of harms, the courts will ignore a defendant's claims where the harms it may suffer "were almost entirely preventable and were the result of its own calculated risk to launch its product pre-judgment." *Sanofi-Synthelabo*, 470 F.3d at 1383. Where, as here, a generic company is making an at-risk launch before a finding on the merits, courts frequently find that the harm to the branded drug's market share greatly outweighs any harm experienced by the generic. *See, e.g.*, *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d 1364, 1382 (Fed. Cir. 2005); *Albany Molecular*, 2010 WL 2516465, at *11. The generic company receives no sympathy from the court for attempting or preparing to infringe.

Fourth, the public interest is well-served by the granting of a preliminary injunction where doing so would enforce valid patent rights and encourage innovation. *See Abbott*, 544 F.3d at 1363. This public interest is not disturbed simply because the infringing generic may be a cheaper alternative to the patented drug. *See Pfizer*, 429 F.3d at 1382. Because companies developing, manufacturing, and marketing brand drugs are innovators, which also provide important services to their customers not provided by their generic competitors, the public may suffer significantly as a result of the branded company's lost sales.

For all the reasons set forth in detail below, each of these four factors weighs strongly in favor of granting GSK's request for a preliminary injunction.

A. GSK Is Likely To Succeed On The Merits Of Its Claim

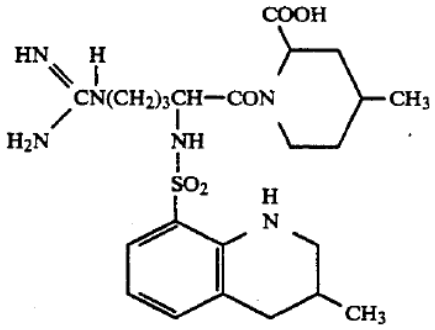
As an initial matter, validity ought not be an issue in the context of this preliminary injunction motion because (1) [redacted] and (2) the '052 Patent has already been adjudged not to be invalid by a district court in the Southern District of New York, *see Mitsubishi*, 718 F. Supp. 2d at 444-45, and the Federal Circuit, *see Mitsubishi*, 435 F. App'x at 936. Therefore, the primary issue here is whether GSK can demonstrate that it is likely to succeed in proving that Hikma infringes one or more claims of the '052 Patent. *See Canon Computer*, 134 F.3d at 1088 ("[W]here the challenger fails to identify any persuasive evidence of invalidity, the very existence of the patent satisfies the patentee's burden on the validity issue.").

1. GSK Is Likely To Prove That Hikma Literally Infringes Claims 1 And 3 Of The '052 Patent

In the context of a preliminary injunction, GSK does not need to demonstrate infringement with certainty, but only that it will likely prove that Hikma infringes at least one claim either literally or under the doctrine of equivalents. *Abbott Labs. v. Andrx Pharms., Inc.*, 473 F.3d 1196, 1201 (Fed. Cir. 2007). Here, GSK will likely succeed in demonstrating that Hikma's generic argatroban injection literally infringes both of the independent claims (claims 1 and

3) of the '052 Patent.[11]

Claims 1 and 3 both relate to argatroban in a solution. Claim 1 recites:

> A method for dissolving an arginineamide, comprising: dissolving N^2-arylsulfonyl-L-argininamide represented by formula (I):
>
> 
>
>
> and/or its salt in a solvent containing ethanol, water and a saccharide.

Claim 3 encompasses a pharmaceutical composition for injection containing the same N^2-arylsulfonyl L-argininamide, ethanol, water, and saccharide elements recited in claim 1.

Hikma's own label and prescribing information for its generic argatroban injection confirm that Hikma's generic product meets each and every limitation recited in claims 1 and 3 of the '052 Patent. (*See* LaWall, Ex. 2.) Specifically, Hikma's generic copy of GSK's Argatroban Injection:

- is a pharmaceutical composition for injection (*see* Byrn ¶ 65);
- contains N^2-arylsulfonyl-L-argininamide (*id.* ¶ 65);
- contains ethanol (*id.* ¶ 66);
- contains water (*id.* ¶ 67);

[11] Even the FDA has recognized that Hikma's generic product is the same as GSK's Argatroban Injection: it gave the generic argatroban injection an AP rating (i.e., therapeutically equivalent to GSK's Argatroban Injection). (LaWall ¶ 27.)

- contains a saccharide (*id.* ¶¶ 68-70);
- is manufactured according to a method where N^2-arylsulfonyl-L-argininamide (i.e. argininеamide) is dissolved in a solvent containing ethanol, water and a saccharide (*id.* ¶¶ 65-68).

