Appeal Nos. 2014-1469, 2014-1504

United States Court of Appeals

for the

Federal Circuit

THE MEDICINES COMPANY,

Plaintiff-Appellant,

– v. –

HOSPIRA, INC.,

Defendant-Cross-Appellant.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
CASE NO. 09-CV-750-RGA, JUDGE RICHARD G. ANDREWS

BRIEF OF PLAINTIFF-APPELLANT
THE MEDICINES COMPANY

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August 13, 2014

CERTIFICATE OF INTEREST

Counsel for Plaintiff-Appellant The Medicines Company certifies the following:

1. The full name of every party or amicus represented by me is:

The Medicines Company.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

None.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

None.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this Court are:

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Frederick L. Cottrell, III, Jason J. Rawnsley, and Laura D. Hatcher (former), all of Richards, Layton & Finger, P.A.

Date: August 13, 2014

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

RULES

TABLE OF ABBREVIATIONS

"'727 patent"	U.S. Patent No. 7,582,727 (A47–61)
"'343 patent"	U.S. Patent No. 7,598,343 (A62–76)
"patents-in-suit"	The '727 patent and the '343 patent
"A____"	Joint Appendix page number(s)
"ANDA"	Abbreviated New Drug Application
"FDA"	United States Food and Drug Administration
"PTO"	United States Patent and Trademark Office
"related New Jersey" action	*The Medicines Company v. Dr. Reddy's Laboratories Ltd.*, No. 11-2456 (D.N.J.) (A5600–22)
the "wherein" term	"wherein the batches have a pH adjusted by a base"

STATEMENT OF RELATED CASES

Plaintiff-appellant The Medicines Company is not aware of any related cases currently pending before this Court.

The following district court cases are related to the instant case, in that each concerns the same patents-in-suit:

- *The Medicines Company v. Dr. Reddy's Laboratories Ltd. et al.*, No. 11-2456 (D.N.J.);
- *The Medicines Company v. Sun Pharma Global FZE et al.*, No. 11-6819 (D.N.J.);
- *The Medicines Company v. Mylan Inc. et al.*, No. 11-1285 (N.D. Ill.);
- *The Medicines Company v. Apotex Inc. et al.*, No. 13-2801 (D.N.J.);
- *The Medicines Company v. Aurobindo Pharma Ltd. et al.*, No. 14-2367 (D.N.J.);
- *The Medicines Company v. Exela Pharma Sciences, LLC et al.*, No. 14-58 (W.D.N.C.); and
- *The Medicines Company v. Accord Healthcare, Inc. et al.*, No. 14-626 (M.D.N.C.).

JURISDICTIONAL STATEMENT

This action arises under the patent laws of the United States, Title 35 of the United States Code. The United States District Court for the District of Delaware has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

The Medicines Company appeals from a Final Judgment entered by the Delaware district court on April 15, 2014. (A1–2.) The Final Judgment disposed of all parties' claims. In accordance with 28 U.S.C. § 2107(a) and Fed. R. App. P. 4(a), The Medicines Company timely filed a notice of appeal on May 9, 2014. (A17083–84.) This Court has jurisdiction over this appeal under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. Did the district court err in construing the claim term "wherein the batches have a pH adjusted by a base" (recited in both the '343 and '727 patents), at least by requiring an "efficient mixing" process, thus: (i) rendering the '343 patent's pre-existing "efficiently mixing" claim term superfluous, and also (ii) transforming the '727 patent's product claims into product-by-process claims that render all of the '343 patent's claims superfluous?

2. Did the district court err in its construction of "efficiently mixing" (recited in only the '343 patent), which imported limitations from part of one embodiment described in a "non-limiting" example in the specification, despite the specification explicitly describing numerous other embodiments that may achieve the same result?

3. Did the district court clearly err in determining that Hospira did not infringe the asserted claims based on its improper claim constructions, when Hospira infringes under correct constructions using the district court's fact determinations?

4. Did the district court clearly err in deciding under its incorrect claim constructions that the asserted claims are not infringed either literally or under the doctrine of equivalents, in that the district court expressly based its construction of

"efficiently mixing" on Example 5, and Hospira's ANDA product falls within the context of Example 5's embodiment?

STATEMENT OF THE CASE
SETTING OUT THE FACTS RELEVANT TO THE ISSUES

I. Invention of the Claimed Drug Product

The patents-in-suit claim pharmaceutical batches of a drug product comprising bivalirudin, a synthetic twenty-amino-acid peptide. Bivalirudin is a substance that is used to prevent blood from clotting. (A48, col.1 ll.44–57; A50, col.5 ll.58–66.) In particular, bivalirudin is regarded as a highly effective anticoagulant for use during catheterization procedures, including coronary angioplasty (a procedure that opens a blocked artery in the heart). (A48, col.1 ll.44–57; A36.) Bivalirudin is typically administered to a patient through intravenous administration. (A50, col.6 ll.27–28.)

When bivalirudin is added to a pharmaceutically acceptable vehicle (such as saline or water) during a process known as compounding, the pH of the resulting solution is very acidic, and thus undesirable for use as an injectable medication. (A3924.) Therefore, when manufacturing the compounded drug product the pH of the bivalirudin is adjusted with a base (such as sodium hydroxide). (*Id.*) This results in pH-adjusted pharmaceutical batches of a bivalirudin drug product that are preferable for administration to a subject in need thereof.

As a pharmaceutical, it is essential that the bivalirudin drug product maintain a high level of purity. (A48, col.2 ll.1–7.) Under certain conditions, however, bivalirudin may degrade and form impurities. (A48, col.2 ll.8–19.) One such

impurity occurs when the ninth amino acid of bivalirudin—asparagine—converts to a different amino acid, aspartic acid ("Asp"). (A48, col.2 ll.8–9.) This impurity is referred to as Asp^9-bivalirudin. (*Id.*)

The Medicines Company's original compounding process—which predated the inventions of the patents-in-suit—resulted in bivalirudin batches with high Asp^9-bivalirudin levels and a high degree of variability in those levels ("original process"). (A58, col.21 l.44–col.22 l.28.) Batches made from the original process had a maximum level of Asp^9-bivalirudin of 3.6%, and a mean level of Asp^9-bivalirudin of 0.5% with a standard deviation of 0.4%. (*Id.*)

Co-inventors Drs. Musso and Krishna developed and conducted detailed studies to determine the cause of the high and variable Asp^9-bivalirudin levels in bivalirudin batches produced according to the original process. (A3718 ¶ 13.) Prior studies taught that shear stress and modest temperature elevations could impact peptide degradation and impurity levels, but the inventors' studies proved that these parameters surprisingly did not significantly contribute to increased Asp^9-bivalirudin levels. (*Id.*) Instead, the inventors found that there is a strong correlation between high pH conditions and high Asp^9-bivalirudin levels. (*Id.*) The inventors also unexpectedly found that when the pH of the initial bivalirudin drug substance is adjusted, high pH values could be obtained and these high levels could persist for an extended time. (*Id.*) The inventors determined that these

conditions could result in high and variable levels of Asp^9-bivalirudin in the finished drug product. (*Id.*)

As a result, the inventors devised a method to assess the impact of adding the base in a controlled manner and effectively dispersing it. (A3719 ¶ 14.) Studies confirmed that by doing so the pH was well controlled, and the resulting Asp^9-bivalirudin levels were similar to the levels in the bivalirudin active ingredient used for the experiments. (*Id.*) In other words, the inventors' new compounding process produced finished drug product with minimized and less variable Asp^9-bivalirudin impurities.

In the patents-in-suit, the inventors described that efficient mixing of these solutions will minimize levels of Asp^9-bivalirudin in the compounding solution and described various methods for how the pH-adjusting solution may be efficiently mixed with the bivalirudin solution to form the compounding solution. (A51, col.8 ll.54–61.) The inventors defined "efficient mixing" as being "characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution." (A52, col.9 ll.34–36.) The inventors unequivocally stated that "efficient mixing" "may be achieved through various methods." (*Id.*) "One such method may be to add or combine the pH-adjusting solution and bivalirudin solution portion-wise, i.e., in portions." (A52, col.9 ll.36–59.) The number of portions may vary, as well as the quantity of pH-adjusting liquid used in each portion, the time

period between portions, and the duration of adding each portion. (A52, col.9 l.60–col.10 l.16.) Further, the pH-adjusting solution for each portion may be added at differing constant or variable rates. (A52, col.10 ll.17–41.)

The inventors also described that "efficient mixing may be achieved through the use of one or more mixing devices." (A52, col.10 l.42–col.11 l.9.) While others thought that bivalirudin could only be compounded with low shear mixing, the inventors found that high shear mixing could optionally be used because "unexpectedly, [] bivalirudin is stable to high shear mixing conditions." (*Id.*; A56, col.18 ll.55–56.) Thus, efficient mixing may use mixing devices that include paddle mixers, magnetic stirrers, shakers, re-circulating pumps, homogenizers, and any combination thereof. (A52, col.10 l.42–col.11 l.9.) The mixing rates of such mixers may vary. (*Id.*) For instance, a paddle mixer may be between about 100 rpm and 1000 rpm. (*Id.*) The mixing rate of a homogenizer may be between about 300 and about 6000 rpm. (*Id.*) Further, when more than one mixing device is used for "efficient mixing," they may be operated at the same or different mixing rates, or at the same or different periods of time. (A52, col.10 l.42–col.11 l.9.)

"Efficient mixing" may also be achieved through adding the pH-adjusting solution to specific sites within the bivalirudin solution, with or without a mixer. (A53, col.11 ll.10–24.) In cases in which a mixer is used, the pH-adjusting solution may be also added to the site of the mixing device. (*Id.*)

The patents-in-suit described that "[e]fficient mixing of the pH-adjusting solution with the bivalirudin solution will minimize levels of Asp^9-bivalirudin in the compounding solution." (A51, col.8 ll.54–61.) "Efficient mixing" results in pharmaceutical batches in which "the generation of [] Asp^9-bivalirudin in the compounding solution [] is less than about 0.6%, or less than about 0.4%, or less than about 0.3%." (*Id.*)

II. Background of the Action

This appeal involves The Medicines Company's patented pharmaceutical formulations of a bivalirudin drug product, which is sold under the trade name Angiomax®. (A48, col.1 ll.52–56, col.2 ll.19–22.) There are two patents-in-suit, which are listed in the FDA's Orange Book as covering Angiomax®. (A165 ¶ 11.) The Medicines Company sued Hospira for infringement of the patents-in-suit on August 19, 2010 in the District of Delaware, based on Hospira filing two Abbreviated New Drug Applications ("ANDAs") seeking FDA approval to sell generic bivalirudin drug products before the expiration of the patents. (A4; A165 ¶ 12.) The infringement issues are the same for both ANDAs, which concern differently-packaged versions of the same bivalirudin drug product. The district court held a three day bench trial on September 23–25, 2013. (A4.)

The patents-in-suit were filed on the same day and share almost identical specifications—U.S. Patent No. 7,582,727 ("the '727 patent") and U.S. Patent No.

7,598,343 ("the '343 patent"). (A36, A47, A62.) Drs. Musso and Krishna are the inventors of the patents-in-suit, which are assigned to The Medicines Company. (*Id.*) The table below illustrates the differences between claim 1 of the '727 product patent and claim 1 of the '343 product-by-process patent:

'727 Patent v. '343 Patent

Product **Claim 1 of '727 Patent**	**Product-by-Process** **Claim 1 of '343 Patent**
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,	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,
	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.	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.

III. The Delaware District Court's Decisions

The Delaware district court construed certain claim terms of the patents, including "wherein the batches have a pH adjusted by a base" (the "wherein" term) and "efficiently mixing." (A6, A38–46.) *See also The Medicines Company v. Teva Parenteral Meds., Inc.*, No. 09-750, 2013 U.S. Dist. LEXIS 97265 (D. Del.

July 11, 2013). A comparison of the district court's and The Medicines Company's proposed constructions follows.

Term	The Delaware District Court's Constructions	The Medicines Company's Constructions
"wherein the batches have a pH adjusted by a base" Note: recited in both the '727 and '343 patents	"wherein said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under efficient mixing conditions"	plain and ordinary meaning In the alternative: "during compounding, the pH of the batches is adjusted using a base"
"efficiently mixing" Note: recited in only the '343 patent	"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)"	"mixing that is characterized by minimizing levels of Asp^{9}-bivalirudin in the compounding solution"

(A39, A42.)

The effect of the district court's "wherein" construction on the '343 patent is illustrated below. The district court's construction made redundant the '343 patent's recitations that "said batches [are] prepared by a compounding process comprising . . . ***efficiently mixing*** a pH-adjusting solution with the first solution to form a second solution." (A76.)

’343 Patent

Claim as Issued (A76 (emphasis added))	District Court’s Construed Claim (emphasis added)
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, said batches prepared by a compounding process comprising: . . . (ii) ***efficiently mixing*** a pH-adjusting solution with the first solution to form a second solution, . . . ; and . . . ***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.	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, said batches prepared by a compounding process comprising: . . . (ii) ***efficiently mixing*** a pH-adjusting solution with the first solution to form a second solution, . . . ; and . . . [*wherein said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under* ***efficient mixing*** *conditions*], 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.

And the effect of the Delaware district court’s “wherein” construction on the ’727 patent is illustrated below. The district court’s construction of the “wherein” term requires that the ’727 patent’s claimed product is made with “efficient mixing,” and thus transforms the ’727 patent’s product claims into product-by-process claims with the very same limitations that the district court ascribed to the ’343 patent’s “efficiently mixing” claim term.

’727 Patent

Claim as Issued (A60 (emphasis added))	District Court’s Construed Claim (emphasis added)
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-bivalirudin that does not exceed about 0.6% as measured by HPLC.	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 said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under* ***efficient mixing*** *conditions*], 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.

After the bench trial, the district court found that the asserted claims of the ’727 and ’343 patents were not invalid (i.e., claims 1–3, 7–10, and 17 of the ’727 patent, and claims 1–3 and 7–11 of the ’343 patent). (A1 ¶¶ 2, 3; A4.) *See also The Medicines Company v. Hospira, Inc.*, No. 09-750, 2014 U.S. Dist. LEXIS 43126 (D. Del. Mar. 31, 2014). But under its claim constructions, the district court also found that Hospira’s proposed generic bivalirudin product did not infringe the asserted claims of the patents-in-suit. (A1 ¶ 4; A6.) The Medicines Company appeals the district court’s July 11, 2013 Claim Construction Opinion (A35–46),

the March 31, 2014 Trial Opinion (A3–34), and any other decision or order adverse to The Medicines Company. (A17083.)

SUMMARY OF THE ARGUMENT

The Delaware district court based its noninfringement ruling on erroneous constructions of two claim terms: "wherein the batches have a pH adjusted by a base" (recited in both patents) and "efficiently mixing" (recited in only the '343 patent).

When construing each of these claim terms, the district court committed a "cardinal sin" of patent law and improperly imported limitations that do not comport with the claim language or the patent's specifications. Furthermore, in construing the "wherein" term, the district court re-wrote the term to add the phrase "efficient mixing," which (i) rendered the '343 patent's pre-existing "efficiently mixing" claim term superfluous, and (ii) transformed the '727 patent's product claims into product-by-process claims, thus rendering all of the '343 patent's claims superfluous with the '727 patent's claims.

The district court's constructions should be vacated because they do not comport with this Court's precedent. This Court should adopt The Medicines Company's constructions because they are consistent with and supported by the intrinsic evidence. In a related action[1] the same terms of the same patents were construed to have constructions that are similar to those offered by The Medicines

[1] *The Medicines Company v. Dr. Reddy's Labs. Ltd*. (the "related New Jersey" action), No. 11-2456, 2013 U.S. Dist. LEXIS 536 (D.N.J Jan. 3, 2013). (A5600–22.)

Company (and markedly different from those of the Delaware district court). (*See* A5622.)

The first term, "wherein the batches have a pH adjusted by a base," should be construed to have its plain and ordinary meaning. In the alternative, it may be construed to mean: "during compounding, the pH of the batches is adjusted using a base."[2] (A39.)

This term is used in both the '343 and '727 patents, but the claims of these two patents are significantly different. The '343 patent has ***product-by-process*** claims, in which the claimed pharmaceutical batches of bivalirudin are made by "efficiently mixing." (A76, claim 1.) In contrast, the '727 patent claims the ***product*** independently of a specific process by which it may be made. (A60, claim 1.)

Despite the patentees' use of the "wherein" term in both product claims and product-by-process claims, the district court construed the term to mean: "wherein said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under efficient mixing conditions." (A39.) The district court's construction is wrong for multiple reasons.

First, the '343 patent's product-by-process claims already recite "efficiently mixing" as a claim term. By rewriting the "wherein" term to include "efficient

[2] This is the construction adopted in the related New Jersey action. (A5622.)

mixing," the district court improperly rendered the '343 patent's pre-existing "efficiently mixing" claim term redundant and superfluous, as shown *supra* at 11. Thus, the district court's construction erroneously repeats the claim limitation that "said batches [are] prepared by a compounding process comprising . . . efficiently mixing a pH-adjusting solution [a base] with the first solution [bivalirudin solution] to form a second solution." The district court's "wherein" construction violates black letter law that requires district courts to interpret claims "with an eye toward giving effect to ***all terms*** in the claim" and "to construe claim terms in light of the surrounding claim language, such that words in a claim are ***not*** rendered ***superfluous***." *Digital-Vending Servs. Int'l, LLC v. Univ. of Phoenix, Inc.*, 672 F.3d 1270, 1275 (Fed. Cir. 2012) (quotation omitted, emphasis added).

Second, there is no basis in the specification or prosecution history for transforming the '727 patent's product claims into product-by-process claims. The Delaware district court fundamentally misunderstood the "wherein" term to require a particular process. In fact, the related New Jersey action's court recognized that such a construction "would improperly rewrite the composition claims of the '727 patent as product-by-process claims, and would add process limitations to those claims." (A5619.) Instead of a process, the term merely describes a property of the batches, i.e. that they have a base-adjusted pH. Moreover, the PTO granted the '727 patent after the patentees argued that the claimed ***product*** was novel and non-

obvious. (*E.g.*, A3923–44.) And "[a] novel product that meets the criteria of patentability is ***not*** limited to the process by which it was made." *Vanguard Prods. Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000) (emphasis added).

Furthermore, the district court's "wherein" construction improperly vitiated the distinction between these patents by transforming the '727 patent's product claims into product-by-process claims (as shown *supra* at 12)—and, thus, made all of the '343 patent's product-by-process claims superfluous with the '727 patent. "Claim differentiation takes on relevance in the context of claim construction that would render additional, or different, language in another independent claim [from another patent] superfluous." *Arlington Indus., Inc. v. Bridgeport Fittings, Inc.*, 632 F.3d 1246, 1254 (Fed. Cir. 2011) (quotation omitted) (comparing independent claims of the '050 and '164 patents). A proper claim construction should respect the differences between the patents, and the '727 patent's claims should remain product claims because "the resulting claim interpretation must, in the end, accord with the words chosen by the patentee to stake out the boundary of the claimed property." *Renishaw plc v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998).

The district court also erred in construing "efficiently mixing," which is recited in only the '343 patent's claims. The Medicines Company's proposed

construction is the same as the definition in the specification: "mixing that is ***characterized*** by minimizing levels of Asp[9]-bivalirudin in the compounding solution."[3] (A41 (emphasis added); A67, col.9 ll.34–35.) After defining the term, the specification describes various methods in which a person of ordinary skill may accomplish "efficiently mixing." (A67–68, col.9 l.34–col.11 l.24.) "The ***characterizations*** of ['efficiently mixing'] in the specification [] are distinctly definitional . . . [and] set forth what the patentee regarded as the meaning of the term [] as used in the claims." *S. Mills, Inc. v. Polartec, LLC*, 377 F. App'x 2, 6 (Fed. Cir. 2010) (emphasis added).

Despite the specification describing many embodiments of "efficient mixing," the district court improperly limited the term to encompass only ***part*** of ***one*** example. The district court construed the term to mean: "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)." (A41–42.) The specification provided no basis to so limit "efficiently mixing." To the contrary, the specification expressly and unequivocally states that its examples are "non-limiting" and should not "be interpreted[] to limit the scope of the invention." (A70, col.16 ll.7–11.) The

[3] In the alternative, the related New Jersey action's construction may be adopted: "mixing that is characterized by minimizing levels of Asp[9]-bivalirudin in the compounding solution and that does not use mixing conditions described in Example 4." (A5622.)

district court committed a "cardinal sin" of claim construction by limiting the scope of the invention by importing limitations from the specification into a claim. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1319–20 (Fed. Cir. 2005) (en banc). And, the district court compounded its error by importing these limitations into its incorrect construction of the "wherein" term, which added "efficient mixing" to the '727 patent.

The district court's constructions of these two claim terms are wrong as a matter of law, and should be vacated. This Court should adopt The Medicines Company's proposed constructions, which are consistent with the language of the claims and the intrinsic evidence as a whole. This Court reviews claim construction *de novo* and need not give deference to the Delaware district court's erroneous constructions. *Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1451 (Fed. Cir. 1998) (en banc). Moreover, no deference should be due to the Delaware district court's legally-incorrect constructions. Instead, this Court should look to the constructions adopted in the related New Jersey action[4] (A5622), which comport with this Court's precedent and are the same as or consistent with the constructions offered by The Medicines Company. "In the interest of uniformity

[4] The related New Jersey action's court also considered claim constructions for the patents-in-suit that were applied in another related action by the Northern District of Illinois. (A5613 (citing *The Medicines Company v. Mylan Inc.*, No. 11-1285, 2012 U.S. Dist. LEXIS 109749 (N.D. Ill. Aug. 6, 2012).) In the related Illinois action, the court did not construe "wherein the batches have a pH adjusted by a base," and adopted a different construction of "efficiently mixing."

and correctness, this court consults the claim analysis of different district courts on the identical terms in the context of the same patent." *Arlington Indus.*, 632 F.3d at 1253 (quotation omitted).

Based on correct constructions of these terms and the record before the district court, this Court should reverse the district court's noninfringement decision. Using The Medicines Company's proposed constructions and the district court's factual findings, Hospira's ANDA products meet every limitation recited in the asserted claims of both patents. Thus, this Court should decide as a matter of law that Hospira's bivalirudin drug products infringe. In the alternative, if factual issues remain, the district court's noninfringement finding should be vacated and the case remanded for further consideration using this Court's claim constructions.

