IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

The Medicines Company, Plaintiff, v. **Hospira, Inc.,** Defendant.	Civil Action No. 09-750-RGA

TRIAL OPINION

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Wilmington, Delaware

ANDREWS, U.S. District Judge:

Plaintiff, The Medicines Company, brought this suit against Hospira, Inc. ("Hospira"), for infringement of U.S. Patent Nos. 7,582,727 ("the '727 patent") and 7,598,343 ("the '343 patent") (collectively, "the patents in suit"). The Medicines Company sells a bivalirudin drug product for injection under the trade name Angiomax and listed the '727 and '343 patents in the Food and Drug Administration's "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly referred to as the "Orange Book") as covering Angiomax. Hospira's Abbreviated New Drug Applications ("ANDAs") seek approval to engage in the commercial manufacture, importation, use, or sale of a bivalirudin drug product for injection before the expiration of the patents in suit. [1]

The Medicines Company asserts that Hospira has infringed, and will continue to infringe, claims 1-3, 7-10, and 17 of the '727 patent, as well as claims 1-3 and 7-11 of the '343 patent. Hospira contends that the asserted claims are invalid under the on-sale bar of 35 U.S.C. § 102(b), are obvious under 35 U.S.C. § 103(a), and are invalid under 35 U.S.C. § 112 because the claims lack written description, are not enabled, and are indefinite. The Court held a three day bench trial on September 23-25, 2013.[2] As explained below, The Medicines Company did not prove infringement by a preponderance of the evidence, and Hospira did not prove invalidity by clear and convincing evidence.

I. INFRINGEMENT

The Medicines Company asserts that Hospira's generic product would infringe claims 1-3, 7-10, and 17 of the '727 patent, as well as claims 1-3 and 7-11 of the '343 patent. Claim 1 of

[1] Angiomax is also covered by U.S. Patent. No. 5,196, 404 ("the 404 patent"), which is listed in the Orange Book. Hospira does not contest the validity of the '404 patent, and certified to the FDA that it would not market generic bivalirudin until the '404 patent expires on June 15, 2015. (D.I. 780 at ¶15).

[2] Transcripts are available at D.I. 815, 816, and 817.

the '727 patent is drawn to pharmaceutical batches of bivalirudin having a maximum impurity level of Asp^9-bivalirudin:

> 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-bivalirudin that does not exceed about 0.6% as measured by HPLC.

(Claim 1 of the '727 patent). Dependent claims 2 and 3 contain additional limitations lowering the maximum Asp^9-bivalirudin level. Claim 7 contains an additional limitation regarding the maximum level of D-Phe^{12}-bivalirudin. Claims 8-10 contain additional limitations regarding the carrier, which is comprised of a bulking or stabilizing agent. Claim 17 contains an additional limitation that the particular base used to adjust the pH of the batches is sodium hydroxide.

Claim 1 of the '343 patent claims the same subject matter as that of claim 1 of the '727 patent, but as a product-by-process:

> 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, said batches prepared by a compounding process comprising:
>
> (i) dissolving bivalirudin in a solvent to form a first solution;
>
> (ii) efficiently mixing a pH-adjusting solution with the first solution to form a second solution, wherein the pH adjusting solution comprises a pH-adjusting solution solvent; and
>
> (iii) removing the solvent and pH-adjusting solution solvent from the second solution;
>
> 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-bivalirudin that does not exceed about 0.6% as measured by HPLC.

(Claim 1 of the '343 patent). Dependent claims 2, 3, and 7-11 of the '343 patent are analogous to those of the '727 patent.

The Court previously construed three claim limitations. (D.I. 732). "Pharmaceutical batches" was construed as, "All batches prepared by a same compounding process, or a single batch wherein the single batch is representative of all commercial batches and wherein the levels of impurities and reconstitution time in a single batch represent levels for all potential batches made by said process." (D.I. 732 at 1-2). "Wherein the batches have a pH adjusted by a base" was construed as, "Wherein said compounding process requires that a pH-adjusting solution containing a base is added to bivalirudin solution under efficient mixing conditions." (D.I. 732 at 4). "Efficient mixing" was construed as, "A pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner, and mixed together by a process comprising high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)." (D.I. 732 at 7).

In its post-trial briefing, Hospira contended that The Medicines Company failed to prove three claim limitations: "efficient mixing," "pharmaceutical batches," and "a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%."[3] (D.I. 818 at 1). Because Hospira does not contest the other claim limitations, I find that they are met. Additionally, because these three claim limitations are present in both independent claims,[4] I deal with the claims together.

A. Legal Standard

The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused product. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575–76

[3] The dependent claims further limit the maximum impurity levels to 0.4% and 0.3%. Hospira treats these as a group, as does the Court.

[4] The "efficient mixing" limitation is present in claim of the '727 patent due to the Court's construction of the term, "wherein the batches have a pH adjusted by a base." While not belaboring the point, the inclusion of this process limitation was necessary because the inventive aspect of the '727 patent relates to the process, and the construction sustains the validity of the claims. (D.I. 732 at 6).

(Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984) (citing *Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1361 (Fed. Cir. 1983)). "Under [35 U.S.C.] § 271(e)(2)(A), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

Where there is no literal infringement, there may still be infringement under the doctrine of equivalents. "The doctrine of equivalents allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733 (2002). A patentee may prove infringement under the doctrine of equivalents "by showing on a limitation by limitation basis that the accused product performs substantially the same function in substantially the same way with substantially the same result as each claim limitation of the patented product." *Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009).

B. Findings of Fact

1. Hospira's Exhibit Batch is representative of future batches.
2. Asp^9-bivalirudin levels may decrease upon compounding.
3. Hospira's Exhibit Batch contains less than 0.6% of Asp^9-bivalirudin.
4. Hospira adds the pH-adjusting solution in three portions.
5. The first two portions of the pH-adjusting solution are added rapidly.
6. The third portion of the pH-adjusting solution is added gradually.
7. Hospira does not add a pH-adjusting solution slowly and in a controlled manner.