[redacted] But Hikma's contention that [redacted] is not a claimed saccharide is directly contrary to the definition of saccharide chosen by the inventors of the '052 Patent and expressly set forth in the patent specification.[12] Because the '052 Patent inventors expressly defined saccharide in the patent, "the patentee's definition controls." *Martek Bioscis. Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009); *see also King Pharm., Inc. v. Sandoz Inc.*, No. 09-3587 (GEB), 2010 WL 3910151, at *2 (D.N.J. Oct. 1, 2010) ("When a patent applicant specifically defines a claim

[12] According to Hikma, Webster's Third New International Dictionary provides a "good definition" of saccharide, which Defendants rely upon as the sole basis for their infringement claims. (Smith, Ex. A, App. I at 5.) But Hikma's reliance on a general usage, non-technical dictionary definition violates the fundamental rule that a court should ***only*** rely on a dictionary to the extent it "can help the court determine what a person of ordinary skill in the art would understand [the] claim term[] to mean." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1319 (Fed. Cir. 2005); *see also Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998) (cautioning against the use of non-technical dictionaries "lest dictionary definitions . . . be converted into technical terms of art having legal, not linguistic, significance."). Webster's Dictionary has nothing to do with pharmaceutical or medical drug products, and is of little relevance in determining what one of skill in the art would understand "saccharide" to mean. (*See* Byrn ¶ 68.)

term in its description of its invention, that definition controls.").

The specification of the '052 Patent sets forth an express definition of saccharide that includes "monosaccharides, oligosaccharides, polysaccharides and their ***reduced derivatives*** (for example ***sugaralcohol***)." (Cmpt., Ex. A, col. 3:61-64 (emphasis added).) GSK's independent expert, Dr. Byrn explains that [redacted] in Hikma's generic argatroban injection is a saccharide because it is a ***reduced derivative of two monosaccharides*** (glyceraldehyde and glucose), and a ***reduced derivative of an oligosaccharide*** (sucrose). (Byrn ¶¶ 68, 70.) Moreover, one of skill in the art would recognize that [redacted] is also a ***sugar alcohol***. (*Id.* ¶ 73.) Thus, in view of the disclosures in the '052 Patent, one of skill in the art would consider [redacted] to be a saccharide, and Hikma's generic argatroban injection to contain a saccharide as that term is defined in the '052 Patent. (*Id.* ¶ 76.)

Hikma's sole non-infringement argument is not only contrary to the controlling definition of saccharide set forth in the specification, but is also premised on a disregard of the very words in the claims. Again, this is improper. *See, e.g.*, *Reckitt Benckiser, Inc. v. Tris Pharma, Inc.*, No. A09-3125 (FLW), 2010 WL 4748648, at *2 (D.N.J. Nov. 16, 2010) ("Claims define the scope of the inventor's right to exclude."). [redacted] But claims 2 and 4 of the '052 Patent provide express examples of various

saccharides, ***including a saccharide with only three carbons***. (Cmpt., Ex. A, claims 2, 4; *see also* Byrn ¶¶ 81-82.) Thus, Hikma's non-infringement argument must necessarily fail because it is based on a faulty assumption regarding the alleged "requirements" of a saccharide.

Because GSK has demonstrated that Hikma's generic argatroban injection literally meets each and every limitation of claims 1 and 3 of the '052 Patent, this Court should find that GSK has established a likelihood of success on the merits. *See, e.g.*, *Celsis*, 664 F.3d at 926; *Andrx*, 473 F.3d at 1213.

2. GSK Is Also Likely To Prove Infringement By Hikma Under The Doctrine Of Equivalents

To the extent that Hikma does not literally infringe the '052 Patent (and it does), it nevertheless infringes claims 1 - 4[13] under the doctrine of equivalents. Under this doctrine, there is infringement if the accused product performs substantially the same function, in substantially the same way, and achieves substantially the same result as set forth in the claim element. *Hilton Davis Chem. Co.* v. *Warner-Jenkinson Co.*, 114 F.3d 1161, 1164 (Fed. Cir. 1997); *see also EKR Therapeutics, Inc. v. Sun Pharm. Indus., Ltd.*, 633 F. Supp. 2d 187, 200 (D.N.J. 2009) (finding infringement by doctrine of equivalents when "insubstantial differences exist between the patented and accused product." (citation and internal quotations omitted)). Equivalence is determined on an "element-by-element basis," such that any element not literally present in the accused product can still

[13] Claims 2 and 4 recite that the saccharide is selected from a group consisting of sorbitol, glucose, glycerin, and sucrose.

be present by equivalence for purposes of the infringement analysis. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 18-19 (1997).