Furthermore, even if the district court's constructions were affirmed, Hospira infringes the asserted claims. The district court's decision expressly relied on Example 5's embodiment when it incorporated part of Example 5's "efficient mixing" embodiment into the claims of both patents. But the district court failed to appreciate that Hospira's mixing process fits within the context of Example 5's embodiment and uses "efficient mixing." Thus, the district court's noninfringement decision using its constructions was clearly erroneous and should be reversed or, if factual questions preclude reversal, vacated and remanded.

ARGUMENT

I. Standard of Review

A court's determination "of patent infringement requires a two-step process: first, the court determines the meaning of the disputed claim terms, then the accused device is compared to the claims as construed to determine infringement." *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 804 (Fed. Cir. 2007).

Construing a patent's claims is a question of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977–78 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370, 388–90 (1996). "This court reviews claim constructions without deference." *Digital-Vending Servs.*, 672 F.3d at 1275 (citing *Cybor*, 138 F.3d at 1451).

Claim construction begins with the language of the claims themselves. *Phillips*, 415 F.3d at 1312 ("It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude."). Further, it is important to "construe claim terms in light of the surrounding claim language, such that words in a claim are not rendered superfluous." *Digital-Vending Servs.*, 672 F.3d at 1275. Claims are to be interpreted "with an eye toward giving effect to all terms in the claim" and "to construe claim terms in light of the surrounding claim language, such that words in a claim are not rendered superfluous." *Id.*

"A novel product that meets the criteria of patentability is not limited to the process by which it was made." *Vanguard Prods.*, 234 F.3d at 1372. "The method of manufacture, even when cited as advantageous, does not of itself convert product claims into claims limited to a particular process." *Id.*

In an infringement analysis, after "determin[ing] the correct claim scope, [the court] compare[s] the properly construed claim to the accused device to determine whether all of the claim limitations are present either literally or by a substantial equivalent." *Renishaw*, 158 F.3d at 1247–48. Infringement may be proven 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).

"What a generic applicant asks for and receives approval to market, if within the scope of a valid claim, is an infringement." *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1279 (Fed. Cir. 2013). Infringement is "proven by a preponderance of the evidence, which simply requires proving that infringement was more likely than not to have occurred." *Warner-Lambert Co. v. Teva Pharm. USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005). Infringement is reviewed for clear error after a bench trial. *Renishaw*, 158 F.3d at 1248.

II. The Delaware District Court's Claim Constructions Do Not Comport with the Claims, the Specifications, and Controlling Federal Circuit Precedent

The Delaware district court improperly construed two claim terms: "wherein the batches have a pH adjusted by a base" and "efficiently mixing." For each term, the district court imported limitations into the claims that are inconsistent with the intrinsic evidence and legally incorrect. In construing "wherein the batches have a pH adjusted by a base," the district court improperly construed the term as a process using "efficient mixing." By doing so, the district court (i) rendered the pre-existing "efficiently mixing" claim term recited in the '343 patent's claims superfluous, and (ii) transformed the '727 patent's product claims into product-by-process claims, which render all of the claims of the '343 patent superfluous. Furthermore, when construing the '343 patent's "efficiently mixing" recitation, the district court committed a "cardinal sin" of claim construction and improperly limited the claims' scope by incorporating limitations from part of one embodiment in the specification. *See Phillips*, 415 F.3d at 1319–20. Under the district court's construction, both the '727 and '343 patents now require that the products be made using a very specific "efficient mixing" process in which "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)."

The Delaware district court's erroneous constructions should be vacated, and this Court should adopt The Medicines Company's constructions. Claim construction is a matter of law, and no deference is due to the district court's erroneous constructions. Even if deference were due, "[i]n the interest of uniformity and correctness" this Court should consider the related New Jersey action's constructions of the same terms. *Arlington Indus.*, 632 F.3d at 1253. Tellingly, the related New Jersey action's constructions are consistent with those proposed by The Medicines Company.

A. The Delaware District Court's Construction of the "wherein" Claim Term Improperly Added "efficient mixing" and Converted It into a Process Term

The claim term "wherein the batches have a pH adjusted by a base" should be construed to have its plain and ordinary meaning. (A39.) "Words of a claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1370 (Fed. Cir. 2008) (quotation omitted). In the alternative, this term should be construed to mean: "during compounding, the pH of the batches is adjusted using a base."[5] (A39.)

[5] The related New Jersey action adopted this construction. (A5622.)

The "wherein" term is used in both the '343 and '727 patents.

'343 Product-by-Process Patent Claim 1 (A76 (emphasis added))	**'727 Product Patent Claim 1 (A60 (emphasis added))**
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, said batches prepared by a compounding process comprising: . . . (ii) ***efficiently mixing*** a pH-adjusting solution with the first solution to form a second solution, . . . ; and . . . ***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.	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-bivalirudin that does not exceed about 0.6% as measured by HPLC.

The district court construed the "wherein" term to mean "wherein said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under ***efficient mixing*** conditions." (A39 (emphasis added).) The district court's construction injected the "efficiently mixing" limitation of step (ii) of the '343 patent into the term, and thus into both the '343 and '727 patents.

The district court's construction conflicts with the intrinsic evidence and should be vacated. As this Court explained, "[i]n determining the meaning of a disputed claim limitation, we look primarily to the intrinsic evidence of record, examining the claim language, the written description, and the prosecution history." *Innogenetics*, 512 F.3d at 1370. The district court's construction of the "wherein" term violates this principle. First, the '343 patent's product-by-process claims already include the "efficiently mixing" claim term, and the district court's erroneous construction renders it superfluous. Second, the construction improperly rewrites the '727 patent's product claims into product-by-process claims by injecting "efficient mixing" into its claims, which renders all of the '343 patent's claims superfluous. The district court's construction reflects a fundamental misunderstanding of the term.

1. The Construction Cannot Include "efficient mixing" Because It Renders a Pre-Existing "efficient mixing" Claim Term in the '343 Patent Superfluous

The '343 patent's claim 1 recites, *inter alia*, pharmaceutical batches comprising bivalirudin and a pharmaceutically acceptable carrier, "said batches prepared by a compounding process comprising: . . . (ii) ***efficiently mixing*** a pH-adjusting solution with the first solution [base] to form a second solution [bivalirudin solution]." (A76.) The district court's construction of the "wherein" term unnecessarily repeats the express "efficiently mixing" claim term: "wherein

said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under ***efficient mixing*** conditions." (A39 (emphasis added).) As illustrated in the table *supra* at 11, this makes the '343 patent's "efficient mixing" claim term superfluous. The district court's "wherein" construction improperly replicates the "efficiently mixing" recitation of the '343 patent, which violates the requirement that courts are "to construe claim terms in light of the surrounding language, such that words in a claim are not rendered superfluous." *Digital-Vending Servs.*, 672 F.3d at 1275. Accordingly, the district court's construction cannot stand because it "is [] contrary to the well-established rule that claims are interpreted with an eye toward giving effect to ***all*** terms in the claim." *Id.* (emphasis added, quotation omitted).

2. The Delaware District Court's Construction Erroneously Rewrites the '727 Patent's Product Claims to Be Product-by-Process Claims Like the '343 Patent, and Thus Makes All of the '343 Patent's Claims Superfluous

The Delaware district court's construction of "wherein the batches have a pH adjusted by a base" should also be rejected because it transforms the '727 patent's product claims into product-by-process claims by improperly incorporating the "efficiently mixing" claim term. "Courts must generally take care to avoid reading process limitations into [a product] claim . . . because the ***process*** by which a product is made is ***irrelevant*** to the question of whether that

product infringes a pure [product] claim." *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1344 (Fed. Cir. 2008) (emphasis added, citation omitted).

The Delaware district court's construction must fail because it does not accord with the words chosen for the '727 patent's claims, which were expressly written as product claims. As the related New Jersey action's claim construction opinion recognized, to include an "efficient mixing" process limitation in the '727 patent "would improperly rewrite the composition claims of the '727 patent as product-by-process claims." (A5619.) "Courts do not rewrite claims; instead, [they] give effect to the terms chosen by the patentee." *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1364 (Fed. Cir. 1999). "[T]he patentee's lexicography must govern the claim construction analysis." *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1356 (Fed. Cir. 2014).

Furthermore, reading "efficient mixing" into the '727 patent's claims improperly eliminates the distinction between the '727 and '343 patents, because the '343 patent's claims already included the "efficient mixing" claim term. *Arlington Indus.*, 632 F.3d at 1254–55. "Unlike the asserted claims of the ['343] patent," the '727 patent's claims "[are] pure [product] claim[s] and ha[ve] no process limitations" and "[t]hus [are] not limited to any process or method of making the claimed [pharmaceutical batch(es)]." *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 873 (Fed. Cir. 2010). The patentees knew how to

claim "efficiently mixing," as they did in the '343 product-by-process patent, but they expressly omitted this process limitation from the '727 patent's product claims, and there is no basis to now insert this limitation. *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1333 (Fed. Cir. 2010). "[T]he resulting claim interpretation must, in the end, accord with the words chosen by the patentee to stake out the boundary of the claimed property." *Renishaw*, 158 F.3d at 1248.

The district court erroneously discounted the patentees' claim language in the '727 patent based on the mistaken reasoning that: "although the claim does not explicitly refer to the process step, the patent defines itself as a product-by-process claim [because] the specification makes clear that this process is characterized by 'efficiently mixing.'" (A40 (citing A51–52, col.8 ll.54–55, col.9 ll.3–17).) But the specification describes the process for making pharmaceutical batches separately from the pharmaceutical batches themselves. (A50, col.6 ll.54–55; A54–55, col.14 l.10–col.15 l.20.) Notably, the district court's reasoning cited the part of the specification that described a "***Process*** for Preparing a Pharmaceutical Batch(es)." (A50, col.6 ll.54–55 (emphasis added).) In contrast, a different and distinct part of the specification describes "Pharmaceutical Batch(es)." (A54–55, col.14 l.10–col.15 l.20.) There, like claim 1 of the '727 patent, the specification describes that "***pharmaceutical batch(es)*** . . . may be characterized by a maximum impurity level

of Asp[9]-bivalirudin . . . not exceeding about 0.6% . . . ." (A54, col.14 ll.43–47 (emphasis added).)

Thus, the specification describes a pharmaceutical batch as a product in terms of its properties, independently of a specific process by which it could be made. That another embodiment of the invention (i.e., product-by-process) is described in the specification is not a proper reason to rewrite and convert product claims into product-by-process claims by importing process limitations into them. "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw*, 158 F.3d at 1250.

The district court's construction of "wherein the batches have a pH adjusted by a base" improperly mandates using a specific "efficient mixing" process to make the product: (i) "wherein said compounding process ***requires*** that a pH-adjusting solution containing a base is added to a bivalirudin solution under ***efficient mixing*** conditions," and (ii), as described *infra*, the district court's construction of "efficient mixing" further limits the term to only part of one example in the specification. (A39 (emphasis added), A42.)

The district court erred by importing "efficiently mixing" from the specification into the '727 patent's claims. "While we construe the claims in light of the specification, limitations discussed in the specification may not be read into

the claims." *3M Innovative Props. Co. v. Tredegar Corp.*, 725 F.3d 1315, 1321 (Fed. Cir. 2013). The difference between reading the claim in light of the specification and importing a limitation turns on whether the patent specification expresses the "clear intention to limit the claim scope." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004). Here, the specification evidences no intent (let alone a clear intent) to limit the '727 patent's product claims to only "batch(es)" made using a specific "efficient mixing" process, as it describes that the "pharmaceutical batch(es) . . . ***may*** be generated by the compounding processes described above" and "[t]hus, the batch(es) ***may*** be prepared by a compounding process comprising . . . efficiently mixing." (A55, col.15 ll.12–20 (emphasis added).)

When describing "pharmaceutical batch(es)" "[t]he specification never asserts that [a specific "efficient mixing" process] is ***required*** to obtain [pharmaceutical batch(es)]". *Sanofi-Aventis U.S. LLC v. Sandoz, Inc.*, 345 F. App'x 594, 598 (Fed. Cir. 2009) (emphasis in original). It instead describes "pharmaceutical batch(es)" based on its properties (the maximum impurity level of Asp^9-bivalirudin (A54, col.14 ll.43–47)), and generally describes "efficiently mixing" as the process "by which the claimed [batches] may be prepared." *Id.* (quotation omitted). "Where a specification does not ***require*** a limitation, that

limitation should not be read from the specification into the claims." *Renishaw*, 158 F.3d at 1249 (quotation omitted, emphasis in original).

The district court's reasoning that such a limitation is nonetheless justified incorrectly assumes that the '727 patent's claim 1 "is not a pure product claim" because it includes the recitations "wherein the batches have a pH adjusted by a base" and "pharmaceutical batches." (A40–41.) But neither term is a process limitation. The district court's construction reflects a fundamental misunderstanding of what "wherein the batches have a pH adjusted by a base" means in the context of the claims as a whole. As recognized in the related New Jersey action, it is not a process recitation and should not be used as a basis for converting the '727 patent's product claims into product-by-process claims. (A5619.) The term merely describes a property of the claimed batches, i.e., that they have a base-adjusted pH, and clarifies that the claimed batches are compounded drug products, not the active pharmaceutical ingredient alone. In other words, the term specifies that the claimed pH and Asp^9-bivalirudin levels are those in the drug product. (A3924; A48, col.2 ll.8–19.)

Further, the district court's reasoning concerning "pharmaceutical batches" is faulty. The district court based its conclusion that "the compounding process element is intrinsic to the claim itself" on its construction of "pharmaceutical batches" to mean, *inter alia*, "batches prepared by a same compounding process."

(A36, A40–41.) The fact that a pharmaceutical batch is prepared using a process, however, does not convert a product claim into a product-by-process claim, "because the process by which a product is made is irrelevant." *Baldwin Graphic Sys.*, 512 F.3d at 1344.

The district court also attempted to justify its construction based on the unsupported statement that "[t]he only novel aspect of both the '727 and '343 Patents is the special compounding process aimed at reliably reducing the amount of Asp^9 in 'pharmaceutical batches.'" (A39.) The district court was wrong to use the novelty of the compounding process as a reason to conflate the '343 and '727 patents (A41), because each patent claims different novel inventions. For the '727 patent, the PTO allowed the product claims after determining that the claimed pharmaceutical "batches [that] have a maximum impurity level of Asp^9-bivalirudin that does not exceed 0.6% . . . is both novel and free of the prior art." (A4124.)

Furthermore, "[a]bsent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language." *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004). There was no such disavowal or contrary definition that could justify limiting the '727 patent's claims to "pharmaceutical batch(es)" produced by a specific "efficient mixing" process. While the specification states that "the batch(es) may be prepared by a compounding process comprising . . .

efficiently mixing" (A55, col.15 ll.14–19), as a matter of law "[t]he method of manufacture, even when cited as advantageous, does not of itself convert product claims into claims limited to a particular process." *Vanguard Prods.*, 234 F.3d at 1372. Moreover, during prosecution the patentees consistently distinguished the '727 patent's claimed product from the prior art by demonstrating that the prior art does not teach or suggest "a pharmaceutical batch of bivalirudin . . . , wherein the batches have [] a maximum impurity level of Asp^{9}-bivalirudin that does not exceed about 0.6% as measured by HPLC." (A3927; *see also* A3928–44.) Thus, the district court's requirement that a specific "efficient mixing" process be used to prepare the claimed product is erroneous. The '727 patent's "specification and prosecution history focus on the property of the [claimed 'pharmaceutical batch(es)'] and not the process used to obtain that property." *Sanofi-Aventis*, 345 F. App'x at 598.

3. The Intrinsic Record Compels Construing "wherein the batches have a pH adjusted by a base" as Having Its Plain and Ordinary Meaning

The Delaware district court's construction of "wherein the batches have a pH adjusted by a base" should be vacated. An ordinarily skilled artisan viewing the claim in light of the intrinsic record would recognize that the plain and ordinary meaning of the term is that the batches have a base-adjusted pH. *See Phillips*, 415 F.3d at 1312–13. "For this claim term the patentee[s] offer[] an ascertainable

definition in the body of the claim, and [this Court's] cases do not support prescribing a more particularized meaning unless a narrower construction is ***required*** by the specification or prosecution history." *3M Innovative Props.*, 725 F.3d at 1329 (emphasis added). "It is axiomatic that we will not narrow a claim term beyond its plain and ordinary meaning unless there is support for the limitation in the words of the claim, the specification, or the prosecution history." *Id.* at 1333. The district court's construction lacks support for any narrowing. Indeed, the district court's narrow construction is inconsistent with the intrinsic record, including by making the '343 patent's "efficiently mixing" claim term superfluous and transforming the '727 patent's product claim into a product-by-process claim. Thus, "wherein the batches have a pH adjusted by a base" should be given its plain and ordinary meaning. (A39.)

In the alternative, the term may be construed as "during compounding, the pH of the batches is adjusted using a base."[6] (A39.) As with the plain and ordinary meaning, the alternative construction informs a person of ordinary skill in the art that the pH of the batches had been adjusted with a base during compounding of the bivalirudin. Either way, "wherein the batches have a pH adjusted by a base" provides context to the claim as a whole, because it describes a property of the claimed batches, i.e., that they have a base-adjusted pH.

[6] This is the construction adopted in the related New Jersey action. (A5622.)

B. "efficiently mixing" Should Be Construed as "mixing that is characterized by minimizing levels of Asp[9]-bivalirudin in the compounding solution"

"Efficiently mixing" is a process step that is recited in the '343 patent's claimed process for making pharmaceutical batches of a bivalirudin drug product. *See supra* at 11. The specification defines "efficiently mixing" as: "[e]fficient mixing is ***characterized*** by minimizing levels of Asp[9]-bivalirudin in the compounding solution." (A67, col.9 ll.34–35 (emphasis added).) "The ***characterizations*** of ['efficiently mixing'] in the specification [] are distinctly definitional . . . [and] set forth what the patentee regarded as the meaning of the term [] as used in the claims." *S. Mills*, 377 F. App'x at 6 (emphasis added). The specification "acts as a dictionary when it expressly defines terms used in the claims or when it defines them by implication." *Phillips*, 415 F.3d at 1321. Thus, "efficiently mixing" should be construed as "mixing that is characterized by minimizing levels of Asp[9]-bivalirudin in the compounding solution." (A41.)

A person of ordinary skill in the art would come to the same conclusion because the specification states that "[e]fficient mixing of the pH-adjusting solution with the bivalirudin solution will minimize levels of Asp[9]-bivalirudin in the compounding solution," and discloses various methods to accomplish it. (A66, col.8 ll.56–58; A67–68, col.9 l.34–col.11 l.24.) The specification unwaveringly describes "efficiently mixing" as a process for minimizing Asp[9]-bivalirudin levels,

and "[t]he definition of a claim term can be affected through repeated and definitive remarks." *Sunovion Pharm*, 731 F.3d at 1278. "[A] person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Phillips*, 415 F.3d at 1313.

The district court erroneously construed this claim term by importing limitations from the specification into its construction, namely only part of Example 5's embodiment. Thus, the district court construed "efficiently mixing" to mean: "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)." (A42, 44.)

As a preliminary matter, neither the claims nor the specification require using high shear mixing conditions with a minimum mixer speed. (A67, col.10 ll.42–58; A76, claim 1.) Indeed, during trial the district court asked Hospira's expert witness Dr. Johnson about this subject, and Dr. Johnson admitted that high shear mixing is not defined by mixing speed:

> THE COURT: Does a person of ordinary skill in the art and talking about high shear mixing have a sort of minimum rpm that makes something high shear?
>
> [Nonresponsive answer]
>
> THE COURT: But you're not answering if there's a general understanding in the art of pharmaceutical

> manufacturing that high shear mixing means above some number of rpms.
>
> THE WITNESS: Outside this patent, that's not usually how it's technically defined. . . .

(A16793–94, 811:11–812:8.) Discussing the same subject, The Medicines Company's expert Dr. Klibanov unequivocally testified that:

> [I]f the Court had asked me that question, I would have said that there's no such number, Your Honor, because it very much depends on what the volume, what the batch volume, is, what the mixer is, what the liquid is, and a lot of other variables, so there is no such fixed number.

(A16902, 920:1–14.)

Furthermore, the district court arrived at its erroneous construction after reasoning that "Example 5 describes the 'efficient mixing' process" because "[it] is entitled, 'Effects of Adding a pH Adjusting Solution at a Constant Rate and Under Efficient Mixing Conditions—Large Scale Study,'" and noted that the specification states that "'the process demonstrated in Example 5 produced batches generally and consistently having lower levels of impurities than the process of Example 4.'" (A44 (citing A58–59, col.22 ll.32–34, col. 23 ll.24–26).)

The district court committed a "cardinal sin" of claim construction and limited "efficiently mixing" to only part of the embodiment disclosed in Example 5 that, among other parameters, used a particular method of adding pH-adjusting solution (slowly and in a controlled manner) and type of mixing conditions (high shear mixing) utilizing a particular mixer speed range (above 1000 rpms). *See*

Phillips, 415 F.3d at 1319–20. This violated this Court's admonition that "although the specification often describes very specific embodiments of the invention, [this Court has] repeatedly warned against confining the claims to those embodiments." *Id.* at 1323 (citations omitted). Even worse, the district court imported only part of Example 5's parameters, and divorced its "efficiently mixing" construction from the full context of the embodiment, as shown below.

Parameters in Example 5's Embodiment (A74)	**The District Court's Construction of "efficiently mixing" (A42)**
110 L (liters) of bivalirudin solution plus 40 L of pH-adjusting solution (equals 150 L total) "the pH-adjusting solution was added to the bivalirudin solution at a controlled rate of 2 L/min" "a homogenizer was used to provide a high shear mixing environment (between about 1000 rpm and 1300 rpm)" "the pH-adjusting solution was added to the bivalirudin solution at a site adjacent to the blades of the homogenizer" "[s]imultaneously, a paddle mixer was used for mixing (mixing rate of between about 300 rpm and 700 rpm) near the surface of the bivalirudin solution"	"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)"

For instance, the district court's construction does not take into account the scale of Example 5, which was a "Large Scale Study" with a batch size of 150 liters (110

liters of bivalirudin solution and 40 liters of pH-adjusting solution). (A74, col.23 ll.16–20.) Further, the district court did not consider the site of base addition, as Example 5's embodiment of "efficiently mixing" added the pH adjusting solution "to an inlet in the homogenizer, so that the pH adjusting solution was added to the bivalirudin solution at a site adjacent to the blades of the homogenizer." (A74, col.23 ll.26–29.) Additionally, the district court's construction overlooked the fact that Example 5's embodiment used a second mixer along with a rate and site of mixing: "Simultaneously, a paddle mixer was used for mixing (mixing rate of between about 300 rpm and 700 rpm) near the surface of the bivalirudin solution." (A74, col.23 ll.29–31.) Thus, the district court's claim construction improperly narrows the claim scope to encompass only a part of a single example in the specification divorced from its context.

