IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

THE MEDICINES COMPANY,	)	
	)	
Plaintiff,	)	
	)	
v.	)	No. 11-cv-1285
	)	
MYLAN INC., MYLAN PHARMACEUTICALS INC., and BIONICHE PHARMA USA, LLC,	)	
	)	
Defendants.	)	

MEMORANDUM OPINION AND ORDER

AMY J. ST. EVE, District Court Judge:

In this patent infringement action, The Medicines Company ("TMC") asserts that Defendants' proposed generic bivalirudin drug product infringes United States Patent No. 7,582,727 (the "'727 patent"). Specifically, TMC claims that Defendants Mylan, Inc., Mylan Pharmaceuticals Inc. and Bioniche Pharma USA, LLC (collectively, "Mylan") proposed generic bivalirudin drug infringes claims 1-3, 7-10, and 17 of the '727 patent. (*See* R.1, Compl.; PTX 397, Parties' Statement of Uncontested Facts, ¶ 38.) Mylan disputes that its proposed drug infringes the '727 patent and asserts that the '727 patent is invalid on grounds of anticipation, obviousness, and non-enablement and unenforceable for inequitable conduct. The Court held a bench trial on TMC's infringement claim and Mylan's counterclaims regarding the '727 patent.[1] Having considered the evidence and the parties' arguments, the Court finds as follows: (1) Mylan failed to prove by clear and convincing evidence that claims 1-3, 7-10, and 17 of the '727

[1] The Court previously granted Mylan summary judgment of non-infringement regarding the other patent-in-suit, United States Patent No. 7,598,343 (the "'343 patent"). (*See* R.309.) Accordingly, only the parties' claims and counterclaims related to the '727 patent were at issue at trial.

patent are invalid or unenforceable; and (2) Mylan's proposed bivalirudin drug product infringes claims 1-3, 7-10, and 17 of the '727 patent.

BACKGROUND

I. The '727 Patent

The '727 patent was filed with the United States Patent and Trademark Office ("PTO") as U.S. Application No. 12/180,553 on July 27, 2008 and issued as the '727 patent on September 1, 2009. (PTX 1, '727 patent; *see* PTX 397, ¶ 6.) The '727 patent is entitled "Pharmaceutical Formulations of Bivalirudin and Processes of Making the Same." (*Id.*) Dr. Gary Musso and Dr. Gopal Krishna are the named inventors of the '727 patent, but TMC owns all rights, title, and interest to the '727 patent.[2] (PTX 397, ¶¶ 8, 9.)

The '727 patent generally pertains to pharmaceutical formulations of bivalirudin, a reversible thrombin inhibitor used to temporarily prevent blood clotting during catherization procedures. (*See id.*, at col. 1:21-56; PTX 397, ¶ 6.) The section of the '727 patent entitled "Background of the Invention" states: "[o]ne class of anticoagulants is direct thrombin inhibitors that disrupt the activity of thrombin, an important protein in the coagulation cascade." (*Id.*, col. 1:49-51.) The '727 further states: "[i]n particular, bivalirudin (ANGIOMAX®), which directly inhibits thrombin by specifically binding to both its catalytic site and to the anion-binding exosite, is regarded as a highly effective anticoagulant for use during catherization [sic] procedures." (*Id.*, col. 1:52-56.) The medical and therapeutic applications of bivalirudin, make it "essential that the bivalirudin formulation maintains a high level of purity." (*Id.*, col. 2:1-3.) The compounding process for the bivalirudin formulation may generate impurities, such as Asp^9-bivalirudin (from deamidation of asparagine at position 9 of bivalirudin to aspartic acid) and

[2] As the Federal Circuit has noted, "[i]nventions are created by individuals, not corporations." *MBO Labs., Inc. v. Becton, Dickinson, & Co.*, 474 F.3d 1323, 1326, n. 1 (Fed. Cir. 2007). For simplicity, however, the Court refers to "TMC" as shorthand for applicants.

D-Phe^{12} impurities (from isomerization of L-phenylalanine at position 12 of bivalirudin to the D-isomer). (*Id.* at col. 2:1-13.) The '727 patent also relates to development of processes for synthesizing bivalirudin that minimize the generation of impurities and pharmaceutical batches produced by such processes. (*Id.* at col. 2:19-22.) By way of background, this compounding process involves three basic steps. (*See* DTX 1080, Compounding Instructions-Bivalirudin Formulation, at MEDMYL4509463, MEDMYL450971.) First, the active pharmaceutical ingredient ("API"), bivalirudin, is dissolved into a mannitol solution to form a bivalirudin solution. Second, the resulting bivalirudin solution is mixed with a pH-adjusting solution, such as sodium hydroxide, to raise the pH of the bivalirudin API to an acceptable level. Third, the mannitol solution and the pH-adjusting solution are removed from the mixture to form the final drug product.[3]

The asserted claims describe pharmaceutical batches of bivalirudin. Specifically, claim 1 of the '727 patent teaches "pharmaceutical batches" of bivalirudin having a maximum Asp^{9} impurity level of 0.6%. (PTX 1, col. 25:56-64.) Dependent claims 2 and 3 contain even stricter limitations on Asp^{9} impurities, reducing the maximum allowable level of Asp^{9} impurities to 0.4% and 0.3%, respectively. (*See id.* at col. 25:65–26:56.) Dependent claims 7-10 and 17 contain all the limitations of claim 1 and additional limitations regarding the maximum level of D-Phe^{12}-bivalirudin impurities (claim 7), the type of pharmaceutically acceptable carrier contained in the final drug product (claims 8-10), and the base used to adjust the pH of the final drug product (claim 17). (*See id.* at col. 27-28.)

[3] Throughout this Opinion, the Court discusses the compounding process used to manufacture bivalirudin final drug products. Although, as the Court previously ruled, the '727 patent does not contain "efficient mixing" process limitations, this compounding process is relevant to the development of the invention in the '727 patent and various other aspects of the parties' infringement and invalidity arguments.

The asserted claims of the '727 patent read as follows:

> 1. Pharmaceutical batches of a drug product comprising bivalirudin (SEQ ID No: 1) and a pharmaceutically acceptable carrier for use as an anticoagulant in a subject in need thereof, wherein the batches have a pH adjusted by a base, said pH is about 5-6 when reconstituted in an aqueous solution for injection, and wherein the batches have a maximum impurity level of Asp^{9}-bivliarudin of about 0.6% as measured by HPLC [high-performance liquid chromatography].
> 2. The pharmaceutical batches of claim 1, wherein the maximum impurity level of Asp^{9}-bivalirudin does not exceed about 0.4% as measured by HPLC.
> 3. The pharmaceutical batches of claim 2, wherein the maximum impurity level of Asp^{9}-bivalirudin does not exceed about 0.3% as measured by HPLC.
> 7. The pharmaceutical batches of claim 1, wherein the batches have a maximum level of D-Phe^{12}-bivalirudin that does not exceed about 2.5% as measured by HPLC.
> 8. The pharmaceutical batches of claim 1, wherein the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent.
> 9. The pharmaceutical batches of claim 8, wherein the bulking agent is a sugar.
> 10. The pharmaceutical batches of claim 9, wherein the sugar is mannitol.
> 17. The pharmaceutical batches of claim 1, wherein the base is sodium hydroxide.

(PTX 1, col. 25:55–28:9.) During claim construction, the Court construed the term "pharmaceutical batches" as follows:

> "Pharmaceutical batches" may include a single batch, wherein the single batch is representative of all commercial batches (see generally, Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 5225.1, Guidance on the Packaging of Test Batches at 1) made by a compounding process, and wherein the levels of, for example, Asp^{9}-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution time represent levels for all potential batches made by said process. "Batches" may also include all batches prepared by a same compounding process.

(*See* R.119, Claim Construction Order.)

The '727 patent specification describes several experiments Dr. Musso and Dr. Krishna ran and provides the resulting Asp^{9} impurity levels for the batches produced in each experiment. Examples 4 and 5 in the specification provide a comparison of an old "inefficient" mixing process (Example 4) and a new "efficient" mixing process (Example 5), and Tables 6 and 7

report the impurity levels and reconstitution times for Original Angiomax® batches produced using inefficient mixing (Table 6) and Improved Angiomax® batches produced using efficient mixing (Table 7). (*See* PTX 397, ¶¶ 13-17.)

Comparison of the results in Table 6 ("inefficient mixing") and Table 7 ("efficient mixing") reveals that the percentage of Asp^9-bivalirudin impurities in the 24 reported batches of Improved Angiomax® (shown in Table 7, recreated below) has a lower mean, standard deviation, and a lower maximum level when compared to the 87 reported batches of Original Angiomax® (shown in Table 6, recreated below):

TABLE 6

Characteristics of the batches generated by the compounding process that features rapid addition of a pH-adjusting solution and **inefficient mixing** rates.

	No. of batches	Mean ± SD	Maximum
Asp^9-bivalirudin (%)	**87**	**0.5 ± 0.4**	**3.6**
Total Impurities (%)	63	1.4 ± 0.5	3.0
Largest unknown impurity (%)	86	0.3 ± 0.1	0.5
Reconstitution Time (seconds)	85	30 ± 12	72

(*See* PTX 1, col. 22:10-20.)

TABLE 7

Characteristics of the batches generated by the compounding process that features addition of a pH-adjusting solution at a constant rate with **efficient mixing**.

	No. of batches	Mean ± SD	Maximum
Asp^9-bivalirudin (%)	**24**	**0.3 ± 0.1**	**0.6**
Total Impurities (%)	24	1.0 ± 0.4	2.0
Largest unknown impurity (%)	24	0.2 ± 0.1	0.3
Reconstitution Time (seconds)	24	18 ± 6	42

(*See id.* at col. 23:1-13.) In addition to the 24 reported batches of Improved Angiomax®, the patent specification discloses that Table 7 did not include the results for one batch because "the method used to generate the batch was not compliant with the protocol established for this study." (*See id.* at col. 23:14-16.)

II. The Present Litigation

TMC is the owner of New Drug Application ("NDA") No. 20-873, which was approved by the U.S. Food and Drug Administration ("FDA"), on December 15, 2000, for the manufacture and sale of a bivalirudin drug product for intravenous injection. (PTX 397, ¶ 19.) TMC's bivalirudin dug product is marketed in the United States under the tradename Angiomax®. (*Id.*, ¶ 20.) Bivalirudin is the active ingredient in TMC's Angiomax® drug, which is indicated for use as an anticoagulant during coronary angioplasty and stenting procedures. (*Id.*, ¶¶ 20-24.)

Mylan submitted Abbreviated New Drug Application ("ANDA") No. 202471 to the FDA, seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of a generic equivalent to Angiomax® prior to the expiration of the '727 patent. (*See* PTX 133; PTX 397, ¶¶ 30-31, 34.) The product specification for Mylan's proposed bivalirudin product seeks approval for a bivalirudin drug with Asp^9 impurities of up to 2.0%

(1.0% α-Asp^9 and 1.0% β-Asp^9). Mylan submitted an exhibit batch of its proposed bivalirudin product to the FDA in support of its ANDA. Mylan's exhibit batch, CMB10001, had total Asp^9 impurities of 0.194%. In November 2011, the FDA sent a deficiency letter to Mylan regarding, among other things, the Asp^9 impurity levels provided in Mylan's specification. Specifically, the FDA wrote, "[y]our drug product impurity release specification is wide, and not supported by the exhibit batch test results." (*See* PTX 162.) To date, Mylan has not submitted a response to the FDA's deficiency letter. An internal draft response prepared in January 2012, however, proposed changing the maximum Asp^9 impurity level to 1.0% (0.5% α-Asp^9 and 0.5% β-Asp^9). (*See* PTX 164.8.)

On February 23, 2011, TMC filed this patent infringement action under the Hatch-Waxman Act, alleging that the manufacture, sale, and offer for sale of Mylan's proposed bivalirudin drug will infringe the '727 patent and United States Patent No. 7,598,343 (the "'343 patent"). (R.1.) Before trial, the Court granted summary judgment of non-infringement in favor of Mylan with respect to the '343 patent. (*See* R.309.) The Court also granted Mylan summary judgment on TMC's willfull infringement claim. (*Id.*) The parties proceeded to trial on TMC's infringement claims and Mylan's counterclaims regarding the '727 patent.

The bench trial on the parties' claims regarding the '727 patent lasted approximately six full days. During the trial, the parties admitted numerous exhibits, including the '727 patent file, Mylan's ANDA, and various e-mails and batch testing documents. Additionally, the following witnesses testified at trial:

- Anthony Flammia, Vice President of New Business Ventures for TMC
- Gary Musso, Co-inventor of the '727 patent
- Julie Simon, formerly the Senior Director of Business Development for Mylan

- Daniel Hoch, an employee of Protocol Link, Inc., a consulting firm that assisted Mylan in preparing its bivalirudin ANDA

- Martina O'Sullivan (via videotaped deposition), Director of Regulatory Affairs for Mylan and Bioniche

- Leena Selvaraj (via videotaped deposition), formerly the Director of External Research and Development and Project Management for Bioniche and Mylan

- Malini Sen (via videotaped deposition), Senior Manager of Quality Assurance at Biocon, the drug manufacturer Mylan contracted with to produce Mylan's ANDA exhibit batch.

- Alexander Klibanov, TMC's expert in the fields of chemistry and in pharmaceutical formulations containing peptides, including their stability

- Wayne Talton, Vice President of Global Regulatory Affairs for Mylan

- Ian McKeague, Mylan's expert in statistics

- David Auslander, Mylan's expert in the field of pharmaceutical formulation and process development

- Rajeshwar Motheram, formerly TMC's Manager of Technical Operations

- Gopal Krishna, Co-inventor of the '727 patent

- Alan Salzberg, TMC's expert in statistics

- Nancy Linck, Mylan's expert in patent prosecution and PTO procedures

- Sandra Kuzmich, TMC's patent prosecution attorney

The parties also submitted deposition designations and videotape clips for the following witnesses: Angela Green; Daniel Robins; James Leary; Lisa-Sue Wood; Pamela Savoy; Russell Garman; Steve McKinnon; and Timothy Smith. During the course of the trial, the Court carefully evaluated the demeanor and credibility of each witness including, where applicable, the witnesses' body language, tone of voice, facial expressions, mannerisms, and other indicative factors. Based on the evidence presented at trial, the Court makes the detailed findings of fact and conclusions of law set forth below.

DISCUSSION

I. Development of the Invention

A. Original Angiomax®

TMC is the owner of NDA No. 20-873, which the FDA approved on December 15, 2000 for the manufacture and sale of a bivalirudin drug product for intravenous injection. (PTX 397, ¶ 19.) TMC's bivalirudin product is marketed under the trade name Angiomax® and among other things, is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty. (*Id.* ¶ 20.) Anticoagulants are substances that prevent blood from clotting and are commonly used during coronary procedures. (*Id.* ¶¶ 23-24.)

Bivalirudin is the API in TMC's Angiomax® product that exhibits anticoagulant activity. (*Id.* ¶¶ 21, 22.) Bivalirudin is a synthetic peptide made up of twenty amino acid residues that are linked in a specific sequence to form a peptide. (*Id.* ¶¶ 22, 25.) The bivalirudin peptide sequence in Angiomax® is: D-Phe-Pro-Arg-Pro-Gly-Gly-Gly-Gly-*Asn*-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu. (PTX 397, ¶ 26 (emphasis added).) The ninth amino acid of the chain, shown above in italics, is asparagine (abbreviated as Asn9 or Asn^9). (*Id.* ¶ 27.) Under certain conditions, an asparagine (Asn) may decompose (undergo deamidation) to form an aspartic acid (Asp). (*Id.* ¶ 28) The impurity "Asp^9-bivalirudin," may form in Angiomax® (or a generic equivalent) when the Asn^9 residue deamidates to an Asp^9 residue. (*Id.* ¶ 29.)

Before the inventions of the '727 and '343 patents, the compounding process used to manufacture TMC's Angiomax® drug resulted in variable and sometimes high levels of Asp^9 impurities in the final drug product. At least two batches of Angiomax® manufactured using the original compounding process ("Original Angiomax®") failed to meet the specification requiring a 1.5% maximum Asp^9 impurity level applicable to Original Angiomax® batches. Lot 716184,

which TMC's drug manufacturer Ben Venue Laboratories ("Ben Venue" or "BVL") produced on June 8, 2005, had an Asp^9 impurity level of 3.6%. (*See* PTX 223.) Ben Venue investigated the failure of Lot 716184 and determined that laboratory error did not cause the failure. In an attempt to avoid future lot failures, Ben Venue and TMC reviewed and implemented changes to its manufacturing instructions, *e.g.,* instructions for adding the pH-adjusting solution to the bivalirudin solution in aliquots. (Tr. 61:22-62:12 (Flammia); Tr. 207:9-208:3 (Musso); PTX 223.15; DTX 1211; DTX 1207; PTX 218 at MEDMYL4399135-36.) Less than a year later, however, Ben Venue produced a second lot with Asp^9 impurity levels that again exceeded the 1.5% specification. (*See* PTX 218; Tr. 1399:23-1402:22 (Klibanov); Tr. 207:9-2008:25 (Musso); Tr. 62:17-64:22 (Flammia).) The second failed lot, Lot 896002, had an Asp^9 impurity level of 2.3%. (*See id*.) Ben Venue could not definitively determine the root cause of either lot failure.

Following this second lot failure, TMC decided to become involved with Ben Venue's investigation into the underlying cause of the high Asp^9 impurity levels for the failed lot. The co-inventors of the '727 patent, Dr. Gopal Krishna and Dr. Gary Musso, led the investigation for TMC. Dr. Krishna was a TMC employee at the time, and TMC hired Dr. Musso as a consultant to assist in the investigation.