8. Hospira's Exhibit Batch was not mixed using high shear mixing.

9. Hospira will not keep impeller size constant during scale up.

10. Hospira does not infringe under the doctrine of equivalents.

C. Conclusions of Law

i. Hospira's Exhibit Batch is a "Pharmaceutical Batch"

"Pharmaceutical batches" refers to, "[a]ll batches prepared by a same compounding process, or a single batch wherein the single batch is representative of all commercial batches and wherein the levels of impurities and reconstitution time in a single batch represent levels for all potential batches made by said process." (D.I. 732 at 1-2). The parties do not dispute that if Hospira were to infringe this limitation, it would be under the single batch alternative. (Tr. 625:2-7). Hospira argues that the Exhibit Batch is not a "pharmaceutical batch" because its impurity levels do not represent the impurity levels which would be present in all of Hospira's future batches. (D.I. 818 at 18). Essentially, Hospira argues that The Medicines Company must prove that every one of Hospira's future batches are represented by the Exhibit Batch. Because of manufacturing process variability, Hospira contends that the Exhibit Batch cannot be representative of every single future batch, and is therefore not a "Pharmaceutical Batch." (Tr. at 461:5-18, 624:10-625:21).

The Medicines Company contends that Hospira's Exhibit Batch is representative of all future batches because ANDAs are typically approved based on a single test batch, and the FDA requires that single test batch be representative of all commercial batches. (D.I. 809 at 10). In support of this assertion, The Medicines Company points out that the '727 patent, in discussing the term "pharmaceutical batches," cites to the "Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 5225.1, Guidance of the Packaging of Test Batches at 1."

('727 patent at 5:25-35). This document states that, "ANDAs and AADAs are usually approved based on data from a single test batch. It is critical that all testing be conducted on samples that represent the entire batch and mimic the product which will be marketed post-approval." (PTX 169.1). Furthermore, in their ANDAs, Hospira stated that, "[t]he commercial scale process contains the same unit operations and utilizes equipment of the same design and operating principles as used to produce the exhibit batches." (PTX 165.32, PTX 166.32). The Medicines Company asserts that this was a representation by Hospira that the exhibit batch is representative of the commercial batches. (D.I. 809 at 10-11).

Hospira replies that this argument neglects the second half of the Court's claim construction, which requires that a batch have impurity levels that "represent levels for all potential batches." (D.I. 818 at 19). Because an Exhibit Batch shows only that a manufacturer can make a drug product within its specifications, (Tr. at 460:21-161:4), Hospira asserts that an Exhibit Batch is not representative of all commercial batches. (D.I. 818 at 19). Furthermore, Hospira asserts that it did not represent to the FDA that the Exhibit Batch was representative, only that it will keep its overall design the same if it scales up its process. *Id.* Essentially, Hospira argues that because of process variability, it would be impossible to make a batch that is representative of all future batches. *Id.* at 20.

Hospira's argument is not persuasive. The '727 patent defines the term "pharmaceutical batches" with reference to a document which essentially defines exhibit batches. To say that exhibit batches cannot be "pharmaceutical batches" would mean that there could not be infringement. Yet the filing of an ANDA is an act of infringement. 35 U.S.C. § 271(e)(2)(A). Hospira's interpretation would negate this. Because the Exhibit Batch must "mimic" the

commercial product, the Exhibit Batch is inherently representative of the commercial product. I therefore find that Hospira's Exhibit Batch meets the "pharmaceutical batch" limitation.

ii. Hospira Literally Infringes the "Maximum Impurity Level of Asp^9-Bivalirudin that Does Not Exceed About 0.6%" Limitation

This claim limitation requires that the batches, "have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6% as measured by HPLC." ('727 patent claim 1). HPLC refers to high performance liquid chromatography, ('727 patent at 16:37-40), which is an analytical technique used to separate peptides from one another, and in this case to determine the amount of Asp^9-bivalirudin. (Tr. at 349:18-24). The Asp^9-bivalirudin[5] in Hospira's Exhibit Batch was measured four times via HPLC, yielding values of 0.1%, 0.1%, 0.1%, and 0.2%. (PTX 165.10, PTX 166.10, PTX 179.19, PTX 180.9). Because the Exhibit Batch is representative of all commercial batches, The Medicines Company contends that this limitation is met.[6]

Hospira makes three arguments in reply. First, that the claim term is invalid under 35 U.S.C. § 112 because a person of ordinary skill cannot determine the number of batches that must be considered to calculate the "maximum" value. Second, that process variability will result in some future batches having Asp^9-bivalirudin levels above 0.6%. Third, that Hospira's ANDA specification provides for Asp^9-bivalirudin levels above 0.6%, both because the starting bivalirudin API ("Active Pharmaceutical Ingredient") may contain up to 0.7% Asp^9-bivalirudin (DTX 191 at H00178612; Tr. at 458:14-20, 629:3-16), and because the ANDA specification calls for up to 1.0% of Asp^9-bivalirudin. (DTX 191 at H00178630; Tr. at 458:24-459:8, 628:19-629:2).

[5] Referred to as "Related Substance 5." (PTX 165.5, PTX 166.5).

[6] Because the Exhibit Batch tested lower than 0.4% and 0.3%, The Medicines Company contends that claims 2 and 3 are also met.

As for the first point, as Hospira correctly notes, this is an invalidity argument, not an infringement argument. (D.I. 818 at 20). Therefore it will be dealt with in the Court's invalidity analysis. As for the second and third points, it is irrelevant that some batches might contain above 0.6% Asp^9-bivalirudin. While Hospira contends that Asp^9-bivalirudin levels do not decrease during compounding, the evidence does not support this assertion. The Asp^9-bivalirudin levels in Hospira's Exhibit Batch actually decreased. (PTX 43.512, PTX 43.517, PTX 57.509, PTX 57.514, PTX 179.10, PTX 180.9). In any event, this argument goes against controlling Federal Circuit case law. In *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013), the Court held that a claim which called for "less than 0.25%" of a particular isomer was infringed by an ANDA application which allowed for up to 0.6% of the isomer. 731 F.3d at 1280. This was because, "[w]hat [a generic manufacturer] has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur." *Id.* at 1278.

Hospira argues that *Sunovion* does not apply because Hospira's ANDA application is not within the scope of the asserted patents. (D.I. 818 at 22). Hospira contends that the ANDA specification "does not permit a product within the claimed *maximum* impurity range of 0-0.6% Asp^9-bivalirudin." (D.I. 818 at 22) (emphasis in original). If the Court's claim construction requires that every batch made by the compounding process not exceed 0.6% Asp^9-bivalirudin, and Hospira's ANDA specification allows for Asp^9-bivalirudin levels above 0.6%, then Hospira's compounding process cannot infringe because it might result in maximum Asp^9-bivalirudin levels above 0.6%.