The facts here support application of the doctrine of equivalents because the claim elements "saccharide" and "glycerin"[14] are equivalent to the [redacted] in Hikma's generic argatroban injection product. [redacted] in Hikma's generic product performs the same function as a saccharide generally (claims 1 and 3), and glycerin in particular (claims 2 and 4), which is to improve solubility of the arginineamide drug. (*See* Byrn ¶¶ 77-79.) [redacted] does so in the same way by forming a co-solvent system along with water and ethanol. (*Id.*) The result is the dissolution of substantially more arginineamide in the co-solvent system than would dissolve in a solvent of either ethanol or aqueous [redacted] alone. (*Id.* ¶ 78.) Accordingly, the [redacted] in Hikma's generic product performs substantially the same function, in substantially the same way, and achieves substantially the same result as both the saccharide element of claims 1 and 3 and the glycerin element of claims 2 and 4. (*Id.* ¶¶ 77, 81.)

Equivalence is further supported by the interchangeability between glycerin and [redacted] in a pharmaceutical composition. As Dr. Byrn explained, one of skill in the art at the time of the '052 invention would have recognized several, significant similarities when comparing [redacted] to glycerin. ***First***, the structures of these two compounds are nearly identical, with only one

[14] The '052 Patent expressly indicates that glycerin is one type of saccharide. (Cmpt., Ex. A, claims 2, 4.)

atom difference between them. (*Id.* ¶ 82.) ***Second***, both glycerin and [redacted] have similar solubilities, such that both are soluble in ethanol and also in water. (*Id.*) ***Third***, both have been widely used as solvents in pharmaceutical formulations, with [redacted] generally accepted as a substitute for glycerin. (*Id.*) Thus, the ***only reasonable conclusion*** that one of skill in the art would reach is that the [redacted] in Hikma's generic argatroban injection is equivalent to the glycerin element claimed in the '052 Patent.

Hikma contends that the doctrine of equivalents is inapplicable here because the inventors of the '052 Patent allegedly disclaimed [redacted] from the claims of the '052 Patent during prosecution. (Smith, Ex. A, App. I at 6.) Once again, Hikma is wrong. The law is clear that "in order to disavow claim scope during prosecution a patent applicant must ***clearly and unambiguously*** express surrender of subject matter." *Voda v. Cordis Corp.*, 536 F.3d 1311, 1321 (Fed. Cir. 2008) (emphasis added, internal quotation and citation omitted).

Contrary to Hikma's assertion, application of the doctrine of equivalents is entirely consistent with the prosecution history of the '052 Patent. Nowhere did the inventors disavow claim scope or narrow subject matter with respect to a saccharide in order to respond to the examiner's rejection of claims or gain allowance of the claims. Indeed, a saccharide element was ***included in the original application*** for the '052 Patent, persisted in the claims after the single substantive amendment, and ***remained in the claims that issued***. There was simply no need to add a saccharide limitation by amendment, since the inventors

had claimed that same element in their initial application. *See Voda*, 536 F.3d at 1326 (finding that prosecution history estoppel applied only to element added via amendment). Similarly, there could be no narrowing of claim scope given that the same saccharide element endured in the issued claims. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*, 535 U.S. 722, 737 (2002) ("A patentee who narrows a claim as a condition for obtaining a patent disavows his claim ***to the broader subject matter***." (emphasis added)). Thus, there was no disclaimer with respect to the "saccharide" limitation of the claims that precludes application of the doctrine of equivalents. Accordingly, Hikma's generic argatroban injection also meets each and every limitation of claims 1-4 of the '052 Patent under the doctrine of equivalents, and thus GSK has established a strong likelihood of success on the merits. *See, e.g.*, *Celsis*, 664 F.3d at 926-27; *Andrx*, 473 F.3d at 1213.

3. Hikma Cannot Raise a Substantial Question of Invalidity

Hikma cannot raise a substantial question as to the invalidity of the '052 Patent. Under 35 U.S.C. § 282, patents enjoy a presumption of validity, and "the burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." *See also Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1365 (Fed. Cir. 2001) ("***Every patent is presumed valid***, so if [defendant] fails to identify any persuasive evidence of invalidity, the very existence of the patent satisfies [plaintiff's] burden on validity." (emphasis added)). In the context of an application for preliminary injunction, the court "must determine whether it is more likely than not that ***the challenger*** will be

able to prove at trial, by clear and convincing evidence, that the patent is invalid." *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1379 (Fed. Cir. 2009) (emphasis added); *see also Andrx*, 473 F.3d at 1201 (to defeat injunction the "***party bearing the burden of proof*** on the issue at trial, must establish a substantial question of invalidity . . . i.e., that it is likely to succeed in proving invalidity . . . of the asserted patents." (emphasis added)).