On July 14, 2006, Dr. Musso and two TMC employees, Anthony Flammia and Angie Green, met with several Ben Venue employees involved in the production of Original Angiomax® to discuss the lot failures. Dr. Krishna was on vacation and did not attend the July 14, 2006 meeting. Discussions at the meeting addressed the taffy or marshmallow-like precipitate formed during the compounding process and suggestions on how to improve the process were made. First, variations in the heights of the two stirrers in the tank were proposed so that one stirrer mixes the upper part of the solution and the other mixes the lower part of the

solution. (*See* PTX 7.) The second proposal involved increasing the stirring speed prior to the addition of the base. (*See id.*) Finally, a proposal regarding addition of the base through a dip tube was made, so that the base dispersed at the bottom of the tank where mixing is still possible. (*See id.*)

After the operators left the meeting, senior Ben Venue staff and TMC discounted the suggestions. The first suggestion—to vary the stirrer heights—was already part of the Original Angiomax® manufacturing instructions, and Ben Venue had used the third suggestion—adding the base through a dip tube—in manufacturing the first failed lot in 2005. With respect to the second suggestion—increasing the stirring speed before addition of the base—Dr. Musso testified that Ben Venue staff expressed concern that this may lead to foaming.[4]

B. Improved Angiomax®

Following the July 14, 2006 meeting, Dr. Musso and Dr. Krishna observed the compounding process used to manufacture Original Angiomax® and developed a set of experiments designed to identify improvements to reduce the formation of Asp^9 impurities during the compounding process. Dr. Musso and Dr. Krishna then supervised and directed the Ben Venue employees who performed the experiments. Ultimately, through these experiments, Dr. Musso and Dr. Krishna developed an "efficient mixing" process that resulted in lower and more consistent Asp^9 impurity levels in the bivalirudin final drug product.

Under the direction of Dr. Musso and Dr. Krishna, Ben Venue manufactured 26 batches of Angiomax® using the improved compounding process ("Improved Angiomax®"). Twenty-four of those batches had a maximum Asp^9 impurity level of about 0.6% or less, but the

[4] Dr. Musso testified that Ben Venue staff informed him that, in a prior batch of bivalirudin, the bivalirudin API foamed when stirred in a tank. The Court accepted Dr. Musso's testimony for non-hearsay purposes only, not for the truth of the matter.

remaining two batches had an Asp^9 impurity level of 12.4% (Lot 116050) and 1.5% (Lot 1344985). Ben Venue conducted investigations into both failed lots. With respect to Lot 116050, Ben Venue concluded after its investigation that operator error had caused the batch failure. With respect to Lot 1344985, however, Ben Venue found no operator error in the manufacturing process and closed its investigation without identifying the root cause of the failure. TMC and the co-inventors challenged Ben Venue's conclusion that the high Asp^9 impurity level in Lot 1344985 was not due to operator error. Ultimately, Ben Venue agreed to destroy the lot and provide a credit to TMC's account for the batch failure. To date, however, neither TMC nor Ben Venue has definitively identified the root cause of the failure.

II. Invalidity

The Court first turns to Mylan's counterclaims that the '727 patent is invalid due to anticipation, obviousness, and non-enablement. Because patents are presumed valid, the party seeking to invalidate a patent—in this case, Mylan—bears the burden of proving the patent's invalidity by clear and convincing evidence. *See Microsoft Corp. v. i4i Ltd. P'ship,* --- U.S. ---, 131 S. Ct. 2238, 2242, 180 L. Ed. 2d 131 (2011) (citing 35 U.S.C. § 282). The presumption of validity creates " 'a heavy burden of persuasion,' requiring proof of the defense by clear and convincing evidence.... [T]he presumption encompassed not only an allocation of the burden of proof but also an imposition of a heightened standard of proof." *Id.*, 131 S.Ct. at 2246; *see also AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.,* 759 F.3d 1285, 1297-98 (Fed. Cir. 2014) ("[P]atents are presumed to be valid, and overcoming this presumption requires clear and convincing evidence."). New evidence supporting an invalidity defense that the PTO did not consider before issuing the patent-in-suit may "carry more weight" in an infringement action than evidence that the PTO previously considered. *See Microsoft Corp.,* 131 S. Ct. at 2251. The

introduction of new evidence not previously considered by the PTO, however, does not lessen the burden of the party seeking invalidity to prove that the patent is invalid by clear and convincing evidence. *Id.* at 2250-51.

A. Anticipation Under 35 U.S.C. § 102

Mylan alleges that claims 1-3, 7-10, and 17 of the '727 patent are invalid as anticipated under 35 U.S.C. § 102(b).[5] (*See* R.553, Mylan's Post-Trial Brief, at 2-11.)

1. Legal Standard

Section 102(b) provides in relevant part: "A person shall be entitled to a patent unless ... the invention was ... in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States ...." 35 U.S.C. § 102(b); *see also ResQNet.com, Inc. v. Lansa, Inc.,* 594 F.3d 860, 866 (Fed. Cir. 2010) ("An offer for sale, sale, or public use, if more than one year before the patent application was filed, will bar patenting of the product."). "The on-sale bar applies when two conditions are satisfied before the critical date [i.e. more than one year before the patent was filed]: (1) the claimed invention must be the subject of a commercial offer for sale; and (2) the invention must be ready for patenting." *Hamilton Beach Brands, Inc. v. Sunbeam Prods., Inc.,* 726 F.3d 1370, 1374 (Fed. Cir. 2013) (citing *Pfaff v. Wells Elecs., Inc.,* 525 U.S. 55, 67, 119 S. Ct. 304, 142 L. Ed. 2d 261 (1998)).

In determining whether claims are invalid due to an on-sale bar, courts should determine "whether the subject of the barring activity met each of the limitations of the claim, and thus was an embodiment of the claimed invention." *Netscape Commc'ns Corp. v. Konrad*, 295 F.3d 1315, 1323 (Fed. Cir. 2002) (citations omitted). In addition, "[o]nly an offer which rises to the level of

[5] The America Invents Act ("AIA"), Pub. L. No. 112–29, took effect on September 16, 2012. Because the application for the '727 patent was filed before that date, the Court refers to the pre-AIA version of § 102. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958, n. 1 (Fed. Cir. 2014).

a commercial offer for sale, one which the other party could make into a binding contract by simple acceptance (assuming consideration), constitutes an offer for sale under [section] 102(b)." *Id* (citations omitted). "To determine if the offer is sufficiently definite, one must examine the language of the proposal in accordance with the principles of general contract law." *Id.* at 1323-24.

2. Analysis

The critical date for the '727 patent is July 27, 2007. (*See* PTX 1.) Mylan relies on five Original Angiomax® batches sold in the United States between 2002 and 2004, prior to the critical date, for its § 102(b) argument. Mylan, for example, submitted evidence alleging TMC sold Lot No. 273786 in the United States to Amerisource Bergen Drug Corp. in Louisville, Kentucky (sold on 12/17/02), and to Morris & Dickson Co., LLC in Shreveport, Louisiana (sold on 12/17/02).[6] (*See* DTX 1658 at MEDMYL4580643-44; *see also* JTX 3028 (McKinnon Dep. 126:13-127:10).) Mylan argues that the sales of these batches satisfy the requirements for an on-sale bar, namely, that TMC made the sales before the critical date, and: (1) the sales constitute the claimed invention as a subject of the commercial offer for sale; and (2) the claimed invention was ready for patenting as of that date. TMC argues that the batches to which Mylan refers represent only a subset of the multiple batches of Original Angiomax® and that the Court would have to consider all the batches in its analysis of whether the subject of the commercial offer for sale was in fact the claimed invention.

[6] Mylan relies on four additional sales that occurred between 2002 and 2004, for Lot Nos. 273787, 335834, 339257, and 515495 in the United States of Original Angiomax® lots in the sales data report from ICS. (*See* DTX 1658 at MEDMYL4580643-46, 4580658; *see* R.553 at 5-6.)

a. TMC Sold Original Angiomax® Batches Prior to the Critical Date

As an initial matter, TMC does not dispute that the sale of Original Angiomax® batches constitutes a commercial offer for sale and the evidence at trial established the same. During prosecution of Application No. 12/180,553, which issued as the '727 patent, TMC admitted the Original Angiomax® batches referenced in Table 6 were sold, stating "[t]he drug products generated from the old compounding process, which were sold/marketed/offered for sale for more than one (1) year prior to the filing date of the accompanying application, comprised a maximum Asp^9-bivalirudin level of about 3.6%, a maximum reconstitution time of about 72 seconds, and a maximum amount of total impurities of about 3.0%." (PTX 3.145 (emphasis added); PTX 3.708-709; *see also* R.560, TMC's Responsive Post-Trial Br., at 17 ("[T]he file history demonstrates that the PTO was made aware that these Original Angiomax® batches were sold . . . ."); *see also* R.418, Pretrial Order, Exhibit M, Mylan's Proposed Findings of Fact and Conclusions of Law on Invalidity and Unenforceability and TMC's Responses, TMC's Response to FF.9, stating "[i]n 2001, TMC only sold pharmaceutical batches of Original Angiomax®.") The evidence at trial also demonstrated that TMC sold Original Angiomax®, through its distributor—Integrated Commercialization Solutions ("ICS")—to various customers in the United States prior to July 27, 2007. (*See* DTX 1658; DTX 1775; Tr. 150:24-154:9 (Flammia); JTX3028 (McKinnon Dep. 126:13:5-14:17.). The Court, therefore, finds that the Original Angiomax® batches constitute a commercial offer for sale.

b. Original Angiomax® Batches Sold Are Not the Claimed Invention

The Court now turns to whether the commercial offers for sale were of the claimed invention. At their core, Mylan's and TMC's arguments regarding the batches of Original

Angiomax® focus on whether a single batch can be used to meet the "pharmaceutical batches" requirement of the '727 patent claims.

During claim construction, the Court construed the term "pharmaceutical batches" as follows:

> "Pharmaceutical batches" may include a single batch, wherein the single batch is representative of all commercial batches (see generally, Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 5225.1, Guidance on the Packaging of Test Batches at 1) made by a compounding process, and wherein the levels of, for example, Asp^9-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution time represent levels for all potential batches made by said process. "Batches" may also include all batches prepared by a same compounding process.

(*See* R.119.) Although the parties agreed to this construction during the claim construction hearing, they now disagree on its meaning. TMC argues that the Court's construction consists of two parts: (1) the first part, regarding a "single batch," refers only to an ANDA test batch, as evidenced by the parenthetical citation to MAPP 5225.1 regarding the packaging of test batches, and (2) the second part, regarding "all batches," refers to prior art like Original Angiomax® in which TMC produced multiple batches. Mylan, on the other hand, argues that the first part of the Court's construction regarding a "single batch" may apply to single batches other than ANDA test batches and that the Court should consider whether *individual* batches of Original Angiomax® on sale before July 27, 2007 anticipate the asserted claims.

The Court need not resolve this dispute, however, because even if the Court accepts Mylan's interpretation, Mylan failed to establish that the individual Original Angiomax® batches on which it relies meet "each of the limitations of the claim, and thus [are] an embodiment of the claimed invention." *See Netscape Commc'ns*, 295 F.3d at 1323 (citations omitted). Namely, Mylan failed to prove that any of the cited Original Angiomax® batches are "representative" as required by the claim. Namely, that the cited Original Angiomax® batches are: (1)

"representative of all commercial batches . . . made by a compounding process," and (2) "wherein the levels of . . . Asp^9-bivalirudin … represent levels for all potential batches made by said process." (PTX 1, claim 1; *see also* R.119.)

i. TMC Batches 339257 and 515495 Are Not "Representative" of All Commercial Batches

Mylan contends that two of its five cited batches—batches 339257 and 515495—satisfy the "single batch" prong of the Court's "pharmaceutical batches" construction because the batches are "representative." Specifically, Mylan argues that TMC's selection of batches 339257 and 515495 as "stability batches" for use in FDA-required testing on the stability, or shelf-life, of its Original Angiomax® drug product demonstrates their "representative" nature. While TMC does not dispute that the batches are from "a compounding process", it argues that the batches are not "representative" as required by the '727 patent claims. TMC contends that any "representative" nature of the single stability batches identified by Mylan pertains only to their stability, not to the general nature of the batch (which would include being representative of properties other than stability, such as level of impurities.) Both parties, however, seem to ignore the fact that the use of "representative" in the claims of the '727 patent has a specialized meaning.

In order for a single batch to be a "pharmaceutical batch" of the '727 patent claims, the single batch must be "representative." The "representative" concept shows up in two portions of the claim language. A single batch is "representative" if it is: "[1] *representative* of all commercial batches . . . made by a compounding process, and [2] wherein the levels of, for example, Asp^9-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution time *represent* levels for all potential batches made by said process." (*See* PTX 1, claim 1 (emphasis added); *see also* R.119.)

Mylan claims that TMC's chemistry expert's (Dr. Klibanov's) reliance on FDA compliance documents that expressly state that lots placed on stability must be "*representative* of the marketed product," further demonstrates the representative nature of TMC's stability batches. (*See* PTX 108.24 (emphasis added); Tr. 1458:5-15 (Klibanov).) The FDA compliance documents use of "representative," however, does not contemplate the use of that term in the '727 patent. As such, the explicit recitation of "representative" in the FDA compliance document does not bear on whether TMC's stability batches meet the "pharmaceutical batches" limitation as used in the '727 patent claims.[7] *See Rembrandt Vision Techs., L.P. v. Johnson & Johnson Vision Care, Inc.*, 725 F.3d 1377, 1379, 1382-83 (Fed. Cir. 2013) (citing Fed. R. Evid. 403) (affirming the district court's exclusion of plaintiff's circumstantial evidence as potentially confusing and non-probative of infringement where the evidence described the accused infringing product as "soft" and "soft gas permeable contact lens" was a claim term the court construed as requiring the lens to have a Short D Hardness less than five).

Mylan also argues that the ICH Harmonized Stability Guidelines support its position that TMC's stability batches are "representative."[8] This argument, however, views the

[7] As Mylan's argument stems from a dispute of the claim term "pharmaceutical batches," the Court's consideration of the ICH Harmonization Stability Guidelines and the FDA compliance documents as evidence of the meaning of the 'representative" nature of the "pharmaceutical batches" equates to reliance on extrinsic evidence, which although it can shed useful light on the relevant art, is not as reliable as the intrinsic evidence of the language of the claim itself. *See Phillips v. AWH Corp.,* 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc) (citations omitted); *see also 01Communique Lab., Inc. v. LogMeIn, Inc.,* 687 F.3d 1292, 1295-96 (Fed. Cir. 2012) ("To ascertain the scope and meaning of the asserted claims, we look to the words of the claims themselves, the specification, the prosecution history, and, if necessary, any relevant extrinsic evidence.") (quoting *Chicago Bd. Options Exch., Inc. v. Int'l Sec. Exch., LLC*, 677 F.3d 1361, 1366 (Fed. Cir. 2012) (emphasis added)); *Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1348 (Fed. Cir. 2009) ("extrinsic sources like expert testimony cannot overcome more persuasive intrinsic evidence"). Here, looking at the intrinsic evidence of the claim language, it is clear that "representative" as defined in the '727 patent claims requires limitations that the Original Angiomax® batches do not meet.

[8] Mylan also argues that the "stability" of a final drug product references the rate at which impurities form while the product is packaged on the shelf, citing the ICH Harmonization Stability

"representative" limitation of the claim with a myopic focus on the "representative of all commercial batches" portion of the limitation. TMC's Annual Product Review for Original Angiomax® identified the stability batches, stating:

> The bivalirudin drug product stability program is performed by BVL, on behalf of MDCO. Per agreement with MDCO, BVL conducts an active bivalirudin drug product stability program with specified lot samples stored at temperatures and conditions in keeping, testing, and reporting *within the ICH Harmonization Stability Guidelines* and in keeping with FDA and EMEA commitments.

(DTX 1698 at MEDMYL4115027 (emphasis added); *see* DTX 1744 (FDA Guidance adopting the ICH Guidelines).) The ICH Harmonized Stability Guidelines § 1.3 states:

> The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

(DTX 1087 at MEDMYL4054113.) The ICH Harmonized Stability Guidelines § 2.2.3 regarding the selection of stability batches state that "[t]he manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that *intended for marketing*." (*See* DTX 1087 at MEDMYL4054114 (emphasis added).)

In an effort to address the "representative" claim limitation, Mylan relies on the ICH Harmonized Stability Guidelines' reference to stability batches as being the same as that *intended for marketing*. TMC's Vice President of Pharmaceutical Development, Dr. Rajeshwar Motheram, however, testified at trial that TMC generally followed ICH guidelines in choosing stability lots and selected stability lots that were "representative" of *the stability* of their commercial batches (as opposed to representative of the batches generally). (*See* Tr. 1101:6-10,

---

Guidelines (DTX 1087) at MEDMYL4054113. The cited reference, however, does not support this assertion as it does not address the rate at which impurities form.

1104:2-10.) While the ICH Harmonized Stability Guidelines may address use of a batch for stability testing that mimics "that intended for marketing," the '727 patent claims require more from a pharmaceutical batch than it simply being "representative of all commercial batches." Namely, in order for a single batch to be "representative" in the '727 patent claims, it must also have "levels of, for example, Asp^9-bivalirudin, . . . [that] represent levels for all potential batches made by said process."

ii. TMC Batches 339257 and 515495 Do Not "Represent" the Asp^9-Bivalirudin Levels For All Potential Batches

Mylan also has not proven by clear and convincing evidence that the two asserted stability batches are "representative" in the sense that "the levels of, for example, Asp^9-bivalirudin, . . . represent levels for all potential batches made by said process." (PTX 1, claim 1.) Mylan asserts that Original Angiomax® batches 273786, 273787, 335834, 339257, and 515495, which TMC sold through its distributor ICS in 2002-2004 (*see* DTX 1658), render the asserted claims invalid under § 102(b). Two of the batches have Asp^9 impurities of 0.5% or less with three of the batches (Lot Nos. 273786, 273787, and 335834) having Asp^9 impurities of 0.3% or less.[9] Several Original Angiomax® batches made by "said process" (*i.e.*, the compounding process of the cited batches), however, have Asp^9 impurity levels above 0.6%. Lot Number 896002, for example, has Asp^9 levels of 2.3% (PTX 218.2) and Lot No. 716184 has Asp^9 levels of 3.6% (PTX 223.2). Both levels exceeded an Asp^9 level of about 0.6%. Even Mylan's expert, Dr. Auslander, admitted that Original Angiomax®, considered as a whole, fails to meet the Asp^9 impurity level limitations in the asserted claims. (*See* Tr. 1022:2-23.)