This argument repeats the same issue raised in connection with "pharmaceutical batch." Batches containing less than 0.6% Asp^9-bivalirudin were known in the prior art. If Hospira uses

a prior art compounding process, then it does not infringe, even if the Asp^9-bivalirudin level is below 0.6%. In order to find infringement, Hospira must make the batch according to the claimed process, and the batch must have an Asp^9-bivalirudin level below 0.6%. However, 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. *See Sunovion*, 731 F.3d at 1278. Therefore, I find that Hospira infringes the "maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%" limitation.

iii. Hospira Does Not Literally Infringe the "Efficient Mixing" Limitation

I previously construed "efficient mixing" as, "[a] pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner, and mixed together by a process comprising high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)." (D.I. 732 at 7). When making the Exhibit Batch, Hospira added the pH-adjusting solution in three portions. (PTX 170.19, PTX 171.19). The first two portions "can be added rapidly with about 2-minute mixing time." (PTX 170.19, PTX 171.19). The third portion is "added gradually over a period of approximately 10 minutes." (PTX 170.19, PTX 171.19). The batch record states that the third portion is added gradually in order to "minimize drastic pH shift." (PTX 170.19, PTX 171.19).

The Medicines Company contends that because the third portion is the "principal" portion, and that portion is added gradually, Hospira's addition meets the "slowly and in a controlled manner" requirement. (D.I. 809 at 14). Hospira responds that the rapid addition of the first two portions entirely negates the "slowly" requirement. (D.I. 818 at 8). In support of this argument, Hospira points to Example 4 of the patent, in which rapid addition of multiple portions was described as inefficient mixing. ('727 patent at 21:45-60). The Medicines Company replies that because the overall pH-adjusting process takes at least 14 minutes (Tr. at 655:10-11), the

addition is slow. This is not persuasive. In Example 1, the pH-adjusting solution was added in four equal portions over the duration of an hour, and yet this was described as inefficient mixing. ('727 patent at 16:43-45, 17:30-35). Whether one looks at the addition of the pH-adjusting solution piecemeal or as an overall process, The Medicines Company has not shown that the addition is "slowly".

In addition to "slowly," the addition must be "in a controlled manner." (D.I. 732 at 7). Hospira argues that "controlled" refers to "constant" and "metered." (D.I. 818 at 10). The Medicines Company contends that the Court's claim construction distinguished between "constant" and "controlled" by using the conjunction "or." (D.I. 822 at 3). The Medicines Company reads too much into the Court's claim construction opinion. In using the term "or," the Court was merely referencing Example 5 of the patent, which used the term "constant" and "controlled" interchangeably. ('727 patent at 22:35-50).

The Medicines Company's attempt to cite to other portions of the patent is also not persuasive. The Medicines Company cites to a portion of the patent which describes that the base may be added in portions, that the period of time between additions may vary, and that each portion can be added at variable rates. (D.I. 822 at 3; '727 patent at 9:52-10:41). However, in its claim construction order, the Court rejected the notion that the specification is dispositive of the term "efficient mixing," as the specification and the examples are contradictory. (D.I. 732 at 10). The Court noted that the specification stated that using a paddle mixer between 400 and 800 rpm was efficient mixing, and yet Example 4 indicated that mixing between 400 and 800 rpm was "inefficient." (D.I. 732 at 10).

Rather than the specification, the Court based its claim construction on the difference between Example 4, which was described as inefficient mixing, and Example 5, which was

described as efficient mixing. In Example 4, the additions were made in portions, yet this is described as "inefficient." Yet again there is an inherent contradiction between the specification and the examples, and again I find that the examples are controlling. Because Example 4, which was "inefficient" mixing, used a portion-wise addition, I find that a portion-wise addition is not efficient mixing, even if other sections of the patent describe it as such.

It is clear from the examples that "slowly and in a controlled manner" requires a constant and metered rate. Both Example 3 and Example 5 describe a "controlled addition," and both use a constant rate of 2 L/min. ('727 patent at 20:34, 22:48). While The Medicines Company argues that Hospira's addition is metered, the evidence does not support this assertion. Hospira's first two additions are rapid. The third addition is added gradually at the operator's discretion, likely using a graduated cylinder. (Tr. at 447:9-448:6). This is not consistent with a constant and metered rate.

The other requirement of efficient mixing is that it is "mixed together by a process comprising high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)." (D.I. 732 at 7). Hospira's Exhibit Batch was mixed at 560 rpm using a convective mixer, *i.e.*, a paddle mixer. (PTX 170.19, PTX 171.19; Tr. at 449:18-19, 619:18-620:1, 632:20-23). Hospira did not use mixing speeds above 1000 rpm. The Medicines Company contends that mixing speed depends on the volume of the batch (D.I. 809 at 15), because the Court's claim construction references Example 5 of the patent, which had a batch size of 150 liters. ('727 patent at 22:40-45). Hospira's Exhibit Batch was 45 liters. (PTX 170.16, PTX 171.16). The Medicines Company contends that a 45 liter batch mixed at 460 rpm is equivalent to a 150 liter batch mixed at 1248 rpm, such that Hospira actually employs high shear mixing. (D.I. 809 at 17).

There are two related arguments at play here, depending on how one interprets the Court's claim construction. If the "mixer speeds above 1000 rpms" language is exemplary, as opposed to required, the argument is that 560 rpm is high shear mixing, because if one adjusts for volume, it is equivalent to 1248 rpm, and that is high shear mixing. The second argument, if the mixer speed language is required, is that because Hospira's ANDAs provide for commercial batch sizes of 150 and 220 liters (PTX 57.1592, PTX 43.689), during scale up Hospira will use mixer speeds above 1000 rpm. Neither argument is persuasive.

In order to show that 560 rpm is equivalent to 1248 rpm when adjusted for volume, Dr. Byrn, The Medicines Company's expert, used a scale-up equation from the McCabe textbook "Unit Operations of Chemical Engineering." (Tr. at 235:5-244:15). Using the McCabe equation, Dr. Byrn calculated that at 560 rpm it would take 26.4 seconds to circulate the 45 liter batch five times. (Tr. at 242:1-24). Then, assuming that the tank to batch volume ratio remained constant (Tr. at 238:1-24), he calculated that in order to circulate a 150 liter batch five times in 26.4 seconds, a mixing speed of 1248 rpm was required. (Tr. at 243:1-244:24).