Hikma cannot raise a substantial question of invalidity in this case. The '052 Patent is entitled to a presumption of validity and to overcome that presumption at trial, Hikma must prove invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2240 (2011). No such evidence exists in this case. [redacted] – the '052 Patent has already survived an invalidity attack both in the district court and at the Federal Circuit. In prior litigation, another generic manufacturer alleged that the '052 Patent was both anticipated and obvious in view of the prior art. Following a 12-day bench trial at which the parties elicited testimony from 15 witnesses, Judge Koeltl, in a detailed, fifty-seven page opinion, confirmed that the '052 Patent was not invalid and enjoined defendants from making, using or selling their infringing product until after the expiration of the '052 Patent. *See Mitsubishi Chem. Corp.*, 718 F. Supp. 2d at 444-45. The Federal Circuit upheld the district court's findings

on appeal, noting that the generic manufacturer failed to show that the claims of the '052 patent were anticipated or obvious in light of the prior art. *See Mitsubishi Chem. Corp.*, 435 F. App'x at 936. Like the generic manufacturer in the prior litigation, Hikma is not likely to satisfy its burden of proving invalidity at trial.

B. GSK Will Suffer Severe, Immediate, And Irreparable Harm Absent Injunctive Relief

GSK's likelihood of success on the merits of its infringement claim and its ability to survive a validity challenge are strong evidence that GSK will be irreparably harmed if Defendants are permitted to launch their generic argatroban injection product. *See Robert Bosch*, 659 F.3d at 1149. Even apart from its likelihood of success, however, GSK clearly demonstrates that it will suffer immediate and irreparable harm as a result of Defendants' product launch. When generic companies like Defendants flood the market with infringing product, the harm to the branded company is swift and irreversible; furthermore, as found in a number of cases in this District and the Federal Circuit, the harm often cannot be sufficiently compensated by monetary damages. *See, e.g.*, *Apotex*, 623 F. Supp. 2d at 608-14 ("[I]f Apotex is not enjoined from launching its generic BIS, AstraZeneca will suffer irreparable, unquantifiable harm in the form of irreversible market share, permanent price erosion, . . . loss of capitalization, adverse impact on employees, reduction of research and development funds, loss of goodwill and consumer confusion."), *aff'd*, 633 F.3d at 1063.

The factor underlying each harm that GSK will suffer is the unit price of

GSK's Argatroban Injection. A company like Hikma can afford to sell its generic product at much lower prices for a number of reasons, not the least of which is that it disregards patents and chooses not to seek a license and pay royalties on the patented drug. By contrast, GSK is required to pay a significant amount of its net sales in royalties to its licensors. (LaWall ¶ 25.)

Nor do Defendants experience many of the costs associated with drug research and development. Generic companies ***are not innovators***, but rather reformulators of drugs innovated by branded companies like GSK and the other plaintiffs in this case. Defendants need not invest in the financial and intellectual resources required to discover and produce new drugs. (LaWall ¶ 25.) They also do not need to expend resources to market their generic versions – rather, the generic rides on the coattails of the branded drug's recognition and reputation.

Moreover, generic companies are in the business of making cheap versions of drugs – ***they are not service providers***. (Sacher ¶ 50.) Companies like GSK spend significant time and financial resources providing customer support and educational programs in support of the drugs they market, services which increase awareness among providers and ensure patient health and safety. (LaWall ¶¶ 20-21; Sacher ¶¶ 42-48.) Generic companies do not provide these services and are therefore able to sell their drugs at bargain prices. (LaWall ¶ 36; Sacher ¶ 50.) As such, when generics enter the market, branded manufactures often cannot reduce their prices enough to compete, and must also cut back on development and service programs that providers and patients depend on. (LaWall ¶ 36; Vellturo ¶ 62.) As

explained below, this is precisely what will happen to GSK if Defendants are allowed to launch their generic version of GSK's Argatroban Injection.

1. GSK Will Suffer Irreversible Losses In Sales, Revenue, And Market Share

Lost sales and revenue: Although lost sales and revenue standing alone are generally not sufficient to prove irreparable harm, *see Automated Merch. Sys., Inc. v. Crane Co.*, 357 F. App'x 297, 301 (Fed. Cir. 2008), they are nevertheless strong evidence of the significant harm that GSK will suffer if Hikma is permitted to launch its generic version of GSK's Argatroban Injection. *See, e.g.*, *Abbott*, 544 F.3d at 1361-62 (affirming that presence of other generic versions on the market did not negate losses in market share and revenue to be experienced upon Sandoz's entry while litigation proceeded); *Bio-Tech. Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1566 (Fed. Cir. 1996) (affirming that loss of revenue, goodwill, and R&D support constituted irreparable harm).