[9] Indeed, the first 12 batches of prior art Angiomax® made using TMC's "inefficient" mixing process each had Asp^9 levels at or below 0.6%. Batch number 273786, manufactured in about May 2002, had an Asp^9 level of 0.0%. Five of these first dozen batches had Asp^9 levels equal to or below 0.3%. Three of these batches had Asp^9 levels less than or equal to 0.2%.

Because the claims require the representative batch to not only be representative of all commercial batches, but also represent levels for all potential batches made by said process, the "stability" batches—Lot Nos. 339257 and 515495—do not meet the "representative" claim limitation. TMC's action in selecting and designating batches 339257 and 515495 as stability batches is insufficient to establish that the Asp^9 impurity levels in those batches represent the impurity levels for all potential Original Angiomax® batches made by the same process, as required by the claim. This is especially true in light of the other evidence at trial which showed just the opposite—*i.e.,* that some batches of Original Angiomax® contained Asp^9 impurities well above the impurity levels observed in batches 339257 and 515495.

Accordingly, Mylan has failed to prove that the Original Angiomax® batches alleged by it to meet the on-sale bar under § 102(b) meet each and every limitation of the claim,[10] and thus Mylan has not established that the *claimed invention* was the subject of a commercial offer for sale by clear and convincing evidence and therefore cannot establish invalidity of the '727 patent claims due to an on-sale bar. *See Netscape Commc'ns*, 295 F.3d at 1323 (explaining that in making a determination as to whether claims are invalid due to an on-sale bar, the court should determine "whether the subject of the barring activity met each of the limitations of the claim, and thus was an embodiment of the claimed invention."). Because Mylan failed to satisfy the first element of the on-sale bar, the Court does not address the second element, namely, whether the invention of the '727 patent was ready for patenting. *See Hamilton Beach*, 726 F.3d at 1374.

[10] Regarding the "maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%" claim limitation, several Original Angiomax® batches contained Asp^9 impurities greater than the limitations in the asserted claims of about 0.6% (claim 1), 0.4% (claim 2), or 0.3% (claim 3). Assuming that a single batch (other than an ANDA batch) meets the "pharmaceutical batches" term of the claim, the Court would only look to the impurity level of the single batch itself regarding the "maximum impurity level" claim limitation. Because TMC's stability batches 339257 and 515495 do not meet the "representative" limitation of the '727 patent claims, the fact that they each have a 0.5% Asp^9-bivalirudin impurity level would in isolation meet the "maximum impurity level" limitation is moot. *See Netscape Commc'ns,* 295 F.3d at 1323.

B. Obviousness

Mylan next contends that Claims 1-3, 7-10, and 17 of the '727 patent are invalid as obvious under 35 U.S.C. § 103.[11] (*See* R.553 at 12-24.)

1. Legal Standard

Section 103 forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill." *See* U.S.C. § 103(a) (2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007). The party seeking to invalidate a patent as obvious must prove by clear and convincing evidence that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *Bristol-Myers Squib Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014) (quoting *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)); *see also Amgen, Inc. v. F. Hoffman–La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.").

Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *See InTouch Techs., Inc. v. CGO Comm'cns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) (citing *Graham v.*

[11] The AIA Pub.L. No. 112–29 took effect on September 16, 2012. Because the application for the '727 patent was filed before that date, the Court refers to the pre-AIA version of § 103. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958, n. 1 (Fed. Cir. 2014); *Q.I. Press Controls, B.V. v. Lee*, 752 F.3d 1371, 1377, n. 3 (Fed. Cir. 2014).

John Deere, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)). If, after assessing these factors, a court concludes that the claimed invention was obvious, the claim is invalid under § 103. *See KSR,* 550 U.S. at 407. The Supreme Court has warned, however, that, while an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR,* 550 U.S. at 415, 419; *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012).

2. Analysis

Mylan identified the references below as alleged prior art, along with the testimony of its expert, Dr. Auslander, on the state of the pharmaceutical industry formulation and mixing arts, in support of its obviousness contentions:

- The Original Angiomax® product and processes;
- The 2005 Original Angiomax® product insert (DTX 1498 at MEDMYL0001916-1919); and/or U.S. Patent No. 5,196,404 (PTX 277);
- Dr. Musso's July 15, 2006 Trip Summary Report ("Musso Trip Summary") (PTX 007; DTX 1246);
- KL Amsberry, et al., *Compatibility and Stability of Bivalirudin in IV Admixtures,* AAPS Pharm. Sci. (1999) ("Amsberry Abstract") (DTX 1498 at MEDMYL0001916-1919);
- R. Bischoff & H. Kolbe, *Deamidation of Asparagine and Glutamine Residues in Proteins and Peptides: Structural Determinants and Analytical Methodology,* 662 J. Chromatography 261-78 (1994) ("Bischoff") (DTX 1021); and
- The 2005 European Medicines Agency ("EMEA") publication (DTX 1498 at MEDMYL0001239-1270).

(*See* R.553 at 12.)

a. The Scope and Content of the Prior Art

In order for prior art to be used in combination to determine obviousness under 35 U.S.C. § 103, the alleged prior art must first qualify as prior art under § 102(a), (b), (e), (f), or (g). *See OddzOn Prods., Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1402 (1997); *see also Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987) ("Before answering *Graham's* 'content' inquiry [under the § 103 obviousness analysis], it must be known whether a patent or publication is in the prior art under 35 U.S.C. § 102 – a legal question."). In this case, the parties do not dispute that the 2005 Original Angiomax® product insert,[12] U.S. Patent No. 5,196,404,[13] Amsberry Abstract,[14] Bischoff,[15] and the 2005 EMEA publication[16] qualify as prior art under § 102(b). (*See* R.553 at 12; R.560 at 6-8.) The parties do, however, dispute whether the Original Angiomax® product and the process used to produce it qualify as prior art under § 102(b). (*See id.*) The parties also dispute whether the Musso Trip Summary qualifies as prior art under § 102(f). (*See id.*) The Court first addresses the teachings of the agreed prior art followed by those references in dispute.

[12] The 2005 Original Angiomax® product insert is dated December 6, 2005 and was available to the public when TMC sold Original Angiomax® in 2005 and is therefore prior art under § 102(b).

[13] The '404 patent issued on March 23, 1993 and is therefore prior art under § 102(b).

[14] The Amsberry Abstract was published in *The AAPS Journal* in 1999 and is prior art under § 102(b).

[15] The Bischoff article was published in the *Journal of Chromatography B* in 1994 and is prior art under § 102(b).

[16] Although Mylan's reference is to a "2005 EMEA publication," the document is the same as that submitted during prosecution of the '727 patent (*see* DTX 1498 at MEDMYL0001239-1270) and referred to as the EMEA publication, dated September 1, 2004 (*see id.* at MEDMYL0001289-90). Under either date, the EMEA publication, which addresses Angiox—the European version of Angiomax® (*see* Tr. 147:20-22 (Flammia))—is prior art under § 102(b).

i. The Undisputed Prior Art

The person of ordinary skill in the art[17] knew that Original Angiomax® was a product manufactured by Ben Venue, distributed by ICS, and marketed by TMC, indicated for use as an anticoagulant and contained bivalirudin as its API. (*See* DTX 1498 at MEDMYL0001916-1919.) The "Description" of the Original Angiomax® product states:

> Angiomax® (bivalirudin) is a specific and reversible direct thrombin inhibitor. The active substance is a synthetic, 20 amino acid peptide. The chemical name id D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucinetrifluoroacetate (salt) hydrate (Figure 1). The molecular weight of Angiomax is 2180 daltons (anhydrous free base peptide). Angiomax is supplied in single-use vials as a white lyophilized cake, which is sterile. Each vial contains 250 mg bivalirudin, 125 mg mannitol, and sodium hydroxide to adjust the pH to 5-6 (equivalent to approximately 12.5 mg sodium). When reconstituted with Sterile Water for injection the product yields a clear to opalescent, colorless to slightly yellow solution, pH 5-6.
>
> (*Id.* at MEDMYL0001916.)

Based on Original Angiomax®, the person of ordinary skill knew that thrombin inhibitors may be formulated using conventional methods to prepare pharmaceutically useful compositions with pharmaceutically acceptable carriers and with suitable fillers or bulking agents, such as mannitol. (DTX 1498 at MEDMYL0001916; *id.* at MEDMYL0001855; *see also id.* at MEDMYL0001239.) Regarding the pH of the reconstituted bivalirudin product (for injection), the person of ordinary skill also knew that the pH could be adjusted by a base to achieve a desired pH range of 5-6. (DTX 1498 at MEDMYL0001916.)

In addition, the person of ordinary skill knew that bivalirudin was composed of 20 amino acids, and that the ninth position of the 20-mer peptide chain was an asparagine (Asn). (*Id.* at

[17] Although the parties presented definitions for the person of ordinary skill that differ, the parties agreed that the differences were essentially irrelevant and neither party argued that the differences had any effect on the ultimate determination of obviousness. (Tr. 830:3-8; 1490:20-1492:6; *see* R.553; R.555; R.558; R.560.)

MEDMYL0001916; *see also id.* at MEDMYL0001240; PTX 277, U.S. Patent No. 5,196,404 (disclosing structure of bivalirudin as a thrombin inhibitor).) The person of ordinary skill also knew that Asn deamidates to Asp, and more specifically that "[a] known degradation product of bivalirudin involves the deamidation of asparagine in position 9 to asp9-bivalirudin." (Amsberry Abstract, DTX 1498 at MEDMYL0001675, 1677; *see also* Bischoff, DTX 1021[18] ("[n]on-enzymatic deamidation of asparagine (Asn) … residues in peptides and proteins is a well-documented phenomenon which may occur under physiological conditions ...).)

ii. The Disputed Prior Art

a) Original Angiomax® Process is Prior Art Under § 102(b)

Mylan argues that sales of the Original Angiomax® product prior to the critical date render the process used to make it a public process. (*See* R.553 at 16.) Mylan further argues that because the process was public, knowledge of the high Asp^9 impurity levels and of TMC's internal efforts to avoid high Asp^9 levels by adjusting the compounding process were also public. (*Id.*, at 17 (referencing TMC's internal documents amending its compounding instructions for Original Angiomax® relating to equal addition of base).) Finally, Mylan contends that the person of ordinary skill would have been motivated to combine the attempt made by TMC to adjust its compounding process with the other prior art to arrive at the claimed invention. (*Id.* at 17.)

Mylan relies on *Torpharm, Inc. v. Ranbaxy Pharms., Inc.*, 336 F.3d 1322, 1326 (Fed. Cir. 2003) and *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1344-45 (Fed. Cir. 2007) to assert that

[18] DTX 1021 was admitted not for the truth of the matter asserted, but rather to establish the state of the prior art. *See* Tr. 837:21-838:3; *see also Abbott Labs. v. Diamedix Corp.*, 969 F.Supp. 1064, 1067, n. 1 (N.D. Ill. 1997) (relying on a reference as non-hearsay when being offered as a verbal act and not to prove the truth of the matter asserted and recognizing its relevance as its very existence and the effect its existence had on the knowledge base of those in the field of the art).

because TMC sold Original Angiomax® product one year before the '727 patent was filed, the process by which Original Angiomax® was produced is public and, hence prior art under § 102(b). In both cases, the claims-at-issue were process claims and the Federal Circuit found because the product made by the claimed process was sold more than one year before the filing of the patent-in-suit, that sale rendered the process prior art under § 102(b), regardless of whether it was disclosed to the public or not. *See Torpharm*, 336 F.3d at 1326; *Dippin' Dots*, 476 F.3d 1337, 1344-45 (Fed. Cir. 2007) (emphasis added) (stating "[t]he public sale of goods produced by a process more than one year before a patent is filed places *that process* in the § 102(b) prior art"); *see also D.L. Auld. Co.*, 716 F.2d 1144, 1147-48 (Fed. Cir. 1983) (holding that "a party's placing of a product of the method invention on sale more than a year before that party's application filing date must act as a forfeiture of any right to the grant of a valid patent on the method to that party if circumvention of the policy animating § 102(b) is to be avoided in respect of patents on method inventions.").

The Court agrees with Mylan that the Original Angiomax® product and the process by which it was made are prior art under § 102(b). The *Torpharm* case supports the Original Angiomax® product as "a reference under section 103 against the claimed invention" because it was sold before the '727 patent's critical date. *See id.,* 336 F.3d at 1327 (explaining that the obviousness inquiry requires the district court to determine whether the Form 1 ranitidine of uncertain genesis sold in 1992, in conjunction with the prior art, rendered obvious TorPharm's claimed process of crystallizing improved Form 1 ranitidine from a three- or four-carbon alcohol solvent."). Because the Court has found that Original Angiomax® was sold before the '727 patent's critical date (*see supra* Discussion,II.A.2.a.), the Original Angiomax® product becomes a reference under § 103 against the claimed invention. The *Dippin Dots* case supports the

premise that because the Original Angiomax® product was sold before the '727 patent's critical date, not only is the Original Angiomax® product prior art, but the process by which Original Angiomax® product was made is also prior art under the § 102(b) on-sale bar and "is also prior art for the purposes of obviousness under § 103." *See id.*, 476 F.3d at 1344.

These cases, however, do not reach as far as Mylan contends. Namely, these cases do not stand for the proposition that everything TMC internally knew about the Original Angiomax® product and the process used to make it amounts to prior art under § 102(b). The claims at issue are directed to pharmaceutical batches of a product made by a compounding process that differs from the process used to make the Original Angiomax® product. In other words, the claims at issue in this case are not the process claims for production of Original Angiomax® like the claims presented in *Torpharm*. Nor are the claims at issue in this case the exact process for production of Original Angiomax®, with additional steps recited, like the claims presented in *Dippin' Dots*. Rather, the claims at issue here are directed to pharmaceutical batches of bivalirudin with maximum impurity levels of Asp^9-bivalirudin impurity of 0.5%. As such, the Court finds consistent with *Torpharm* and *Dippin' Dots*, that the Original Angiomax® product and the process used to produce Original Angiomax® qualify as prior art for the purposes of obviousness under § 103. The Court does not find, however, that all of TMC's internal efforts to avoid high Asp^9 levels by adjusting the Angiomax® compounding process also become prior art, absent a showing that this knowledge was disclosed to the public. (*See infra* Discussion, II.B.2.a.ii.c).)

The Court finds, therefore, that the person of ordinary skill in the art being aware of the Original Angiomax® product, knew bivalirudin to be a 20 amino acid peptide with an asparagine residue at the ninth position, and knew it was used as an anticoagulant. The Original

Angiomax® product also taught that bivalirudin drug product was formulated as a dry, lyophilized cake and when reconstituted, the pH was adjusted with base (sodium hydroxide) to reach a pH of 5-6. The Original Angiomax® product was also known to be produced by a compounding process. The compounding process creates the final pharmaceutical product and involves three basic steps. First, the bivalirudin API is dissolved into a mannitol solution to form a bivalirudin solution. Second, the resulting bivalirudin solution is mixed with a pH-adjusting solution, such as sodium hydroxide, to raise the pH of the bivalirudin API to an acceptable level. Third, the mannitol solution and the pH-adjusting solution are removed from the mixture to form the final drug product. More specifically, the original manufacturing process for commercial batches of Original Angiomax® was disclosed in the '727 patent as Example 4. (*See* PTX 1, col.21:44-col.22:27; Tr. 211:8-11; 235:6-14; 269:23 (Musso).)

b) Portions of the Musso Trip Summary Are Prior Art Under § 102(f)

Section 102(f) is a derivation provision which provides that a person shall be entitled to a patent unless "he did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f). Thus, § 102(f) "requires that the patentee be the actual inventor of the subject matter patented." *See New England Braiding Co., Inc. v. A.W. Chesterton Co.*, 970 F.2d 878, 883 (Fed. Cir. 1992).

Mylan argues that "the July 14, 2006 communication from BVL employees to named inventor Musso" is prior art under 35 U.S.C. § 102(f). (*See* R.553 at 17.) The Musso Trip Summary is an internal report prepared by Dr. Musso on July 15, 2006, summarizing a meeting that occurred at Ben Venue on July 14, 2006 "to follow-up on a recent failure of a bivalirudin batch due to high Asp^9 levels (Limit NMT 1.5%)." (PTX 7.) TMC responds that in order to find the Musso Trip Summary prior art under § 102(f), Mylan must prove by clear and convincing

evidence "both *prior conception* of the invention by another and *communication* of the conception to the patentee . . . ." (*See* R.560 at 6 (emphasis original).) TMC further argues that "[t]he communication must be sufficient to enable one of ordinary skill in the art to make the patented invention." (*Id.*) TMC's recited requirements, however, apply when a party is attempting to prove invalidity by derivation under § 102(f), not when a party is attempting to use the disclosure as prior art under § 102(f) in an obviousness analysis. *See Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1313 (Fed. Cir. 2011) (citing *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1344 (Fed. Cir. 2003) (explaining that to prove derivation under § 102(f), a patent challenger must prove both prior conception of the invention by another and communication of that conception to the patentee by clear and convincing evidence); *Galderma Labs, LP v. Paddock Labs, Inc.*, No. 2:09cv002Y, 2011 WL1119700, at *7 (N.D. Tex. March 28, 2011); *see also Gambro Lundia AB v. Baxter Healthcare Corp.,* 110 F.3d 1573, 1577 (Fed. Cir. 1997) (explaining the requirements of a showing of prior conception and an enabling disclosure for an anticipation argument of derivation under § 102(f) and emphasizing there is not a determination of obviousness in a § 102(f) analysis).

Mylan relies on *OddzOn Products, Inc. v. Just Toys, Inc.,* and its holding that "subject matter derived from another not only is itself unpatentable to the party who derived it under § 102(f), but, when combined with other prior art, may make a resulting obvious invention unpatentable to that party under a combination of §§ 102(f) and 103." 122 F.3d 1396, 1403-04 (Fed. Cir. 1997). In *OddzOn*, the Federal Circuit found that the district court did not err by considering confidential disclosures known to the inventor to be prior art under the combination of §§ 102(f) and 103. *See id.* at 1404; *see also IGT v. Bally Gaming Int'l., Inc.*, 610 F. Supp. 2d 288, 321 n.24 (D. Del. 2009) (referencing *OddzOn's* holding that "§ 102(f) non-public subject

matter can be used to reject a claim of invention by another in possession of the § 102(f) subject matter under a combination of § 102(f) and § 103"). The confidential disclosures in *OddzOn* were two design references provided to the inventor by another.[19] 122 F.3d at 1403-04.