While the equivalency and the scale up arguments can be understood as separate and distinct lines of reasoning, they share the same faults. First, Hospira does not use a high shear mixer, but a convective or paddle mixer. (Tr. at 449:18-19, 619:18-620:1, 632:20-23). The patents themselves differentiate between paddle mixers and homogenizers ('727 patent at 10:48-50), of which only homogenizers are described as providing high shear mixing. ('727 patent at 10:50-51, 10:56-57). Even the two inventors of the patent are not in agreement over whether a paddle mixer can provide high shear mixing. Dr. Musso, while conceding that a paddle mixer is not a high shear mixer, maintained that a paddle mixer can achieve high shear mixing. (Tr. at 153:5-18). Dr. Krishna, on the other hand, described high shear mixing as "provid[ing]

mechanical shearing effect." (Tr. at 509:13-16). When asked if paddle mixers could provide a mechanical shearing effect, Dr. Krishna answered, "I don't think so." (Tr. at 153:17-19).

The Medicines Company's equivalency argument did not account for mechanical shearing effect. The equation Dr. Byrn applied deals with miscible[7] liquids (Tr. at 258:9-11), and is based on the understanding that "essentially complete mixing (99 percent) should be achieved if the contents of the tank are circulated about 5 times." (DTX 628 at H00182367). In fact, Dr. Byrn only calculated how long it would take to mix in the base, not how long it would take to disperse and dissolve the bivalirudin. (Tr. at 257:21-258:2). Dr. Byrn calculated that for a 45 liter batch mixed at 560 rpm, which corresponds to Hospira's Exhibit Batch, the base would be fully mixed in 26.4 seconds. (Tr. at 242:5-23). If mixing in the base were all that mattered, why then did Hospira mix its Exhibit Batch for 4 hours and 52 minutes? (PTX 170.19, PTX 171.19; Tr. at 257:6-10). At trial, Dr. Byrn maintained that factor was not relevant to his calculation, because "[t]hat length of time is involved in trying to get the mass[8] dissolved." (Tr. at 257:13-16). And yet the patents contemplate that rapid re-dissolution of the precipitate is important to efficient mixing. ('727 patent at 9:3-17). Simply put, The Medicines Company did not meet its burden to show why Dr. Byrn's calculations are relevant.

In addition to the relevancy of Dr. Byrn's calculations, they are based on flawed assumptions. In his scale up calculation, Dr. Byrn keeps impeller size constant, and yet increases the size of the tank to accommodate the larger batch size. (Tr. at 241:7-22). Dr. Byrn admitted that a larger impeller could achieve the same mixing at the same mixing speed. (Tr. at 254:11-12). While Dr. Byrn did not believe Hospira would use a larger impeller size (Tr. at 264:8-24), Dr. Bernat testified that Hospira would typically use a larger impeller size when scaling up

[7] Miscible liquids form a homogenous solution. For example, water and ethanol are miscible. Oil and water are not.
[8] The mass is the bivalirudin precipitate, which is also referred to as a white solid, gel, or glob. (Tr. at 258:19-259:7).

because, "a larger tank will have a larger impeller."[9] (Tr. at 462:10-24). Lastly, if larger batches really did require faster mixing speeds, why do the patents' examples not follow this trend? For instance, Example 3 mixes two 562.5 mL batches at 1500 rpm and 3000 rpm ('727 patent at 20:35-50), whereas Example 5 mixes a 150 L batch at between 1000 and 1300 rpm. ('727 patent at 22:40-60). If mixer speed really did depend on batch size, one would expect that the nearly 300 fold increase in batch size would necessitate at least some increase in mixer speed. In actuality, the larger batch was mixed at a lower speed. The Medicines Company did not meet its burden to prove literal infringement.

iv. Hospira Does Not Infringe the "Efficient Mixing" Limitation Under the Doctrine of Equivalents

The Medicines Company's final infringement argument is that Hospira infringes under the doctrine of equivalents. In order to infringe under this doctrine, The Medicines Company must show that Hospira performs "substantially the same function in substantially the same way with substantially the same result." *Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009). The parties disagree on the function, way, and result of "efficient mixing." The Medicines Company asserts that the function is to achieve a desired mixing through the addition of a pH-adjusting solution slowly and in a controlled manner, the way is through high shear mixing conditions, and the result is minimizing levels of Asp^9-bivalirudin formation. (D.I. 809 at 18-19). This merely parrots The Medicines Company's literal infringement argument, and, as such, was dealt with above. Hospira treats the base addition step and the mixing step as separate limitations, the function of the base addition step being operator

[9] I accept Dr. Bernat's testimony over Dr. Byrn's testimony. It makes more sense. Further, Dr. Byrn presents more as an advocate than as an expert seeking the truth, and thus I reject his testimony on this point.

independence and the function of the mixing step being particle dispersion through mechanical shearing forces. (D.I. 818 at 25-27).

I need not reach Hospira's arguments. Nevertheless, I do not agree with them either. The patents contemplate "efficient mixing" as one limitation involving a combination of slow addition and high shear mixing, so the combination should be dealt with as one limitation. However, I believe that the real function of "efficient mixing" is minimizing precipitate. The patents describe that, "without efficient mixing, a dense precipitate may form. This dense precipitate may result in a slower dissolution and surrounding solution being maintained at a high pH for extended time." ('727 patent at 9:3-7). In contrast, the patents describe that, "if the pH-adjusting solution is efficiently mixed with the bivalirudin solution, the formed precipitate is amorphous. The amorphous character allows for a more rapid re-dissolution of the precipitate and a better control of pH throughout the compounding process." ('727 patent at 9:10-13). Slow addition and high shear mixing both achieve the desired result of minimizing precipitate. Slow addition prevents a rapid buildup of precipitate in the first place. High shear mixing makes sure that any precipitate is quickly dissolved. It is this combination that is the novel aspect of the patents in suit. Hospira does not use this combination, literally or via the doctrine of equivalents.

II. ANTICIPATION

Hospira contends that the asserted claims are invalid under the on-sale bar of 35 U.S.C. § 102(b), are obvious under 35 U.S.C. § 103, and are invalid under 35 U.S.C. § 112 because the claims lack written description, are not enabled, and are indefinite. Hospira argues that the invention was sold or offered for sale before the critical date[10] because The Medicines Company paid its contract manufacturer, Ben Venue Laboratories ("Ben Venue"), to manufacture

[10] Both patents in suit were filed on July 27, 2008. (PTX 1.2, PTX 2.2). Therefore, the critical date is July 27, 2007.