[redacted]

[15] This is a conservative estimate. For example, when Apotex launched its generic version of Plavix in 2006, it claimed 75% of all new prescriptions and 60%

[redacted]

This economic harm to GSK is likely to be substantial, long-lasting, and unpredictable. While sales lost directly to Hikma's generic argatroban injection may be quantifiable at trial for damages up to that point, determining the quantity of potential losses to RTU generics or other branded drug introductions would be extremely difficult: it would require an understanding of the changes in the marketplace for HIT treatment at that time, which would be impossible to predict with any reasonable accuracy. (Vellturo ¶ 53.) Furthermore, the calculation of these harms may be further complicated because one cannot predict the timing of re-entry by the RTU products. (*Id.*) Such potential future damages are difficult to assess and quantify and are therefore irreparable.

Market share: All argatroban products together captured 82% share of the

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of all prescriptions in just two weeks; by week 4, it had captured 80% of all prescriptions. (Vellturo ¶ 43.) The at-risk launch of generic versions of Protonix by Teva and Sun showed similar numbers. (*Id.*)

[16] These estimates are imprecise because the ultimate effect of Hikma's premature launch will depend on the particular market conditions that exist at that time (*e.g.*, whether Hikma is the only generic competitor or whether one or the other or both of Sandoz or TMC re-enter the market at full capacity).

HIT-treatment market as of January 2012; of this market, GSK's Argatroban Injection had an 80% share. (LaWall ¶ 17.) Correspondingly, GSK's Argatroban Injection accounted for 97% of the argatroban-only market. (*Id.*) If Hikma's generic argatroban injection is allowed to launch, it is likely that hospital pharmacies will remove GSK's Argatroban Injection from their formularies altogether – and replace it with cheaper alternatives like Hikma's generic product or an RTU generic. (LaWall ¶ 27; Vellturo ¶¶ 50-51.); *see also Hoffmann-La Roche Inc. v. Cobalt Pharm. Inc.*, No. 07-4539, 2010 WL 4687839, at *11 (D.N.J. Nov. 10, 2010). Several courts have found that a generic could capture approximately 80% of the branded drug's market within months of launch. *See, e.g.*, *Ortho McNeil*, 2009 WL 2182665, at *9 (drop of 80% net sales in first twelve months); *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 609 F. Supp. 2d 786, 811 & n.23 (S.D. Ind. 2009) (loss of 80% within two months of launch; further noting that other brandeds Pravacol and Zoloft had lost approximately 80% of prescriptions to generics within 3 weeks of entry).

Furthermore, generic companies making at-risk launches – those made with the knowledge of the patentee's rights – will often "flood the market" by pumping many months' supply of product in the first few weeks of its launch, rapidly pushing out the branded drug. (Vellturo ¶ 52.) This flooding effect can be felt many months later,[17] and could be particularly damaging for GSK because the '052

[17] When Apotex launched its generic version of Plavix in 2006, it released so much generic product into supply channels in its three-week launch that even nine months later, it still claimed over 20% of all prescriptions. (Vellturo ¶ 52.)

Patent is set to expire in June 2014. (Cmpt., Ex. A.) As a result, Hikma's generic entrance could sound the death knell for GSK's remaining years of branded-level revenue, to which it should otherwise be guaranteed as the exclusive sublicensee of the '052 Patent. *See King Pharm., Inc. v. Corepharma*, LLC, No. 10-1878 (GEB-DEA), 2010 WL 1850200, at *4 (D.N.J. May 7, 2010) (noting that "two and a half years is not necessarily a 'short period of time' in the pharmaceutical industry" and that in the time period, generic entry could eviscerate the branded's market share).

2. GSK Will Suffer Permanent Price Erosion

The permanent price erosion that a branded product will suffer upon the entrance of a competing generic is clear and consistently-affirmed evidence of irreparable and unquantifiable harm. *See, e.g., Celsis*, 664 F.3d at 930; *Canon, Inc. v. GCC Int'l Ltd.*, 263 F. App'x 57, 62 (Fed. Cir. 2008). Most clearly, such harm is found where a lower-priced generic enters the market, and the brand-name seller is forced to drop its price to compete but can "never increase the price [of the branded] to pre-generic levels." *Hoffmann-La Roche*, 2010 WL 4687839, at *12 ("The phenomenon of price erosion in the pharmaceutical industry is wellknown." (citing *Sanofi-Synthelabo*, 470 F.3d at 1382)).

[redacted] GSK will most likely have to discount its price even further if Hikma enters the market, and once it does so, it will not be

able re-raise its price to pre-generic entry levels once Hikma leaves the market.[18] (*Id.* ¶ 19; Vellturo ¶ 58.) *See Corepharma*, 2010 WL 1850200, at *3 (finding persuasive King's argument that generic entry will cause a "sharp downward pressure" on the market, which will "be permanently altered in ways that will irreversibly deprive King of its 'patent-protected first-entrant advantages").