Moreover, the specification warns skilled artisans away from the very same construction adopted by the district court. The specification unequivocally makes clear that its examples are "***non-limiting*** examples, which further illustrate the invention, and are not intended, nor should they be interpreted to, limit the scope of the invention." (A70, col.16 ll.8–11 (emphasis added).) "[I]t is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment—into the claims absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited." *Liebel-Flarsheim*,

358 F.3d at 913. The patentees did not intend for the claims to be limited to Example 5, let alone only part of it. Example 5's "embodiment is just that—one way of [efficiently mixing]. That disclosure alone does not clearly and unambiguously disavow other ways of [efficiently mixing] within the scope of the claim language." *Home Diagnostics*, 381 F.3d at 1357.

Nowhere does the specification suggest that Example 5 is the only way to perform "efficiently mixing." To the contrary, the specification provides a fulsome description of "efficiently mixing" with many ways in which an ordinarily skilled artisan may employ it. (*See, e.g.*, A66–68, col.8 l.24–col.11 l.24.) For example, it states:

> ***Efficient mixing is characterized by minimizing levels of Asp[9]-bivalirudin in the compounding solution***. This may be achieved through various methods. One such method may be to add or combine the pH-adjusting solution and bivalirudin solution portion-wise, i.e., in portions. For instance, the pH-adjusting solution may be added to the bivalirudin solution in portions of set quantities, wherein each addition is separated by a period of time. The quantity of pH-adjusting solution may be approximately equal or may vary among the portions. . . .
>
> The pH-adjusting solution may also be added in portions such that there is a combination of equal and unequal quantities. . . .
>
> The period of time between the addition of each portion may vary. . . .
>
> ***The pH-adjusting solution may also be added to the bivalirudin solution portion-wise, wherein each portion is added at a constant or variable rate***. The portions

> may be added in equal amounts, unequal amounts, or a combination thereof. Further, each portion may be added at the same or different constant rates, or the same or different variable rates, or a combination thereof. . . .
>
> Furthermore, ***efficient mixing may be achieved through the use of one or more mixing devices***. Examples of mixing devices that may be used in various embodiments of the present invention may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. ***The mixing rate of, for instance, a paddle mixer may be between about 100 rpm and 1000 rpm***, or between about 400 rpm and about 800 rpm. The mixing rate for, as an example, a homogenizer (i.e., high shear mixing) may be between about 300 and about 6000 rpm, or between about 1500 rpm and about 3000 rpm.

(A67, col.9 l.34–col.10 l.52 (emphasis added).)

In other words, as the related New Jersey action recognized, "[t]he specification clearly states that 'efficient mixing' can be achieved by a variety of methods, including through the use of different mixing devices, by mixing at different speeds and temperatures, and by adding the two solutions together rapidly all at once, or in portions, or at a constant rate." (A5615.) Regardless of the particular method used, the inventors discovered that "[e]fficient mixing of the pH-adjusting solution with the bivalirudin solution will minimize levels of Asp^{9}-bivalirudin in the compounding solution." (A67, col.8 ll.56–58.) "Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and

intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw*, 158 F.3d at 1250 (internal citation omitted).

The district court's construction, however, did not align itself with the patent's description of the invention. It erroneously eviscerates all of the other "various methods" in which "efficiently mixing" may be achieved (A67, col.9 ll.34–36) by limiting the claim to only part of Example 5's particular embodiment. For example, the district court's construction requires that "a pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner" (A42), but the specification also describes adding "the bivalirudin solution portion-wise, wherein each portion is added at a constant or variable rate." (A67, col.10 ll.30–32.)

Additionally, the district court's construction improperly limited "efficiently mixing" to "high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)." (A42.) The district court's requirement that only high shear mixing conditions be used disregards the specification's teaching that high shear mixing conditions are merely one acceptable means of mixing—low shear mixing conditions, for example, are also an acceptable alternative. (A67, col.10 ll.42–58.) Indeed, "it was initially thought that bivalirudin could only be formulated using a compounding process employing low shear" mixing. (*Id.*)

Moreover, there was no disclaimer that would justify limiting "efficient mixing" to only "mixer speeds above 1000 rpms." "[This Court's] cases emphasize that an alternative means of accomplishing the claimed result weighs against a claim construction that would exclude that alternative." *3M Innovative Props.*, 725 F.3d at 1331. Contrary to the district court's "mixer speeds above 1000 rpms" construction, the specification taught other speed ranges. For instance, the specification describes "efficient mixing" in which "[t]he mixing rate of [] a paddle mixer may be between about 100 rpm and 1000 rpm." (A67, col.10 ll.42–49.) And the mixing speed of "a homogenizer (i.e., high shear mixing) may be between about 300 and about 6000 rpm." (A67, col.10 ll.49–52.)

Unlike the district court's construction, the specification also allows for the use of more than one mixing device and type of mixing device, different mixing rates, or a combination thereof. (A67–68, col.10 l.63–col.11 l.3.) Moreover, the specification explains that the mixing devices may be used at the same or different times, or a combination thereof. (A68, col.11 ll.3–9.)

Further, "efficient mixing" may also be achieved through adding the pH-adjusting solution to specific sites within the bivalirudin solution, and with or without a mixing device. (A68, col.11 ll.10–24.) "In cases wherein a mixing device is used, the pH-adjusting solution may be added to the site of the mixing

device, e.g., at the site of the paddles of the paddle mixer or the blades of the homogenizer." (A68, col.11 ll.14–17.)

Thus, the district court's construction of "efficiently mixing" improperly limited the claims in ways that are contrary to the clear disclosures of the specification. The district court's construction should be vacated because "[w]here a specification does not ***require*** a limitation, that limitation should not be read from the specification into the claims." *Renishaw*, 158 F.3d at 1249 (emphasis in original, quotation omitted).

The district court's incorrect construction sought to keep "the processes used in Example 4 [] outside the scope of 'efficient mixing.'" (A44–45.) Example 4's process resulted in "batches [that] displayed a maximum level of Asp^9-bivalirudin of 3.6%, while the mean level of Asp^9-bivalirudin was 0.5%. Furthermore, the standard deviations relative to the means were larger." (A73–74, col.22 l.66–col.23 l.4.) These results demonstrate that the Asp^9-bivalirudin levels of the batches generated by the Exhibit 4 process are high and variable. (*Id.*) In other words, Example 4's "inefficient mixing conditions" (A73, col.22 ll.25–26) do the opposite of the claimed invention, because the claimed "[e]fficient mixing is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution." (A67, col.9 ll.34–35.)

But the district court's construction went too far by construing "efficiently mixing" so that it encompassed only parts of Example 5's specific embodiment. (A44–45.) In describing Example 5, the patentees did not disclaim all other methods of "efficiently mixing." In the specification, the patentees merely disclosed that Example 4's particular combination of "inefficient mixing conditions" (A73, col.22 l.21–col.23 l.4) fell outside of the claim scope, because Example 4 did not minimize levels of Asp^9-bivalirudin to less than 0.6%. As this Court has explained, when construing claims "[w]e do not read limitations from the specification into claims; we do not redefine words. Only the patentee can do that. To constitute disclaimer, there must be a clear and unmistakable disclaimer." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1366–67 (Fed. Cir. 2012). There was no disclaimer of other methods of mixing here, let alone clear and unmistakable disclaimer. Furthermore, the district court compounded its error by importing these parts of Example 5's embodiment into its construction of the "wherein" term, and thus adding these limitations into the '727 patent's product claims.

Thus, the Delaware district court erred in construing "efficiently mixing." The patentees' definition of "efficiently mixing" is the correct one because the specification makes clear that "[e]fficient mixing is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution." (A67, col.9 ll.34–35.)

The specification describes (as the court in the related New Jersey action recognized (A5615)) that "efficiently mixing" may be achieved by a variety of methods. (A67, col.9 l.34–col.10 l.52.) An ordinarily skilled artisan, viewing claim 1 in the context of the specification, would appreciate that when "efficiently mixing" is used as a part of the compounding process, the levels of Asp^{9}-bivalirudin are minimized in the compounding solution.

The Medicines Company's construction of "efficiently mixing," namely "mixing that is characterized by minimizing levels of Asp^{9}-bivalirudin in the compounding solution," should be adopted because it stays true to the claim language and most naturally aligns with the patent's description of the invention.[7] *Renishaw*, 158 F.3d at 1250.

III. Using Correct Claim Constructions, Hospira's ANDA Products Infringe the Asserted Claims of the '727 and '343 Patents

Hospira's generic products infringe claims 1–3, 7–10, and 17 of the '727 patent, and claims 1–3 and 7–11 of the '343 patent. (A4.) After a bench trial, the district court found that Hospira only contested infringement of three claim limitations in the '343 and '727 patents: "efficient mixing," "pharmaceutical batches," and "a maximum impurity level of Asp^{9}-bivalirudin that does not exceed

[7] In the alternative, the related New Jersey action's construction—"mixing that is characterized by minimizing levels of Asp^{9}-bivalirudin in the compounding solution and that does not use mixing conditions described in Example 4" (A5622)—may be adopted.

about 0.6%." (A6.) The district court further found that "[b]ecause Hospira does not contest the other claim limitations, [] they are met." (A6.)

With regard to the contested limitations, the district court "[found] that Hospira's Exhibit Batch meets the 'pharmaceutical batch' limitation" and "that Hospira infringes the 'maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%' limitation." (A10, A12 (citing *Sunovion Pharm.*, 731 F.3d at 1278).) Thus, "efficient mixing" is the only limitation at issue here.

A. Hospira's ANDA Product Literally Infringes the '727 Patent's Product Claims under a Correct Construction of "wherein the batches have a pH adjusted by a base"

The district court found that "[t]he 'efficient mixing' limitation is present in claim[s] of the '727 patent due to the [c]ourt's construction of ['wherein the batches have a pH adjusted by a base']." (A6 n.4.) As discussed *supra*, the district court's construction of the "wherein" term is erroneous, and a proper construction does not include "efficient mixing." Under a correct construction, this term should be given its plain and ordinary meaning or, in the alternative, the construction that "during compounding, the pH of the batches is adjusted using a base." (A39.)

There is no dispute that Hospira infringes the "wherein the batches have a pH adjusted by a base" limitation in the '727 patent's (and '343 patent's) claims using a correct claim construction. Hospira's proposed ANDA product

unquestionably has a pH adjusted by a base, namely sodium hydroxide. (A13958, A14021.)

Furthermore, the district court already found that every other limitation of the ’727 patent’s claims is met by Hospira’s ANDA product. (A6, A10, A12.) The only reason that the district court incorrectly found that the ’727 patent was not infringed was because of the erroneous addition of “efficient mixing” into the the claims. (*Id.*) Thus, The Medicines Company respectfully requests that the district court’s noninfringement finding as to the ’727 patent be reversed. In the alternative, if this Court finds that further factual analysis is necessary, The Medicines Company respectfully requests that the district court’s noninfringement finding be vacated and remanded for further consideration.

B. Hospira’s ANDA Products Literally Infringe the “efficiently mixing” Claim Term under a Correct Construction

Based on its erroneous construction, the district court found that Hospira’s ANDA product did not infringe the “efficiently mixing” limitation (and consequently both the ’343 and ’727 patents). (A6, A12.) But under a correct construction of “efficiently mixing” that comports with the specification, namely “mixing that is characterized by minimizing levels of Asp^{9}-bivalirudin in the compounding solution” (to levels less than 0.6%) (A66–67, col.8 ll.54–61, col.9 ll.34–35), Hospira literally infringes the “efficiently mixing” claim term.

As the district court found, "[t]he Asp[9]-bivalirudin[] in Hospira's Exhibit Batch was measured four times via HPLC, yielding values of 0.1%, 0.1%, 0.1%, and 0.2%." (A10 & n.5 (noting that Asp[9]-bivalirudin is referred to as "Related Substance 5" (A13835, A13886), and citing A13840, A13891, A14284 [sic PTX 179.10], and A14295).) Furthermore, the district court found that "[t]he Asp9-bivalirudin levels in Hospira's Exhibit batch actually decreased" during compounding. (A11 (citing A9197, A9202, A11376, A11381, A14284, A14295).) Thus, Hospira used "efficient mixing" in compounding its ANDA product, which resulted in minimized Asp[9]-bivalirudin levels in its compounding solution. (*See* A66, col.8 ll.54–61.) Moreover, the district court did not find that Hospira's exhibit batches were produced by the method of Example 4. (*See generally* A12–17.) Accordingly, Hospira literally infringes the "efficiently mixing" limitation under a proper claim construction.

The district court's noninfringement finding is clearly erroneous under a proper construction of "efficiently mixing." Based on the record established by the district court, Hospira literally infringes the '343 patent and, for the reasons given *supra*, the '727 patent. Accordingly, The Medicines Company respectfully requests that the district court's noninfringement finding be reversed. In the alternative, The Medicines Company respectfully requests that the district court's noninfringement finding be vacated and remanded for further consideration.

IV. If This Court Were to Use the Delaware District Court's "efficient mixing" Claim Construction, the District Court's Noninfringement Judgment Should Be Reversed, or Vacated and Remanded

Under the district court's construction of "efficient mixing," Hospira infringes the patents-in-suit. Notably, the district court's "efficient mixing" construction was expressly based on part of Example 5. (A44.) Hospira's method of making pharmaceutical batches employs "efficient mixing," and falls within the context of Example 5's embodiment. Despite this, the district court decided that Hospira did not infringe either the '727 product patent or the '343 product-by-process patent because it limited "efficiently mixing" to only part of Example 5's embodiment without regard to context.

Specifically, the district court incorrectly found that Hospira did not meet either of the following terms in the district court's "efficiently mixing" construction: (A) "[a] pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner," and (B) is "mixed together by a process comprising high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)." (A12.) In doing so, the district court noted that "[r]ather than the specification, the [c]ourt 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." (A13–14.) But the district court's analysis of Example 5 erroneously considered part of Example 5's embodiment divorced from its context.

The district court's noninfringement decision is clearly erroneous because Hospira's ANDA product fits within the context of Example 5's embodiment. Hospira infringes the asserted claims either literally or under the doctrine of equivalents. The district court's noninfringement holding should be reversed. In the alternative, should this Court determine that factual questions prevent reversal, the decision should be vacated and remanded.

A. Hospira's "pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner"

The Delaware district court found that Hospira did not meet this portion of its claim construction while noting that:

> When making the Exhibit Batch, Hospira added the pH-adjusting solution in three portions. ([citing A13958, A14021].) The first two portions 'can be added rapidly with about 2-minute mixing time.' ([*Id.*].) The third portion is 'added gradually over a period of approximately 10 minutes.' ([*Id.*].) The batch record states that the third portion is added gradually in order to 'minimize drastic pH shift.' ([*Id.*].)

(A12.) The district court incorrectly found that this "portion-wise addition is not efficient mixing, even if other sections of the patent describe it as such" and that Hospira's method of adding its pH-adjusting solution in three portions, including a third portion that "is added gradually," was not "slowly and in a controlled manner." (A14.)

The district court's finding is clearly erroneous. As the district court noted (A13), the patent teaches that "efficient mixing" may be performed by adding the bivalirudin solution portion-wise, wherein each portion is added at a constant or variable rate. (A52, col.9 l.34–col.10 l.41.) But the district court erroneously disregarded such teachings and "[found] that portion-wise addition is not efficient mixing," because "[i]n Example 4, the additions were made in portions." (A14.) In doing so, the district court overlooked the fact that Example 4's "pH-adjusting solution was added to the bivalirudin solution either all at once, or ***rapidly*** in multiple portions." (A73, col.22 ll.37–38 (emphasis added).) Thus, ***no*** portion of Example 4's pH-adjusting solution was mixed slowly and in a controlled manner.

In contrast, The Medicines Company's expert Dr. Klibanov explained that Hospira adds its pH-adjusting solution (sodium hydroxide) to the bivalirudin solution slowly and in a controlled manner. (A16296–97, 316:20–317:21; A16319–20, 338:20–339:8; A13958; A14021.) Hospira's batch records instruct that the third and last portion of pH-adjusting solution is "added gradually over a period of approximately 10 minutes." (A12; A13958; A14021; A16319–20, 338:20–339:8.) The third portion is the "critical" step in Hospira's process because that portion brings about a significant pH change. (A16320–21, 339:9–340:20.) At that point, the pH has already been raised by the earlier portions, and a higher pH is more likely to result in the formation of Asp^{9}-bivalirudin impurity.

(A16321, 340:4–7.) Indeed, Hospira's batch records explain that "last portion [is] added gradually to minimize drastic pH shift." (A13958; A14021; A16319–20, 338:20–339:8.) Thus, Hospira's adds its pH-adjusting solution to a bivalirudin solution "slowly and in a controlled manner." (A16320–21, 339:9–340:20.) Accordingly, Hospira infringes this part of the district court's "efficiently mixing" construction.

B. Hospira's Batch Is "mixed together by a process comprising high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)"

The Delaware district court erroneously found that this portion of the claim construction was not infringed because "Hospira's Exhibit batch was mixed at 560 rpm using a convective mixer, *i.e.*, a paddle mixer." (A14 (citing A13958, A14021; A16430, 449:18–19; A16600–01, 619:18–620:1; A16613, 632:20–23).) Based on this, the district court found that "Hospira did not use mixing speeds above 1000 rpm" and "does not use a high shear mixer, but a convective or paddle mixer." (A14, A15.)

As an initial matter, the district court's construction requires "high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)," that is to say 1000 rpms but not a particular type of mixer. (A42.) Moreover, the specification describes "efficient mixing" using a paddle mixer, and that "[t]he mixing rate of [] a paddle mixer may be between about 100 rpm and 1000 rpm, or between about 400 rpm and about 800 rpm." (A67, col.10 ll.42–49.) Nowhere does the specification

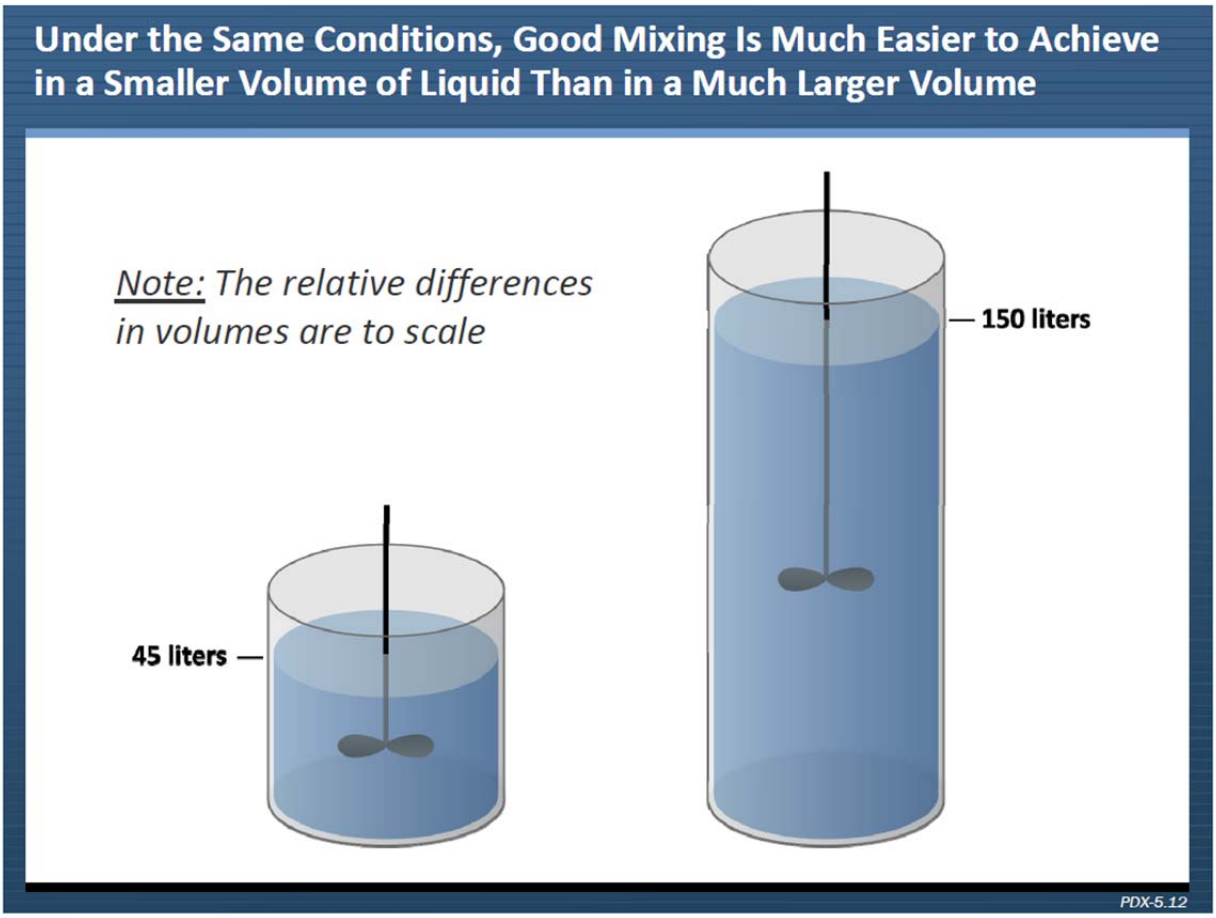
require high speed mixing conditions, mixer speeds above 1000 rpms, or a particular kind of mixer. (A67, col.10 ll.42–58.)

Indeed, the distinction between "low shear" and "high shear mixing conditions" is not based on "some number of rpms"—as Hospira's expert Dr. Johnson admitted when questioned by the district court (see also *supra*)—because "that's not usually how it's technically defined necessarily." (A16793–94, 811:4–812:8.) As Dr. Klibanov explained, there are "a lot of other variables, so there is no such fixed number." (A16902, 920:8–14.) Accordingly, in Hospira's small batch, "high shear mixing conditions" should be viewed in terms of the result of the mixing with respect to a certain batch size, and not in terms of an absolute speed in rpms. Hospira's paddle mixer in a small batch does comprise "high shear mixing conditions." (A16387, 406:10–16; A16902, 920:1–14.)