Angiomax according to the new method, and because The Medicines Company offered to sell the new Angiomax to its distributor, Integrated Commercial Solutions ("ICS"). Hospira also argues that the inventions would have been obvious to one of ordinary skill in the art at the time of the invention, that because the patents fail to disclose the impurity levels of the starting material, they fail to comply with the written description requirement, and that the term "maximum" is indefinite and not enabled.

Since 1997, Ben Venue has manufactured Angiomax for The Medicines Company. (Tr. at 78:8-17). In 2005, a batch of Angiomax failed due to high Asp^9-bivalirudin levels. (Tr. at 75:4-77:6). Ben Venue investigated the problem and attempted to fix the issue. (Tr. at 76:21-82:16). Unable to solve the problem, The Medicines Company retained Dr. Gary Musso to consult with Ben Venue to modify the compounding process. (Tr. at 87:23-88:11). Dr. Musso's work led to the new compounding process claimed in the patents in suit. (Tr. at 95:7-15). In October 2006, the new process was incorporated into a revised Master Batch Record ("MBR"), and since then all batches have been made using the new process. (Tr. at 616:22-617:22, 680:19-682:5, 885:18-886:16). After The Medicines Company revised its MBR, it asked Ben Venue to perform a process validation study in order to confirm that the process worked as intended. (Tr. at 689:3-693:6). Ben Venue manufactured three validation batches, for which The Medicines Company was invoiced. (Tr. 693:15-695:17, 856:5-17, 886:9-13).

Generally, after Ben Venue would manufacture a batch, it would create a batch record, which was sent to The Medicines Company. (Tr. at 815:11-24, 820:16-821:13). The Medicines Company would review the batch records and issue a Certificate of Manufacture if the records met the specifications. (Tr. at 816:1-22, 819:10-820:15, 822:13-824:13). Once The Medicines Company issues the Certificate of Manufacture, it clears the product for delivery to the packager.

(Tr. at 822:13-824:13, 890:18-23). After the packager applies the required labeling and boxing, the batch is released and sent to the distributor, ICS, under "quarantine" conditions. (Tr. at 824:14-825:14, 875:19-24). Once The Medicines Company conducts a final review, the batch is removed from quarantine status and is available for sale. (Tr. at 862:10-22).

On February 27, 2007, The Medicines Company entered into a new "Distribution Agreement" with ICS. (DTX 84, Tr. at 849:10-851:1). The Distribution Agreement made ICS the exclusive authorized distributor of Angiomax in the U.S., and states that, "[t]itle to and risk of loss to each order of Product shipped to Distributor hereunder [passed] to Distributor upon receipt of Product at the distribution center." (DTX 84 at ¶ 4.1). Hospira asserts that Ben Venue sold the claimed invention before the critical date when it sold the validation batches to The Medicines Company, and The Medicines Company contracted to sell batches made by the new process when it entered into the Distribution Agreement with ICS. The Medicines Company opposes these contentions, and asks that Hospira's invalidity claims be dismissed because Hospira improperly relies on documents not disclosed in its § 282 notice.

A. Legal Standard

A patent claim is invalid under the on-sale bar of 35 U.S.C. § 102(b) if "the invention was… on sale in this country, more than one year prior to the date of the application for patent in the United States." The on-sale bar requires proof of two conditions: (i) the product is "ready for patenting," and (ii) the invention is "the subject of a commercial offer for sale." *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 66-68 (1998). To invalidate a claim under the on-sale bar, "the record must show by clear and convincing evidence that the claimed invention was in public use before the patent's critical date." *Clock Spring, L.P. v. Wrapmaster, Inc.*, 560 F.3d 1317, 1325 (Fed. Cir. 2009).

B. Findings of Fact

1. The Medicines Company's invention was ready for patenting prior to July 27, 2007.

2. The Medicines Company paid Ben Venue to manufacture validation batches.

3. The Medicines Company's payment to Ben Venue for the validation batches was for experimental purposes.

4. The Medicines Company's Distribution Agreement with ICS was not an offer for sale.

C. Conclusions of Law

i. Hospira Met Its Obligations Under 35 U.S.C. § 282

Under § 282 a party asserting invalidity is required to give notice "in the pleadings or otherwise in writing" of:

> the title, date, and page numbers of any publication to be relied upon as anticipation of the patent in suit or... as showing the state of the art, and the name and address of any person who may be relied upon as the prior inventor or as having prior knowledge of or as having previously used or offered for sale the invention of the patent in suit. In the absence of such notice proof of the said matters may not be made at the trial except on such terms as the court requires.

35 U.S.C. § 282(c). At trial, The Medicines Company objected to Hospira's use of documents that were not identified in its § 282 notice. (Tr. at 704:15-706:8, 709:3-711:3). Hospira argued that it had complied with the notice requirement because its § 282 statement "incorporates by reference all pleading discovery responses, expert reports, and references cited therein as providing notice under § 282." (Tr. at 704:21-705:4, D.I. 779). The Court expressed doubt that such a blanket statement provided adequate notice, but reserved judgment until after post-trial briefing. (Tr. at 710:4-711:2).

The Medicines Company objects to the following documents: DTX 110, DTX 205, DTX 600A, DTX 624, and DTX 645. Hospira's initial argument is that because The Medicines Company did not object to the latter four exhibits, any objection to their admission has been

waived. At trial, the Court expressly reserved judgment until after post-trial briefing. Making The Medicines Company object to every document would have accomplished nothing, and therefore any objections are not deemed waived.

Hospira next argues that § 282 does not apply to the exhibits because they are not anticipatory references, nor do they show the state of the art. This is persuasive. DTX 205, DTX 600A, and DTX 645 relate to Hospira's on-sale defense, and are not anticipatory references. Section 282 deals specifically with the on-sale bar, requiring only "the name and address of any person who may be relied upon... as having previously used or offered for sale the invention of the patent in suit." 35 U.S.C. § 282(c).