The July 15, 2006 Musso Trip Summary, however, is not the same as the confidential disclosures in *OddzOn*, because it is not a disclosure provided to Dr. Musso from another. Instead, Dr. Musso prepared the report himself to memorialize the meeting with Ben Venue, and dated it the following day. (PTX 7; DTX 1246; Tr. 199:21-201:7 (Musso).) Mylan's request that the "July 14, 2006 communication from BVL employees to named inventor Musso is prior art under § 102(f)," when the report is actually dated as prepared by Dr. Musso on July 15, 2006 is not a mistake on Mylan's part, but rather reflects the complex nature of Mylan's request. The Musso Trip Summary contains Dr. Musso's recollection of discussions he had on July 14, 2006 with Ben Venue employees working with the bivalirudin batches for Original Angiomax® and TMC, discussions that addressed the recent failure of bivalirudin batches due to high Asp^9 levels (*i.e.* levels beyond the 1.5% allowed for in the product specification). (*See* PTX 7.1.) As such, the report contains both summaries of information Ben Venue employees allegedly provided to Dr. Musso on July 14, 2006, as well as Dr. Musso's own thoughts, reactions, and proposals experienced during and after that meeting. Mylan specifically advocates for consideration of the "*July 14, 2006* communication from Ben Venue employees to named inventor Musso" as prior art under § 102(f), and not consideration of the Musso Trip Summary in its entirety created on July 15, 2006.

[19] Although the patent in *OddzOn* was a design patent, the obviousness inquiry "applies with equal force." *See Litton Systems, Inc., v. Whirlpool Corp.*, 728 F.2d 1423, 1441 (Fed. Cir. 1984) (*overruled on other grounds, Braun Inc. v. Dynamics Corp. of America*, 975 F.2d 815 (Fed. Cir. 1992)) ("Accordingly, 35 U.S.C. § 103 (and all the case law interpreting that statute) applies with equal force to a determination of the obviousness of either a design or a utility patent.")

Employees of both TMC and Ben Venue, along with the inventor Dr. Musso, attended the July 14, 2006 meeting. (PTX 7; DTX 1245; Tr. 67:19-68:18 (Flammia); Tr. 200:6-202:19 (Musso); Smith Dep. 71:06-71:18, June 10, 2014.) Dr. Musso testified that the Musso Trip Summary was an accurate memorialization of what happened during the meeting. (*See* Tr. 200:6-201:11 (Musso).) Dr. Musso further testified that Ben Venue operators shared their experiences regarding the compounding process, and referred to the section of three bullet points in the report, shown below, which states:

> The operators shared their experience based comments which included:
> - Vary the stirrer heights so that one mixed the upper and one mixed the lower level of the tank
> - Increase the stir speed prior to base addition
> - Add base through a dip tube so that it is dispersed in the bottom of the tank where mixing is still possible (the marshmallow solid was suggested to be more on the top portion of the formulation).

(PTX 7.2; Tr. 202:17-204:7 (Musso).) Dr. Musso also testified about the operators insights regarding the compounding process, and referred to the section of five bullet points in the report as referring to the Original Angiomax® compounding process, also described in Example 4 of the '727 patent. (Tr. 261:263:8 (Musso).)[20] The portion of the Musso Trip Summary that Dr.

[20] TMC employee, Angie Green, worked on the commercial side of Angiomax® and was a part of the Ben Venue and TMC team as a liaison to facilitate communication between the companies. (Deposition Video, Angie Green, 44:22-45:17; 47:25-48:25.) Ms. Green testified that she attended the meeting with Ben Venue on July 14, 2006 and kept minutes from that meeting. (*See* DTX 1245.) The "Comments" section of those minutes reflects various comments made by employees of Ben Venue and TMC (including Musso) throughout the meeting. (*Id.*) The minutes indicate the Ben Venue provided Dr. Musso with information, but the conclusions regarding what the problem may be are attributed to inventor Gary Musso, "BVL gave Gary the sequence of the cleaning process. Gary does not believe this is the problem." In addition, numerous suggestions are attributed to inventor, Musso, e.g., a suggestion of "testing ph at bottom of mixers," (DTX 1245, at MEDMYL0007884); "3 different mixing times," (*id.*); "using glass for container in order to see solution at the bottom" (*id.*). The numerous contributions noted by inventor Musso as well as by other TMC employees highlight the challenge in parsing out what portions of the Musso Trip Summary correlate to statements communicated from Ben Venue or TMC during that meeting.

Musso testified contained the comments from the Ben Venue operators is shown below, and states:

> The two operators provided some interesting insights such as:
> - There is no safety issue with base addition, so stirring could be rapid in the base addition
> - They had no problem adding all the base at once (both operators appeared physically strong)
> - They do not recall shutting off the stirrers during base addition
> - They also commented that with the low speed stir, the mixture is like a "marshmallow" after ¾ of the base addition and the stirrer is ineffective at low speed.
> - Under low speed mixing, the formulation is generally not stirred at the end of the addition as the solid mass is too thick. In a discussion of portion-wise addtion [sic] the operators also indicated that the last base addition just sat on top of the marshmallow and did not mix – similar to the comments related to viscosity discussion held previously.

(PTX 7.2; Tr. 261:263:8 (Musso).) The evidence revealed that at some point later in the meeting when the participants were still discussing the issues, Ben Venue operators were no longer present. (Tr. 68:9-10 (Flammia); Tr. 264:10 (Musso).) Timothy Smith, Director of Product and Process Development at Ben Venue at the relevant time, also testified that he attended the meeting with TMC on July 14, 2006. (Smith Dep. 71:06-71:18; *see* Gezzar Dep. 89:14-89:25, January 18, 2013.) Mr. Smith testified that Ben Venue operators were asked to join the meeting, identifying one of the operators by name. (Smith Dep. 73:08-73:19.) In response to questions from Mylan's counsel regarding the Musso Trip Summary, Mr. Smith testified that he "presumed" what the document was referring to, but provided no testimony regarding whether the Ben Venue operators provided the recited information to Musso and TMC or whether the meeting participants discussed the recited information, and Mylan never asked. (*See* Smith Dep. 74:04-79:11.) Mylan's scientific expert, Dr. Auslander, provided a conclusory opinion regarding the Musso Trip Summary, but later conceded that without having attended the meeting, it was not possible for him to tell who had led the discussion, what dialogue took place, or the dynamic

of the discussion (*e.g.*, who asked who what), and that it would be speculation to attempt to know. (Tr. 1013:6-1017:13 (Auslander).) In fact, Dr. Musso testified that the cause of the high Asp[9] failure was not identified at the meeting. (Tr. 201:19-21.) Dr. Musso further stated that he and Dr. Krishna "came up with the ideas on how to fix and make the improved product. Ben Venue did not contribute to those inventions." (Tr. 205:19-21.)

Based on this record, and in particular on Dr. Musso's testimony and the Musso Trip Summary itself (a document created by Dr. Musso very close to the date of communication with Ben Venue), Mylan has established by clear and convincing evidence that the two bulleted portions from the Musso Trip Summary cited above qualify as prior art under § 102(f) in a § 103 obviousness analysis.[21] Mylan has failed, however, to establish by clear and convincing evidence whether any additional portions of the Musso Trip Summary qualify as prior art communications from Ben Venue to TMC and Musso under § 102(f) for the § 103 obviousness inquiry. The Court, therefore, is unable to rely on the disclosures in the summary, in whole, as prior art.

c) TMC's Efforts Associated With Production of Original Angiomax® Identified in Internal Documentation Are Not Prior Art Under § 102(b)

Mylan contends that the efforts TMC made associated with Original Angiomax® production identified in internal TMC documentation are also prior art and were known to the person of ordinary skill. (R.553 at 16-17.) The Court disagrees.

[21] Although the second bullet point seems to memorialize not only what Ben Venue operators communicated to Dr. Musso, but also includes additional information that appears to be reflective of Dr. Musso's own thoughts or impressions ("both operators appeared physically strong"), the remaining portions of the report are clearly understood as attributable to comments made by Ben Venue operators. (*See* PTX 7.2.)

Again relying on the Federal Circuit's decision in *Torpharm*, Mylan asserts that TMC's 2005 effort to avoid high Asp[9] levels by adjusting the Angiomax® compounding process constitutes prior art. (*Id.* at 17.) Specifically, Mylan argues that TMC's amendment to its compounding instructions in 2006, reflected only in TMC's internal documents, is prior art. (*Id.* at 17.) Mylan references the confidential copies of the Master Production Record for Bivalidurdin, 50 mg/ml from Ben Venue to TMC. (*See* DTX 1211.) The *Torpharm* and *Dippin' Dots* cases do not, however, stand for the proposition that because the Original Angiomax® product and the process used to make the sold batches of Original Angiomax® product are prior art, all TMC's internal and confidential knowledge about that product and its process also become prior art. The Court has already found that the process as disclosed in Example 4 of the '727 patent is prior art based on the sales of Original Angiomax®. (*See supra* Discussion, II.B.2.a.ii.a).) This discussion indicates the process change that was implemented in the 2006 amendment. In particular, the addition of the pH-adjusting solution to the bivlirudin solution as "either all at once, or rapidly in multiple portions, while the bivalirudin solution was mixed by two paddle mixers located at the top and bottom of the bivalirudin solution." (PTX 1, col. 59-62.)

The fact that this process change is included in the prior art disclosure of the bivalirudin compounding process, however, does not equate to a finding that all of TMC's internal efforts surrounding that product and its process or problems with that process and the evolution of the process also become prior art. Indeed, TMC and Mylan both agree and the evidence at trial demonstrated that the two failed Original Angiomax® batches—Lot Nos. 716184 and 896002 with Asp[9] levels above the 1.5% specification—were not sold and, thus, were not publicly available. (*See* Tr. 59:4-9 (Flammia); *see* R.553 at 9 ("When Original Angiomax batches were

not representative of this approved process … such batches were not representative and destroyed …").) The batches of Original Angiomax® that TMC sold to the public were those batches that followed the original compounding process and met the regulatory requirements of the specification. These batches would, therefore, if tested by the person of ordinary skill, not demonstrate any problems with levels of Asp^9 that fell outside of the product and process specification's maximum level of 1.5% Asp^9 impurity.

The internal efforts TMC made to adjust its compounding process over time and the internal, confidential communications surrounding those adjustments do not become prior art based on *Torpharm* and *Dippin' Dots*, and Mylan has not cited any case law that supports such a proposition. Mylan also failed to offer any evidence surrounding public disclosure of TMC's internal documents addressing the problem of high Asp^9 levels in Original Angiomax® or the steps TMC undertook to combat that problem. *See In re Lister*, 53 F.3d 1307, 1311 (Fed. Cir. 2009) (citing *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004)) (explaining the public accessibility of a reference "is determined on a case-by-case basis based on the facts and circumstances surrounding the reference's disclosure to members of the public."). The Court, therefore, finds no evidentiary support that those documents were "sufficiently accessible to the public interested in the art" and as such, cannot rely on TMC's internal documents as prior art under § 102(b). *See In re Lister*, 583 F.3d at 1311 (citations omitted) (explaining that "[i]n order for a printed publication to qualify as prior art within the meaning of § 102, a reference 'must have been sufficiently accessible to the public interested in the art.'").

b. Differences Between the Claimed Invention and the Prior Art

In order to determine whether the claimed invention of the '727 patent was obvious to the person of ordinary skill at the time the invention was filed (July 27, 2006), the Court must

determine the differences between the claimed invention and the prior art. *See InTouch Techs., Inc.,* 751 F.3d at 1347. The '727 patent's claimed invention is directed to "pharmaceutical batches" of "bivalirudin" and a "pharmaceutically acceptable carrier for use as an anticoagulant" wherein the batches have a pH adjusted by a base (pH of 5-6) and wherein the batches "have a maximum Asp^9 impurity level of 0.6%." (PTX 1, col. 25:56-64.)

The differences between the prior art and the claims of the '727 patent are narrow when compared to Original Angiomax® as prior art. The prior art Original Angiomax® meets a number of the limitations of claim 1 of the '727 patent. (*See* R.553 at 15; (Tr. 1431:10-1432:22 (Klibanov).) The person of ordinary skill knew that Original Angiomax® contained bivalirudin formulated with a pharmaceutically acceptable carrier (*e.g.*, including a bulking agent such as mannitol) for use as an anticoagulant. (DTX 1498 at MEDMYL0001916; *id.* at MEDMYL0001855; *see also id.* at MEDMYL0001239.) The person of ordinary skill also knew that the pH of the reconstituted bivalirudin product (for injection) could be adjusted by a base to achieve a desired pH range of 5-6. (DTX 1498 at MEDMYL0001916.) Regarding bivalirudin and its impurities, the person of ordinary skill knew that bivalirudin was composed of 20 amino acids, and that the ninth position of the 20-mer peptide chain was asparagine. (*Id.* at MEDMYL0001916; *see also id.* at MEDMYL0001240; PTX 277, U.S. Patent No. 5,196,404 (disclosing structure of bivalirudin as a thrombin inhibitor).) Further, the person of ordinary skill knew that asparagine (Asn) deamidates to aspartic acid (Asp), and more specifically that "[a] known degradation product of bivalirudin involves the deamidation of asparagine in position 9 to asp9-bivalirudin." (Amsberry Abstract, DTX 1498 at MEDMYL0001675, 1677; *see also* Bischoff, DTX 1021 ("[n]on-enzymatic deamidation of asparagine (Asn) … residues in peptides

and proteins is a well-documented phenomenon which may occur under physiological conditions ...).)

i. The Prior Art Does Not Disclose All Elements of the Claimed Invention

The prior art does not, however, disclose the remaining limitations of claim 1 requiring that the "pharmaceutical batches" and the "maximum impurity level of Asp^9-bivalirudin does not exceed about 0.6%" claim limitations. (*See* R.553 at 15; (Tr. 1431:10-1432:22 (Klibanov).)

In an attempt to overcome this absence, Mylan first relies on the story of the invention. (*See* R.553, 13-15.) The story of the Improved Angiomax® invention, as recounted by Mylan, however, repeatedly relies on evidence that does not qualify as prior art under § 102 – namely, internal TMC documents and knowledge that indicate the problems with the Asp^9-bivalirudin levels. In particular, Mylan relies on these documents for disclosure of the problem with Asp^9 levels in the prior art. Without the support provided by these documents as prior art, the obviousness analysis requiring the information they contain fails. (*See infra* Part II.B.2.b.ii.)

Second, Mylan essentially repeats its anticipation argument and relies on internal TMC documents showing that 79 of 87 prior art Angiomax® batches had Asp^9 levels at or below about 0.6% and that TMC sold dozens of these batches prior to the critical date for the '727 patent. The Court must, however, consider the claimed subject matter as a whole and, in doing so, it cannot focus only on the Asp^9 levels in isolation. *See* 35 U.S.C. § 103; *see also KSR,* 550 U.S. at 406 (holding that a party asserting obviousness must show "the subject matter [of the asserted claims] *as a whole* would have been obvious") (emphasis added). To ignore the "pharmaceutical batches" limitation of the '727 patent claims would, therefore, be improper in the obviousness analysis. As noted above, in relation to Mylan's anticipation argument and the parties' dispute regarding the "pharmaceutical batches" limitation, Mylan failed to establish that the Original

Angiomax® batches on which it relies meet each and every limitation of the asserted claims. (*See supra* Part II.A.2.) In particular, Mylan failed to prove that any of the cited Original Angiomax® batches are: (1) "representative of all commercial batches . . . made by a compounding process," and (2) have "levels of . . . Asp^9-bivalirudin … [that] represent levels for all potential batches made by said process." (PTX 1, claim 1; *see also* R.119.) As such, the Court finds that the evidence of prior art provided in this case, does not meet all the limitations of the claimed invention.

ii. The Prior Art Did Not Provide a Motivation for a Person Skilled in the Art to Combine the Prior Art Elements – the Asp^9 Problem Was Not Known or Predictable

In addition, Mylan asserts that the above limitations were obvious to the person of ordinary skill in the art, a person who understood the generation of the Asp^9 impurity in a bivalirudin compounding process. (*See* R.553 at 17.) Mylan relies on the Amsberry Abstract and Bischoff for teaching the person of ordinary skill about generation of the Asp^9 impurity in the bivalirudin compounding process. Further, Mylan argues that the person of ordinary skill would apply this knowledge to bivalirudin because he or she: (1) knew that the bivalirudin peptide contained an asparagine residue (Asn) preceded and followed by glycine residues (Gly); (2) knew that the bivalirudin compounding process included a pH-adjustment step wherein the bivalirudin solution is exposed to sodium hydroxide, a strong base (*see* DTX 1080, at MEDMYL4509447-75 (compounding instructions for mannitol solution (Part I), sodium hydroxide/mannitol solution (Part II), and bivalirudin formulation (Part III)); PTX 223); and (3) knew the specific Asp^9 levels of prior art Original Angiomax® as they had access to the product and would have been motivated to measure the Asp^9 levels of prior art Original Angiomax®. (*See* R.553 at 17-18.)

The Court agrees that the prior art teaches the bivalirudin peptide sequence and teaches that asparagine residues, generally, can be susceptible to deamidation under basic conditions. The prior art also teaches that a known degradation product of bivalirudin involves deamidation of asparagine in position 9 to asp9-bivalirudin. The Court also agrees that the prior art teaches the presence of a pH-adjustment step of the Original Angiomax® compounding process. Mylan's argument fails, however, from its reliance on the presence of a problem with the levels of Asp^9-bivalirudin impurity and, hence has no basis for a motivation to measure the Asp^9 levels of prior art Original Angiomax®. This motivation presumes the person of ordinary skill has knowledge of the problem of high and variant Asp^9 levels with prior art Original Angiomax®. The prior art does not specifically teach that asparagine deamidation or high and variant Asp^9 levels were a problem with the bivalirudin peptide. Mylan did not establish that the specification parameters for Original Angiomax® were available as prior art,[22] nor did it establish that the person of ordinary skill would be aware of any problems with the Original Angiomax® batches falling out of specification.