Regardless, a correct infringement analysis under the district court's construction should take into account the context of Example 5's embodiment (i.e., scale), because the district court's construction was expressly based on "Example 5, which was described as efficient mixing." (A13–14.) Using the district court's construction, the volume of Hospira's exhibit batch must be considered in relation to the scale of Example 5. (A16298–99, 318:15–319:2.) Example 5 was based on a batch size of 150 liters (approximately 110 liters of bivalirudin solution plus approximately 40 liters of pH-adjusting solution). (A74, col.23 ll.16–20; A16299,

319:9–16.) In contrast, Hospira's exhibit batch is 45 liters. (A13955; A14018; A16299, 319:19–22.)

Thus, as shown below, there is a more than three-fold difference in the volumes of the batches, which is a significant change when mixing. (A16311–12, 330:12–331:8; A16314–15, 333:21–334:3.)



(A15859 (citing A16314–17, 333:22–336:14).)

All else being the same, "efficient mixing" is easier to achieve in a smaller volume of liquid than in a much larger volume. (A16212, 232:5–17; A16315–17, 334:4–336:14.) Mixing in a tank having a larger volume of liquid is more difficult

to achieve because areas close to the surface and the bottom of the tank will not be engaged in the same mixing, and thus the mixing will not be as good. (A16315–16, 334:19–335:9.) Hospira and its expert Dr. Johnson agreed that a way to improve the mixing would be to increase the rate of mixing. (A16029–30, 49:23–50:8; A16224–25, 244:16–245:1; A16316–17, 335:9–336:2; A16749–50, 767:12–768:13; A16751–52, 769:8–770:6.) To scale up Hospira's mixing speed of 560 rpm for its 45-liter batch, the equivalent mixing speed in a 150-liter batch would be 1248 rpms.[8] (A16211, 231:6–19; A16215–24, 235:5–244:15; A16298–99, 318:2–319:22; A16310–18, 329:14–337:3.)

Viewed in light of the relative batch size, Hospira infringes the "mixed together by a process comprising high shear mixing conditions (i.e., mixer speeds above 1000 rpms)" part of the district court's "efficiently mixing" claim construction.

C. Qualitative Evidence Further Demonstrates That Hospira Uses "efficient mixing"

The Delaware district court's decision shows that Hospira's method of producing its ANDA product demonstrates that Hospira uses "efficient mixing" when compounding pharmaceutical batches. The district court stated:

[8] Notably, the master production batch records in Hospira's ANDAs indicate that Hospira's commercial batch sizes will be 150 or 220 liters. (A9374; A12459; A10847; A12825; A16214–15, 234:18–235:3; A16313–14, 332:1–333:8.)

> 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." ([A52] 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." ([A52] at 9:10–14.)

(A18.) The Medicines Company does not agree that the "real function" of "efficient mixing" is minimizing precipitate, because it is not the precipitate itself that causes the formation of the Asp^9-impurity. (A16913, 931:8–10.) Furthermore, as described *supra*, the district court wrongly concluded that slow addition and high shear mixing were, per se, the combination that is required to achieve such results. (A18.) But the fact of the matter is that Hospira's method of mixing does not form a dense precipitate (A13958; A14021), which further demonstrates that Hospira uses "efficient mixing" in its process of making batches of bivalirudin. As the inventors explained, such a dense precipitate has a marshmallow- or taffy-like consistency. (A8681.) In contrast to the dense precipitate caused by inefficient mixing, Hospira's process employs "efficient mixing" and, thus, in its process only an amorphous "white cloudy precipitate will

form with the addition of the Sodium Hydroxide." (A13958; A14021; *see also* A52, col.9 ll.10–17.)

Consequently, in addition to performing its mixing process using a method that falls within the patent's description of "efficiently mixing" and the context of Example 5's embodiment, the fact that Hospira's method does not form a "dense precipitate" demonstrates that Hospira uses "efficient mixing." (A13958; A14021.) Hospira "efficiently mix[es]" its pharmaceutical batches and, thus, infringes.

D. Hospira Infringes the Delaware District Court's Construction of "efficiently mixing" Either Literally or Under the Doctrine of Equivalents

Hospira's proposed ANDA product infringes "efficient mixing" or infringes it by substantial equivalent by performing substantially the same function in substantially the same way with substantially the same result. *See Crown Packaging Tech.*, 559 F.3d at 1312; *Renishaw*, 158 F.3d at 1247–48.

As described *supra*, Hospira literally infringes the Delaware district court's "pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner" part of its "efficiently mixing" construction, at least because Hospira adds the third and critical portion of its pH-adjusting solution "gradually over a period of approximately 10 minutes." (A13958; A14021; A16319–21, 338:20–340:20.) Thus, the function of the "efficiently mixing" claim element is met because

Hospira achieves a desired mixing though the addition of a pH-adjusting solution slowly and in a controlled manner.

The way that the pH-adjusting solution and the bivalirudin solution are mixed is the same or substantially the same as the district court's "mixed together by a process comprising high shear mixing conditions (i.e., mixer speeds above 1000 rpms)" construction. (A42; A16322, 341:15–24.) Hospira's mixing of a 45-liter batch at 560 rpms is the same as or equivalent to mixing a 150-liter batch at 1248 rpms. (A16215–24, 235:5–244:15; A16323–24, 342:1–343:8.)

Furthermore, the result of "efficiently mixing" is reliably minimizing levels of Asp^9-bivalirudin formed in the compounding solution to not exceed about 0.6%. (A16324, 343:9–20.) The levels of Asp^9-bivalirudin in Hospira's exhibit batches were 0.1%, 0.1%, 0.1%, and 0.2%—which were even less than the starting levels in the bivalirudin active ingredient. (A14284 (Related Substance 5); A14295 (same); A16169–72, 189:5–192:11; A16324–26, 343:21–345:24; A16755–57, 773:4–775:18.) Additionally, the precipitate formed by Hospira's mixing demonstrates that Hospira uses "efficient mixing." (A13958; A14021; *see also* A52, col.9 ll.10–17.) Therefore, Hospira achieves substantially the same result as the "efficiently mixing" claim element.

Thus, Hospira literally infringes the "efficiently mixing" claim element or infringes it under the doctrine of equivalents. (A16327, 346:1–9.) The district

court found that Hospira infringed every other element of the asserted claims. (A6, A10, A12.) Accordingly, even if this Court upholds the district court's claim construction, The Medicines Company respectfully requests that the district court's noninfringement finding be reversed. If factual questions preclude reversal, the district court's decision should be vacated and remanded.

CONCLUSION

The Delaware district court's constructions of "wherein the batches have a pH adjusted by a base" and "efficiently mixing" are legally erroneous and should be vacated, because they render an expressly recited claim term and all of the claims of an entire patent superfluous, and commit a "cardinal sin" of claim construction by importing "slowly and in a controlled manner" and "a process comprising high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)" limitations from an example into the claim. "Wherein the batches have a pH adjusted by a base" should be construed to have its plain and ordinary meaning or, in the alternative, "during compounding, the pH of the batches is adjusted using a base." And "efficiently mixing" should be construed to mean "mixing that is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution."

The district court's judgment of noninfringement rested on its erroneous claim constructions. Using correct constructions, this Court should reverse the

district court's noninfringement ruling, and decide as a matter of law that based on the district court's factual determinations Hospira infringes claims 1–3, 7–10, and 17 of the '727 patent, and claims 1–3 and 7–11 of the '343 patent. In the alternative, if this Court decides that factual issues remain to be considered under proper claim constructions, the district court's noninfringement finding should be vacated and remanded.

Finally, even using the district court's constructions, the district court's noninfringement decision was clearly erroneous. Hospira's mixing process is encompassed within the context of Example 5's embodiment, from which the district court expressly based its construction. Under a proper interpretation of the district court's construction, Hospira should be found to infringe either literally or under the doctrine of equivalents. Hospira uses "efficient mixing" when producing its pharmaceutical batches. Even if this Court were to affirm the district court's constructions, the district court's noninfringement finding should be reversed or, in the alternative, vacated and remanded.

Dated: August 13, 2014

Respectfully submitted,

By: /s/ Edgar H. Haug

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ADDENDUM

ADDENDUM

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE MEDICINES COMPANY, Plaintiff, v. HOSPIRA, INC., Defendant.	)	C.A. No. 09-750 (RGA)

~~[PROPOSED]~~ FINAL JUDGMENT

For the reasons stated in the Court's March 31, 2014 Trial Opinion (D.I. 827), IT IS HEREBY ORDERED AND ADJUDGED ON THIS 15th day of April 2014 that:

1. The Medicines Company has standing and is a proper plaintiff in this case.

2. The asserted claims, i.e., claims 1-3, 7-10, and 17 of U.S. Patent No. 7,582,727 ("the '727 patent") and claims 1-3 and 7-11 of U.S. Patent No. 7,598,343 ("the '343 patent"), are not invalid (i) under the on-sale bar of 35 U.S.C. § 102(b), (ii) for obviousness under 35 U.S.C. § 103, or (iii) for failing to comply with the written-description, lack-of-enablement, or definiteness requirements of 35 U.S.C. § 112.

3. Judgment of validity of each asserted claim of the '727 and '343 patents is entered in favor of The Medicines Company and against Hospira, Inc. ("Hospira")

4. Hospira's Abbreviated New Drug Applications (Nos. 90-811 and 90-816) do not infringe the asserted claims of the '727 and '343 patents.

5. Judgment of noninfringement of each asserted claim of the '727 and '343 patents is entered in favor of Hospira and against The Medicines Company.

The Honorable Richard G. Andrews
United States District Judge

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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March 31, 2014
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. <u>The Invention Was Not Sold or Offered for Sale Before the Critical Date</u>

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

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[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,

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[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.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE MEDICINES COMPANY,	:	
	:	
Plaintiff,	:	
	:	
v.	:	C.A. 09-750-RGA
	:	
TEVA PARENTERAL MEDICINES, INC., ET AL.	:	
	:	
Defendants.	:	

CLAIM CONSTRUCTION

Frederick L. Cottrell, III, Esq., Wilmington, Delaware; Porter F. Fleming, Esq. (argued), New York, New York; Attorneys for Plaintiff The Medicines Company.

Richard K. Hermann, Esq., Wilmington, Delaware; William F. Long, Esq. (argued), Atlanta, Georgia; Attorneys for Defendants.

July 11, 2013
Wilmington, Delaware

ANDREWS, UNITED STATES DISTRICT JUDGE:

This is a claim construction opinion for United States Patent Nos. 7,582,727 and 7,598,343 (the "'727 Patent" and "'343 Patent," respectively). Plaintiff The Medicines Company has asserted both patents in response to the Defendants' filing of Abbreviated New Drug Applications with the FDA. The '727 Patent and '343 Patent are familial patents with identical specifications, and both seek to facilitate the production of bivalirudin. Bivalirudin is an anticoagulant drug compound used during angioplasty procedures. The process of making pharmaceutical formulations of bivalirudin, however, can be prone to producing high levels of an unwanted impurity known as Asp^9-bivalirudin ("Asp^9"). The '727 Patent is a product patent that claims pharmaceutical batches of bivalirudin with less than specified impurity levels of Asp^9, while the '343 Patent is a method patent claiming certain compounding processes for the production of bivalirudin with low levels of Asp^9.

The disputed terms follow.

(1) "Pharmaceutical batches"

The Medicines Company's Proposed Construction:	A single batch, wherein the single batch is representative of all commercial batches, and wherein the levels of, for example, impurities represent levels for all potential batches made by said process, or all batches prepared by a same compounding process.
Defendants' Proposed Construction:	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. Pharmaceutical batches are bulk batches, not unit doses, of an active pharmaceutical ingredient and a pharmaceutically acceptable carrier.
The Court's Construction	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.

The parties dispute the construction of "pharmaceutical batches" as used in both of the patents. The term is used in claim 1 of the '343 Patent 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, said batches prepared by a compounding process comprising…

Both parties agree that the following quotation from the specification explicitly defines "pharmaceutical batches," while differing as to the interpretation of the definition:

> As used here, "batch" or "pharmaceutical batch" refers to material produced by a single execution of a compounding process of various embodiments of the present invention. "Batches" or "pharmaceutical batches" as defined herein 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), 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.

Id. at 5:24-36. The parties dispute the significance of the first sentence of this quotation. Defendants argue that the first sentence of this quotation expressly limits a "pharmaceutical batch" to a product made by the "compounding process of various embodiments of the present invention." The Medicine Company disagrees, arguing that the sentence refers to embodiments of the invention and should thus not be limiting. The Medicine Company further argues that limiting "pharmaceutical batches" to only batches created according to the described compounding processes will convert the '727 Patent from a formulation patent into a formulation-by-process patent.

The Court agrees with Defendants. The definition defines "pharmaceutical batches" as batches made by "said process." *Id.* at 5:34 ("[T]he reconstitution time represent levels for all potential batches made by said process."). The antecedent of "said process" is "a compounding process of various embodiments of the present invention." This indicates that the "pharmaceutical batches" are only those made by the "compounding process." "When the intrinsic record reveals that a process step is essential to the invention as a whole, that step is a required limitation of the claims." *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1367-68 (Fed. Cir. 2007). The intrinsic record reveals that "pharmaceutical batches" of the invention must be prepared according to the special compounding process. This is because the patentee does not claim to have invented the bivalirudin drug compound itself. *See* '343 Patent at 1:62-64. Instead, the patentee refers to the present invention as an improved compounding process for the production of bivalirudin. *See id.* at 2:29-34. The patentee cannot claim to have invented formulations of bivalirudin with less than .6% Asp^9 without regard to the process used, as batches with low Asp^9 levels existed in the prior art. Table 6 represents batches produced by the prior art compounding processes, and shows that a certain percentage of the time, those processes created at least some batches with less than .6% Asp^9. The "pharmaceutical batches" should be defined as those resulting from the novel compounding process.

Defendants argued in their briefing that "pharmaceutical batches" should be restricted to "bulk batches" that exclude "unit doses," but also stated they were "willing to remove" the restriction from their proposed construction. (D.I. 716, p. 28 ll. 6-7). Thus, the Court construes "pharmaceutical batches" as only those batches produced by the compounding process of the patents, but does not construe the term as excluding unit doses.

(2) Wherein the batches have a pH adjusted by a base

The Medicines Company's Proposed Construction:	Plain and ordinary meaning In the alternative: During compounding, the pH of the batches is adjusted using a base
Defendants' Proposed Construction:	Wherein said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under efficient mixing conditions
The Court's Construction	Wherein said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under efficient mixing conditions

The next term is "wherein the batches have a pH adjusted by a base." As oral argument developed, it became clear that the actual issue in dispute is not so much the construction of "wherein the batches have a pH adjusted by a base,"[1] but whether the "efficient mixing" process should be added to the formulation claims of the `727 Patent. (D.I. 716, p. 58). Defendants argue that the "efficient mixing" process is necessary to the `727 Patent, as that is the only inventive feature of the patent, and the patentee distinguished the invention on that basis. The Medicine Company disagrees, arguing that "efficient mixing" was intentionally omitted and its addition would improperly transform claim 1 from a product claim into a product-by-process claim. Claim 1 of the `727 Patent 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 –bivalirudin that does not exceed about .6% as measured by HPLC.

The Court agrees with Defendants. The only novel aspect of both the '727 and '343 Patents is the special compounding process aimed at reliably reducing the amount of Asp^9 in "pharmaceutical batches." The term "pharmaceutical batches" is explicitly defined in the

[1] The phrase standing on its own deserves its plain and ordinary meaning.

specification as resulting from the compounding process, and "pharmaceutical batches" is the product of the '727 Patent. Thus, although the claim does not explicitly refer to the process step, the patent defines itself as a product-by-process claim. The specification makes clear that this process is characterized by "efficiently mixing." *See id.* at 8:54-55 ("The pH-adjusting solution will be efficiently mixed with the bivalirudin solution to form the compounding solution"); *id.* at 9:3-17.[2]

The Medicines Company argues that it is error to read a process limitation into the product claim. It is generally correct to say that product claims should not be limited by how the product is manufactured. *See Vanguard Prods. Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000). "The method of manufacture, even when cited as advantageous, does not of itself convert product claims into claims limited to a particular process…A novel product that meets the criteria of patentability is not limited by the process by which it was made." *Id.* Nevertheless, the Court is convinced that the exception to this general rule is correct here. First, claim 1 already has a process step of "wherein the batches have a pH adjusted by a base," meaning that it is not a pure product claim. Second, as discussed, by virtue of the explicit definition of "pharmaceutical batches," the compounding process element is intrinsic to the

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[2] The following quotation from the specification explains the necessity of "efficient mixing" to the process of controlling Asp^9 levels:

> For example, if the pH-adjusting solution is introduced without efficient mixing, a dense precipitate may form. This dense precipitate may result in a slower dissolution and the surrounding solution being maintained at a high pH for extended time. Although the concentration of bivalirudin in the solution phase is low, it is also very susceptible to Asp^9-bivalirudin generation at this high pH.
>
> Conversely, 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. Thus, process operations to control the pH transition through efficient mixing provide a significant process improvement and control of Asp^9-bivalirudin levels.

'727 Patent at 9:03-17.

claim itself. Third, again as already discussed, there is nothing novel here about the product alone, i.e., "[p]harmaceutical batches of a drug product comprising bivalirudin… wherein the batches have a maximum impurity level of Asp^9 –bivalirudin that does not exceed about .6%[.]" `727 Patent, claim 1. Table 6 of the patent shows that pharmaceutical batches containing less than .6% Asp^9 existed in the prior art. The problem in the prior art was not that batches with low Asp^9 were unheard of, the problem was that no process existed to reliably produce these batches. This was only solved by the new compounding process.

This finding is bolstered by the prosecution history. The application for the `727 Patent was rejected for failing to recite the "compounding process of preparing the pharmaceutical composition." (D.I. 467, J.A. 358). In response, the declaration of inventor Dr. Musso described a "process improvement strategy to assess the impact of process control wherein the base was added in a controlled (metered) and effectively dispersed (at the bivalirudin precipitate stage) manner." (D.I. 468, J.A. 518 at ¶ 14). In overcoming the rejection, the inventor emphasized the process, not the product. Thus, although it is recited as a product claim, it falls into the exception that "arise[s] when the product's distinction from the prior art depends on how it was produced, for when the validity of the patent depends on use of a particular process, the claims are construed in the manner that will sustain their validity, when such construction is supported by the record." *AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 224 F. App'x 956, 958 (Fed. Cir. 2007). For these reasons, the Court adopts Defendants' construction.

3. "Efficient mixing"

The Medicines Company's Proposed Construction:	Mixing that is characterized by minimizing levels of Asp^9- bivalirudin in the compounding solution.
Defendants' Proposed Construction:	A pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner, and mixed

	together under high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms), but not solely under slow mixing conditions (*i.e.*, mixer speeds less than 800 rpms). The pH adjusting solution is not added rapidly to the bivalirudin solution; neither rapidly all at once nor rapidly in multiple portions.
The Court's Construction	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).

The next term is "efficient mixing." This term is explicitly found in the claims of the '343 Patent, but is also relevant to the '727 Patent as discussed above. "Efficient mixing" as used in claim 1 of the '343 Patent 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, 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 .6% as measured by HPLC.

The Medicines Company argues that the patent explicitly defines "efficient mixing" as "mixing that is characterized by minimizing levels of Asp^9 in the compounding solution." Defendants argue that this is not an explicit definition, as it merely describes the desired results from the process, and that "efficient mixing" is a coined term that must be construed with reference to the specification and examples. Defendants' proposal follows:

> A pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner, and mixed together under high shear mixing conditions (*i.e.*, mixer speeds above

1000 rpms), but not solely under slow mixing conditions (*i.e.*, mixer speeds less than 800 rpms). The pH adjusting solution is not added rapidly to the bivalirudin solution; neither rapidly all at once nor rapidly in multiple portions.

"Efficient mixing" is the second step of a three step process. These steps are (1) "dissolving bivalirudin to form a first solution;" (2) "efficiently mixing a pH-adjusting solution with the first solution to form a second solution," and (3) "removing the solvent and the pH adjusting solution solvent from the second solution." The "Background of the Invention" makes clear that the patent's inventive aspect is a compounding process for making "pharmaceutical batches" of bivalirudin that consistently have low levels of undesirable impurities, including Asp^9-bivalirudin. '727 Patent at 2:16-23.

The Medicines Company cites the following as support of its explicit definition argument: "Efficient mixing is characterized by minimizing levels of Asp^9 –bivalirudin in the compounding solution." *Id.* at 9:34-35. The Court does not agree that this is definitional language, especially in contrast with other terms in the specification that are clear explicit definitions, set off with quotation marks and accompanied with the language of "as used herein" or "refers to." *See id.* at 5:24-54. Further, The Medicines Company's proposed construction does not do much to help determine the metes and bounds of the invention. It cannot be any mixing process that results in batches with less than .6% Asp^9. "Efficient mixing" is a distinct step that must be given a meaningful construction. As discussed, it is the compounding process that is the inventive aspect of the patents. Further, construing "efficient mixing" as offered by The Medicines Company would give the term a construction that captures all new compounding processes that achieve the same results, even if those methods were truly novel and achieved those results in a superior fashion.

Defendants argue that Examples 4 and 5 of the specification provide guidance, as they expressly contrast "inefficient mixing" processes with "efficient mixing" processes. Example 4 is entitled, "Effects of Rapidly Adding pH Adjusting Solution to the Bivalirudin Solution Under Inefficient Mixing Conditions—Large Scale Study." *Id.* at 21:46-48. Example 4 implies that "inefficient mixing conditions" are equivalent to "slow mixing conditions" between about 400 and 800 rpm. *See id.* at 21:50, 63-65. The Court agrees that the processes used in Example 4 are outside the scope of "efficient mixing," as the specification explains that the methods used in Example 4 failed to consistently produce "pharmaceutical batches" with low impurities, which is the goal of the inventive process.