Hospira also argues that DTX 624 and DTX 110 are outside the scope of § 282, and that DTX 110, DTX 205, and DTX 600A were disclosed, either in its § 282 document or in its expert report. While these arguments appear persuasive, I do not reach them. The purpose of § 282 is "to prevent patentees being surprised, at the trial of the cause, by evidence of a nature which they could not be presumed to know, or be prepared to meet, and thereby to subject them either to most expensive delays, or to a loss of their cause." *Eaton Corp. v. Appliance Valves Corp.*, 790 F.2d 874, 879 (Fed. Cir. 1986). Most of these documents belong to The Medicines Company and as such there is no surprise. As for those that belong to Hospira, *i.e.*, DTX 624, there is no prejudice to The Medicines Company, as will become evident *infra.*

ii. The Invention Was Ready for Patenting Before the Critical Date

In order to show that an invention was ready for patenting, there must be proof of a reduction to practice before the critical date or proof that the inventor prepared enabling drawings or descriptions of the invention. *Pfaff*, 525 U.S. at 67-68. Hospira contends that The Medicines Company developed two sets of drawings and instructions which enabled Ben Venue

to manufacture the invention. (D.I. 810 at 9). The first purported enabling disclosure is the MBR, which was printed on October 25, 2006, and which Ben Venue followed in order to manufacture a batch on October 31, 2006. (Tr. at 680:19-683:15, DTX 598 at MEDCO4103510). The second purported enabling disclosure is a validation study protocol, signed by the inventors in November 2006, which describes the compounding process. (DTX 205 at MEDCO4043391, MEDCO4043419-27; Tr. at 688:12-689:2, 690:15-693:14).

The Medicines Company's only argument in response is that the invention was not ready for patenting because the maximum Asp^9-bivalirudin level of about 0.6% was not determined until after the critical date. (D.I. 819 at 8-9). The Medicines Company states this same argument in a different way by claiming that the validation batches are not enabling disclosures because they do not disclose the maximum level of Asp^9-bivalirudin. (D.I. 819 at 10-11). This argument is not persuasive. The invention was the process itself. The process produced a batch having an Asp^9-bivalirudin level of 0.3%. (DTX 598 at MEDCO4103356, DTX 599 at MEDCO4103635, DTX 600A at MEDCO4071518). The MBR and validation protocol disclose how to use the process according to the invention. Nothing more is needed. Alternatively, the invention was actually reduced to practice prior to the critical date, since batches according to the invention were produced.

iii. The Invention Was Not Sold or Offered for Sale Before the Critical Date

The existence of an invalidating offer for sale or actual sale is determined according to traditional contract principles. *Electromotive Div. of Gen. Motors Corp. v. Transp. Sys. Div. of Gen. Elec. Co.*, 417 F.3d 1203, 1209 (Fed. Cir. 2005). Hospira asserts that two different transactions trigger the on-sale bar. (D.I. 810 at 10). First, Hospira contends that Ben Venue sold The Medicines Company the three validation batches made by the new compounding process.

Second, Hospira contends that The Medicines Company contracted to sell to ICS Angiomax made by the new process. (D.I. 810 at 11).

The parties describe the Ben Venue transaction very differently. Hospira describes the transaction as a sale of the validation batches. (D.I. 810 at 11). The Medicines Company describes the transaction as a contract manufacturer relationship in which Ben Venue was paid to manufacture Angiomax for The Medicines Company, but wherein title to the Angiomax always resided with The Medicines Company. (D.I. 819 at 11-12). The Medicines Company's characterization is the better understanding, as the invoices clearly stated, "Charge to manufacture Bivalirudin lot." (DTX 29 at MEDCO4550164-65). However, this does not end the inquiry.

Hospira cites to *Plumtree Software, Inc. v. Datamize, LLC*, 473 F.3d 1152, 1163 (Fed. Cir. 2006), for the proposition that payment for the performance of a claimed process constitutes a sale under § 102(b). What *Plumtree* actually stated is that, "performing the patented method for commercial purposes before the critical date constitutes a sale under § 102(b)." 473 F.3d at 1163. The reasoning behind this statement is that the purpose of § 102(b) "is to preclude attempts by the inventor or his assignee to profit from commercial use of an invention for more than a year before an application for patent is filed." *Id.* Hospira admits that the batches were for validation purposes. (D.I. 810 at 12). Therefore, at the time of the supposed sale, the batches were not for commercial purposes, but experimental batches made in order to verify that the invention worked for its intended purpose.[11]

[11] The same reasoning applies to the "service provider" argument. The Medicines Company "purchased" the validation batches for its own secret use, as did the patentee in *Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1362 (Fed. Cir. 2010). The fact that the batches were subsequently sold does not change the underlying transaction from experimental to commercial. At the time of the transaction, the intent was experimental.

The second transaction which Hospira contends is an invalidating sale is the amendment of the Distribution Agreement between The Medicines Company and ICS. Hospira mischaracterizes the agreement. In its briefing, Hospira states that the Distribution Agreement replaced a prior "3PL Agreement" (D.I. 810 at 13), and yet the Distribution Agreement itself states that the 3PL Agreement "will continue in effect."[12] (DTX 84 a ¶ 2.2). Hospira also stated that title passes to ICS upon receipt of the product (D.I. 810 at 13), but, as was shown during trial, title only passes when product is received at an ICS distribution center, not an ICS 3PL facility. (Tr. at 861:6-865:13; DTX 84 at MEDCO4555475). In order to receive product, ICS was required to submit individual purchase orders. (DTX 84 at ¶ 3.1). The Medicines Company would invoice ICS on the same day that the product was shipped. (DTX 84 at ¶ 4.2).

Hospira contends that the Distribution Agreement was a requirements contract, which would be an offer for sale, because the agreement requires that ICS "place orders for such quantities of Product as are necessary to maintain an appropriate level of inventory based on customers' historical purchase volumes. Any purchase order not rejected in whole or in part by TMC within two (2) business days after receipt will be deemed accepted." (DTX 84 at ¶ 3.1). This does not rise to the level of a requirements contract, but merely states the contemplated scope of the agreement. The Distribution Agreement was just what it said it was, an agreement for ICS to be the sole U.S. distributor of Angiomax. It was not an offer to sell Angiomax, as individual purchase orders were required. In the payment section of the agreement, one paragraph deals with payment for product orders, and another paragraph deals with payment for distribution services. (DTX 84 at ¶ 5.1, 5.3). In order to be a commercial offer for sale, "[o]nly an offer which... the other party could make into a binding contract by simple acceptance

[12] Hospira argues that the language only applies to activity outside the U.S. (D.I. 824 at 12). The language is not conclusive.