Mylan's argument relies on the inferences to link the prior art disclosures that create a drawn out hypothetical scenario that does not render the claims obvious by clear and convincing evidence. First, Mylan's argument relies on the person of ordinary skill in the art to have known to produce batches of bivalirudin drug product following a version of the prior art process disclosed in Example 4 of the '727 patent and in doing so, to have recreated the Asp^9-bivalirudin impurity level problem experienced by TMC and Ben Venue. Second, Mylan's argument relies on that person of ordinary skill understanding that because the known degradation product of the

[22] Mylan's expert testified that the term "out of specification" was a colloquial term that "refers to a specification that's been generally filed with the government, with the FDA, or it could be an internal specification." (Tr. 798:25-799:11.)

Asp^{9}-bivalirudin impurity was produced by exposure to basic conditions, that the pH-adjustment step in the compounding process was the culprit of the problem (meanwhile ignoring the prior art that indicates other problems could occur and affect the rate of deamidation). Mylan's argument then relies on the person of ordinary skill to have known that changes to the compounding process, namely to the mixing conditions, would result in a more effective process and a lower Asp^{9}-bivalirudin impurity level. In short, Mylan's argument is fraught with unsupported assumptions, which the Court addresses below.

While it is true that the Amsberry Abstract teaches that Asp^{9}-bivalirudin was a known degradation product of bivalirudin. Amsberry also indicates that under the conditions examined, "no significant change in the concentration of asp9-bivalidurin" was observed and further concludes that "[b]ivaliridin is stable to deamidation during the normal course of IV administration in PTCA and AMI clinical trials." (DTX 1498 at MEDMYL0001677.) This disclosure would not lead the person of ordinary skill in the art to believe that bivalirudin had problems with high and variant Asp^{9} levels, either in production or in practice.[23] The general disclosure of Bischoff is no more convincing. Bischoff does teach the person of ordinary skill that generally, a deamidation of asparagine can occur (at neutral and basic pH values) in peptides and proteins containing asparagine residues, but the prior art also teaches that other residues contained in bivalirudin, *e.g.*, aspartic acid at position 11, were susceptible to changes in pH and to reactions such as isomerization. (*See* DTX 1023; *see also* PTX 1, claim 1 ("… wherein the

[23] Mylan's reliance on Dr. Klibanov is unpersuasive and misconstrues his testimony. Mylan alleges Dr. Klibanov "readily admits that the susceptibility of asparagine to deamidation when it is followed by a glycine was 'widely known.'" (R.553 at 18.) In response to Mylan's questions regarding the adverse effects of a high level of the Asp9 impurity, Dr. Klibanov testified, however, that "[i]t's widely known in the industry that when you produce the aspartic acid residue [from deamidation of asparagine], which is followed by glycine, *that particular peptide bond* [Asp-Gly] *will be susceptible to hydrolysis*." (Tr. 1428:12-1429:13.) Dr. Klibanov was therefore testifying about the susceptible nature of an Asp-Gly peptide bond that has already formed (after deamidation of the Asn residue), not the susceptibility of the occurrence of the deamidation reaction, itself.

batches have a pH adjusted by a base, said pH is about 5-6 when reconstituted in an aqueous solution for injection).) The bivalirudin peptide contains both asparagine and aspartic acid residues. (*See* PTX 397, ¶ 26.) Mylan provided no testimony to justify ignoring Aswad's disclosure for the potential problems of pH changes and aspartic acid isomerization, but accepting Bischoff's disclosure for asparagine deamidation. Therefore, while the person of ordinary skill may have been aware that asparagine residues, followed by glycine, can be susceptible to deamidation, they would also have been aware that other residues, like aspartic acid, were susceptible to isomerization and would not have, therefore, been led by the prior art to focus on the deamidation of asparagine as a problem with bivalirudin.

Mylan's reliance on an internal memorandum dated in 1994 from Biogen, Inc. to TMC, admittedly not prior art, (DTX 1020) is unpersuasive. The evidence showed that even after receiving the information from Biogen, Inc., TMC still experienced high variable Asp^9 levels. (Tr. 1397:9 – 1399:10 (Klibanov).) In addition, the batches made by Biogen, Inc. did not all report Asp^9 levels, as such, it is impossible to determine if the production of batches from Biogen, Inc.'s compounding process changes would have resulted in "pharmaceutical batches" as required by the claims of the '727 patent. (*Id.*) Mylan admits that the Biogen solution "produc[ed] batches that *appeared to satisfy all the requirements* of the asserted claims. (R.553 at 23.) Because Mylan did not prove by clear and convincing evidence that the Biogen batches meet each and every limitation of the claimed invention and were made within a comparatively short period of time, however, they do not suffice as evidence of obviousness. *See Geo M. Martin Co. v. Alliance Machine Sys. Int'l. LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (citing *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184, 46 S.Ct. 42, 70 L.Ed. 222 (1925) (finding a simultaneous invention made one year prior to be strong evidence of what constitutes

the level of ordinary skill in the art as it was "[i]ndependently made, simultaneous inventions, made 'within a comparatively short space of time," and therefore "persuasive evidence the claimed apparatus 'was the product only of ordinary mechanical or engineering skill.'").

Without the internal documentation of the prior specification, the problem, and the entire Musso Trip Summary available as prior art, Mylan has little to no evidentiary support for its obviousness argument. Mylan failed to establish that the person of ordinary skill was aware of TMC's problems with the Original Angiomax® process – more specifically, the problem with the Asp^9 levels falling out of specification. Further, Mylan failed to establish that the prior art taught the person of ordinary skill what the product specification for Original Angiomax was, as Mylan consistently refers to confidential, internal TMC and Ben Venue documents for this premise. (*See e.g.,* DTX 1080; DTX 1076; DTX 1240; DTX 1216; DTX 1263; DTX 1366; DTX 1406; 1645.)[24] Even if the specification limit of 1.5% Asp-bivalirudin impurity level for Original Angiomax® had been established as known in the prior art, however, it is counter-intuitive that the person of ordinary skill knowing that an FDA approved product had a specification of 1.5% maximum for use as an injectable would find that limit to be a problem, and Mylan failed to prove otherwise. (*See* Tr. 1429:25-1430:3 (Klibanov) ("Q. And, in fact, TMC believed it was safe to sell Angiomax to doctors to inject into patients for those years with Asp^9 levels of 1.5 percent, correct? A. That's my understanding.")

The person of ordinary skill would have had access to the prior art batches of Original Angiomax® sold and had the ability to test those batches, including the ability to test the Asp^9

[24] Indeed, during cross examination of Dr. Klibanov, Mylan's questioning indicated that even generic filers do not know what the Asp^9-bivalirudin levels are for the Angiomax® products. (*See* Tr. 1434:8-10 ("Q. Right. Because, of course, the generic filers don't know what the Asp^9 level is of Angiomax set by the FDA, right? A. I'm not sure about that."); *see also* DTX 1526, Portion of TMC's NDA for Angiomax, dated 2/23/2011, and marked "Confidential.") Mylan also admits that DTX 1080 and DTX 1216 are internal reports, both produced under the "Highly Confidential-Outside Counsel Only designation and that neither is a patent or publication. (*See* R.553 at 39.)

levels of those batches. Those sold batches, however, did not contain problematic Asp^9 levels. Mylan argues the person of ordinary skill would have been aware that the bivalirudin compounding process included a pH-adjustment step that exposed the bivalirudin solution to a strong base, sodium hydroxide, and paired this knowledge with the prior art's teaching of susceptibility of the Asn residue in the ninth position of bivalirudin to deamidation. Even knowing this information, however, when asked if the person of ordinary skill would predict a deamidation problem for bivalirudin, Mylan's own expert testified that he would "say that a scientist or a person of ordinary skill in the art [would] say that's a very plausible or possible pathway and would do those experiments." (Tr. 972:24-975:3.) Plausible and possible, however, do not rise to the level of clear and convincing. *See Buildex Inc. v. Kason Industries, Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988) (citing *Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433, 2437-38, 81 L.Ed.2d 247 (1984)) ("Although not susceptible to precise definition, 'clear and convincing' evidence has been described as evidence which produces in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions are highly probable.'"); *see also United States v. Boos*, 329 F.3d 907, 911 (7th Cir. 2003) ("highly probable" is the Supreme Court's definition of clear and convincing standard of proof).

Given that the problem of high and variant Asp^9 levels remained unknown, as TMC points out, a finding of obviousness is precluded. The Court recognizes that "[o]ne of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR*, 550 U.S. at 419–20. When a problem is "known in the field of endeavor at the time of invention and addressed by the patent," that problem "can provide a reason for combining the elements in the manner claimed." *Id.* at 420. In this case, however, Mylan has not

presented evidence that the person of ordinary skill knew of the problem with high and variant Asp^9 levels. The evidence at trial provided only conclusory and factually unsupported testimony of a general motivation in the drug formulation business to minimize the level of impurities and that the person of ordinary skill in the art would have been motivated to minimize or eliminate the level of Asp^9 impurity in the bivalirudin drug product. (Tr. 839:13-19 (Auslander); (Tr. 366:22-23 (Musso) ("one always seeks to control and limit impurities …").) Mylan did not provide facts to explain how the person of ordinary skill would know to combine the prior art addressing the presence of Asp^9 impurities in Asn-containing peptides generally with the bivalirudin Original Angiomax® product specifically, especially in light of the evidence presented at trial that there are other scientific considerations that must be taken into account with peptides, such as bivalirudin. (*See infra* Part II.B.2.b.iii.) The inventor of the '727 patent testified that addressing the high degree of variability in Asp^9 impurity levels was the inventors' motivation, a motivation that was not known to the person of ordinary skill. (*See* Tr. 328:3-23 (Musso).)

Without the problem of variability or high Asp^9 levels known in the prior art, Mylan has failed to establish by clear and convincing evidence a reason to combine the elements in the manner claimed. *See KSR*, 550 U.S. at 420; *see also Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) ("The problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable. Therefore the claimed invention would not have been obvious to try to one of ordinary skill in the art. Indeed ordinary artisans would not have thought to try at all because they would not have recognized the problem."). To ignore prior art teaching such as Aswad, and to focus on the Amsberry Abstract and Bischoff, without also having knowledge of the problem with Asp^9 levels

in Original Angiomax® or evidence that it would be predictable, becomes an improper analysis driven by hindsight. *See Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (finding it impermissible to use "hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention."); *see also KSR*, 550 U.S. at 421 ("A factfinder should be aware … of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning."). Thus, the Court finds that the prior art did not provide a motivation for a person skilled in the art to combine the prior art elements.

iii. Mylan Failed to Prove That a Person of Ordinary Skill Would Not Have Had a Reasonable Likelihood of Success in Creating the Claimed Invention

The Federal Circuit has observed that "in the medical arts 'potential solutions are less likely to be genuinely predictable,' as compared with other arts such as the mechanical devices in *KSR*." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). In terms of deamidation of a peptide sequence, Mylan's expert testified that the person of ordinary skill in the art would not be able to predict the rate (or existence) of deamidation based on a peptide sequence without experimentation or pre-formulation analysis, but rather would be "very encouraged to do this work" if the peptide sequence contained an amide bond (*e.g.*, asparagine residue). (Tr. 968:4-973:7 (Auslander) (asked if one could predict a deamidation problem in bivalirudin without experimentation, Dr. Auslander responded: "to predict the chemistry of a molecule that hasn't been handled before is unrealistic ….").) Mylan's expert acknowledged that his analysis focused on deamidation because it was allegedly a known problem at the time[25]

[25] The basis for Dr. Auslander's knowledge of deamidation as a problem, however, was internal documents from Biogen that Mylan acknowledges are not prior art. (*See* Tr. 941:14-24 ("Q. Well why did you focus on deamidation? A. Based upon the Biogen experiences, it was a known sensitivity of

and that he did not consider other possible reactions. (Tr. 941:2-12 (Auslander).) A peptide sequence, like that of bivalirudin, however, is not only composed of asparagine residues with amide bonds, and the person of ordinary skill would have also been aware of the susceptibilities surrounding other amino acid residues to undergo interaction during a compounding process *e.g.*, hydrolysis of peptide bonds, isomerization, racemization, oxidation, aggregation, precipitation, adsorption. The evidence at trial established other types of degradation reactions can occur with a peptide, including isomerization of aspartic acid residues (present at position 11 of bivalirudin), (Tr. 937:12-946:18 (Auslander); *see also* DTX 1021, Bishchoff, at 276 ("The present review is mainly concerned with deamidation of Asn residues and with isomerization at Asp-Gly sites as one of the more common modifications found in both natural and recombinant proteins.").) The evidence at trial also demonstrated that other concerns existed surrounding potential changes in the compounding process that affect the peptide, *e.g.*, susceptibility of peptides to pH changes or high-shear mixing. (DTX 1023; PTX 224; Tr. 997:24-98:21 (Auslander); 1394:6-15 (Klibanov).)

The evidence of the unpredictable nature of the chemical response of bivalirudin in a compounding process to produce "pharmaceutical batches" of bivalirudin with "a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6% as measured by HPLC," provides the person of ordinary skill, in light of the prior art, no reasonable expectation of success. Moreover, Mylan did not present evidence to overcome the "difficult hurdle" of unpredictability to establish its burden of a clear and convincing standard that a person of ordinary skill would have a reasonable expectation of success to achieve "pharmaceutical batches" as claimed in the '727 patent. *See also Eisai Co. Ltd.,* 533 F.3d at 1359 ("To the extent

---

bivalirudin . . . .").) In fact, at one point, Dr. Auslander stated "I don't know how much public information was available about bivalirudin." (Tr. 942:23-24.)

an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.")

c. Objective Indicia of Nonobviousness

In an obviousness analysis, courts must consider objective evidence of nonobviousness in the form of secondary considerations, as it "play[s] a critical role in the obviousness analysis." *Leo Pharm. Prods,* 726 F.3d at 1358. The Federal Circuit has repeatedly emphasized that objective indicia "may often be the most probative and cogent evidence of nonobviousness in the record." *Mintz v. Dietz & Watson, Inc.,* 679 F.3d 1372, 1378 (Fed. Cir. 2012) (quoting *Ortho–McNeil Pharm. Inc. v. Mylan Labs., Inc.,* 520 F.3d 1358, 1365 (Fed. Cir. 2008)). These indicia "provide objective evidence of how the patented device is viewed in the marketplace, by those directly interested in the product" at the time of the invention. *See Mintz*, 679 F.3d at 1378 (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.,* 851 F.2d 1387, 1391 (Fed. Cir. 1988)). In doing so, they help "inoculate the obviousness analysis against hindsight." *Id.*; *see also Graham,* 383 U.S. at 36 (recognizing that the objective indicia of obviousness "guard against slipping into use of hindsight" and help "resist the temptation to read into the prior art the teachings of the invention in issue"). Here, TMC points to failure of others, Mylan's alleged copying of TMC's product, and unexpected results, as objective indicia of nonobviousness. (R.560 at 14-16; *see also* R.416 at 39-48.)

i. Failure of Others

First, TMC argues that the evidence at trial demonstrated the failure of others to solve the problem of high Asp^{9}-bivalirudin levels. (*See* R.560 at 13-14.) Evidence that others tried but failed to develop a claimed invention "may carry significant weight in an obviousness inquiry."

In re Cyclobenzaprine, 676 F.3d at 1081; *see also Galderma Labs., L.P.v. Tolmar, Inc.,* 737 F.3d 731, 736 (Fed. Cir. 2013). TMC contends that the evidence showed that Ben Venue could not solve the problem with the high Asp^9-bivalirudin levels despite its ten plus years of experience in formulating bivalirudin. (Tr. 59:21-61:1; 62:17-24 (Flammia); PX223.) Ben Venue investigated the lot failure and, with TMC, reviewed and implemented manufacturing process changes, ***e.g.***, instructions for adding the pH-adjusting solution to the bivalirudin solution in aliquots. (Tr. 61:22-62:12 (Flammia); Tr. 207:9-208:3 (Musso); PTX 223.15; DTX 1211.) This attempt, however, was unsuccessful as a lot Ben Venue manufactured after implementing the changes failed due to an Asp^9-bivalirudin level of 2.3%. (PTX 218; Tr. 1399:23-1402:22 (Klibanov); Tr 207:9-2008:25 (Musso); Tr. 62:17-64:22 (Flammia).)

Mylan argues that the Court should afford this evidence little weight in the obviousness context because at the time Ben Venue was working with bivalirudin, it was TMC that owned the Angiomax® NDA and the compounding instructions from the master batch record used to make the bivalirudin product required TMC's approval. (Tr. 81:4-8 (Flammia); *see also* R.418 at 10, TMC's Response to FF.18, stating "[a]dmit that TMC 'has ultimate approval authority concerning the content of, and modifications to, the [Master Batch Record]".) The Court agrees and does not place substantial weight on any lack of success that Ben Venue had in changing a process that TMC had joint control over.

ii. Copying of TMC's product

Second, TMC argues that Mylan and other generic drug companies copied the Improved Angiomax® drug product, with many stipulating to infringement. (*See* R.560 at 14-15.) In some cases, evidence that the defendant or other competitors have copied a product embodying the claimed invention can provide objective evidence of nonobviousness. *See Wm. Wrigley Jr.*

Co. v. Cadbury Adams USA LLC, 683 F.3d 1356, 1364 (Fed. Cir. 2012.) Courts, however, have questioned whether copying can serve as evidence of nonobviousness in the ANDA context. *See Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 Fed App'x 978, 983 (Fed. Cir. 2010) (unpublished). The Hatch-Waxman Act requires a generic drug manufacturer to demonstrate that its generic formulation has the same active ingredients, route of administration, dosage form, strength, and bioequivalency as an approved drug. *See* 35 U.S.C. § 355(j)(2)(A)(ii)-(iv). As the Court has previously noted, the claim of copying has little force in the Hatch-Waxman context. *Bayer,* 713 F.3d at 1377 ("copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval").