Example 5 describes the "efficient mixing" process. Example 5 is entitled, "Effects of Adding a pH Adjusting Solution at a Constant Rate and Under Efficient Mixing Conditions—Large Scale Study." '727 Patent at 22:32-34. Example 5 states that the solutions were combined at a "controlled" or "constant" rate and mixed using a "high shear mixing environment (between about 1000 rpm and 1300 rpm)," and further states that "the process demonstrated in Example 5 produced batches generally and consistently having lower levels of impurities than the process of Example 4." *Id.* at 22:38; 22:49-50; 23:24-26. Based on these passages, Defendants argue that "efficient mixing conditions" should be construed to require two acts: (1) add the pH-adjusting solution in a slow, controlled manner; and (2) mix the pH-adjusting solution and bivalirudin solution using high shear mixing.

The Medicines Company disagrees, arguing that Defendants' proposed construction is contradicted by the specification that allows low shear mixing, citing the following:

> Furthermore, efficient mixing may be achieved through the use of one or more mixing devices. Examples of mixing devices that may be used in various

> embodiments of the present invention may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing rate of, for instance, a paddle mixer may be between about 100 rpm and 1000 rpm, or between about 400 rpm and about 800 rpm. The mixing rate, for, as an example, a homogenizer (i.e., high shear mixing) may be between about 300 and about 6000 rpm, or between about 1500 rpm and about 3000 rpm.

Id. at 10:42-53. Here, the specification states that a paddle mixer may be used at between 100 rpm and 1000 rpm, or between about 400 rpm and about 800 rpm. This presents a contradiction as Example 4 clearly indicates mixing between 400 and 800 rpms is "inefficient." The contradiction should be resolved in favor of relying on what the inventor excluded from the scope of the patent. First, the Example 4 process is explicitly referred to as "inefficient," and "efficient mixing" should thus not be construed to include that process. Second, the public should be able to rely on a patent's statements of exclusion, even if the patent is not entirely consistent as to what is excluded. Third, the discussions within the Examples more cohesively frame which processes are novel and reliably reduce Asp^9, in comparison with the somewhat vague discussion cited by The Medicines Company. The discussion of the Examples should thus be given more weight.

With all of this in mind, the Court agrees with Defendants that "efficient mixing" requires high shear mixing conditions. Example 5 makes clear that addition of the pH-adjusting solution at a constant rate or controlled rate is required, as well as the necessity of high shear mixing. The proposal that the pH-adjusting solution be added in a "controlled manner" receives further support from the inventor's description of a "process improvement strategy to assess the impact of process control wherein the base was added in a controlled (metered) and effectively dispersed (at the bivalirudin precipitate stage) manner." (D.I. 468, J.A. 518 at ¶ 14). Defendants' construction, however, contains some elements that are not justified. First, the

proposed construction states that the mixing occurs both "under high shear mixing conditions" and "not solely under slow mixing conditions[.]" If the mixing requires high shear mixing conditions, then by definition it does not occur "solely under slow mixing conditions." The "not solely under slow mixing conditions" is therefore redundant. Second, the proposed requirement excluding any and all rapid addition of the pH-adjusting solution to the bivalirudin solution is unnecessary. Example 4 of the patent does show generally that rapid addition of the pH-adjusting solution is inconsistent with "efficient mixing." That is why "slowly" is appropriate. The "not rapidly all at once" and "not rapidly in multiple portions" limitations are therefore redundant of the "slowly" limitation. For these reasons, the Court construes "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)."

US007582727B1

(12) **United States Patent**
Krishna et al.

(10) **Patent No.: US 7,582,727 B1**
(45) **Date of Patent: *Sep. 1, 2009**

(54) **PHARMACEUTICAL FORMULATIONS OF BIVALIRUDIN AND PROCESSES OF MAKING THE SAME**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/180,553**

(22) Filed: **Jul. 27, 2008**

(51) **Int. Cl.**

A61K 38/55	(2006.01)
C07K 7/08	(2006.01)
C07K 7/64	(2006.01)
C07K 1/00	(2006.01)
C07K 1/04	(2006.01)
C07K 14/00	(2006.01)

(52) **U.S. Cl.** **530/326**; 530/324; 530/333; 530/334; 530/335; 514/13

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Pharmaceutical batch(es) or pharmaceutical formulation(s) comprising bivalirudin as the active ingredient, and a method of preparing the pharmaceutical batch(es) or pharmaceutical formulation(s). The pharmaceutical batch(es) or pharmaceutical formulation(s) may have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. Also, the pharmaceutical batch(es) or pharmaceutical formulation(s) may have a reconstitution time that does not exceed about 42 seconds. The method of preparing the pharmaceutical batch(es) or pharmaceutical formulation(s) may comprise dissolving bivalirudin in a solvent to form a first solution, efficiently mixing a pH-adjusting solution with the first solution to form a second solution in which the pH-adjusting solution may comprise a pH-adjusting solution solvent, and removing the solvent and the pH-adjusting solution solvent from the second solution.

20 Claims, No Drawings

PHARMACEUTICAL FORMULATIONS OF BIVALIRUDIN AND PROCESSES OF MAKING THE SAME

INCORPORATION BY REFERENCE

The foregoing applications, and all documents cited therein or during their prosecution ("appln cited documents") and all documents cited or referenced in the appln cited documents, and all documents cited or referenced herein ("herein cited documents"), and all documents cited or referenced in herein cited documents, together with any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

FIELD OF THE INVENTION

Various embodiments of the present invention are generally directed towards a method for preparing a pharmaceutical batch(es) or a pharmaceutical formulation(s) comprising bivalirudin as the active ingredient. Some embodiments of the present invention are also directed towards a pharmaceutical batch(es) or a pharmaceutical formulation(s) comprising bivalirudin as the active ingredient. For example, certain embodiments of the present invention relate to pharmaceutical batch(es) or pharmaceutical formulation(s) of a drug product having reduced levels of a major degradation product, i.e., Asp^9-bivalirudin, which may contribute to improved stability and shelf-life. In some embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In various embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) of the present invention are characterized by a reconstitution time that does not exceed about 42 seconds. Various embodiments of the invention further generally relate to an injectable dosage form comprising a pharmaceutical formulation and a vehicle, and methods of administering the injectable dosage form.

BACKGROUND OF THE INVENTION

Anticoagulants are substances that prevent blood from clotting. They are commonly used during percutaneous coronary intervention (PCI) and other catherization techniques in order to reduce bleeding complications. One class of anticoagulants is direct thrombin inhibitors that disrupt the activity of thrombin, an important protein in the coagulation cascade. In 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 procedures.

Bivalirudin, also known as Hirulog-8, is a synthetic congener of the naturally occurring thrombin peptide inhibitor hirudin, which is found in the saliva of the medicinal leech *Hirudo medicinalis*. Hirudin consists of 65 amino acids, although shorter peptide segments have proven to be effective as thrombin inhibitors. U.S. Pat. No. 5,196,404 (incorporated herein by reference) discloses bivalirudin among these shorter peptides that demonstrate an anticoagulant activity. However, in contrast to hirudin, bivalirudin is a reversible inhibitor, which is ideal for temporary prevention of blood clotting during catherization procedures.

In light of the medical and therapeutic applications of bivalirudin, it is essential that the bivalirudin formulation maintains a high level of purity. The bivalirudin formulation is a compounded formulation containing bivalirudin, e.g., bivalirudin undergoes a compounding process following its synthesis so that it is usable and stable for medical and therapeutic applications.

Impurities such as Asp^9-bivalirudin (deamidation of asparagine at position 9 of bivalirudin to aspartic acid) and D-Phe^{12}-bivalirudin (isomerization of L-phenylalanine at position 12 of bivalirudin to the D-isomer) may be generated during the synthesis of bivalirudin. Consequently, processes for synthesizing bivalirudin have been developed to minimize the generation of impurities. However, impurities can also be produced during the compounding process, i.e., the process to generate a formulation of bivalirudin. It has been shown that various compounding processes can result in formulations that have up to 12% of Asp^9-bivalirudin, which may affect product stability and shelf-life. Therefore, development of a compounding process for formulating bivalirudin that consistently generates formulations having low levels of impurities is desirable.

Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention.

SUMMARY OF THE INVENTION

Various embodiments of the present invention relates to a compounding process for preparing a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient. In certain embodiments, the compounding process comprises (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 Asp^9-bivalirudin in the second solution is minimized; and (iii) removing the solvent from the second solution.

In some embodiments, the pH of the second solution does not exceed about 8. In some embodiments, the pH of the second solution does not exceed about 7. In further embodiments, the pH of the second solution does not exceed about 6.

In certain embodiments, efficient mixing is achieved by adding the pH-adjusting solution to the first solution, by adding the first solution to the pH-adjusting solution, or a combination thereof. In some embodiments, the pH-adjusting solution is added to the first solution in portions. In further embodiments, the pH-adjusting solution is added to the first solution at a constant rate.

In some embodiments, efficient mixing is achieved by using one or more mixing devices. In certain embodiments, the mixing device is selected from a group consisting of a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. In some embodiments, the mixing device is a homogenizer, a paddle mixer, or a combination thereof.

In further embodiments, the efficient mixing is achieved through high shear mixing.

In certain embodiments, removal of the solvent from the second solution is achieved through lyophilization.

In some embodiments, the compounding process may further comprise sterilization of the second solution before removal of the solvent. In certain embodiments, sterilization is achieved by aseptic filtration.

Various embodiments of the present invention also relate to a pharmaceutical batch(es) or a pharmaceutical formulation(s) prepared by the compounding process of the

invention. In certain embodiments, a pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In some embodiments, a pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum total impurity level that does not exceed about 2%. In additional embodiments, a pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

In addition, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) 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; and (iii) removing the solvent from the second solution.

In certain embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In some embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.4%. In further embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.3%.

In some embodiments of the present invention, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum total impurity level that does not exceed about 2%. In certain embodiments, the maximum total impurity level does not exceed about 1%. In additional embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum level of D-Phe^{12}-bivalirudin that does not exceed about 2.5%.

In other embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds. In some embodiments, the maximum reconstitution time does not exceed about 30 seconds. In further embodiments, the maximum reconstitution time does not exceed about 21 seconds.

In some embodiments of the present invention, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In additional embodiments, the bulking agent is a sugar. In further embodiments, the sugar is mannitol.

In certain embodiments, efficient mixing is achieved by adding the pH-adjusting solution to the first solution, by adding the first solution to the pH-adjusting solution, or a combination thereof. In some embodiments, the pH-adjusting solution is added to the first solution at a constant rate. In further embodiments, efficient mixing is achieved by using one or more mixing devices. In yet additional embodiments, the efficient mixing is achieved through high shear mixing.

Moreover, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) 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; and (iii) removing the solvent from the second solution; wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) are characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%.

Certain embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) 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; and (iii) removing the solvent from the second solution; wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

Furthermore, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof. Some embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%.

In some embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.4%. In certain embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.3%.

In additional embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is further characterized by a maximum total impurity level that does not exceed about 2%. In certain embodiments, the maximum total impurity level does not exceed about 1%. In some embodiments, the maximum total impurity level does not exceed about 0.5%.

In certain embodiments of the invention, the pharmaceutical batch(es) or pharmaceutical formulation(s) is further characterized by a maximum level of D-Phe^{12}-bivalirudin that does not exceed about 2.5%.

In some embodiments, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In further embodiments, the bulking agent is a sugar. In yet additional embodiments, the sugar is mannitol.

Some embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

In certain embodiments, the maximum reconstitution time does not exceed about 30 seconds. In some embodiments, the maximum reconstitution time does not exceed about 21 seconds.

In some embodiments of the invention, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In further embodiments, the bulking agent is a sugar. In yet additional embodiments, the sugar is mannitol.

Also, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active

ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%, a maximum total impurity level that does not exceed about 2%, and a maximum reconstitution time that does not exceed about 42 seconds.

These and other embodiments are disclosed or are obvious from and encompassed by, the following Detailed Description.

DETAILED DESCRIPTION

Various embodiments of the present invention relate to a compounding process for preparing a pharmaceutical batch(es) of a drug product, which results in pharmaceutical formulations comprising bivalirudin and a pharmaceutically acceptable carrier. Certain embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product, resultant pharmaceutical formulation(s) comprising bivalirudin and a pharmaceutically acceptable carrier, and an injectable dosage form comprising the pharmaceutical formulation and a vehicle.

As used here, "batch" or "pharmaceutical batch" refers to material produced by a single execution of a compounding process of various embodiments of the present invention. "Batches" or "pharmaceutical batches" as defined herein 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), 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.

The term "drug product" herein refers to an active ingredient and a pharmaceutically acceptable carrier.

The term "formulation" or "pharmaceutical formulation" refers to a unit dose of an active pharmaceutical ingredient and a pharmaceutically acceptable carrier, which is prepared by the various processes in certain embodiments of the present invention. In the case of the present pharmaceutical formulation, the active pharmaceutical ingredient is bivalirudin.

The term "carrier" refers to any component of the pharmaceutical batch(es) or pharmaceutical formulation(s) that, for example, serves as a bulking agent or functions as a stabilizing agent for the active ingredient. A bulking agent refers to any material that fills or provides volume to the active ingredient. Examples of appropriate bulking agents may include, but are not limited to, sugars such as mannitol, sucrose, lactose, fructose and trehalose.

A stabilizing agent refers to any material which serves to minimize degradation of the active ingredient. Examples of stabilizing agents may include, but are not limited to, antioxidants, buffering agents, preservatives, etc.

Bivalirudin has the chemical name of 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-Leucine trifluoroacetate (salt) hydrate and has a molecular weight of 2180 daltons. Bivalirudin is made up of the amino acid sequence: (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu (SEQ ID NO: 1). Methods for the synthesis of bivalirudin may include, but are not limited to, solid-phase peptide synthesis, solution-phase peptide synthesis, or a combination of solid-phase and solution-phase procedures (e.g., U.S. Pat. No. 5,196,404; Okayama et al., *Chem. Pharm. Bull.* 1996, 44: 1344-1350; Steinmetzer et al., *Eur. J. Biochem.* 1999, 265: 598-605; PCT Patent Application WO 91/02750).

As described above, Asp^9-bivalirudin is formed due to deamidation of asparagine at position 9 of bivalirudin to aspartic acid. The amino acid sequence of Asp^9-bivalirudin is: (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu (SEQ ID NO: 2). Further, D-Phe^{12}-bivalirudin is generated from isomerization of L-phenylalanine at position 12 of bivalirudin to the D-isomer. The amino acid sequence of D-Phe^{12}-bivalirudin is (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-(D-Phe)-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu (SEQ ID NO: 3)

Bivalirudin inhibits blood clotting by binding to thrombin, a key serine protease in blood clot formation. This synthetic 20 amino acid peptide binds to thrombin at the catalytic site and at the anion-binding exocite, thereby inhibiting thrombin. Thrombin plays a central role in hemostasis. The coagulation pathway initiates clotting when thrombin, a serine protease, converts fibrinogen into fibrin. Additionally, thrombin activates Factor XIII into Factor XIIIa (the latter which links fibrin polymers covalently), Factors V and VIII (which promote thrombin generation), and platelets (which help propagate the thrombus).

The method of delivery of bivalirudin may be through intravenous administration. Bivalirudin may be supplied in single-use vials as a white lyophilized sterile cake. Each single-use vial may contain about 250 mg of bivalirudin. When reconstituted with a sterile aqueous solution for injection, the product yields a clear to opalescent, colorless to slightly yellow, solution. Such a solution has a pH of about 5-6.

The pharmaceutical batch(es) or pharmaceutical formulation(s) according to certain embodiments of the present invention may be used in any application which requires altered or inhibited thrombin activity. The pharmaceutical batch(es) or pharmaceutical formulation(s) may be used to alter or inhibit the coagulation cascade, for example, as an anticoagulant.

Approved indications include treatment in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty; administration with the provisional use of glycoprotein IIb/IIIa inhibitor for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI); and treatment in patients with, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. Also, the pharmaceutical batch(es) or pharmaceutical formulation(s) according to various embodiments of the present invention can be used for the prevention and treatment of venous thromboembolic disease.

Process for Preparing a Pharmaceutical Batch(es) or a Pharmaceutical Formulation(s)

Various embodiments of the present invention relate to a compounding process for preparing a pharmaceutical batch(es) or pharmaceutical formulation(s) comprising bivalirudin.

1) Dissolving Bivalirudin in a Solvent to Form a Bivalirudin Solution

In the compounding process of various embodiments of the present invention, bivalirudin may be dissolved in a solvent to form a bivalirudin solution. Bivalirudin may be commercially purchased or synthesized by various procedures as described above. The concentration of bivalirudin in the solvent may be

between about 0.010 g/mL and about 1 g/mL, or between about 0.050 g/mL and about 0.1 g/mL. Solvents may include aqueous and non-aqueous liquids, including but not limited to, mono- and di-alcohols such as methanol, ethanol, isopropyl alcohol, and propylene glycol; polyhydric alcohols such as glycerol and polyethylene glycol; buffers; and water.

The solvent may comprise carriers such as sugars. For example, the sugar may be a monosaccharide such as glucose or fructose; a disaccharide such as sucrose, maltose, or trehalose; an oligosaccharide; or a polysaccharide. Alternatively, the sugar may be a sugar alcohol, such as sorbitol or mannitol. The quantity of carrier in the solvent may be adjusted to provide a pharmaceutical batch or pharmaceutical formulation preferably having a ratio of the carrier to the active ingredient of between about 5:1 and about 1:10, or between about 1:1 and about 1:4, or more preferably about 1:2.

Bivalirudin can be dissolved in the solvent by methods known in the art, preferably by adding the bivalirudin to the solvent. For example, bivalirudin may be added to the solvent rapidly, slowly, in portions, at a constant rate, at a variable rate, or a combination thereof. A mixing device known in the art may be used to dissolve bivalirudin. Examples of mixing devices may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing device may be applied at a mixing rate between about 100 and about 2000 rpm, or between about 300 and about 1500 rpm. The solution resulting from dissolving the bivalirudin in the solvent is referred to here as the "bivalirudin solution" or alternatively the "first solution."

2) Mixing a pH-Adjusting Solution with the Bivalirudin Solution to Form a Compounding Solution

The compounding process may comprise mixing a pH-adjusting solution with the bivalirudin solution to form a compounding solution. The pH-adjusting solution may be prepared before, after, or simultaneously with, the bivalirudin solution.

The pH-adjusting solution may comprise a base dissolved in a solvent, wherein the solvent is referred to here as the "pH-adjusting solution solvent." In other words, the solution resulting from the combination of the base with the pH-adjusting solution solvent is referred to here as the "pH-adjusting solution." The pH-adjusting solution may also comprise a neat base such as pyridine or a volatilizable base such as ammonium carbonate.

The base may be an organic base or an inorganic base. The terms "inorganic base" and "organic base," as used herein, refer to compounds that react with an acid to form a salt; compounds that produce hydroxide ions in an aqueous solution (Arrhenius bases); molecules or ions that capture hydrogen ions (Bronsted-Lowry bases); and/or molecules or ions that donate an electron pair to form a chemical bond (Lewis bases). In certain processes, the inorganic or organic base may be an alkaline carbonate, an alkaline bicarbonate, an alkaline earth metal carbonate, an alkaline hydroxide, an alkaline earth metal hydroxide, an amine, or a phosphine. For example, the inorganic or organic base may be an alkaline hydroxide such as lithium hydroxide, potassium hydroxide, cesium hydroxide, or sodium hydroxide; an alkaline carbonate such as calcium carbonate or sodium carbonate; or an alkaline bicarbonate such as sodium bicarbonate.

Solvents may include aqueous and non-aqueous liquids, including but not limited to, mono- and di-alcohols such as methanol, ethanol, isopropyl alcohol, and propylene glycol; polyhydric alcohols such as glycerol and polyethylene glycol; buffers; and water. The pH-adjusting solution solvent may comprise carriers such as dissolved sugars. For instance, the sugar may be a monosaccharide such as glucose or fructose; a disaccharide such as sucrose, maltose, or trehalose; an oligosaccharide; or a polysaccharide. The sugar may also be a sugar alcohol, such as sorbitol or mannitol. The quantity of the carrier in the pH-adjusting solution solvent may be adjusted to provide the final product as described above.

The base is mixed or dissolved in the pH-adjusting solution solvent. The mixing or dissolution can be performed by methods known in the art. For instance, the base may be added to the pH-adjusting solution solvent rapidly, slowly, in portions, at a constant rate, at a variable rate, or a combination thereof. Also, a mixing device known in the art may be used to mix the base and the pH-adjusting solution solvent. Examples of mixing devices may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing device may be applied at a mixing rate between about 100 and about 1500 rpm, or between about 300 and about 1200 rpm. The base is added/mixed with the pH-adjusting solution solvent in a quantity that will result in a pH-adjusting solution that is characterized as being between about 0.01 N and about 5 N, or between about 0.1 N and 1 N.

The pH-adjusting solution may then be mixed with the bivalirudin solution. This mixing may occur by adding the pH-adjusting solution to the bivalirudin solution. Alternatively, the bivalirudin solution may be added to the pH-adjusting solution, or the pH-adjusting solution and the bivalirudin solution may be added simultaneously (into a separate vessel), or there may be a combination of these addition methods thereof. It is important during the adding or mixing of the pH-adjusting solution and the bivalirudin solution that pH is controlled. See below. The solution resulting from mixing the pH-adjusting solution and the bivalirudin solution is referred to here as the "compounding solution," or the "second solution." The compounding solution or the second solution can refer to the bivalirudin solution during or after the pH-adjusting solution is added, or can refer to the pH-adjusting solution during or after the bivalirudin solution is added, or can refer to the resulting solution formed during or after both the pH-adjusting solution and the bivalirudin solution are added together.

The mixing of the pH-adjusting solution and the bivalirudin solution may occur under controlled conditions. For example, temperature may be controlled by means known in the art, such as by mixing the pH-adjusting solution and the bivalirudin solution in a vessel inside a cooling jacket. The temperature may be set between about 1° C. and about 25° C., or between about 2° C. and about 10° C. In some instances, the temperature may exceed 25° C. for limited periods of time. Also, the mixing of the pH-adjusting solution and the bivalirudin solution may occur under controlled conditions such as under nitrogen, etc.

The pH-adjusting solution will be efficiently mixed with the bivalirudin solution to form the compounding solution. Efficient mixing of the pH-adjusting solution with the bivalirudin solution will minimize levels of Asp^9-bivalirudin in the compounding solution. "Minimize" as used herein refers to the generation of a level of Asp^9-bivalirudin in the compounding solution that is less than about 0.6%, or less than about 0.4%, or less than about 0.3%.