While some amount of permanent price erosion will occur, it is difficult to predict to what extent generic entry will drive down the price of GSK's Argatroban Injection. Many hospitals will choose the cheaper generic drug because price matters – it is the main driver of generic adoption. (Vellturo ¶¶ 50, 55.) [redacted] If and when the RTU products re-enter the market, the pressure on GSK to offer additional discounts will only increase. (Vellturo ¶¶ 54-55, 58.) [redacted]

In addition, there is great uncertainty regarding the quality and supply of the resulting generic product. As noted earlier, GSK's Argatroban Injection is a sterile injectable drug used in the critical care setting, where hospitals depend on the drug

[18] Customers will consider the new pricing to be the "true" value of the drug and will be unwilling to accept a return to the list price. (LaWall ¶ 19.) [redacted]

to treat HIT in critically ill patients. (LaWall ¶ 11; Vellturo ¶ 16.) Supply or quality issues have resulted in both RTU products being pulled from the market, and similar issues with Hikma's generic argatroban injection could negatively impact GSK's sales by association. (LaWall ¶¶ 15, 40; Vellturo ¶¶ 27, 30, 65.)

It is unclear how individual hospitals or institutions will weigh these competing factors, and as such, to what extent GSK will have to drop its prices in order to compete with Defendants' generic product. The only things that are certain here, after evaluating all of these considerations, are that the extent of these effects will be difficult to ascertain or quantify, and that the resulting harm to GSK will be irreparable.

3. GSK Will Suffer Incalculable And Irreversible Harm From Lost Goodwill And Consumer Confusion

The adverse effect of Defendants' generic entry on GSK's educational efforts extends beyond the harm described above. Defendants' unauthorized launch would also result in intangible and unquantifiable damages to GSK's reputation and goodwill. *See, e.g.*, *Apotex*, 623 F. Supp. 2d at 613-14. Because GSK's Argatroban Injection was the first high-concentration injectable treatment for HIT on the market, it has gained a loyal following among prescribing physicians and pharmacists, both because of the high and dependable quality of its product and because of its dedication to educational support and customer service, all of which have earned the company substantial credibility and customer goodwill. (LaWall ¶¶ 20, 34, 37, 40; Vellturo ¶ 62.) With Hikma's launch,

however, GSK may have to reduce or eliminate its educational programs, which will likely result in significant damage to GSK's customer relationships, goodwill, and reputation. (LaWall ¶ 36-40; Vellturo ¶ 62.) These negative effects, indirectly related to Defendants' generic competition, are impossible to quantify and will result in significant harm to GSK, its customers, and the public. *See, e.g.*, *Ortho McNeil*, 2009 WL 2182665, at *10 (noting that lost goodwill is among the harms that "cannot be undone" or "readily or accurately quantified").

Furthermore, there is likely to be a loss in hospital goodwill associated with changes in price following the exit of Hikma's generic argatroban injection. Hikma's generic argatroban injection is likely to replace GSK's Argatroban Injection on many, if not most, hospital formularies. (LaWall ¶ 27-28; Vellturo ¶ 59.) If Hikma's generic argatroban injection is subsequently withdrawn from the marketplace either as a result of this litigation or due to quality or supply issues, there is no guarantee that GSK's Argatroban Injection will return to its prior formulary position – especially if the RTU products re-enter the market in the meantime. (LaWall ¶ 31; Vellturo ¶¶ 57, 59.)[19]

Just as critical to the value of its reputation, GSK will no longer have control over the quality and service aspects of consumer satisfaction for any sales of

[19] Even if Argatroban Injection were to return to its prior formulary position, economics and marketing studies suggest GSK would lose its customers' goodwill because they would have become accustomed to purchasing the lower priced generic product and would be unhappy being forced to accept a price increase. (Vellturo ¶ 68.)

argatroban to hospitals during the term of generic entry. (Vellturo ¶ 65.) As mentioned above, GSK's Argatroban Injection and Hikma's proposed generic product both use the name "Argatroban Injection," since it is the name of the actual active ingredient and not a brand name. (LaWall ¶¶ 24, 42.) Thus, there is little to separate nominally the products from each other, especially since they are both injectable products. (*Id.*)

The entry of Hikma's generic version could have significant reputational costs for GSK if consumers are confused as to the source of the argatroban being used. *See, e.g.*, *Albany Molecular*, 2010 WL 2516465, at *11. To the extent that there are quality issues associated with Hikma's product, GSK may suffer unquantifiable harm from negative perceptions of "Argatroban Injection" in general – like guilt-by-association. (LaWall ¶ 42; Vellturo ¶¶ 65-66.)