(assuming consideration), constitutes an offer for sale under § 102(b)." *Grp. One, Ltd. v. Hallmark Cards, Inc.*, 254 F.3d 1041, 1048 (Fed. Cir. 2001).

The Distribution Agreement is a contract to enter into a contract. ICS is bound to place an order at some later date, which could be rejected by The Medicines Company.[13] The contract deals mainly with ICS providing distribution services, not with the sale of Angiomax from The Medicines Company to ICS. Hospira only cites to one case in which such a distribution agreement was held to be an invalidating offer for sale. In *Cardiac Sci., Inc. v. Koninklijke Philips Elecs. N.V.*, 2006 WL 2038625 (D. Minn. July 19, 2006), the court invalidated a patent because the patentee entered into a distribution agreement prior to the critical date. However, in *Cardiac*, the patentee reported to its shareholders that it had, "entered into a distribution agreement ...to market and sell the [product]." *Id.* at *2. The court relied on the "to sell" language as an admission that the distribution agreement was a sales contract. *Id.* at *4 ("Gilman and Bourgraf's testimony is contrary to both the clear language of the contract and to Gilman's description of the Distribution Agreement to the Survivalink shareholders"). In any event, *Cardiac* is not binding on this Court, and I therefore decline to follow its reasoning. I hold that the ICS Distribution Agreement was not an offer to sell Angiomax made by the new method.[14]

III. OBVIOUSNESS

Hospira asserts that claim 1 of each patent is invalid because "efficient mixing" was an obvious change to the prior art compounding process. (D.I. 810 at 16). The prior art consists of the old compounding process for Angiomax, literature and patents related to bivalirudin, and scientific literature, including FDA materials, related to process optimization, drug formulation,

[13] Of course, rejecting an order would be unlikely given the parties' course of dealing. (Tr. at 854:17-855:3, 864:20-865:8).

[14] Because I hold that there was no offer to sell, I need not reach whether the Distribution Agreement concerned Angiomax made by the new method as opposed to Angiomax made by the original method.

mixing, and peptides and proteins. (Tr. at 700:2-701:4). The old compounding process for Angiomax is prior art because The Medicines Company sold bivalirudin made by that process before the critical date. (Tr. at 78:8-17). It was also known in the prior art literature that a "known degradation product of bivalirudin involves the deamidation of asparagine in position 9 to [A]sp[9]-bivalirudin." (DTX 273). Additionally, it was known in the art that peptides such as bivalirudin are sensitive to degradation when exposed to basic conditions (Tr. at 159:4-11), and that base must be added to bivalirudin to make it safe for human injection. (Tr. at 703:12-24).

The only difference between the claims of the patents and the prior art compounding process is "efficient mixing," which reliably yields batches having low levels of Asp^9-bivalirudin. (D.I. 732 at 4). Therefore, the claimed invention differs from the prior art only in that the base addition step is done slowly and in a controlled manner and with high shear mixing. Furthermore, there is no dispute that a person of ordinary skill in the art has a B.S., M.S., or Ph.D. with at least several years' experience working as a professional in pharmaceutical process development, scale characterization and/or validation of manufacturing processes for pharmaceutical formulations. (Tr. at 698:4-20, 912:10-17).

A. Legal Standard

Under 35 U.S.C. § 103(a) a patent "may not be obtained... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." Obviousness is a question of law that depends on the following factual inquiries: (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 relevant art; and (4) any objective considerations such as commercial success, long felt but unsolved need, and the failure of others. *Transocean Offshore*

Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc., 699 F.3d 1340, 1347 (Fed. Cir. 2012). The improvement over the prior art must be "more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007).

To prove obviousness, Defendants must show that a person skilled in the art would be motivated to combine the claimed combinations with a reasonable expectation of success. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013). Evidence of obviousness, especially when that evidence is proffered in support of an "obvious-to-try" theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were "finite," "small," or "easily traversed," and that skilled artisans would have had a reason to select the route that produced the claimed invention. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012). Obviousness must be proven by clear and convincing evidence. *Id.* at 1078.

B. Findings of Fact

1. The old compounding process for Angiomax is prior art.
2. Asp^9-bivalirudin was a known degradation product of bivalirudin in basic conditions.
3. High shear mixing was a known method of dispersion.
4. It would not have been obvious to a person of ordinary skill in the art to use high shear mixing with bivalirudin.

C. Conclusions of Law

i. <u>The Asserted Claims Are Not Obvious Under 35 U.S.C. § 103(a)</u>

Hospira contends that a person of ordinary skill would be motivated to reduce Asp^9-bivalirudin levels in order to minimize the presence of drug impurities. The person of ordinary skill would identify the base addition and mixing step as the source of the problem because it

was known that peptides degrade in base. Because the base addition and mixing step comprises only addition and mixing, the person of ordinary skill would have only two variables to manipulate. (Tr. at 713:2-6). First, it would have been obvious to add the base more slowly and in a controlled manner because it removes undesirable human variability. (Tr. at 162:7-11, 719:12-720:20). Second, because base addition causes the formation of bivalirudin precipitate (Tr. at 512:21-513:7, 711:17-713:1), which must be dissolved (Tr. at 177:3-10, 454:2-21, 714:23-715:10), the person of ordinary skill would have used high shear mixing because such mixers were used in the prior art to dissolve solids. (Tr. at 714:23-716:14).

While this argument seems fairly logical, it fails to overcome the burden of proving obviousness by clear and convincing evidence. First of all, there were more than just two variables at play. During his investigation, Dr. Musso identified ten potential causes for the high Asp^9-bivalirudin problem: residual peroxides, residual perchlorates, speed of base addition, base viscosity, timing of the base addition, mixing speed, properties of the precipitated bivalirudin, the location of pH addition, stirrer heights and location, and batch scale. (PTX 27; Tr. at 116:11-23). The question of residual peroxides and perchlorates as causing the impurities was quickly dismissed (PTX 27.2), yet that still left eight potential variables, all of which deal with the base addition step.