Critical to the efficient mixing is the fact that the isoelectric point of bivalirudin is about 3.6. As the bivalirudin solution itself has a pH of between about 2.5 and about 2.8, and the compounding solution is adjusted to a final pH of between about 5.1 and about 5.5, a portion of bivalirudin precipitates out during the addition of the pH-adjusting solution. The

characteristics of this precipitate are critical to regulating and controlling Asp^9-bivalirudin levels.

For example, if the pH-adjusting solution is introduced without efficient mixing, a dense precipitate may form. This dense precipitate may result in a slower dissolution and the surrounding solution being maintained at a high pH for extended time. Although the concentration of bivalirudin in the solution phase is low, it is also very susceptible to Asp^9-bivalirudin generation at this high pH.

Conversely, 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. Thus, process operations to control the pH transition through efficient mixing provide a significant process improvement and control of Asp^9-bivalirudin levels.

Not wishing to be bound by theory, Asp^9-bivliarudin may also be generated by high pH or "hot spots," which are defined here as concentrated sites in the compounding solution that have much higher pH levels than the surrounding environment. An example of a hot spot is a site in the compounding solution having a pH of about 12, while the surrounding solution has a pH of about 5. Asp^9-bivliarudin may also be generated by high pH levels in the compounding solution in general. It has been found that efficient mixing reduces the generation of "hot spots" or high levels of pH in the compounding solution while the pH-adjusting solution and the bivalirudin solution are being added/mixed. Thus, efficient mixing may control the overall pH level of the compounding solution to a level not exceeding about 8, or a level not exceeding about 7, or a level not exceeding about 6, or even a level not exceeding about 5.5.

Efficient mixing is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution. This may be achieved through various methods. One such method may be to add or combine the pH-adjusting solution and bivalirudin solution portion-wise, i.e., in portions. For instance, the pH-adjusting solution may be added to the bivalirudin solution in portions of set quantities, wherein each addition is separated by a period of time. The quantity of pH-adjusting solution may be approximately equal or may vary among the portions. For example, the pH-adjusting solution may be added in four portions, wherein each portion comprises about 25% of the total pH-adjusting solution volume. As another example, the pH-adjusting solution may be added in three portions, such that the first portion comprises about 45% of the total pH-adjusting solution volume, the second portion comprises about 30% of the total pH-adjusting solution volume, and the third portion comprises about 25% of the total pH-adjusting solution volume.

The pH-adjusting solution may also be added in portions such that there is a combination of equal and unequal quantities. For instance, the pH-adjusting solution may be divided into four portions, wherein the first portion comprises about 45% of the total pH-adjusting solution volume, the second portion comprises about 25% of the total pH-adjusting solution volume, and the third and fourth portions each comprise about 15% of the total pH-adjusting solution volume.

The period of time between the addition of each portion may vary. This period may be a set duration of time regardless of the number of portions and/or volume of the portions to be added. Alternatively, the period of time may vary according to the number of portions and/or volume of the portions to be added. For example, the period of time between adding four equal portions may be about 5 minutes between each addition. As another example, the period of time after adding a first portion comprising about 60% of the total pH-adjusting solution volume may be about 15 minutes, while the period of time after adding a second portion comprising about 40% of the total pH-adjusting solution volume may be about 5 minutes.

The period of time between the addition of each portion may also be based upon a set total time for adding the pH-adjusting solution. For instance, if the total time for adding a pH-adjusting solution is set at about 20 minutes, then the period of time after adding each portion comprising about 25% of the total pH-adjusting solution volume may be about 5 minutes. In certain embodiments of the present invention, the total time for adding the pH-adjusting solution may be a duration of between about 5 minutes and about 40 minutes, or between about 10 minutes and about 30 minutes, or between about 15 minutes and about 25 minutes.

Efficient mixing may also be achieved by adding the pH-adjusting solution to the bivalirudin solution at a constant rate. The pH-adjusting solution may be added at a rate of between about 0.5% and about 50% of the total pH-adjusting solution volume, per minute; or between about 1% and about 25% of the total pH-adjusting solution volume, per minute; or between about 3% and about 8% of the total pH-adjusting solution volume, per minute.

The pH-adjusting solution may alternatively be added at a variable rate to the bivalirudin solution. As an example, the rate may increase from about 5% to about 20% of the total pH-adjusting solution volume per minute during the addition of the pH-adjusting solution.

The pH-adjusting solution may also be added to the bivalirudin solution portion-wise, wherein each portion is added at a constant or variable rate. The portions may be added in equal amounts, unequal amounts, or a combination thereof. Further, each portion may be added at the same or different constant rates, or the same or different variable rates, or a combination thereof. As an example, the first portion comprising 60% of the total pH-adjusting solution may be added at 5% of the portion volume per minute, while four subsequent portions each comprising about 10% of the total pH-adjusting solution may be added at 10% of the portion volume per minute.

Furthermore, efficient mixing may be achieved through the use of one or more mixing devices. Examples of mixing devices that may be used in various embodiments of the present invention may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing rate of, for instance, a paddle mixer may be between about 100 rpm and 1000 rpm, or between about 400 rpm and about 800 rpm. The mixing rate for, as an example, a homogenizer (i.e., high shear mixing) may be between about 300 and about 6000 rpm, or between about 1500 rpm and about 3000 rpm.

Since most proteins and peptides are susceptible to degradation by high shear, it was initially thought that bivalirudin could only be formulated using a compounding process employing low shear. Surprisingly, high shear mixing, such as through the use of a homogenizer, could successfully be used in the compounding process.

The mixing device may mix continuously during the addition of the pH-adjusting solution, or at specific periods of time, e.g., between the additions of portions, after the pH-adjusting solution is added, etc.

In addition, more than one mixing device may be used when the pH-adjusting solution is added to the bivalirudin solution. For example, a paddle mixer may be used at the surface of the bivalirudin solution and a homogenizer may be used near the bottom of the bivalirudin solution. When more

than one mixing device is used, they may be operated at the same mixing rate or different mixing rates, or a combination thereof. The mixing devices may also be operated at the same periods of time, at different periods of time, or a combination thereof, during the addition of the pH-adjusting solution. Similarly, a mixing device may be used with the addition of the bivalirudin solution to the pH-adjusting solution, or with the addition of the pH-adjusting solution and the bivalirudin solution together.

Moreover, efficient mixing may be achieved through adding the pH-adjusting solution to specific sites within the bivalirudin solution. For instance, the pH-adjusting solution may be added to the surface of the bivalirudin solution or to the bottom of the bivalirudin solution. In the cases wherein a mixing device is used, the pH-adjusting solution may be added to the site of the mixing device, e.g., at the site of the paddles of the paddle mixer or the blades of the homogenizer. The pH-adjusting solution may also be added to more than one site in the bivalirudin solution; for example, the pH-adjusting solution may be added simultaneously at the top of the bivalirudin solution and at the site of the mixing device. Alternatively, the bivalirudin solution may be added to the pH-adjusting solution at specific sites and at more than one site within the pH-adjusting solution, as described above.

Optionally, once the compounding solution is formed, the pH or the final volume of the compounding solution may be adjusted to a specified level before removal of the solvent (see below). The pH or volume can be adjusted using methods known in the art, for instance, the addition of a pH-adjusting solution as described above.

The compounding solution may also be sterilized before the removal of solvent. The compounding solution may undergo aseptic filtration using, for example, a 0.2 μm disposable membrane filter, to sterilize the compounding solution. Techniques of sterilizing the compounding solution are known in the art (see, e.g., Berovic, *Biotechnol. Annu. Rev.* 2005, 11:257-79).

Furthermore, following sterilization, the compounding solution may be aliquoted into containers such as vials, bottles, ampoules, syringes, etc.

3) Removal of Solvent from the Compounding Solution

The compounding process of various embodiments of the invention may comprise removing solvents from the compounding solution in order to produce a pharmaceutical batch(es) or pharmaceutical formulation(s).

Removal of the solvent from the compounding solution may be achieved through lyophilization, which comprises freezing the compounding solution and then reducing the surrounding pressure to allow the frozen solvent/moisture in the material to sublime directly from a solid phase to a gas phase. The lyophilization process may be performed by methods known in the art (see, e.g., Liu, *Pharm. Dev. Technol.* 2006, 11: 3-28; Tang et al., *Pharm. Res.* 2004, 21: 191-200; Nail et al., *Pharm. Biotechnol.* 2002, 14: 281-360; U.S. Pat. Nos. 7,351,431, and 6,821,515, which are incorporated by reference).

For example, the compounding solution may be frozen using such techniques as, but not limited to, mechanical refrigeration, dry ice, and liquid nitrogen. The temperature may be cooled to a range of between about 0° C. and about −80° C., or between about −20° C. and about −55° C. The primary lyophilization step may be characterized by a lowered pressure of between about 0.05 torr and about 10 torr, or between about 1 torr and about 5 torr. The secondary lyophilization step may be characterized by a pressure between about 0.05 torr and about 5 torr, or between about 0.1 torr and about 3 torr. In other instances, only one lyophilization step may be required.

The solvent may also be removed from the compounding solution through other techniques such as spray drying and spray-freeze drying (see, e.g., Lee, *Pharm. Biotechnol.* 2002, 13: 135-58; Maa et al., *Curr. Pharm. Biotechnol.* 2000, 1:283-302), vacuum drying, super critical fluid processing, air drying, or other forms of evaporative drying, as known in the art.

Alternative Compounding Process

In other embodiments, an alternative compounding process for preparing a pharmaceutical batch(es) or a pharmaceutical formulation(s) comprising bivalirudin may comprise (1) preparing a bivalirudin solution, (2) mixing the bivalirudin solution with a pH-adjusting solution, (3) mixing the bivalirudin/pH-adjusting solution with a carrier to form a compounding solution.

The bivalirudin solution may be prepared by mixing bivalirudin in an aqueous or non-aqueous solvent as described above. The resulting bivalirudin solution may be mixed with a pH-adjusting solution as described above, including adding the bivalirudin solution to the pH-adjusting solution, or vice-versa.

The combined bivalirudin/pH-adjusting solution may then be mixed with a carrier such as a bulking agent or stabilizing agent as described above. For example, the carrier may be a sugar such as mannitol. The bivalirudin/pH-adjusting solution and the carrier may be efficiently mixed using methods described in this application.

Pharmaceutical Batch(es) or Pharmaceutical Formulation(s) Generated by the Compounding Process

In the characterization of the pharmaceutical batch(es) and pharmaceutical formulation(s) generated by the compounding process, the levels of a parameter determined from the pharmaceutical formulation(s) prepared by a single execution of a compounding process are representative of the entire batch. Moreover, values for impurity levels include those amounts generated by the synthesis of the active pharmaceutical ingredient together with those levels generated by the compounding process.

Each pharmaceutical batch or pharmaceutical formulation prepared by the compounding process may be characterized by an impurity level of Asp^{9}-bivalirudin not exceeding about 1.5%, or not exceeding about 1%, or not exceeding about 0.6%, or not exceeding about 0.4%, or not exceeding about 0.3%.

The pharmaceutical batch(es) or the pharmaceutical formulation(s) prepared by the compounding process may be characterized by a total impurity level not exceeding about 6%, or not exceeding about 3%, or not exceeding about 2%, or not exceeding about 1%, or not exceeding about 0.5%. "Total impurity level" refers to the combined total of all measurable impurities in the pharmaceutical batch(es) or the pharmaceutical formulation(s).

The reconstitution time, i.e., time required to prepare the pharmaceutical batch(es) or the pharmaceutical formulation(s) for use, for the pharmaceutical batch(es) or the pharmaceutical formulation(s) may be characterized by a reconstitution time not exceeding about 180 seconds, or not exceeding about 72 seconds, or not exceeding about 42 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds, or not exceeding about 15 seconds.

Reconstitution time may be determined, for example, by adding 5 mL of water to a unit dosage vial comprising the bivalirudin pharmaceutical formulation. Immediately after adding the appropriate diluent (e.g., water, saline, etc.), a

timer is started. The vial is shaken vigorously, with inversion, for approximately 10 seconds. The vial is viewed to determine if the solid has dissolved. If the solid has not completely dissolved, the vial is shaken for another 10 seconds. These steps are repeated until all the solid dissolves, at which point the time is stopped and recorded.

The pharmaceutical batch(es) or the pharmaceutical formulation(s) prepared by the compounding process may relate to one or more of the characteristics described above.

Collectively, the compounding process of certain embodiments of the invention described herein may consistently generate pharmaceutical batches or pharmaceutical formulations having the same characteristics. As used herein, the use of the terms "consistent" or "consistently" in reference to the compounding process indicates that about 85% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have a specific characteristic, or wherein about 90% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have the characteristic, or about 95% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have the characteristic, or about 99% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have said characteristic, or 100% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have said characteristic.

In various embodiments of the present invention, the pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a maximum impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 1%, or not exceeding about 0.6%, or not exceeding about 0.4%, or not exceeding about 0.3%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) prepared by the compounding process may be characterized by consistently having a mean impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 0.5%, or not exceeding about 0.4%, or not exceeding about 0.3%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a maximum total impurity level not exceeding about 6%, or not exceeding about 3%, or not exceeding about 2%, or not exceeding about 1%, or not exceeding about 0.5%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a mean total impurity level not exceeding about 2%, or not exceeding about 1.3%, or not exceeding about 1.1%, or not exceeding about 0.5%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a maximum largest unknown impurity level not exceeding about 1%, or not exceeding about 0.5%, or not exceeding about 0.4%, or not exceeding about 0.3%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a mean largest unknown impurity level not exceeding about 1.0%, or not exceeding about 0.27%, or not exceeding about 0.25%, or not exceeding about 0.2%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a maximum reconstitution time not exceeding about 180 seconds, or not exceeding about 72 seconds, or not exceeding about 42 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a mean reconstitution times not exceeding about 60 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds, or not exceeding about 15 seconds.

Moreover, the pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may relate to one or more of the characteristics described above.

Pharmaceutical Batch(es) and Pharmaceutical Formulation(s)

Certain embodiments of the present invention relate to a pharmaceutical batch(es) or pharmaceutical formulation(s) comprising bivalirudin and a pharmaceutically acceptable carrier. The carrier is any component of the pharmaceutical batch(es) or pharmaceutical formulation(s) that, for example, serves as a bulking agent or functions as a stabilizing agent for the active ingredient.

The solvent may comprise carriers such as sugars. For example, the sugar may be a monosaccharide such as glucose or fructose; a disaccharide such as sucrose, maltose, or trehalose; an oligosaccharide; or a polysaccharide. Alternatively, the sugar may be a sugar alcohol, such as sorbitol or mannitol.

A pharmaceutical batch(es) or pharmaceutical formulation(s) may be characterized by an impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 1%, or not exceeding about 0.6%, or not exceeding about 0.4%, or not exceeding about 0.3%.

A pharmaceutical batch(es) or pharmaceutical formulation(s) may be characterized by a total impurity level not exceeding about 6%, or not exceeding about 3%, or not exceeding about 2%, or not exceeding about 1%, or not exceeding about 0.5%.

A pharmaceutical batch(es) or pharmaceutical formulation(s) may also be characterized by a reconstitution time not exceeding about 180 seconds, or not exceeding about 72 seconds, or not exceeding about 42 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds, or not exceeding about 15 seconds.

Further, a pharmaceutical batch(es) or pharmaceutical formulation(s) may relate to one or more of the characteristics described above.

A pharmaceutical batch(es) or pharmaceutical formulation(s) may be characterized by a maximum impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 1%, or not exceeding about 0.6%, or not exceeding about 0.4%, or not exceeding about 0.3%. The pharmaceutical batch(es) or pharmaceutical formulation(s) may also be characterized by a mean impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 0.5%, or not exceeding about 0.4%, or not exceeding about 0.3%.

Moreover, a pharmaceutical batch(es) or formulation(s) may be characterized by a maximum total impurity level not exceeding about 6%, or not exceeding about 3%, or not exceeding about 2%, or not exceeding about 1%, or not exceeding about 0.5%. In addition, the batch(es) may be characterized by a mean total impurity level not exceeding about 2%, or not exceeding about 1.3%, or not exceeding about 1.1%, or not exceeding about 0.5%.

The batch(es) may also be characterized by a maximum largest unknown impurity level not exceeding about 1%, or not exceeding about 0.5%, or not exceeding about 0.4%, or not exceeding about 0.3%. The batch(es) may further be characterized by a mean largest unknown impurity level not exceeding about 1%, or not exceeding about 0.27%, or not exceeding about 0.25%, or not exceeding about 0.2%.

Yet, the batch(es) may be characterized by a maximum reconstitution time not exceeding about 180 seconds, or not exceeding about 72 seconds, or not exceeding about 42 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds. Also, the batch(es) may be characterized by a mean reconstitution time not exceeding about 60 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds, or not exceeding about 15 seconds.

Moreover, the pharmaceutical batch(es) or pharmaceutical formulation(s) may relate to one or more of the characteristics described above.

The pharmaceutical batch(es) or pharmaceutical formulation(s) may be generated by the compounding processes described above. Thus, the batch(es) may be prepared by a compounding process comprising dissolving bivalirudin in a solvent to form a bivalirudin solution, efficiently mixing a pH-adjusting solution with the bivalirudin solution to form a compounding solution, and removing solvents from the compounding solution. This compounding process includes all of the embodiments as described above.

Administering the Pharmaceutical Formulation

Various embodiments of the present invention further relate to a method of administering the pharmaceutical formulation of certain embodiments of the present invention to a subject, which comprises preparing an injectable dosage form, and then delivering the injectable dosage form to the subject parenterally.

The injectable dosage form is prepared by reconstituting the pharmaceutical formulation in a pharmaceutically acceptable vehicle. Methods of reconstituting the pharmaceutical formulation are well known in the art. Pharmaceutically acceptable vehicles are also well known in the art and can include, but are not limited to, water and saline for injection.

As an example, the injectable dosage form may be prepared by adding water to the pharmaceutical formulation and dissolving the pharmaceutical formulation. This solution can then be further diluted in 5% dextrose in water or 0.9% sodium chloride for injection.

Methods of delivering the injectable dosage form parenterally are well known in the art. For example, the injectable dosage form may be delivered intravenously.

The dosage form may be an intravenous bolus dose of between about 0.25 mg/kg and about 1.50 mg/kg, or between about 0.50 mg/kg to about 1.00 mg/kg, or about 0.75 mg/kg. This may be followed by an infusion of between about 1.25 mg/kg/h and about 2.25 mg/kg/h, or about 1.75 mg/kg/h for the duration of the procedure or treatment protocol. Five minutes after the bolus dose is administered, an additional bolus of between about 0.1 mg/kg and about 1.0 mg/kg, or about 0.3 mg/kg, may be given if needed.

The dosage form of various embodiments of the present invention can be indicated for use as an anticoagulant. Also, the dosage form can be used for the prevention and treatment of venous thromboembolic disease. Approved indications include treatment in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty; administration with the provisional use of glycoprotein IIb/IIIa inhibitor for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI); and treatment in patients with, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. Also, the dosage form can be used for the prevention and treatment of venous thromboembolic disease.

The injectable dosage form may be administered with other drug products such as glycoprotein (GP) IIb/IIIa inhibitor ((see, e.g., Allie et al., *Vasc. Dis. Manage.* 2006, 3: 368-375). Alternatively, the injectable dosage form may be combined with blood thinners including, but not limited to, coumadin, warfarin, and preferably, aspirin.

The invention will now be further described by way of the following non-limiting examples, which further illustrate the invention, and are not intended, nor should they be interpreted to, limit the scope of the invention.

EXAMPLES

Example 1

Generation of High Levels of Asp^9-Bivalirudin

A study was performed in three parts to determine levels of Asp^9-bivalirudin generated in batches prepared by compounding processes having different methods of mixing the pH-adjusting solution with the bivalirudin solution to form a compounding solution. More specifically, the study examined the effects of adding the pH-adjusting solution to the bivalirudin solution in portions with inefficient mixing, the effects of having high levels of pH in the compounding solution, and the effects of high shear mixing of the compounding solution on Asp^9-bivalirudin levels.

In a first part of the study, the bivalirudin solution (~600 mL) comprised bivalirudin at a concentration of ~0.1 mg/mL in a 2.64% w/w mannitol solution. The pH-adjusting solution (233 mL) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution. Asp^9-bivalirudin levels were measured throughout the experiment by high-performance liquid chromatography (HPLC). pH was also measured through the experiment. One measurement of Asp^9-bivalirudin was taken immediately after the bivalirudin solution was formed (baseline).

The pH-adjusting solution was added to the bivalirudin solution in four equal portions over the total duration of about 1 hour at a temperature of 5-8° C., each addition separated by about 15 minutes. The resulting compounding solution was mixed at between 600 rpm and 700 rpm throughout the addition of the first and second portions of the pH-adjusting solution, and the pH and Asp^9-bivalirudin levels were recorded (measurements #1 and #2). During the addition of the third portion, the mixer was turned off and the pH and Asp^9-bivalirudin levels were recorded (measurement #3A). The mixture was then subjected to high shear mixing at 4000 rpm for 30 seconds and the pH and Asp^9-bivalirudin levels were recorded (measurement #3B). During addition of the fourth portion, the mixer was turned off and the levels of pH and Asp^9-bivaluridin were recorded (measurement #4A). Mixing was then continued for, at least, two minutes at 5300 rpm and the pH was and Asp^9-bilvairudun levels were recorded (measurement #4B). The mixing rate was decreased to about 3600 rpm for 1 hour and the pH and Asp^9-bivalirudin levels were recorded (measurement #5). A portion of the material from measurement #4a was allowed to stand for 7 hours and the pH and Asp^9-bivalirudin levels were recorded (measurement #6). The pH and Asp^9-bivalirudin levels are shown in Table 1.