Customers who have experienced an adverse safety event while using a poor quality generic product are likely to conclude that GSK's Argatroban Injection would not work for them either. (LaWall ¶ 42.) For instance, TMC has already been forced to remove its argatroban drug from the market due to quality concerns. Moreover, West-Ward, Hikma's distribution partner for the generic argatroban injection product (*see* LaWall, Ex. 3 at 22.), has also had quality and supply problems, affecting several of its injectable products. (LaWall ¶¶ 40-41.) For example, in 2010, West-Ward recalled two of its injectable drugs, ondansetron and metronidazole, because of safety concerns due to the presence of floating matter and non-sterility. (*Id.* ¶ 40.) This recall likely led, in part, to West-Ward's

discontinuation of these products. (*Id.*) As of February 29, 2012, there are continued market shortages of both ondansetron and metronidazole.[20] (*Id.*)

This sort of reputational harm is impossible to predict and difficult to estimate reliably. Moreover, the future impact of this effect post-trial is inherently difficult to assess and quantify, since quality control would not be in GSK's hands. (Vellturo ¶ 66.)

In addition to quality issues, supply shortages have recently plagued drug markets. If Defendants are allowed to launch, the risk of an argatroban shortage is likely to increase. The previous entry of the RTU generics did little to affect the supply of argatroban, because TMC and Sandoz were on the market for only a short time, but more importantly because the RTU products are formulated differently than GSK's Argatroban Injection. (LaWall ¶ 43.) As a result, GSK was able to compete effectively with the RTU products and could justify maintaining its production of Argatroban Injection. Thus, when both RTU products were removed from the market, GSK was able to meet the demand for argatroban products. (*Id.*)

However, if Hikma is permitted to launch its product, the resulting decline in the sales and market share for GSK's Argatroban Injection would leave GSK no choice but to decrease its production of its Argatroban Injection. (*Id.*) If Hikma were to encounter supply or quality problems – as both TMC and Sandoz have

[20] *See* American Society of Health Pharmacists, Current Drug Shortages, http://www.ashp.org/DrugShortages/Current/Bulletin.aspx?id=510; http://www.ashp.org/DrugShortages/Current/Bulletin.aspx?id=643.

with the RTU argatroban products, and as West-Ward has in the past – GSK could be unable to ramp up production quickly enough to fill in the supply gap. (*Id*.)

This supply concern is particularly significant at the current time. According to the American Society of Health-System Pharmacists, over 250 drugs have suffered from supply problems in the past year, including lifesaving drugs such as doxorubicin and methotrexate. (LaWall ¶ 44.) Signifying the critical nature of these shortages, President Obama signed Executive Order 13588 on October 31, 2011, which allows the FDA to undertake expedited review of manufacturers to prevent shortages of life-saving drugs, stating:

> Shortages of pharmaceutical drugs pose a serious and growing threat to public health. While a very small number of drugs in the United States experience a shortage in any given year, the number of prescription drug shortages in the United States nearly tripled between 2005 and 2010, and shortages are becoming more severe as well as more frequent. The affected medicines include cancer treatments, anesthesia drugs, and other drugs that are critical to the treatment and prevention of serious diseases and life threatening conditions.
>
> For example, over approximately the last 5 years, data indicates that the use of sterile injectable cancer treatments has increased by about 20 percent, without a corresponding increase in production capacity. While manufacturers are currently in the process of expanding capacity, it may be several years before production capacity has been significantly increased. Interruptions in the supplies of these drugs endanger patient safety and burden doctors, hospitals, pharmacists, and patients. They also increase health care costs, particularly because some participants in the market may use shortages as opportunities to hoard scarce drugs or charge exorbitant prices.

(LaWall ¶ 37, n.11.) If GSK became associated with such a shortage of argatroban, its customer goodwill would be seriously and additionally harmed.

Such losses could negatively affect GSK's reputation as an innovative branded drug producer and would restrict its strategic options in the face of likely, though unquantifiable, future competitive challenges. (Vellturo ¶¶ 62, 69.)

4. Defendants' Unrestrained Launch Will Result In Other Unquantifiable Harm To GSK

Other types of irreparable injury recognized in case law include significant reduction in R&D funding and loss of business opportunities. *See, e.g.*, *Apotex*, 623 F. Supp. 2d at 608-14, *aff'd*, 633 F.3d at 1063. [redacted]

[redacted]

These kinds of collateral harm – resulting from Hikma's launch and GSK's subsequent reduction in or loss of other programs and relationships – are inherently difficult to quantify, and as such, are plainly irreparable. (*Id.* ¶ 65.)

C. The Balance Of Hardships Strongly Favors Injunctive Relief

In stark contrast to the devastating effect that entry of Hikma's generic argatroban injection will have on GSK, the injunctive relief sought here would have little or no adverse effect on Defendants. First, Hikma has yet to launch its product. Injunctive relief merely "preserve[s] the relative positions of the parties until a trial on the merits can be held," and as such, Defendants are not harmed by maintaining the status quo. *See Abbott*, 544 F.3d at 1344-45.