Second, other than a conclusory opinion that a person of ordinary skill would add base slowly and in a controlled manner, Hospira offers little support for such an assertion. Naturally, the removal of variability is an important parameter for anyone working in the pharmaceutical industry. (Tr. at 162:7-11, 719:12-720:20). However, without evidence that the variability actually caused a problem, the argument is circular. Ostensibly, Hospira argues that the person of ordinary skill would be motivated to reduce variability in order to decrease impurity levels, but

the person of ordinary skill does not know that reducing variability decreases impurity levels until after variability is reduced. Of course, the person of ordinary skill could have a different reason for attempting to implement controlled addition. But incorporating controlled addition for its own sake is not sufficient motivation.

Third, while Hospira contends that a person of ordinary skill in the art would not have been dissuaded from using a high shear mixer, the evidence is in equipoise. Dr. Johnson, Hospira's expert, testified that high shear mixers were routinely used with peptides similar to bivalirudin. (Tr. at 716:15-718:17). However, the inventor, Dr. Musso, testified that peptides often experience foaming under vigorous mixing (Tr. at 120:13-121:3), and The Medicines Company's expert, Dr. Klibanov, testified that foaming leads to degradation. (Tr. at 914:18-915:7). Additionally, the patents state that most proteins and peptides are susceptible to degradation by high shear. ('727 patent at 10:53-55). Hospira also contends that only peptides with structural complexity are subject to degradation during mixing, and since bivalirudin does not have such a structure, the person of ordinary skill would not be concerned about using high shear mixing. (Tr. at 440:6-442:10, 716:15-717:24). Even assuming that foaming does not cause degradation of the bivalirudin, foaming itself is not desirable, as it can lead to solution loss via the foam coming out of the compounding vessel. (DTX 216.75). I therefore find that Hospira has not met its burden of proving obviousness by clear and convincing evidence.

IV. 35 U.S.C. § 112

Hospira asserts that the claims at issue do not comply with 35 U.S.C. § 112 because they do not satisfy the written description, are not enabled, and are indefinite.

A. Legal Standard

A patent specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same..." 35 U.S.C. § 112 ¶ 1. The test for written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

A patent's specification must enable the claimed invention. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999). Furthermore, "[t]he scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *Nat'l Recovery Technologies, Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999). Whether a patent claim is enabled is a question of law based upon the underlying facts of the case. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). Here, the burden of proof must be carried by the Defendant, and must be proven by clear and convincing evidence. *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013). "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Id.*

A claim is indefinite if it does not reasonably apprise those skilled in the art as to its scope. *Morton Int'l v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993). This occurs only when "it is not 'amenable to construction' or 'insolubly ambiguous.'" *Biosig Instruments, Inc. v. Nautilus, Inc.*, 715 F.3d 891, 898 (Fed. Cir. 2013) (citations omitted).

B. Conclusions of Law

i. The Asserted Claims Satisfy the Written Description Requirement

Hospira contends that the patents in suit do not satisfy the written description because the specification does not disclose the amount of Asp^9-bivalirudin in the API starting material. (D.I. 810 at 26). Because the patents in suit are directed at minimizing the Asp^9-bivalirudin impurity, Hospira argues that the person of ordinary skill would expect to see an assessment of the invention's effect on that impurity level. Without knowing the impurity level of the starting material, the person of ordinary skill in the art would not be able to gauge the effectiveness of the invention. Additionally, Hospira argues that claim 7 of each patent, which limits the level of D-Phe^{12}-bivalirudin, is invalid because the claimed levels of D-Phe^{12}-bivalirudin were known in the prior art.

This argument is not persuasive. The specifications explain that the Asp^9-bivalirudin levels in the final product account for the Asp^9-bivalirudin levels in the API. ('727 patent at 12:38-41). The person of ordinary skill in the art, reading the specification, would understand that the inventor had possession of the claimed subject matter. The claimed subject matter is the finished "pharmaceutical batch," not the starting compound. It appears that Hospira's argument is premised on the assumption that Asp^9-bivalirudin levels do not decrease during compounding (D.I. 824 at 18), which is contrary to my factual findings. As for the D-Phe^{12}-bivalirudin levels, there is no requirement that every limitation be novel over the prior art. Where an independent claim is novel, the dependent claims do not have to add further novel features. Hospira has not met its high burden of proving lack of written description by clear and convincing evidence.[15]

[15] Hospira also argues that claims 2 and 3 fail to meet the written description requirement because the patents do not disclose any means to lower the maximum level of Asp^9-bivalirudin to 0.3-0.4%. (D.I. 824 at 18-19). This appears to be an enablement argument, not a written description argument. In any event, it was not raised until the reply brief, and is therefore waived.

ii. The Asserted Claims Are Enabled and Not Indefinite

Hospira next contends that the claims are not enabled because the claim term "maximum" does not reasonably apprise those skilled in the art how to determine the number of samples needed to calculate the "maximum" impurity level for a pharmaceutical batch. (D.I. 810 at 28). Essentially, because the specification does not state how many samples are needed to determine the maximum impurity level, the person of ordinary skill could not determine the maximum, because the next batch could increase the maximum. Alternatively, Hospira argues that a person of ordinary skill could never obtain a maximum impurity level of all potential batches, and because the impossible cannot be enabled, the claims are invalid.

This argument is not persuasive. The Court's claim construction allowed for "pharmaceutical batches" to be a "single batch wherein the single batch is representative of all commercial batches and wherein the levels of impurities and reconstitution time in a single batch represent levels for all potential batches made by said process." (D.I. 732 at 1-2). Certainly the person of ordinary skill could determine the impurity level of a single batch. As discussed *supra*, representative does not mean identical.

Hospira rephrases this argument as an indefiniteness argument: the person of ordinary skill in the art cannot know the scope of the claimed "maximum impurity level" for all batches because a maximum might increase the more one practices the invention. Hospira argues therefore that the term "maximum" is itself indefinite. This is not persuasive. The claim construction allows for one batch to be representative of other batches. Where the Asp^9-bivalirudin levels of a representative batch can be determined, the person of ordinary skill can determine the "maximum" impurity levels. The term "maximum" does not rise to the level of "insolubly ambiguous" and was in fact "amenable to construction," so it is not indefinite.

V. CONCLUSION

Plaintiff has failed to prove that Hospira's generic product infringes claims 1-3, 7-10, and 17 of the '727 patent, or claims 1-3 and 7-11 of the '343 patent. The Defendants have not proven by clear and convincing evidence that any of the asserted claims of the '727 or '343 are invalid.

The Plaintiffs should submit an agreed upon form of final judgment within two weeks.