TABLE 1

pH and average Asp^9-bivalirudin levels after addition of pH-adjusting solution in four equal portions with inefficient mixing.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample taken after bivalirudin solution was formed	~2.5	~0.42
#1	Sample taken from compounding solution after addition of first portion of pH-adjusting solution to bivalirudin solution	3.0	—
#2	Sample taken from compounding solution after addition of second portion of pH-adjusting solution to bivalirudin solution	4.2	0.43
#3A	Sample taken from compounding solution after addition of third portion of pH-adjusting solution to bivalirudin solution with no mixing	~6 to 8	0.45
#3B	Same as #3A, but after mixing	5.0	0.74
#4A	Sample taken from compounding solution after addition of fourth portion of pH-adjusting solution to bivalirudin solution, and after compounding solution sat for 10 minutes with no mixing	~8.5 to 9	0.60
#4B	Same as #4A, but after mixing	6.0 to 6.5	0.57
#5	Same as #4A, but after high speed mixing for 1 hour	5.0	0.71
#6	Same as #4A, but 7 hours later with no mixing	~8.5 to 9	2.05

These results suggest that inefficient mixing of the compounding solution generates Asp^9-bivalirudin. Notably, during the addition of the pH-adjusting solution, a precipitate formed which may contain bivalirudin. Since the level of Asp^9-bivalirudin is based on a % analysis by HPLC of the amount of bivalirudin in solution, the level of Asp^9-bivalirudin appears to increase and decrease during the compounding process.

In a second part of the study, four portions of the final compounding solution from the first part of the study were removed. The pH levels of these portions were adjusted to 8, 9, 10, and 12, respectively, using additional pH-adjusting solution and high shear mixing on a Silverson Laboratory Emulsifier (Model L4RT).

Samples of the portion of the compounding solution adjusted to pH 8 were taken immediately, and after about 80 minutes, 300 minutes, and 370 minutes. Samples of the portion of the compounding solution adjusted to pH 9 were taken immediately, after about 80 minutes, and 300 minutes. Further, samples of the portion of the compounding solution adjusted to pH 10 and 12 were taken immediately, after about 80 minutes and 170 minutes. The results of the analyses for levels of Asp^9-bivalirudin in these samples are shown in Table 2.

TABLE 2

Asp^9-bivalirudin levels of portions adjusted to various pH levels.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample measured after bivalirudin solution was formed	5	0.71
#1	Sample measured after pH was adjusted	8	0.71
	Sample measured after ~80 minutes		0.77
	Sample measured after ~300 minutes		1.11
	Sample measured after ~370 minutes		1.26
#2	Sample measured after pH was adjusted	9	0.84
	Sample measured after ~80 minutes		1.07
	Sample measured after ~300 minutes		1.84
#3	Sample measured after pH was adjusted	10	1.24
	Sample measured after ~80 minutes		2.08
	Sample measured after ~170 minutes		2.59
#4	Sample measured after pH was adjusted	12	4.71
	Sample measured after ~80 minutes		8.20
	Sample measured after ~170 minutes		10.95

These results appear to show a relationship between pH, time, and the generation of Asp^9-bivalirudin.

In a third part of the study, the final compounding solution from the first part of the study was placed into a recirculation vessel for use in a recirculation water bath (Precision Model 181) to be subjected to high shear mixing using a Silverson Laboratory Emulsifier (Model L4RT). Prior to this study, it was thought that bivalirudin solutions were unstable to both heat and shear, thus requiring extreme care in handling bivalirudin during the compounding process. Before subjecting the compounding solution to high shear mixing, the level of Asp^9-bivalirudin was recorded (measurement #1). The compounding solution was then subjected to high shear mixing at ~6000 rpm for 30 minutes without use of the recirculation water bath; the temperature of the compounding solution due to the high shear mixing rose to about 36° C. A sample was then measured for Asp^9-bivalirudin level (measurement #2). The mixing speed was then slowed to 5000 rpm for 120 minutes and the temperature was measured at about 33° C., and another sample was analyzed for Asp^9-bivalirudin level (measurement #3). The Asp^9-bivalirudin levels are shown in Table 3.

TABLE 3

Asp^9-bivalirudin levels of the compounding solution undergoing different high shear mixing rates.

Measurement	Sample	Temperature	% Asp^9-bivalirudin
#1	Sample taken from the compounding solution before high shear mixing	RT~20° C.	0.71
#2	Sample taken from the compounding solution after high shear mixing at 6000 rpm for 30 minutes	36° C.	0.71
#3	Sample as #2, but after mixing rate was reduced to 5000 rpm for 120 minutes	33° C.	0.75

These results also show that, unexpectedly, that bivalirudin is stable to high shear mixing conditions. Also, the temperature of the compounding solution did not, surprisingly, affect Asp^9-bivalirudin generation in this study.

Example 2

Effects of Adding the pH-Adjusting Solution in Two Portions to the Bivalirudin Solution on Asp^9-Bivalirudin Levels

A study was performed to determine levels of Asp^9-bivalirudin generated in compounding solutions prepared by a

compounding process involving the addition of the pH-adjusting solution to the bivalirudin solution in two portions.

The bivalirudin solution (~760 mL) comprised bivalirudin at a concentration of 0.050 mg/ml dissolved in a 2.64% w/w mannitol solution. The pH-adjusting solution (233 mL) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution. The experiment was conducted at a temperature of about 8° C.

The pH-adjusting solution was divided into a 75% portion and a 25% portion of the total pH-adjusting solution volume. First, the pH and Asp^9-bivalirudin levels were measured before addition of the pH-adjusting solution (baseline). During addition of the 75% portion, at about 400 rpm, the pH was monitored during mixing until the pH achieved a constant level at which time the Asp^9-bivalirudin level was also measured (measurement #1). A portion of this material was allowed to sit for about 6.5 hours and the amount of Asp^9-bivaliridn was again measured (measurement #2). The 25% portion of the pH-adjusting solution was added about 30 minutes after the last base addition and mixing was continued at 400 rpm. The pH was initially recorded and then both the pH and Asp^9-bivalirudin levels were measured after about 30 minutes of mixing (measurement #3). The pH and Asp^9-bivalirudin levels were again recorded after mixing at 400 rpm overnight (measurement #4). The pH and Asp^9-bivalirudin levels are shown in Table 4.

Notably, after the 75% portion of the pH-adjusting solution was added, a large white mass precipitated from the compounding solution and formed a mass at the bottom of the vessel. The addition of the 25% portion did not induce any physical changes in the appearance of the mixture, and there was no additional precipitation. The white mass displayed little change after mixing for 30 minutes after the 25% portion was added, but dissolved after mixing overnight.

TABLE 4

pH and average Asp^9-bivalirudin levels after addition of pH-adjusting solution in two portions of 75% and 25% at 400 rpm.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample taken after bivalirudin solution was formed	1.71	0.42
#1	Sample of the compounding solution taken after addition of 75% portion of the pH-adjusting solution to the bivalirudin solution	Peak at 12.2, then dropped to 8-9	0.44
#2	Same as #1, but after sitting for 6.5 hours with no stirring	—	0.88
#3	Remaining 25% of pH-adjusting solution added	12.4 initially, then dropped to 7.7 after 30 minutes	1.85 (taken from the top) 2.19 (taken from the bottom)
#4	Same as #3, but after mixing overnight	5.0	1.57

These results indicate that addition of the pH-adjusting solution in two portions with inefficient mixing produces high levels of Asp^9-bivalirudin.

Example 3

Effect of Controlled Addition of pH Adjusting Solution at Different Mixing Rates on Asp^9-Bivalirudin Levels

Asp^9-bivalirudin levels were assessed in compounding solutions prepared by a compounding process which comprised adding the pH-adjusting solution at a constant rate to the bivalirudin solution and mixing under high shear conditions.

The bivalirudin solution (675 mL) comprised 64.4 g dissolved in 2.64% w/w mannitol solution. The bivalirudin solution was divided in half for evaluation of adding the pH-adjusting solution at two different mixing rates. The bivalirudin solution was placed in a vessel with a high shear mixer.

The pH-adjusting solution (131.2 mL) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution. The pH-adjusting solution was loaded into a burette, which was connected on the bottom to a tube with a hose. The tube was positioned at the base of the high shear mixer blade inside the mixing vessel containing the bivalirudin solution. A clamp was used to restrict the pH-adjusting solution from passing through the hose.

The speed of the high shear mixer (Silverson Laboratory Emulsifier Model L4RT) was set to either 1500 rpm or 3000 rpm. The clamp on the hose was removed and the pH-adjusting solution was then added to the bivalirudin solution at a controlled, constant rate of approximately 2 L/min.

For the solution mixed at 3000 rpm, addition of approximately 10 mL of the pH-adjusting solution resulted in a pH of the compounding solution of 5.25. The volume of the compounding solution was then adjusted to a final volume of 562.5 mL.

For the compounding solution mixed at 1500 rpm, after the pH-adjusting solution was added, the mixing speed was increased to approximately 4500 rpm for a short period of time to allow faster and complete dissolution, and then reduced to 1500 rpm until the solution was completely dissolved. After complete dissolution, the resulting compounding solution was moved from the vessel to a beaker which contained a stir bar. The solution was adjusted to a target pH of 5.3 using 19 mL of the pH-adjusting solution, and then the volume was adjusted to a final volume of 562.5 mL.

For both mixing conditions, the pH was monitored throughout the addition of the pH-adjusting solution to the bivalirudin solution to form the compounding solution. The level of Asp^9-bivalirudin was measured by HPLC before (baseline) addition of the pH-adjusting solution, after the addition of the pH-adjusting solution (measurement #2), and after the volume of the compounding solution was adjusted to mark (measurement #3). The results of the HPLC analysis are shown in Tables 5a and 5b.

Notably, when the compounding solution was mixed at 3000 rpm, a material precipitated as the pH-adjusting solution was added, first as a milky white dispersion, and then as a semi-transparent aggregate. By the time that all of the pH-adjusting solution was added, most of the precipitated material had dissolved.

Similarly, when the compounding solution was mixed at 1500 rpm, a material also precipitated as the pH-adjusting

solution was added, first as a milky white dispersion, and then as a semi-transparent aggregate.

TABLE 5a

pH and average Asp^9-bivalirudin levels before and after addition of pH-adjusting solution at 1500 rpm.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample taken before addition of pH-adjusting solution	~2.5	0.38
#1	Sample taken of the compounding solution after addition of pH-adjusting solution	~6.0	0.31
#2	Sample taken of the compounding solution after compounding solution was adjusted to mark	5.3	0.34

TABLE 5b

pH and average Asp^9-bivalirudin levels before and after addition of pH-adjusting solution at 3000 rpm.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample taken from bivalirudin solution before addition of pH-adjusting solution	~2.5	0.43
#1	Sample taken of the compounding solution after addition of pH-adjusting solution	~5.6	0.41
#2	Sample taken of the compounding solution after compounding solution was adjusted to mark	5.25	0.40

These results indicate that there were no changes in Asp^9-bivalirudin levels before and after the addition of the pH-adjusting solution at a constant rate, and under high shear mixing conditions. Moreover, it was surprising that bivalirudin was not susceptible to degradation by high shear mixing even up to 4500 rpm, even though many peptides are susceptible to degradation by high shear mixing or by high temperatures.

Example 4

Effects of Rapidly Adding pH Adjusting Solution to the Bivalirudin Solution Under Inefficient Mixing Conditions—Large Scale Study

The effects of rapidly adding the pH-adjusting solution to the bivalirudin solution under slow mixing conditions were studied. Multiple batches were generated by the same method.

The bivalirudin solution (~110 L) comprised bivalirudin at a concentration of 0.050 mg/ml dissolved in a 2.64% w/w mannitol solution. The pH-adjusting solution (~40 L) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution.

The pH-adjusting solution was added to the bivalirudin solution 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. Both paddle mixers operated at a rate of between about 400 and about 800 rpm. When the pH-adjusting solution was added to the bivalirudin solution, a large amount of a material precipitated. The precipitated material eventually dissolved after continued mixing. After the pH-adjusting solution was completely added and mixed, the compounding solution was sterile filtered and lyophilized, and the lyophilizate was analyzed by HPLC for impurity levels.

This study analyzed impurity levels and reconstitution times of the lyophilizate of 89 batches. Results from the study are displayed in Table 6 (note that not all of the samples were analyzed for each characteristic).

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

According to these results, the batches displayed a maximum level of Asp^9-bivalirudin of 3.6%, while the mean level of Asp^9-bivalirudin was 0.5%. Furthermore, the standard deviations relative to the means were larger. These results suggest that the characteristics of the batches generated by this process may be variable.

Example 5

Effects of Adding pH Adjusting Solution at a Constant Rate and Under Efficient Mixing Conditions—Large Scale Study

The effects of adding the pH-adjusting solution to the bivalirudin solution at a constant rate and under efficient mixing condition were studied. Multiple batches were generated by the same method.

The bivalirudin solution (~110 L) comprised bivalirudin at a concentration of 0.050 mg/ml dissolved in a 2.64% w/w mannitol solution. The pH-adjusting solution (~40 L) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution.

The pH-adjusting solution was added to the bivalirudin solution at a controlled rate of 2 L/min using a peristaltic pump. A homogenizer was used to provide a high shear mixing environment (between about 1000 rpm and 1300 rpm) within the bivalirudin solution as the pH-adjusting solution was added, A feed tube extended from the peristaltic pump to an inlet in the homogenizer, so that the pH-adjusting solution was added to the bivalirudin solution at a site adjacent to the blades of the homogenizer. Simultaneously, a paddle mixer was used for mixing (mixing rate of between about 300 rpm and 700 rpm) near the surface of the bivalirudin solution. As the pH-adjusting solution was added, a small amount of material precipitated which later dissolved. After the pH-adjusting solution was completely added, the compounding solution was sterile filtered and lyophilized, and the lyophilizate was analyzed by HPLC for impurity levels.

In this study, which prepared 25 batches, analysis of impurity levels and reconstitution times for the lyophilizate are shown in Table 7.

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

The results of one batch was not included in the data presented in Table 7, as the method used to generate the batch was not compliant with the protocol established for this study.

Comparison of the batches of Example 5 to the batches of Example 4 revealed that the batches of Example 5 displayed significantly lower mean levels of Asp^9-bivalirudin, total impurities, and largest unknown impurity. The batches of Example 5 also showed smaller standard deviations relative to the means for levels of Asp^9-bivalirudin, total impurities, and largest unknown impurity. Together, these results suggest that the process demonstrated in Example 5 produced batches generally and consistently having lower levels of impurities than the process of Example 4.

In addition, the batches of Example 5 displayed significantly shorter mean reconstitution times, and smaller standard deviations relative to the mean, as compared to the batches of Example 4. These results suggest that the process of Example 5 generated batches generally and consistently having shorter reconstitution times than the batches generated by the process of Example 4.

A comparison between the batches generated in Example 4 and Example 5 is shown in Table 8 which assesses the mean values of the characteristics of the batches, and Table 9, which examines the maximum values of the characteristics of the batches:

TABLE 8

Comparison of mean values of the characteristics of the batches generated by the compounding process of Example 4 and the characteristics of the batches generated by the compounding process of Example 5 ($p < 0.05$).

	Batches of Example 4 Mean ± SD	Batches of Example 5 Mean ± SD	% change*	p
Asp^9-bivalirudin (%)	0.5 ± 0.4	0.3 ± 0.1	−40%	<0.0003
Total impurities (%)	1.4 ± 0.5	1.0 ± 0.4	−29%	<0.004
Largest unknown impurity (%)	0.3 ± 0.1	0.2 ± 0.1	−33%	0.03
Reconstitution time (seconds)	30 ± 12	18 ± 6	−40%	<0.000001

*% change = 100 × [(mean value from Example 5 batches) − (mean value from Example 4 batches)]/(mean value from Example 4 batches)

TABLE 9

Comparison of maximum values of the characteristics of the batches generated by the compounding process of Example 4 and the characteristics of the batches generated by the compounding process of Example 5 ($p < 0.05$).

	Batches of Example 4 Maximum	Batches of Example 5 Maximum	% change*
Asp^9-bivalirudin (%)	3.6	0.6	−83%
Total impurities (%)	3.0	2.0	−33%
Largest unknown impurity (%)	0.5	0.3	−40%
Reconstitution time (seconds)	72	42	−42%

*% change = 100 × [(maximum value from Example 5 batches) − (maximum value from Example 4 batches)]/(maximum value from Example 4 batches)

As shown in Table 8, the levels of Asp^9-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution time are all significantly less in the batches made by the process of Example 5 as compared to the batches made by the process of Example 4. Further, Table 9 shows that the maximum values for the levels of Asp^9-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution time are also greatly less in the batches made by the process of Example 5 as compared to the batches made by the process of Example 4

Example 6

Generation of D-Phe^{12}-Bivalirudin in Stored Bivalirudin Pharmaceutical Formulations

The bivalirudin pharmaceutical formulations prepared in Examples 1-3 were stored in refrigerated conditions and then evaluated by HPLC to compare the level of D-Phe^{12}-bivalirudin impurities among the different formulation methods. The results show that the levels of D-Phe^{12}-bivliarudin were similar across each formulation method, which indicated that the methods did not influence the generation of D-Phe^{12}-bivliarudin.

Having thus described in detail embodiments of the present invention, it is to be understood that the invention defined by the above paragraphs is not to be limited to particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit or scope of the present invention.

SEQUENCE LISTING

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1               5                   10                  15

Glu Glu Tyr Leu
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```

What is claimed is:

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

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.

4. The pharmaceutical batches of claim **1**, wherein the batches have a maximum total impurity level that does not exceed about 2% as measured by HPLC.

5. The pharmaceutical batches of claim **4**, wherein the maximum total impurity level does not exceed about 1% as measured by HPLC.

6. The pharmaceutical batches of claim **5**, wherein the maximum total impurity level does not exceed about 0.5% 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.

11. 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 reconstitution time that does not exceed about 42 seconds and a maximum total impurity level that does not exceed about 2% as measured by HPLC.

12. The pharmaceutical batches of claim 11, wherein the maximum reconstitution time does not exceed about 30 seconds.

13. The pharmaceutical batches of claim 12, wherein the maximum reconstitution time does not exceed about 21 seconds.

14. The pharmaceutical batches of claim 11, wherein the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent.

15. The pharmaceutical batches of claim 14, wherein the bulking agent is a sugar.

16. The pharmaceutical batches of claim 15, wherein the sugar is mannitol.

17. The pharmaceutical batches of claim 1, wherein the base is sodium hydroxide.

18. The pharmaceutical batches of claim 11, wherein the base is sodium hydroxide.

19. Pharmaceutical batches of a drug product comprising bivalirudin (SEQ ID NO: 1) and mannitol for use as an anticoagulant in a subject in need thereof, wherein the batches have a pH adjusted by sodium hydroxide, said pH is about 5-6 when reconstituted in an aqueous solution for injection, and wherein the batches have a maximum reconstitution time that does not exceed about 42 seconds and a maximum total impurity level that does not exceed about 2% as measured by HPLC.

20. The pharmaceutical batches of claim 19, wherein the batches have a maximum impurity level of Asp^{9}-bivalirudin that does not exceed about 0.6% as measured by HPLC.

* * * * *

US007598343B1

(12) **United States Patent**
Krishna et al.

(10) **Patent No.: US 7,598,343 B1**
(45) **Date of Patent: *Oct. 6, 2009**

(54) **PHARMACEUTICAL FORMULATIONS OF BIVALIRUDIN AND PROCESSES OF MAKING THE SAME**

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(73) Assignee: **The Medicines Company**, Parsippany, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/180,551**

(22) Filed: **Jul. 27, 2008**

(51) **Int. Cl.**

A61K 38/55	(2006.01)
C07K 7/08	(2006.01)
C07K 7/64	(2006.01)
C07K 1/00	(2006.01)
C07K 1/04	(2006.01)
C07K 14/00	(2006.01)

(52) **U.S. Cl.** **530/325**; 530/324; 530/333; 530/334; 530/335; 514/13

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Pharmaceutical batch(es) or pharmaceutical formulation(s) comprising bivalirudin as the active ingredient, and a method of preparing the pharmaceutical batch(es) or pharmaceutical formulation(s). The pharmaceutical batch(es) or pharmaceutical formulation(s) may have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. Also, the pharmaceutical batch(es) or pharmaceutical formulation(s) may have a reconstitution time that does not exceed about 42 seconds. The method of preparing the pharmaceutical batch(es) or pharmaceutical formulation(s) may comprise dissolving bivalirudin in a solvent to form a first solution, efficiently mixing a pH-adjusting solution with the first solution to form a second solution in which the pH-adjusting solution may comprise a pH-adjusting solution solvent, and removing the solvent and the pH-adjusting solution solvent from the second solution.

20 Claims, No Drawings

PHARMACEUTICAL FORMULATIONS OF BIVALIRUDIN AND PROCESSES OF MAKING THE SAME

INCORPORATION BY REFERENCE

The foregoing applications, and all documents cited therein or during their prosecution ("appln cited documents") and all documents cited or referenced in the appln cited documents, and all documents cited or referenced herein ("herein cited documents"), and all documents cited or referenced in herein cited documents, together with any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

FIELD OF THE INVENTION

Various embodiments of the present invention are generally directed towards a method for preparing a pharmaceutical batch(es) or a pharmaceutical formulation(s) comprising bivalirudin as the active ingredient. Some embodiments of the present invention are also directed towards a pharmaceutical batch(es) or a pharmaceutical formulation(s) comprising bivalirudin as the active ingredient. For example, certain embodiments of the present invention relate to pharmaceutical batch(es) or pharmaceutical formulation(s) of a drug product having reduced levels of a major degradation product, i.e., Asp^9-bivalirudin, which may contribute to improved stability and shelf-life. In some embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In various embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) of the present invention are characterized by a reconstitution time that does not exceed about 42 seconds. Various embodiments of the invention further generally relate to an injectable dosage form comprising a pharmaceutical formulation and a vehicle, and methods of administering the injectable dosage form.

BACKGROUND OF THE INVENTION

Anticoagulants are substances that prevent blood from clotting. They are commonly used during percutaneous coronary intervention (PCI) and other catherization techniques in order to reduce bleeding complications. One class of anticoagulants is direct thrombin inhibitors that disrupt the activity of thrombin, an important protein in the coagulation cascade. In 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 procedures.

Bivalirudin, also known as Hirulog-8, is a synthetic congener of the naturally occurring thrombin peptide inhibitor hirudin, which is found in the saliva of the medicinal leech *Hirudo medicinalis*. Hirudin consists of 65 amino acids, although shorter peptide segments have proven to be effective as thrombin inhibitors. U.S. Pat. No. 5,196,404 (incorporated herein by reference) discloses bivalirudin among these shorter peptides that demonstrate an anticoagulant activity. However, in contrast to hirudin, bivalirudin is a reversible inhibitor, which is ideal for temporary prevention of blood clotting during catherization procedures.