According to TMC, Mylan's copying of Improved Angiomax® far exceeded its legal obligations under the Hatch-Waxman Act by copying the inactive ingredients and impurity profile of the Improved Angiomax® product. (*See* R.560 at 16; *see also* R.488 at 7; Tr. 1404:5-13.) Mylan responds that its use of inactive ingredients such as mannitol and sodium hydroxide mirrors the use of the same excipients from the Original Angiomax® product and is therefore nothing more than the use of prior art excipients. The evidence of copying presented here – that other ANDA applicants have copied TMC's formulation with some stipulating to infringement – is afforded little weight by the Court because of the FDA's bioequivalence mandate for approval of a generic drug application.

iii. Unexpected Results

Lastly, TMC argues that the inventors of the '727 patent were unexpectedly surprised "that bivalirudin is stable to high shear mixing conditions." (*See* R.560 at 16.) TMC interweaves its teaching away argument with its alleged unexpected results that because the prior

art taught away from high shear mixing with peptides, it was surprising to find that high shear mixing did not negatively impact bivalirudin. (*See also* Tr. 1402:23-1403:4.) The claims of the '727 patent are not limited to high speed mixing, and as such, this argument is unpersuasive.

The results that TMC obtained with the Improved Angiomax® product (less than 0.6% Asp^9-bivalirudin levels) are not unexpected results probative of nonobviousness. TMC argues that the achieved lowering of Asp^9-bivalirudin impurity levels were unexpected in light of the fact that the person of ordinary skill in the art would have been discouraged from using high speed mixing. This is nothing more than a reframing of TMC's teaching away argument and as an unexpected result indicative of nonobviousness is afforded little weight.

3. Conclusion

After consideration of the parties' arguments[26] and the evidence presented at trial, the Court finds that Mylan has failed to prove the asserted claims of the '727 patent invalid due to obviousness. After a thorough examination of the evidence and analysis of the established teachings of the prior art and the elements of the claimed invention, the Court finds there is no motivation for a person of ordinary skill to combine the teachings of the prior art and arrive at the claimed invention with a reasonable expectation of success. The Court therefore finds that

[26] Mylan also argues that the changes TMC made to reduce the Asp^9 maximum are nothing more than a routine optimization of its Original Angiomax® product and process and the changes made to the prior art compounding process are "few and routine." (*See* R.553 at 19-21.) First, Mylan's argument ignores the fact that the claims of the '727 patent are not limited to a compounding process. Second, Mylan makes conclusory attorney arguments that are undeveloped and unsupported by the evidence at trial. In alleged support of its arguments, Mylan cites its expert's testimony that provides no substantive opinion about the differences between the changes, but rather notes only that such differences exist. (Tr. 823:15-16 (Auslander).) Even with the benefit of the evidence presented at trial, Mylan failed to establish that TMC's optimization of its prior art process and the resulting batches produced by the improved process constitute routine experimentation. This is especially true where the prior art was not proven to include the prior specification for Original Angiomax, nor the knowledge of the problems with the out of specification Asp^9-bivalirudin impurity levels. As such, Mylan has failed to prove by clear and convincing evidence that the alleged differences between the prior art and improved compounding processes, to achieve a reduced level of Asp^9-bivalirudin impurities in "pharmaceutical batches" as claimed in the '727 patent, were obvious as routine optimization.

Mylan has failed to prove obviousness of claims 1-3, 7-10,[27] and 17 of the '727 patent by clear and convincing evidence.

C. Enablement

Mylan also alleges that claims 1-3, 7-10, and 17 of the '727 patent are invalid for lack of enablement under 35 U.S.C. § 112.[28] (*See* R.553 at 25-29.)

1. Legal Standard

Under 35 U.S.C. § 112, a patent specification must include

> 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*, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112, ¶ 1 (emphasis added). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *MagSil Corp. v. Hitachi Global Storage Techs., Inc.,* 687 F.3d 1377, 1380 (Fed. Cir. 2012). Enablement is determined as of the effective filing date of the patent's application. *See ALZA Corp. v. Andrx Pharms., LLC,* 603 F.3d 935, 940 (Fed. Cir. 2010). The Federal Circuit has provided the framework for the enablement analysis:

> To prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without "undue experimentation." . . .

---

[27] Because the Court has found claim 1 valid and nonobvious, Mylan's arguments regarding claim 7 are moot as this claim contains the novel limitations set forth in claim 1 from which it depends and is therefore nonobvious for the reasons presented herein. This is true, even if the additional element provided by claim 7, namely, the D-Phe[12] limitation, is taught by the prior art and imparts no additional novelty. For these reasons, Mylan has failed to meet its burden in proving claim 7 of the '727 patent obvious.

[28] Paragraph 1 of 35 U.S.C. § 112 was replaced with newly designated § 112(a) by § 4(c) of the AIA, Pub. L. No. 112–29, and AIA § 4(e) makes those changes applicable "to any patent application that is filed on or after" September 16, 2012. Because the application resulting in the '727 patent was filed before that date, the Court will refer to the pre-AIA version of § 112. *See Alcon*, 745 F.3d 1180, 1183, n. 1 (Fed. Cir. 2014).

> After the challenger has put forward evidence that some experimentation is needed to practice the patented claim, the factors set forth in *Wands* then provide the factual considerations that a court may consider when determining whether the amount of that experimentation is either "undue" or sufficiently routine such that an ordinarily skilled artisan would reasonably be expected to carry it out.

Alcon Research Ltd. v. Barr Labs, Inc., 745 F.3d 1180, 1188 (Fed. Cir. 2014) (citing *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988).) The Court may consider the following factors when determining if 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.

2. Analysis

Mylan advances two arguments in support of its contention that the specification does not teach those skilled in the art how to make the full scope of the claimed invention. (*See* R.553 at 25-28.) First, Mylan argues that the patent specification does not enable the asserted claims because, as shown by failed Lot 1344985, even the co-inventors of the '727 patent, Dr. Musso and Dr. Krishna, could not produce the claimed invention (*i.e.*, the maximum 0.6% Asp^9-bivalirudin impurity level of claims 1, 7-10, and 17). Second, Mylan argues that even if asserted claims 1, 7-10, and 17 are enabled, claims 2 and 3, which teach pharmaceutical batches having maximum Asp^9 impurity levels of 0.4% and 0.3%, respectively, are not enabled because some Improved Angiomax® batches actually had Asp^9 impurity levels greater than the allowed maximums. The Court addresses each set of claims and arguments in turn.

a. Claims 1, 7-10, and 17

The Court finds that Mylan has failed to show by clear and convincing evidence that claims 1, 7-10, and 17 are invalid due to lack of enablement. Mylan's non-enablement argument with respect to these claims hinges upon Mylan establishing that Lot 1344985 was made according to a compounding process and without experiencing any operator error or investigation concerns. Lot 1344985 was one of two failed batches (the other being Lot 1116050) that Ben Venue manufactured purportedly using the Improved Angiomax® compounding process described in Example 5 of the '727 specification. Lot 1116050 had an Asp^9 impurity level of 12.4%, and Lot 1344985 had an Asp^9 impurity level of 1.5%. The inventors disclosed the Asp^9 impurity results for Lot 1116050 to the PTO, explaining that the data presented regarding Improved Angiomax® batches did not include the results for Lot 1116050 because "the method used to generate the batch was not compliant with the protocol established for [the] study." (*See* PTX 1, col. 23:14-16.) The inventors, however, did not disclose the Asp^9 impurity results of Lot 1344985 to the PTO or explain why they had omitted those results from the data regarding Improved Angiomax® batches.

Mylan essentially argues inoperability of the '727 patent claims, asserting that the 1.5% Asp^9 impurity level of Lot 1344985 establishes not only that the patentees were not able to make the claimed invention, but that the '727 patent fails to teach those skilled in the art to produce the claimed invention (*i.e.*, pharmaceutical batches of bivalirudin with a maximum Asp^9 impurity level of about 0.6%). Mylan, however, failed to prove that Ben Venue did not properly follow the compounding process in manufacturing Lot 1344985.

Mylan relies heavily on the fact that Ben Venue's investigation into the high Asp^9 impurity level in Lot 1344985 found that no operator error had occurred during the compounding

process. The evidence at trial, however, does not establish this fact under a clear and convincing standard. Indeed, the evidence showed persuasive reasons to question the results of Ben Venue's investigation. This evidence substantially decreases the weight of Ben Venue's investigation.

First, around the time period that Ben Venue manufactured Lot 1344985 in May 2008, the FDA had issued a warning letter to Ben Venue for, among other reasons, not closing its quality investigations timely and not complying with scientific standards in performing those investigations. The FDA issued the warning letter to Ben Venue in May 2007, and, in June 2008, Ben Venue recognized its need to "implement[] . . . improved systems" in a Comprehensive Corrective Action Plan. (*See* DTX 1407.)

Second, Ben Venue had failed to follow the manufacturing instructions for another failed batch, Lot 116050, prior to manufacturing Lot 1344985. Ben Venue's initial investigation into Lot 116050—like its initial investigation into Lot 1344985—found that the high Asp^9 impurity level was not the result of operator error in the compounding process. Only after Ben Venue reopened its investigation into Lot 116050 at TMC's urging did Ben Venue identify operator error as responsible for the batch failure. Lot 116050 is the only Improved Angiomax® batch other than Lot 1344985 to have Asp^9 impurity levels above about 0.6%. Given all the evidence, Ben Venue's failure to follow the manufacturing process with respect to Lot 116050 suggests that Ben Venue also may have failed to follow the manufacturing process with respect to Lot 1344985. Ben Venue's failure to identify operator error in its initial investigation into Lot 116050 gives further reason to question the similar finding of no operator error in Ben Venue's initial investigation into Lot 1344985. Ultimately, Ben Venue agreed to destroy Lot 1344985 and issue a credit to TMC's account for the cost of manufacturing Lot 1344985, although it is unclear if Ben Venue agreed to this resolution because it determined that the batch failure was

the result of operator error or for other reasons, such as maintaining a good business relationship with TMC.

Third, the evidence at trial showed an unidentified peak in the chromatogram for Lot 1344985 similar to an unidentified peak in the chromatogram for Lot 1116050. Lot 1344985 and Lot 1116050 are the only Improved Angiomax® batches that showed this unidentified peak, and they are the only batches that had Asp^9 impurity levels greater than about 0.6%. This evidence further suggests that Ben Venue failed to follow the manufacturing process for Lot 1344985 as it had for Lot 1116050.

Mylan failed to submit sufficient evidence to support an affirmative finding that Lot 1344985 was made by the improved compounding process and did not encounter operator error or some other issue related to Ben Venue's incompliance with regard to the timeliness and standards of its quality investigations (*see* DTX 1407, Ben Venue's Comprehensive Corrective Action Plan related to receipt of FDA warning letter). At best, the evidence at trial raised questions regarding whether Ben Venue followed the Improved Angiomax® compounding process in manufacturing Lot 1344985. Further, Mylan failed to present sufficient evidence to meet its clear and convincing burden on this issue. Put simply, Mylan failed to prove by clear and convincing evidence that the Improved Angiomax® process, rather than another reason, *e.g.*, operator error, caused the high Asp^9 impurity level in Lot 1344985.

Even if the Court had found that Mylan established that the invention of claims 1, 7-10, and 17 was inoperable based on the high Asp^9 impurity level in Lot 1344985, that showing alone would not establish invalidity due to lack of enablement. Mylan still needed to show that the person of ordinary skill would not be able to practice the claimed invention without "undue experimentation." *See Alcon,* 745 F.3d at 1190-91 (reversing the district court's finding of

invalidity for lack of enablement because defendant failed to provide evidence that established the person of ordinary skill would need to engage in "undue experimentation" in order to practice the asserted claims). Mylan has the burden to establish that TMC's patent lacked enabling disclosures, yet it "failed to make the threshold showing that any experimentation is necessary to practice the claimed methods." *See id.* at 1189. Putting aside the fact that Mylan's briefing was silent as to the legal requirement under *Wands* for "undue experimentation", Mylan failed to present evidence at trial that would satisfy a requirement for any experimentation with bivalirudin, let alone undue experimentation under the clear and convincing standard.

Indeed, Mylan's own expert, Dr. Auslander, admitted the focus of all his testimony was deamidation, rather than other possible reactions (*e.g.*, hydrolysis, racemization, oxidation, aggregation, precipitation) that can occur with aspartate peptides, such as bivalirudin. (Tr. 941:2-13.) Dr. Auslander further testified on cross examination that in focusing on deamidation, he considered the effects of pH and oxidation, but did not consider the effects of temperature, ionic strength, and excipients (*e.g.*, mannitol), and was not able to provide conclusive answers as to what those effects may be other than that they "may" have one. (Tr. 956:17-966:20.) In *Alcon*, the defendant's expert testified that "[v]arious parameters including pH, buffer, buffer concentration, preservatives, chelating agents, and other excipients *may* affect the chemical stability of prostaglandins in ophthalmic formulations." 745 F.3d at 1189 (citations omitted) (emphasis original). The Federal Circuit found the "unsubstantiated conclusory statement" insufficient to establish evidence of undue experimentation. *Id.* In particular, the Federal Circuit reasoned that while adjusting variables may be relevant to optimizing the claimed invention, the defendants offered no evidence that any experimentation, let alone undue experimentation, with those variables would be necessary in order to practice the claimed invention. *See id.* Similarly,

Mylan provided no evidence that any experimentation, let alone undue experimentation, would be required with variables its own expert admitted could have an effect on asparate peptides.

Therefore, Mylan failed to show that the embodiments of claims 1, 7-10 and 17 would be inoperable and failed to provide evidence that a person of ordinary skill in the art would have been unable to practice the asserted claims without resorting to any experimentation, let alone undue experimentation. *See id.* at 1191. Mylan had the burden of proof to show that TMC's patents lacked enabling disclosures, but failed to carry that burden. As such, claims 1, 7-10, and 17 are not invalid based on nonenablement.

b. Claims 2 and 3

Mylan also failed to satisfy its burden on its non-enablement counterclaim regarding claims 2 and 3, which teach pharmaceutical batches having a maximum Asp^9 impurity level of 0.4% and 0.3%, respectively. Mylan argues that the '727 patent specification fails to disclose any method that even purports to produce batches of bivalirudin having Asp^9 impurity levels not exceeding "about 0.4%" or "about 0.3%." The only arguably enabling disclosure, Mylan notes, is Example 5 which reports a maximum Asp^9 impurity level of 0.6% (not 0.4% or 0.3%). TMC responds that "Mylan ignores Example 3 of the '727 patent which discloses different processes that resulted in batches having maximum values of Asp^9 after sodium hydroxide addition of 0.34% for one experiment (PTX 1, col. 21, Table 5a) and 0.40% (Table 5b) in another experiment." (R.560 at 21.)

The Court, however, does not need to resolve this dispute because even if the Court found that Mylan proved that the specification did not teach the full scope of the claimed invention, the inquiry does not end there. Mylan must also establish that the person of ordinary skill would not be able to practice the claimed invention without "undue experimentation." *See*

Alcon, 745 F.3d at 1190-91; *see also Johns Hopkins Univ. V. CellPro, Inc.,* 152 F.3d 1342, 1360 (Fed. Cir. 1998) ("[I]t is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to [practice] the claimed invention without undue experimentation"). As addressed above, Mylan has the burden of proof to show that TMC's patent lacked enabling disclosures and Mylan has "failed to make the threshold showing that any experimentation is necessary to practice the claimed methods." *See Alcon*, 745 F.3d at 1189. Because the evidence is insufficient under the clear and convincing standard to satisfy a requirement of "undue experimentation", the Court concludes that claims 2 and 3 are not invalid based on nonenablement.

III. Unenforceability for Inequitable Conduct

Mylan alleges that the '727 patent is unenforceable due to inequitable conduct. (*See* R.553 at 29-34.)

A. Legal Standard

"Inequitable conduct is an equitable defense to patent infringement that, if proved, bars enforcement of a patent." *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1285 (Fed. Cir. 2011) (*en banc*). To prevail on an inequitable conduct defense, the accused infringer must show by clear and convincing evidence (1) that "the applicant misrepresented or omitted material information" on patentability and (2) the applicant had "the specific intent to deceive the PTO." *Id.* at 1287; *see also American Calcar, Inc. v. American Honda Motor Co., Inc.*, No. 2013-1061, __ F.3d __, 2014 WL 4783613, at *3 (Fed. Cir. Sept. 26, 2014) (quoting *Ohio Willow Wood Co. v. Alps S., LLC,* 735 F.3d 1333, 1344 (Fed. Cir. 2013)). Materiality and intent must be separately established. *See Therasense*, 649 F.3d at 1290*; see also In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 519 (2012).

A patent challenger can establish materiality by showing that the PTO would not have issued the claim but for the applicant's misrepresentation or omission. *Therasense*, 649 F.3d at 1291; *see also American Calcar*, 2014 WL 4783613, at *3. Because the Court assesses but-for materiality from the PTO's perspective, the Court applies the preponderance of the evidence standard in assessing whether the withheld or allegedly misrepresented information would have blocked patentability. *Therasense*, at 1291-92. Absent but-for materiality, a patent challenger also can prove presumptive materiality by showing that TMC "has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit." *Id.* at 1292; *see also Ohio Willow Wood*, 735 F.3d at 1345.

A patent challenger must also prove that the patentee acted with the specific intent to deceive the PTO. *Therasense*, 649 F.3d at 1290. Because it is rare to find direct evidence of intent to deceive, courts may "infer [deceptive] intent from indirect and circumstantial evidence." *Id; see also American Calcar*, 2014 WL 4783613, at *5. To meet the clear and convincing standard, however, the specific intent to deceive must be "the single most reasonable inference able to be drawn from the evidence." *Therasense*, 649 F.3d at 1290 (quoting *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008)); *see also Therasense*, 649 F.3d at 1290 (emphasis added) (quoting *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 873 (Fed. Cir. 1988)) (explaining that to prove inequitable conduct, the circumstantial evidence "'must be sufficient to *require* a finding of deceitful intent in light of all the circumstances.'").