Second, any harm to Defendants at this point would be entitled to little weight in the balance of harms: Hikma cannot legitimately argue prejudice where it knew of Argatroban Injection's status under-patent and GSK's marketing of the drug. *See Sanofi-Synthelabo*, 470 F.3d at 1383 (affirming grant of preliminary injunction where defendant's "harms were almost entirely preventable and were the result of its own calculated risk to launch its product pre-judgment"). In comparable circumstances, numerous courts have concluded that the effects of

generic entry on a branded drug's ***existing*** market share greatly outweigh the effect of injunctive relief on the generic drug's ***future*** market share. *See, e.g.*, *Albany Molecular*, 2010 WL 2516465, at *11 ("Any sales that [the generic] would lose if this injunction is improvidently granted would be time-shifted, and lost sales will not be destroyed. [The branded], on the other hand, would suffer devastating and irreversible losses if an injunction is not issued."); *Ortho McNeil*, 2009 WL 2182665, at *11 ("[T]he hardship to Ortho from allowing a generic competitor into the marketplace far outweighs any hardship to Barr."). "Simply put, an alleged infringer's loss of market share and customer relationships, without more, does not rise to the level necessary to overcome the loss of exclusivity experienced by a patent owner due to infringing conduct." *Pfizer*, 429 F.3d at 1382.

Finally, Hikma cannot successfully argue that it will be burdened or prejudiced because GSK did not file suit immediately following the issue of the Paragraph IV Notice. First, GSK never received the Paragraph IV Notice from Hikma. (Smith ¶ 7.) GSK did not learn of Hikma's impending infringement until approximately January 19, 2012, and did not receive a copy of the Paragraph IV Notice until February 13, 2012, when Mitsubishi's outside counsel emailed GSK an electronic copy. (*Id.* ¶¶ 8-9.) From that point forward, GSK has been diligently preparing to file this suit.

Second, Hikma could have taken any number of actions to minimize any perceived harm to itself. For instance, it could have filed an action for declaratory judgment that the '052 Patent was invalid or not infringed by its proposed generic

product. Hikma instead chose to forego this form of relief in favor of infringement. GSK should not be required to suffer the consequences of such a careless choice where it – not Hikma – possesses the exclusive right to practice the '052 Patent in the United States.

D. The Public Interest Favors Injunctive Relief

Finally, granting injunctive relief in this case will strongly serve the public interest in enforcing patent rights and encouraging innovation. *See Abbott*, 544 F.3d at 1363 ("The patent laws promote this progress by offering a right of exclusion for a limited period as an incentive to inventors to risk the often enormous costs in terms of time, research, and development." (citation omitted)). The public interest analysis "includes consideration of whether, by shifting market benefits to the infringer while litigation is pending for patents that are likely to withstand the attack, the incentive for discovery and development of new products is adversely affected." *Id.* at 1362. Permitting Defendants' launch of an infringing product would shift the lawful economic benefits of GSK's licensed patent to the Defendants, a precedent that would adversely affect drug developers' incentives to take risks in pursuit of new products that benefit the public.

The public interest in obtaining lower-priced generic alternatives to brand name prescription drugs does not overcome these considerations. *See Pfizer*, 429 F.3d at 1382 ("Selling a lower priced product does not justify infringing a patent." (citation omitted)). In this case, the public interest is threatened by Hikma's infringement: doctors and ultimately patients will suffer the consequences of

GSK's inability to pursue the development and launch of the new hospital-driven products in its pipeline. (LaWall ¶ 39.)

Nor does the Hatch-Waxman Act alter the balance of public interests. *See Pfizer*, 429 F.3d at 1382 ("[W]hile the statutory framework under which Ranbaxy filed its ANDA does seek to make low cost generic drugs available to the public, ***it does not do so by entirely eliminating the exclusionary rights conveyed by pharmaceutical patents***." (emphasis added)). Moreover, courts confronted with circumstances similar to those present here have repeatedly held that the public interest in encouraging and incentivizing pharmaceutical R&D outweighs the public's interest in expedited access to generic drugs. *See, e.g.*, *Sanofi-Synthelabo*, 470 F.3d at 1383-85 (affirming district court's finding that "the interest in encouraging [and incentivizing] pharmaceutical research and development" outweighed the public interests advanced by the generic manufacturer); *Hoffman-La Roche*, 2010 WL 4687839, at *13 (holding that the public interest in "encouraging investment in drug development" outweighed the interest in "availability of low cost drugs").

IV. CONCLUSION

For the reasons set forth above, GSK respectfully requests that the Court grant its Motion and enter a preliminary injunction prohibiting Defendants from making, using, selling, offering for sale, or importing their generic copy of GSK's Argatroban Injection pending resolution of this litigation.

Dated: April 3, 2012

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