B. Analysis

Mylan contends Drs. Musso and Krishna engaged in inequitable conduct by (1) failing to disclose and misrepresenting to the PTO the Asp^9 impurity level in Lot 1344985,

(2) misrepresenting the number of Original Angiomax® batches that contained an Asp^9 impurity level greater than about 0.6% in Table 6 of the '727 patent, (3) failing to fully disclose the process used to produce Original Angiomax® batches, and (4) failing to disclose the contributions of Ben Venue employees as inventors. (R.553 at 29.) The Court addresses each argument in turn.

1. Failure to Disclose the Asp^9 Impurity Level of Lot 1344985

Mylan first argues that the PTO would not have issued the '727 patent due to non-enablement if the inventors had disclosed the Asp^9 impurity level in Lot 1344985. As explained above, Mylan failed to prove its non-enablement argument based on Lot 1344985 by clear and convincing evidence. Mylan also failed to prove its inequitable conduct argument based on Lot 1344985 because Mylan failed to establish that the inventors intended to deceive the PTO by not disclosing the Asp^9 impurity level for Lot 1344985.

Both Dr. Musso and Dr. Krishna credibly testified at trial regarding their reasons for not disclosing the results of Lot 1344985. Dr. Musso testified that he did not believe Ben Venue had manufactured Lot 1344985 according to the Improved Angiomax® process, and, therefore, did not believe he had a duty to disclose it to the PTO. (Tr. 507:9-18.) Dr. Musso based his belief on a number of factors. First, he took into account the ongoing FDA investigations at Ben Venue. (*See id.* at 389:19-20, 393:9-14, 412:2-9.) Dr. Musso knew of Ben Venue's past manufacturing problems, including the operator error identified in manufacturing Lot 1116050. (*See id.* at 423:20-25.) Second, Dr. Musso knew that Ben Venue's and TMC's investigation into Lot 1344985 was ongoing during the '727 patent's prosecution. (*See id.* at 435:23-436:10.) It was Dr. Musso's belief that because Lot 1344985 was still under investigation and he believed the lot failure was due to operator error, he did not need to disclose Lot 1344985 to the PTO.

(*See id.* at 413:14-20.) Third, Dr. Musso expressed his distrust of the results of Ben Venue's internal investigations into failed lots. (*See id.* at 426:23-427:4.) Based on his experience, he did not find Ben Venue's preliminary "no root cause" finding regarding failure of Lot 1344985 reliable. (*Id.*) Dr. Musso testified that, in light of these considerations, he "never considered" whether he should disclose Lot 1344985 to the PTO. (*See id.* at 436:18-21.)

Dr. Krishna gave similar testimony regarding Lot 1344985. Like Dr. Musso, Dr. Krishna did not believe he had a duty to disclose the Asp^9 level of Lot 1344985 to the PTO. (Tr. 1206:5-9, 1206:24-1207:7.) Dr. Krishna testified that he based his determination on the fact that, from TMC's standpoint, the investigation into Lot 1344985 was ongoing. (*See id.* at 1183:18-22, 1201:14-19.) Furthermore, Dr. Krishna believed that Ben Venue had not followed the Improved Angiomax® process in manufacturing Lot 1344985. (*See id.* at 1187:6-11, 1220:22-1221:3.) Dr. Krishna believed that had Ben Venue followed the Improved Angiomax® process, Lot 1344985 would have had an Asp^9 level below about 0.6%. (*See id.* at 1220:22-1221:3.) For these reasons, Dr. Krishna believed that the results for Lot 1344985 were not relevant to the claimed subject matter. (*See id.* at 1206:5-9, 1206:24-1207:7.) Having observed Dr. Musso's and Dr. Krishna's demeanor on the stand and ability to withstand cross examination as well as the evidence surrounding Ben Venue, the Court finds the co-inventors' testimony to be credible.

Mylan called Dr. Linck, its expert in patent prosecution and PTO procedures, to testify on the issue of inequitable conduct and Lot 1344985. Dr. Linck noted that Dr. Musso became aware of the 1.5% Asp^9 level in Lot 1344985 prior to signing a petition to the PTO claiming a bivalirudin drug product with a "maximum impurity level of Asp^9-bivalirudin not exceeding about 0.6%." (Tr. 1306:18-23.) Dr. Linck testified that she "saw no evidence supporting the allegations that Lot 1344985 was not made by the so-called efficient process." (*Id.* at 1314:14-

16.) Dr. Linck also questioned the inventors' stated reasons for not disclosing Lot 1344985 when they had disclosed Lot 1116050. (*Id.* at 1318:20-25.)

While the inventors' disclosure of failed Lot 1116050 due to operator error raises questions regarding why they did not also disclose failed Lot 1344985 even if they believed the failure was due to operator error, the evidence at trial did not establish that intent to deceive the PTO is "the single most reasonable inference" the Court can draw. *See Therasense,* 649 F.3d at 1290. The credibility of Dr. Musso's and Dr. Krishna's testimony at trial and the evidence corroborating their testimony regarding problems with Ben Venue's manufacturing process and investigations into failed batches weighs against a finding of intent to deceive the PTO. In sum, Mylan failed to present evidence "sufficient to *require* a finding of deceitful intent in light of all the circumstances. *See Therasense*, 649 F.3d at 1290 (emphasis in original). Mylan's inequitable conduct theory based on Lot 1344985 therefore fails.

2. Misrepresentation of the Data in Table 6

Mylan next argues that the inventors misrepresented the number of Original Angiomax® batches that contained an Asp^9 impurity level greater than about 0.6% in Table 6 of the '727 patent. Table 6 discloses the mean, standard deviation, and maximum Asp^9 impurity level for the 87 Original Angiomax® batches analyzed:

TABLE 6

Characteristics of the batches generated by the compounding process that features rapid addition of a pH-adjusting solution and inefficient mixing rates.

	No. of batches	Mean ± SD	Maximum
Asp^9-bivalirudin (%)	87	0.5 ± 0.4	3.6
Total impurities (%)	63	1.4 ± 0.5	3.0
Largest unknown impurity (%)	86	0.3 ± 0.1	0.5
Reconstitution time (seconds)	85	30 ± 12	72

(PTX 1, col. 22:10-20.) Mylan's statistical expert, Dr. Ian McKeague, however, opined that the Table 6 is misleading because applying a normal distribution to the data suggests that only 60% of Original Angiomax® batches had Asp^9 impurity levels of less than 0.6% (*see* Tr. 647:7-649:2) when, in actuality, 87% of Original Angiomax® batches had Asp^9 impurity levels below 0.6%. Mylan argues that if the inventors had disclosed to the PTO that nearly 90% of Original Angiomax® batches met the '727 claim limitation regarding Asp^9 impurity levels, the PTO would not have issued the '727 patent.

Mylan's argument is unpersuasive. First, Dr. McKeague's assumption that a normal distribution applied to the data in Table 6 is highly questionable. TMC's statistics expert, Dr. Alan Salzberg, calculated that given that the mean value (0.5%) is close to zero and the maximum value (3.6%) is "nearly eight standard deviations away from the mean," (*see* Tr. 1271:22-1272:8 (Dr. Salzberg testimony)), the chance that the data followed a normal distribution is less than 1 in 2.5 trillion. (*See id.* at 1272:19-1273:20.) Accordingly, Dr. Salzberg opined that Dr. McKeague's assumption of a normal distribution was inappropriate. (*See id.* at 1273:21-24.) Although Dr. McKeague challenged Dr. Salzberg's 1 in 2.5 trillion calculation, Dr. McKeague did not provide an alternative calculation to show that the data supported his assumption of a normal distribution. Instead, he appears to have based his assumption on the form in which Table 6 presented the data, rather than the data itself. (*See id.* at 647:17-25 (assuming a normal distribution because (1) Table 6 reported the mean and standard deviation, which characterize a normal distribution, and (2) the "±" sign before the standard deviation indicates a symmetrical distribution).)

Furthermore, while Dr. McKeague acknowledged during cross-examination that alternatives to a normal distribution for the data in Table 6 exist, he offered no persuasive reason

why he failed to analyze whether one of those alternatives may better fit the data than a normal distribution. (*See id.* at 721:16-724:3.) Dr. McKeague admitted that given the mean and standard deviation, a normal distribution is "not a perfect choice," but rather "a quick back-of- – back-of-the-envelope choice." (*See id.* at 704:13-705:2.) The Court puts more weight on Dr. Salzberg's testimony than Dr. McKeague's based both on the substance of his testimony and his demeanor on the stand. Mylan, in sum, failed to prove that the inventors withheld or misrepresented information regarding the number of Original Angiomax® batches that had an Asp^9 impurity level below about 0.6% that, if accurately disclosed, would have led the PTO to reject the asserted claims. *See Ohio Willow Wood*, 735 F.3d at 1345.

Mylan also failed to prove by clear and convincing evidence that the inventors intended to deceive the PTO about the Asp^9 impurity levels of Original Angiomax® batches. *See Therasense*, 649 F.3d at 1290. Dr. Musso and Dr. Krishna credibly testified that they believed the data in Table 6 fully disclosed the characteristics of the 87 Original Angiomax® batches analyzed, and they had never even considered whether to disclose the Asp^9 impurity levels of all 87 batches. (*See, e.g.,* Tr. 329:15-330:20; 435:9-22; 1243:18-1244:19.) This testimony was unrebutted at trial. Mylan, therefore, failed to prove either prong of its inequitable conduct theory based on the data in Table 6.

3. Failure to Disclose the Original Angiomax® Compounding Process

Mylan argues that the inventors deceived the PTO by failing to disclose how similar the Original Angiomax® compounding process described in Example 4 of the patent specification was to the Improved Angiomax® compounding process described in Example 5. Specifically, Mylan argues that the inventors should have disclosed that (1) the Original Angiomax® compounding process involved initially operating the mixers at a rate between 400 and 800

RPMs and then increasing the rate to 900 and 1300 RPMs upon completion of the base addition step, and (2) in making Original Angiomax®, the base solution "was sometimes added by a third method—via a nitrogen pressurized hose." (*See* Mylan Post-Trial Br. at 33.) Mylan's arguments are unpersuasive.

First, Mylan failed to prove that the increase in the mixing rate after the completion of the base-addition step was material to the asserted claims and the '727 patent would not have issued if the inventors had disclosed it. *See Ohio Willow Wood*, 735 F.3d at 1345. The comparison of the Example 4 and Example 5 processes in the patent specification focused on the rate of mixing *during* the base-addition step—*i.e.,* the time at which the precipitate formed—not the mixing rate *after* addition of the base solution. (*Compare* PTX 1, col. 21:59-64 *with id.*, col. 22:47-52.) The patent specification accurately disclosed the mixing rates used during the base-addition steps in the two processes. (*See* Tr. 316:2-18.) Furthermore, the patent specification also omitted the fact that the mixing rate increased after addition of the base solution in the Example 5 process, like in the Example 4 process. (*See id.* at 318:9-14 ("[A]lso in Example 5, the increase in speed after base addition is also increased and not described.").)

Second, Mylan failed to prove that the fact that, in the original compounding process, the base solution sometimes was added via a pressurized hose was material to the asserted claims. The comparison of the Example 4 and Example 5 processes focused on the rate at which the base solution was added, not the mechanism for adding the base. In Example 4, the base solution was added "either all at once, or rapidly in multiple portions," whereas in Example 5, the base solution was added "at a controlled rate of 2 L/min." (*Compare* PTX 1, col. 21:60 *with id.,* col. 22:49.) The evidence at trial confirmed that the rate at which the base solution was added in the Example 4 process—even when a nitrogen pressurized hose was used—was significantly more

rapid than the rate at which the base solution was added in the Example 5 process. Adding the solution through the nitrogen pressurized hose in the Example 4 process took a period of "much less than five minutes" (*see* Tr. 315:3-18; *see also* PTX 223), whereas, in the Example 5 process, the base solution was added over a twenty-minute period. (*See* Tr. 750:22-751:7.) Mylan, therefore, failed to prove that the fact that the Example 4 process sometimes involved the use of a pressurized nitrogen hose was material to the asserted claims and the '727 patent would not have issued if the inventors had disclosed it. *See Ohio Willow Wood*, 735 F.3d at 1345.

Third, Mylan failed to prove that the inventors intended to deceive the PTO about the similarities between the Example 4 and Example 5 processes. As discussed, to meet the clear and convincing standard for proving deceptive intent, "the specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence.'" *Therasense,* 649 F.3d at 1290. That is not the case here. Dr. Musso credibly testified that he believed the patent specification disclosed the important aspects of the Example 4 and Example 5 processes to the PTO. (*See* Tr. 319:10-320:11.) Dr. Musso explained that the patent specification described the mixing rate during the base-addition step, rather than following the base-addition step, because the base-addition step is the important point in the process in which the marshmallow-like precipitate formed. (*See* Tr. 318:9-319:4.) He further explained that adding the base solution through a pressurized nitrogen hose came within the umbrella of adding the solution "all at once," as disclosed in the description of the Example 4 process. (*See, e.g.,* Tr. 314:2-315:24.) This evidence supports an inference that the inventors omitted the aspects of the Original Angiomax® compounding process at issue because they did not believe the information to be material to the asserted claims, not because they intended to deceive the PTO. Accordingly,

Mylan failed to prove the specific intent element of its inequitable conduct theory. *See Therasense,* 649 F.3d at 1290.

4. Failure to Disclose Ben Venue Employees' Contributions as Inventors

Finally, Mylan argues that the inventors failed to disclose the contributions of Ben Venue's operators as co-inventors. In patent law, the "inventor" is the person or persons who conceived of the invention. *See Ohio Willow Wood,* 735 F.3d at 1350. Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Invitrogen Corp. v. Clontech Labs., Inc.,* 429 F.3d 1052, 1063 (Fed. Cir. 2005). In the case of co-inventors, "each joint inventor must generally contribute to the conception of the invention." *Ethicon, Inc. v. U.S. Surgical Corp.,* 135 F.3d 1456, 1460 (Fed. Cir. 1998). "One who simply provides the inventor with well-known principles or explains the state of the art without ever having 'a firm and definite idea' of the claimed combination as a whole does not qualify as a joint inventor." *Id.* Inventorship can be material to patentability. *See Leviton Mfg., Co. v. Universal Sec. Instruments, Inc.,* 606 F.3d 1353, 1360 (Fed. Cir. 2010).

During the July 14, 2006 meeting attended by Dr. Musso and several TMC and Ben Venue employees, Ben Venue operators familiar with the Original Angiomax® compounding process joined the meeting and engaged in some discussions regarding how to minimize the formation of Asp^9 impurities during the process. Specifically, Mylan argues that the operators suggested: (1) varying the stirrer heights so that one stirrer mixes the upper part of the solution and one mixes the lower part; (2) increasing the mixing speed prior to base addition; and (3) adding the base solution through a dip tube so that it dispersed at the bottom of the tank where mixing is still possible. (*See* PTX 7.) Mylan contends that Dr. Musso incorporated these

concepts without attribution into the Improved Angiomax® compounding process described in Example 5, and, in doing so, materially misled the PTO regarding the inventorship of the patent. (*See* R.553, Mylan Post-Trial Br. at 33-34.) The Court disagrees.

As discussed above (*see* Part II.B.2.a.ii.b)), Mylan established that some portions of the report, authored by Dr. Musso, are attributable to Ben Venue employees. Employees of both TMC and Ben Venue, along with the inventor Dr. Musso, attended the July 14, 2006 meeting. (PTX 7; DTX 1245; Tr. 67:19-68:18 (Flammia); Tr. 200:6-202:19 (Musso); Smith Dep. 71:06-71:18, June 10, 2014.) The evidence Mylan presented did not support a finding that the information in the Musso Trip Summary in its entirety came from Ben Venue operators. Indeed, the evidence revealed that at some point later in the meeting when the participants were still discussing the issues, Ben Venue operators were no longer present. (Tr. 68:9-10 (Flammia); Tr. 264:10 (Musso).) In addition, attendees of the meeting who testified at trial, namely Timothy Smith – Ben Venue employee – and Angie Green – TMC employee, did not recall who specifically provided the suggestions and more importantly, the respective roles of inventor Musso and TMC in the discussion and in making the suggestions. Dr. Musso also testified that the cause of the high Asp^9 failure was not identified at the meeting and that he and Dr. Krishna "came up with the ideas on how to fix and make the improved product. Ben Venue did not contribute to those inventions." (Tr. 201:19-21; 205:19-21.) Even treating the suggestions and insights from the Ben Venue operators as prior art, the Court already found the claims valid and therefore, the "but-for" materiality of the operators' disclosures to Dr. Musso is not established here. Mylan provided no additional evidence that despite this lack of "but-for" materiality, TMC "engaged in affirmative acts of egregious misconduct." *See Therasense*, 649 F.3d at 1291-92 (assessment of but-for materiality in an inequitable conduct defense is assessed by a

preponderance of the evidence standard to determine whether the withheld or allegedly misrepresented information would have blocked patentability); *see also Ohio Willow Wood*, 735 F.3d at 1345.

Furthermore, Mylan failed to establish that TMC and Musso intended to deceive the PTO about the contents of the Musso Trip Summary from the July 14, 2006 meeting. Dr. Musso credibly testified that it was he and Dr. Krishna who "came up with the ideas on how to fix and make the improved product," not Ben Venue. (*See* Tr. 201:19-21; 205:19-21.) Mylan's allegations of TMC's pattern of withholding information to establish specific intent fails. (*See* R.553 at 34-35.) The Court does not find that Dr. Musso's intent to deceive the PTO is the single most reasonable inference drawn from the evidence. *See Therasense*, 649 F.3d at 1290. Instead, the evidence at the very least supports a reasonable inference that Dr. Musso worked collaboratively with a team of scientists at TMC and Ben Venue on the production of bivalirudin batches and that he and Dr. Krishna identified the underlying problems responsible for generation of the high and variable Asp^9 levels, and discovered a solution to that problem.

Hence, Mylan failed to establish by clear and convincing evidence that the inventors of the '727 patent (1) misrepresented or omitted material information on patentability, and (2) had a specific intent to deceive the PTO.

IV. Infringement

A. Legal Standard

A determination of infringement requires a two-step analysis. First, the asserted claims are interpreted by the courts to determine their scope and meaning. *See Presidio Components, Inc. v. American Tech. Ceramics Corp.,* 702 F.3d 1351, 1358 (Fed. Cir. 2012). Second, the fact-finder compares the properly construed claims to the allegedly infringing product. *See id.*

To establish infringement, TMC must prove by a preponderance of the evidence that Mylan's proposed drug product contains every limitation in the asserted claims. *See Trebro Mfg., Inc. v. Firefly Equip., LLC,* 748 F.3d 1159, 1166 (Fed. Cir. 2014); *Meyer Intellectual Props. Ltd. v. Bodum, Inc.,* 690 F.3d 1354, 1370 (Fed. Cir. 2012).

For claims of infringement brought under 35 U.S.C. § 271(e)(2), the infringement inquiry is whether the proposed commercial ANDA product will infringe if manufactured or sold in the United States, *i.e*., whether it will contain each and every limitation of the asserted patent claims. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000). Because the ANDA may not yet be approved and a product may not yet be marketed, this inquiry is necessarily a hypothetical one focusing on "what the ANDA applicant will likely market if its application is approved, an act that has not yet occurred." *Bayer AG,* 212 F.3d at 1248 (quoting *Glaxo, Inc. v. Novopharm, Ltd.,* 110 F.3d 1562, 1569 (Fed. Cir. 1997)). "[T]his hypothetical inquiry is properly grounded in the ANDA application and the extensive materials typically submitted in its support." *Id.* (quoting *Glaxo,* 110 F.3d at 1569). "[I]f a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue. *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013) (citing *Abbott Labs. v. TorPharm, Inc.,* 300 F.3d 1367, 1373 (Fed. Cir. 2002)). In other words, "[w]hat a generic applicant asks for and receives approval to market, if within the scope of a valid claim, is an infringement." *Sunovion*, 731 F.3d at 1279.

B. Analysis

TMC claims that Mylan's proposed drug product infringes claims 1-3, 7-10, and 17 of the '727 patent under 35 U.S.C. § 271(e)(2)(A).[29] (*See* R.555, TMC's Op. Post-Trial Br.) The parties do not dispute that Mylan's proposed drug meets many limitations of claim 1—*i.e.,* that it constitutes a drug product comprising bivalirudin and a pharmaceutically acceptable carrier, it is indicated for use as an anticoagulant, and it has a pH adjusted by a base and said pH is about 5-6 when reconstituted in an aqueous solution for injection. (*See* Tr. 553:8-561:14 (Dr. Klibanov testimony and exhibits cited therein); R.558, Mylan's Post Tr. Reply Br. (contesting only the two disputed terms recited above); *see also e.g.,*PTX 133.203-204; PTX 133.42-44, PTX 133.47.) The parties also do not dispute that Mylan's proposed drug meets the additional limitations in dependent claims 7-10 and 17—*i.e.,* that it has a maximum level of D-Phe^{12}-bivalirudin that does not exceed about 2.5% as measured by HPLC (claim 7); that the pharmaceutically acceptable carrier in the drug is a bulking agent, more specifically, the sugar mannitol (claims 8-10); and that the base used to adjust the drug's pH level is sodium hydroxide (claim 17). (*See* Tr. 566:1-568:12 (Dr. Klibanov testimony and exhibits cited therein); R.558 at 8-18 (contesting only the two disputed terms recited above) *see also e.g.,* PTX 133.203-204; PTX 133.42-44, PTX 133.47.) The dispute regarding infringement of the asserted claims centers around two claim limitations "pharmaceutical batches" and "wherein the batches have a maximum impurity level of Asp^{9}-bivalirudin of about 0.6%."[30] The Court finds that Mylan's proposed ANDA product infringes asserted claims 1-3, 7-10, and 17 of the '727 patent for the reasons stated below.

[29] TMC did not advance arguments at trial regarding infringement under the doctrine of equivalents, therefore, TMC's infringement allegations for the asserted claims are treated as allegations of literal infringement. (*See* R.309 at 22-23; R.366; R.485.)

[30] For asserted claims 2 and 3, which depend from claim 1, the maximum impurity level of Asp^{9}-bivalirudin is about 0.4% and 0.2%, respectively.

TMC's primary argument for infringement is that Mylan's proposed drug product infringes the asserted claims as a matter of law under the Federal Circuit's recent opinion in *Sunovion*. (R.555 at 11-14.) To the extent *Sunovion* is not dispositive – TMC argues that Mylan's representations in its ANDA and its ANDA exhibit batch demonstrate that its proposed drug product will infringe the asserted claims. (*Id.* at 14-30.) The Court agrees that *Sunovion* is dispositive on the infringement issue and, under *Sunovion*, Mylan's proposed ANDA drug product infringes the asserted claims as a matter of law.

1. The Federal Circuit's Decision in *Sunovion*

In *Sunovion,* another Hatch-Waxman case, the plaintiff owned the rights to a patent directed to a pharmaceutical composition containing the drug eszopiclone, the active ingredient in Lunesta®. The patent claimed a pharmaceutical composition containing eszopiclone "essentially free of its levorotatory isomer," which the district court construed as meaning "less than 0.25% of [the] levorotatory isomer." *See Sunovion*, 731 F.3d at 1273, 1274 (alteration in original). Defendant submitted its ANDA seeking FDA approval to manufacture, use, and sell a generic version of Lunesta® before the expiration of the patent-in-suit. *See id.* The defendant originally sought approval for levorotatory isomer levels "[n]ot less than 0.3% and [n]ot more than 1.0%," but after the FDA required the defendant to "tighten" the proposed levorotatory isomer levels, defendant amended the levorotatory isomer levels in its ANDA to "not more than 0.6% (*i.e.,* 0.0-0.6%)". *See id.* at 1274-75. The district court granted the defendant's motion for summary judgment of noninfringement despite the fact that the amended ANDA specification allowed the proposed drug product to have levorotatory isomer levels within the claimed range of 0.0 – 0.25%. *Id.* at 1275. The district court relied on the defendant's internal manufacturing guidelines that the levels "would likely be 'outside the infringing range of less than 0.25% …'"

Id. The district court also relied on a "certification" submitted as a declaration from the defendant's employee vowing to only market eszopiclone with levorotatory isomer levels above the claimed range, namely between 0.3-0.6%. *Id.*

The Federal Circuit reversed the district court's grant of summary judgment of noninfringement and instead found defendant's ANDA infringed as a matter of law. *Id.* at 1280. Because the defendant's ANDA allowed the defendant to market a drug product within the patent-in-suit's claimed levorotatory isomer range, the Federal Circuit held that the proposed drug product infringed as a matter of law. *See id.* at 1280. The Federal Circuit instructed that "[w]hat a generic applicant asks for and receives approval to market, if within the scope of a valid claim, is an infringement." *Id.* at 1279 (citing *Abbott*, 300 F.3d at 1373). The Hatch-Waxman framework establishes that the act of filing an ANDA, in and of itself, constitutes a technical infringement for jurisdictional purposes under 35 U.S.C. § 271(e)(2)(A). *Id.* at 1278. "But the ultimate infringement question is determined by traditional patent law principles and, if a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." *Id*. Also, the Federal Circuit was not persuaded by the defendants' certification to the court that its product would remain outside the claimed range. *See id.* at 1279-80. What defendant "has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur," and any filing in court "does not overcome the basic fact that [the defendant] has asked the FDA to approve, and hopes to receive from the FDA, approval to market a product within the scope of the issued claims." *Id.* at 1278.

2. Mylan's Proposed ANDA Drug Product Infringes as a Matter of Law

Like the defendant in *Sunovion,* Mylan seeks FDA approval for a drug product that falls within the scope of the asserted '727 patent claims. TMC has alleged that Mylan's ANDA infringes the '727 patent under § 271(e)(2)(A). (R.1, Compl. ¶ 25.) Mylan's ANDA specification allows it to market drug product with Asp^9 impurity levels from 0.0%-2.0% (*see* PTX 133.1785; PTX 159.2), a range that includes the '727 patent's claimed ranges of 0.0-0.6% (claim 1), 0.0-0.4% (claim 2) and 0.0-0.3% (claim 3).[31] (*See* PTX 1, col. 25:62–26:56; PTX 133 at MYL0001785.) Mylan's ANDA specification references the drug product as produced from a batch or batches. (*See, e.g.*, PTX 133.1852; PTX 133.205-208 (Quality Overall Summary referring to "batch records" in the manufacturing steps and "the manufactured batch.").) Because Mylan's ANDA specification seeks approval for a bivalirudin drug product made from pharmaceutical batches allowed to have a maximum impurity level for Asp^9 within the scope of the '727 patent's issued claims, Mylan infringes as a matter of law. *See Sunovion*, 731 F.3d. at 1278, 1280.

Mylan's attempts to distinguish this case from *Sunovion* fail. First, Mylan argues *Sunovion* is distinguishable because the claims in *Sunovion* were directed to individual compounds below the defined maximum impurity level and whether they would infringe the patent, whereas in the present case, the claims of the '727 patent are directed to all batches containing Asp^9 impurities below 0.6% and whether they infringe TMC's '727 patent. Mylan's argument is unavailing. Mylan's ANDA specification allows it to produce all batches having less than 0.6% Asp^9 impurities. (PTX 133.1785; PTX 159.2; *see also* Tr. 609:19-23 (Wayne

[31] The same reasoning that applies to determining whether Mylan's proposed drug meets the Asp^9 impurity limitation in claim 1 also applies to determining whether Mylan's proposed drug meets the Asp^9 impurity limitations in claims 2 and 3. For the sake of simplicity, the Court will refer only to the Asp^9 impurity range in claim 1 (*i.e.,* 0.0-0.6%) for the remainder of the infringement analysis.

Talton, Mylan's Vice President of Global Regulatory Affairs) ("Q. There is nothing in Mylan's ANDA that prevents, from a regulatory standpoint, selling a product that has an Asp^9 level below .6 for every batch, correct? A. That would be an acceptable result.") As the Federal Circuit stated in *Sunovion*, "[w]hat a generic applicant asks for and receives approval to market, if within the scope of a valid claim, is an infringement." *Id.* (citing *Abbott*, 300 F.3d at 1373). What Mylan seeks approval for (a bivalirudin drug product made from pharmaceutical batches with Asp^9 impurity levels ranging from 0.0-2.0%) allows it to make product that falls within the scope of the '727 patent's asserted claims (a bivalirudin drug product made from pharmaceutical batches with Asp^9 impurity levels ranging from 0.0-0.6%).[32] Mylan, therefore, infringes the '727 patent as a matter of law. *See id.* at 1280.

Second, Mylan argues that its compounding process likely will lead to some batches having Asp^9 impurity levels above 0.6%.[33] It is not, however, Mylan's batch production likelihoods that govern the infringement analysis under § 271(e)(2)(A). Rather it is what Mylan

[32] Both TMC and Mylan cite the Delaware district court's judgment in the related case of *The Medicines Co. v. Hospira, Inc.*, No. 09-750-RGA, 2014 WL 1292802 (D. Del. Mar. 31, 2014). As Mylan notes, the Delaware court found that Hospira's ANDA product did not infringe the '727 patent due to Hospira's use of inefficient mixing. The Delaware court's finding of noninfringement was due to the fact that, unlike in the present case, that court construed the '727 patent claims to include an "efficient mixing" limitation (*id.* at *2, n.4), and the Delaware court found that Hospira's proposed ANDA product did not meet that limitation (*id.* at *5-*8). As Mylan also has noted, in this case, the Court has held that "efficient mixing" is not a limitation of the '727 patent claims. The Delaware court did, however, make an express finding that based on *Sunovion*, Hospira's ANDA product infringed the "maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%" limitation. *Id.* at *5.

[33] Mylan also argues that the Court decided the infringement issue as it relates to whether the ANDA specification is dispositive in the Court's summary judgment opinion. This argument fails as the issue on summary judgment was whether viewing the evidence in the light most favorable to TMC, the Court found that TMC offered sufficient evidence to establish a genuine issue of material fact, not whether Mylan's proposed ANDA product specification infringed the asserted claims as a matter of law under *Sunovion*. *See HK Systems, Inc. v. Eaton Corp.*, 553 F.3d 1086 (7th Cir. 2009) (explaining that although the standard for granting judgment as a matter of law and granting summary judgment is the same, the record compiled in a trial is bound to differ from the record on which a motion for summary judgment was based); *see also Aycock Eng'g, inc. v. Airflite, Inc.*, 560 F.3d 1350, 1356 (Fed. Cir. 2009) (explaining that law of the case doctrine does not apply to a denial of summary judgment).

has asked the FDA to approve as a regulatory matter that is the subject matter for a determination of whether infringement will occur. *See Sunovion*, 731 F.3d at 1278. The Federal Circuit rejected a similar argument in *Sunovion* by finding infringement despite both the defendant's promise to only market product outside of the patent's claimed impurity range and the likelihood that internal manufacturing guidelines would produce drug product outside of the claimed 0.0-0.25% levorotatory isomer range. *See id.* at 1275, 1278 (explaining that even a certification to the court to market only product outside the claimed range does not overcome infringement when the ANDA specification is "within the scope of the issued claims."). Allowing such an "unconventional and unenforceable 'guarantee' " to the court when Mylan is asking for and may receive FDA approval to market a product within the scope of TMC's patent, "would be incompatible with the basic principles of patent law." *See id.* at 1279. "If it had no intent to infringe, [Mylan] should not have requested, or should not accept, approval to market a product within the scope of the ['727 patent claims]." *See id.* at 1279.

Lastly, Mylan argues that *Sunovion* is distinguishable because the methods of Mylan's ANDA, namely, "inefficient mixing," produce variable and randomly high Asp^9 results exceeding the claimed maximum and that Mylan has committed to using the "inefficient mixing" process. The claims of the '727 patent, however, are not limited to "efficient mixing" either explicitly or as construed by the Court. (*See* R.119, Claim Construction Order; R.309, Summary Judgment Order, at 35-39; R.558 at 22, n.11.) Therefore, Mylan's use of an "inefficient mixing" method does not rescue its ANDA specification from falling within the scope of the claims.

In the present case, Mylan's ANDA test batch, produced using Mylan's proposed manufacturing process, did in fact have an Asp^9 impurity level below 0.6%. (PTX 159.2.)[34] Indeed, Mylan's ANDA allows it to produce all batches below 0.6% Asp^9 impurity levels. *See Sunovion*, 731 F.3d at 1279. *Sunovion* renders it irrelevant that some batches may end up outside the '727 patent's claimed maximum impurity level. *See id.*; *see also The Medicines Co. v. Hospira, Inc.*, No. 09-750-RGA, 2014 WL 1292802, at *4-5 (D. Del. Mar. 31, 2014) (finding the limitation of the "Asp^9 impurity level below 0.6%" of the '727 patent claims met by defendant's ANDA specification which sought approval for drug product with Asp^9 impurity levels up to 1.0%, noting "the fact that the ANDA application includes Asp^9-bivalirudin levels above 0.6%, and at some point Hospira might make a batch with levels above 0.6%, does not negate a finding of infringement").

Finally, the supplemental cases Mylan submitted to the Court do not alter the Court's decision that Mylan has infringed as a matter of law under *Sunovion*. In both cases—*Ferring B.V. v. Watson Labs., Inc.-Florida,* 764 F.3d 1382, (Fed. Cir. 2014) (hereinafter, *Apotex*) and *Ferring B.V. v. Watson Labs., Inc.-Florida,* 764 F.3d 1401 (Fed. Cir. 2014) (hereinafter, *Watson*)—the ANDA at issue was silent with respect to the claim limitations of the patents-in-suit. *See Apotex,* 764 F.3d at 1387; *Watson,* 764 F.3d at 1409. In *Apotex,* the ANDA specification provided a dissolution release rate for the proposed drug in which "NLT [not less than] 80% of the labeled amount of tranexamic acid dissolved in 60 minutes," whereas the claim limitations in the patents-in-suit pertained to the dissolution release rates only at 15 minutes, 45 minutes, 90 minutes, and 120 minutes. *See Apotex,* 764 F.3d at 1385-86. Because the ANDA at

[34] The Court refers to the test batch as merely an example of Mylan's proposed ANDA product, as the specific impurity levels of this test batch are not necessary for the infringement analysis under *Sunovion*.

issue was silent with respect to the claim limitations of the patents-in-suit, which did not specify the dissolution rate at 60 minutes, the Federal Circuit held that *Sunovion* did not apply. *Id.* at 1387-88. Similarly, in *Watson*, the ANDA at issue was silent with respect to the claim limitations of the patents-in-suit concerning the drug's dissolution release rate in water. *See Watson,* 764 F.3d at 1409. Accordingly, the Federal Circuit held that the ANDA specification alone did not resolve the question of infringement, and *Sunovion* therefore did not apply. *See id.* at 1408-09.

Here, unlike in *Apotex* and *Watson*, Mylan's ANDA specification speaks directly to the disputed claim limitations in the '727 patent and therefore resolves the question of infringement. As explained above, Mylan's ANDA specification, if approved, will allow it to market a drug with Asp^9 impurity levels from 0.0%-2.0%, a range that includes the '727 patent's claimed range of 0.0-0.6%. Because Mylan's ANDA specification clearly describes a product that meets the limitations of the asserted claims, *Sunovion* is directly on point and establishes that Mylan's proposed drug product infringes claims 1-3, 7-10 and 17 of the '727 patent as a matter of law. *See Sunovion*, 731 F.3d. at 1278, 1280.

CONCLUSION

For the reasons explained above, the Court finds that: (1) Mylan failed to prove by clear and convincing evidence that claims 1-3, 7-10, and 17 of the '727 patent are invalid or unenforceable; and (2) Mylan's proposed bivalirudin drug product infringes claims 1, 7-10, and 17 of the '727 patent as a matter of law under *Sunovion*. Accordingly, the Court enters judgment in favor of TMC on its infringement claim regarding the '727 patent and on Mylan's counterclaims regarding claims 1-3, 7-10, and 17.

DATED: October 27, 2014 **ENTERED**

AMY J. ST. EVE
United States District Court Judge