In light of the medical and therapeutic applications of bivalirudin, it is essential that the bivalirudin formulation maintains a high level of purity. The bivalirudin formulation is a compounded formulation containing bivalirudin, e.g., bivalirudin undergoes a compounding process following its synthesis so that it is usable and stable for medical and therapeutic applications.

Impurities such as Asp^9-bivalirudin (deamidation of asparagine at position 9 of bivalirudin to aspartic acid) and D-Phe^{12}-bivalirudin (isomerization of L-phenylalanine at position 12 of bivalirudin to the D-isomer) may be generated during the synthesis of bivalirudin. Consequently, processes for synthesizing bivalirudin have been developed to minimize the generation of impurities. However, impurities can also be produced during the compounding process, i.e., the process to generate a formulation of bivalirudin. It has been shown that various compounding processes can result in formulations that have up to 12% of Asp^9-bivalirudin, which may affect product stability and shelf-life. Therefore, development of a compounding process for formulating bivalirudin that consistently generates formulations having low levels of impurities is desirable.

Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention.

SUMMARY OF THE INVENTION

Various embodiments of the present invention relates to a compounding process for preparing a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient. In certain embodiments, the compounding process comprises (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 Asp^9-bivalirudin in the second solution is minimized; and (iii) removing the solvent from the second solution.

In some embodiments, the pH of the second solution does not exceed about 8. In some embodiments, the pH of the second solution does not exceed about 7. In further embodiments, the pH of the second solution does not exceed about 6.

In certain embodiments, efficient mixing is achieved by adding the pH-adjusting solution to the first solution, by adding the first solution to the pH-adjusting solution, or a combination thereof. In some embodiments, the pH-adjusting solution is added to the first solution in portions. In further embodiments, the pH-adjusting solution is added to the first solution at a constant rate.

In some embodiments, efficient mixing is achieved by using one or more mixing devices. In certain embodiments, the mixing device is selected from a group consisting of a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. In some embodiments, the mixing device is a homogenizer, a paddle mixer, or a combination thereof.

In further embodiments, the efficient mixing is achieved through high shear mixing.

In certain embodiments, removal of the solvent from the second solution is achieved through lyophilization.

In some embodiments, the compounding process may further comprise sterilization of the second solution before removal of the solvent. In certain embodiments, sterilization is achieved by aseptic filtration.

Various embodiments of the present invention also relate to a pharmaceutical batch(es) or a pharmaceutical formulation(s) prepared by the compounding process of the

invention. In certain embodiments, a pharmaceutical batch (es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In some embodiments, a pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum total impurity level that does not exceed about 2%. In additional embodiments, a pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

In addition, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) 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; and (iii) removing the solvent from the second solution.

In certain embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%. In some embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.4%. In further embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.3%.

In some embodiments of the present invention, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum total impurity level that does not exceed about 2%. In certain embodiments, the maximum total impurity level does not exceed about 1%. In additional embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum level of D-Phe^{12}-bivalirudin that does not exceed about 2.5%.

In other embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds. In some embodiments, the maximum reconstitution time does not exceed about 30 seconds. In further embodiments, the maximum reconstitution time does not exceed about 21 seconds.

In some embodiments of the present invention, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In additional embodiments, the bulking agent is a sugar. In further embodiments, the sugar is mannitol.

In certain embodiments, efficient mixing is achieved by adding the pH-adjusting solution to the first solution, by adding the first solution to the pH-adjusting solution, or a combination thereof. In some embodiments, the pH-adjusting solution is added to the first solution at a constant rate. In further embodiments, efficient mixing is achieved by using one or more mixing devices. In yet additional embodiments, the efficient mixing is achieved through high shear mixing.

Moreover, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) 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; and (iii) removing the solvent from the second solution; wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) are characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%.

Certain embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, said pharmaceutical batch(es) or pharmaceutical formulation(s) 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; and (iii) removing the solvent from the second solution; wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

Furthermore, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof. Some embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product or a pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%.

In some embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.4%. In certain embodiments, the maximum impurity level of Asp^9-bivalirudin does not exceed about 0.3%.

In additional embodiments, the pharmaceutical batch(es) or pharmaceutical formulation(s) is further characterized by a maximum total impurity level that does not exceed about 2%. In certain embodiments, the maximum total impurity level does not exceed about 1%. In some embodiments, the maximum total impurity level does not exceed about 0.5%.

In certain embodiments of the invention, the pharmaceutical batch(es) or pharmaceutical formulation(s) is further characterized by a maximum level of D-Phe^{12}-bivalirudin that does not exceed about 2.5%.

In some embodiments, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In further embodiments, the bulking agent is a sugar. In yet additional embodiments, the sugar is mannitol.

Some embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum reconstitution time that does not exceed about 42 seconds.

In certain embodiments, the maximum reconstitution time does not exceed about 30 seconds. In some embodiments, the maximum reconstitution time does not exceed about 21 seconds.

In some embodiments of the invention, the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent. In certain embodiments, the pharmaceutically acceptable carrier is a bulking agent. In further embodiments, the bulking agent is a sugar. In yet additional embodiments, the sugar is mannitol.

Also, various embodiments of the present invention relate to a pharmaceutical batch(es) of a drug product or pharmaceutical formulation(s) comprising bivalirudin as an active

ingredient for use as an anticoagulant in a subject in need thereof, wherein the pharmaceutical batch(es) or pharmaceutical formulation(s) is characterized by a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%, a maximum total impurity level that does not exceed about 2%, and a maximum reconstitution time that does not exceed about 42 seconds.

These and other embodiments are disclosed or are obvious from and encompassed by, the following Detailed Description.

DETAILED DESCRIPTION

Various embodiments of the present invention relate to a compounding process for preparing a pharmaceutical batch(es) of a drug product, which results in pharmaceutical formulations comprising bivalirudin and a pharmaceutically acceptable carrier. Certain embodiments of the present invention also relate to a pharmaceutical batch(es) of a drug product, resultant pharmaceutical formulation(s) comprising bivalirudin and a pharmaceutically acceptable carrier, and an injectable dosage form comprising the pharmaceutical formulation and a vehicle.

As used here, "batch" or "pharmaceutical batch" refers to material produced by a single execution of a compounding process of various embodiments of the present invention. "Batches" or "pharmaceutical batches" as defined herein 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), 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.

The term "drug product" herein refers to an active ingredient and a pharmaceutically acceptable carrier.

The term "formulation" or "pharmaceutical formulation" refers to a unit dose of an active pharmaceutical ingredient and a pharmaceutically acceptable carrier, which is prepared by the various processes in certain embodiments of the present invention. In the case of the present pharmaceutical formulation, the active pharmaceutical ingredient is bivalirudin.

The term "carrier" refers to any component of the pharmaceutical batch(es) or pharmaceutical formulation(s) that, for example, serves as a bulking agent or functions as a stabilizing agent for the active ingredient. A bulking agent refers to any material that fills or provides volume to the active ingredient. Examples of appropriate bulking agents may include, but are not limited to, sugars such as mannitol, sucrose, lactose, fructose and trehalose.

A stabilizing agent refers to any material which serves to minimize degradation of the active ingredient. Examples of stabilizing agents may include, but are not limited to, antioxidants, buffering agents, preservatives, etc.

Bivalirudin has the chemical name of 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-Leucine trifluoroacetate (salt) hydrate and has a molecular weight of 2180 daltons. Bivalirudin is made up of the amino acid sequence: (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu (SEQ ID NO: 1). Methods for the synthesis of bivalirudin may include, but are not limited to, solid-phase peptide synthesis, solution-phase peptide synthesis, or a combination of solid-phase and solution-phase procedures (e.g., U.S. Pat. No. 5,196,404; Okayama et al., *Chem. Pharm. Bull.* 1996, 44: 1344-1350; Steinmetzer et al., *Eur. J. Biochem.* 1999, 265: 598-605; PCT Patent Application WO 91/02750).

As described above, Asp^9-bivalirudin is formed due to deamidation of asparagine at position 9 of bivalirudin to aspartic acid. The amino acid sequence of Asp^9-bivalirudin is: (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu (SEQ ID NO: 2). Further, D-Phe^{12}-bivalirudin is generated from isomerization of L-phenylalanine at position 12 of bivalirudin to the D-isomer. The amino acid sequence of D-Phe^{12}-bivalirudin is (D-Phe)-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-(D-Phe)-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu (SEQ ID NO: 3)

Bivalirudin inhibits blood clotting by binding to thrombin, a key serine protease in blood clot formation. This synthetic 20 amino acid peptide binds to thrombin at the catalytic site and at the anion-binding exocite, thereby inhibiting thrombin. Thrombin plays a central role in hemostasis. The coagulation pathway initiates clotting when thrombin, a serine protease, converts fibrinogen into fibrin. Additionally, thrombin activates Factor XIII into Factor XIIIa (the latter which links fibrin polymers covalently), Factors V and VIII (which promote thrombin generation), and platelets (which help propagate the thrombus).

The method of delivery of bivalirudin may be through intravenous administration. Bivalirudin may be supplied in single-use vials as a white lyophilized sterile cake. Each single-use vial may contain about 250 mg of bivalirudin. When reconstituted with a sterile aqueous solution for injection, the product yields a clear to opalescent, colorless to slightly yellow, solution. Such a solution has a pH of about 5-6.

The pharmaceutical batch(es) or pharmaceutical formulation(s) according to certain embodiments of the present invention may be used in any application which requires altered or inhibited thrombin activity. The pharmaceutical batch(es) or pharmaceutical formulation(s) may be used to alter or inhibit the coagulation cascade, for example, as an anticoagulant.

Approved indications include treatment in patients with unstable angina undergoing percutaneous translumnial coronary angioplasty; administration with the provisional use of glycoprotein IIb/IIIa inhibitor for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI); and treatment in patients with, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. Also, the pharmaceutical batch(es) or pharmaceutical formulation(s) according to various embodiments of the present invention can be used for the prevention and treatment of venous thromboembolic disease.

Process for Preparing a Pharmaceutical Batch(es) or a Pharmaceutical Formulation(s)

Various embodiments of the present invention relate to a compounding process for preparing a pharmaceutical batch(es) or pharmaceutical formulation(s) comprising bivalirudin.

1) Dissolving Bivalirudin in a Solvent to Form a Bivalirudin Solution

In the compounding process of various embodiments of the present invention, bivalirudin may be dissolved in a solvent to form a bivalirudin solution. Bivalirudin may be commercially purchased or synthesized by various procedures as described above. The concentration of bivalirudin in the solvent may be

between about 0.010 g/mL and about 1 g/mL, or between about 0.050 g/mL and about 0.1 g/mL. Solvents may include aqueous and non-aqueous liquids, including but not limited to, mono- and di-alcohols such as methanol, ethanol, isopropyl alcohol, and propylene glycol; polyhydric alcohols such as glycerol and polyethylene glycol; buffers; and water.

The solvent may comprise carriers such as sugars. For example, the sugar may be a monosaccharide such as glucose or fructose; a disaccharide such as sucrose, maltose, or trehalose; an oligosaccharide; or a polysaccharide. Alternatively, the sugar may be a sugar alcohol, such as sorbitol or mannitol. The quantity of carrier in the solvent may be adjusted to provide a pharmaceutical batch or pharmaceutical formulation preferably having a ratio of the carrier to the active ingredient of between about 5:1 and about 1:10, or between about 1:1 and about 1:4, or more preferably about 1:2.

Bivalirudin can be dissolved in the solvent by methods known in the art, preferably by adding the bivalirudin to the solvent. For example, bivalirudin may be added to the solvent rapidly, slowly, in portions, at a constant rate, at a variable rate, or a combination thereof. A mixing device known in the art may be used to dissolve bivalirudin. Examples of mixing devices may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing device may be applied at a mixing rate between about 100 and about 2000 rpm, or between about 300 and about 1500 rpm. The solution resulting from dissolving the bivalirudin in the solvent is referred to here as the "bivalirudin solution" or alternatively the "first solution."

2) Mixing a pH-Adjusting Solution with the Bivalirudin Solution to Form a Compounding Solution

The compounding process may comprise mixing a pH-adjusting solution with the bivalirudin solution to form a compounding solution. The pH-adjusting solution may be prepared before, after, or simultaneously with, the bivalirudin solution.

The pH-adjusting solution may comprise a base dissolved in a solvent, wherein the solvent is referred to here as the "pH-adjusting solution solvent." In other words, the solution resulting from the combination of the base with the pH-adjusting solution solvent is referred to here as the "pH-adjusting solution." The pH-adjusting solution may also comprise a neat base such as pyridine or a volatilizable base such as ammonium carbonate.

The base may be an organic base or an inorganic base. The terms "inorganic base" and "organic base," as used herein, refer to compounds that react with an acid to form a salt; compounds that produce hydroxide ions in an aqueous solution (Arrhenius bases); molecules or ions that capture hydrogen ions (Bronsted-Lowry bases); and/or molecules or ions that donate an electron pair to form a chemical bond (Lewis bases). In certain processes, the inorganic or organic base may be an alkaline carbonate, an alkaline bicarbonate, an alkaline earth metal carbonate, an alkaline hydroxide, an alkaline earth metal hydroxide, an amine, or a phosphine. For example, the inorganic or organic base may be an alkaline hydroxide such as lithium hydroxide, potassium hydroxide, cesium hydroxide, or sodium hydroxide; an alkaline carbonate such as calcium carbonate or sodium carbonate; or an alkaline bicarbonate such as sodium bicarbonate.

Solvents may include aqueous and non-aqueous liquids, including but not limited to, mono- and di-alcohols such as methanol, ethanol, isopropyl alcohol, and propylene glycol; polyhydric alcohols such as glycerol and polyethylene glycol; buffers; and water. The pH-adjusting solution solvent may comprise carriers such as dissolved sugars. For instance, the sugar may be a monosaccharide such as glucose or fructose; a disaccharide such as sucrose, maltose, or trehalose; an oligosaccharide; or a polysaccharide. The sugar may also be a sugar alcohol, such as sorbitol or mannitol. The quantity of the carrier in the pH-adjusting solution solvent may be adjusted to provide the final product as described above.

The base is mixed or dissolved in the pH-adjusting solution solvent. The mixing or dissolution can be performed by methods known in the art. For instance, the base may be added to the pH-adjusting solution solvent rapidly, slowly, in portions, at a constant rate, at a variable rate, or a combination thereof. Also, a mixing device known in the art may be used to mix the base and the pH-adjusting solution solvent. Examples of mixing devices may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing device may be applied at a mixing rate between about 100 and about 1500 rpm, or between about 300 and about 1200 rpm. The base is added/mixed with the pH-adjusting solution solvent in a quantity that will result in a pH-adjusting solution that is characterized as being between about 0.01 N and about 5 N, or between about 0.1 N and 1 N.

The pH-adjusting solution may then be mixed with the bivalirudin solution. This mixing may occur by adding the pH-adjusting solution to the bivalirudin solution. Alternatively, the bivalirudin solution may be added to the pH-adjusting solution, or the pH-adjusting solution and the bivalirudin solution may be added simultaneously (into a separate vessel), or there may be a combination of these addition methods thereof. It is important during the adding or mixing of the pH-adjusting solution and the bivalirudin solution that pH is controlled. See below. The solution resulting from mixing the pH-adjusting solution and the bivalirudin solution is referred to here as the "compounding solution," or the "second solution." The compounding solution or the second solution can refer to the bivalirudin solution during or after the pH-adjusting solution is added, or can refer to the pH-adjusting solution during or after the bivalirudin solution is added, or can refer to the resulting solution formed during or after both the pH-adjusting solution and the bivalirudin solution are added together.

The mixing of the pH-adjusting solution and the bivalirudin solution may occur under controlled conditions. For example, temperature may be controlled by means known in the art, such as by mixing the pH-adjusting solution and the bivalirudin solution in a vessel inside a cooling jacket. The temperature may be set between about 1° C. and about 25° C., or between about 2° C. and about 10° C. In some instances, the temperature may exceed 25° C. for limited periods of time. Also, the mixing of the pH-adjusting solution and the bivalirudin solution may occur under controlled conditions such as under nitrogen, etc.

The pH-adjusting solution will be efficiently mixed with the bivalirudin solution to form the compounding solution. Efficient mixing of the pH-adjusting solution with the bivalirudin solution will minimize levels of Asp^9-bivalirudin in the compounding solution. "Minimize" as used herein refers to the generation of a level of Asp^9-bivalirudin in the compounding solution that is less than about 0.6%, or less than about 0.4%, or less than about 0.3%.

Critical to the efficient mixing is the fact that the isoelectric point of bivalirudin is about 3.6. As the bivalirudin solution itself has a pH of between about 2.5 and about 2.8, and the compounding solution is adjusted to a final pH of between about 5.1 and about 5.5, a portion of bivalirudin precipitates out during the addition of the pH-adjusting solution. The

characteristics of this precipitate are critical to regulating and controlling Asp^9-bivalirudin levels.

For example, if the pH-adjusting solution is introduced without efficient mixing, a dense precipitate may form. This dense precipitate may result in a slower dissolution and the surrounding solution being maintained at a high pH for extended time. Although the concentration of bivalirudin in the solution phase is low, it is also very susceptible to Asp^9-bivalirudin generation at this high pH.

Conversely, 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. Thus, process operations to control the pH transition through efficient mixing provide a significant process improvement and control of Asp^9-bivalirudin levels.

Not wishing to be bound by theory, Asp^9-bivliarudin may also be generated by high pH or "hot spots," which are defined here as concentrated sites in the compounding solution that have much higher pH levels than the surrounding environment. An example of a hot spot is a site in the compounding solution having a pH of about 12, while the surrounding solution has a pH of about 5. Asp^9-bivliarudin may also be generated by high pH levels in the compounding solution in general. It has been found that efficient mixing reduces the generation of "hot spots" or high levels of pH in the compounding solution while the pH-adjusting solution and the bivalirudin solution are being added/mixed. Thus, efficient mixing may control the overall pH level of the compounding solution to a level not exceeding about 8, or a level not exceeding about 7, or a level not exceeding about 6, or even a level not exceeding about 5.5.

Efficient mixing is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution. This may be achieved through various methods. One such method may be to add or combine the pH-adjusting solution and bivalirudin solution portion-wise, i.e., in portions. For instance, the pH-adjusting solution may be added to the bivalirudin solution in portions of set quantities, wherein each addition is separated by a period of time. The quantity of pH-adjusting solution may be approximately equal or may vary among the portions. For example, the pH-adjusting solution may be added in four portions, wherein each portion comprises about 25% of the total pH-adjusting solution volume. As another example, the pH-adjusting solution may be added in three portions, such that the first portion comprises about 45% of the total pH-adjusting solution volume, the second portion comprises about 30% of the total pH-adjusting solution volume, and the third portion comprises about 25% of the total pH-adjusting solution volume.

The pH-adjusting solution may also be added in portions such that there is a combination of equal and unequal quantities. For instance, the pH-adjusting solution may be divided into four portions, wherein the first portion comprises about 45% of the total pH-adjusting solution volume, the second portion comprises about 25% of the total pH-adjusting solution volume, and the third and fourth portions each comprise about 15% of the total pH-adjusting solution volume.

The period of time between the addition of each portion may vary. This period may be a set duration of time regardless of the number of portions and/or volume of the portions to be added. Alternatively, the period of time may vary according to the number of portions and/or volume of the portions to be added. For example, the period of time between adding four equal portions may be about 5 minutes between each addition. As another example, the period of time after adding a first portion comprising about 60% of the total pH-adjusting solution volume may be about 15 minutes, while the period of time after adding a second portion comprising about 40% of the total pH-adjusting solution volume may be about 5 minutes.

The period of time between the addition of each portion may also be based upon a set total time for adding the pH-adjusting solution. For instance, if the total time for adding a pH-adjusting solution is set at about 20 minutes, then the period of time after adding each portion comprising about 25% of the total pH-adjusting solution volume may be about 5 minutes. In certain embodiments of the present invention, the total time for adding the pH-adjusting solution may be a duration of between about 5 minutes and about 40 minutes, or between about 10 minutes and about 30 minutes, or between about 15 minutes and about 25 minutes.

Efficient mixing may also be achieved by adding the pH-adjusting solution to the bivalirudin solution at a constant rate. The pH-adjusting solution may be added at a rate of between about 0.5% and about 50% of the total pH-adjusting solution volume, per minute; or between about 1% and about 25% of the total pH-adjusting solution volume, per minute; or between about 3% and about 8% of the total pH-adjusting solution volume, per minute.

The pH-adjusting solution may alternatively be added at a variable rate to the bivalirudin solution. As an example, the rate may increase from about 5% to about 20% of the total pH-adjusting solution volume per minute during the addition of the pH-adjusting solution.

The pH-adjusting solution may also be added to the bivalirudin solution portion-wise, wherein each portion is added at a constant or variable rate. The portions may be added in equal amounts, unequal amounts, or a combination thereof. Further, each portion may be added at the same or different constant rates, or the same or different variable rates, or a combination thereof. As an example, the first portion comprising 60% of the total pH-adjusting solution may be added at 5% of the portion volume per minute, while four subsequent portions each comprising about 10% of the total pH-adjusting solution may be added at 10% of the portion volume per minute.

Furthermore, efficient mixing may be achieved through the use of one or more mixing devices. Examples of mixing devices that may be used in various embodiments of the present invention may include, but are not limited to, a paddle mixer, magnetic stirrer, shaker, re-circulating pump, homogenizer, and any combination thereof. The mixing rate of, for instance, a paddle mixer may be between about 100 rpm and 1000 rpm, or between about 400 rpm and about 800 rpm. The mixing rate for, as an example, a homogenizer (i.e., high shear mixing) may be between about 300 and about 6000 rpm, or between about 1500 rpm and about 3000 rpm.

Since most proteins and peptides are susceptible to degradation by high shear, it was initially thought that bivalirudin could only be formulated using a compounding process employing low shear. Surprisingly, high shear mixing, such as through the use of a homogenizer, could successfully be used in the compounding process.

The mixing device may mix continuously during the addition of the pH-adjusting solution, or at specific periods of time, e.g., between the additions of portions, after the pH-adjusting solution is added, etc.

In addition, more than one mixing device may be used when the pH-adjusting solution is added to the bivalirudin solution. For example, a paddle mixer may be used at the surface of the bivalirudin solution and a homogenizer may be used near the bottom of the bivalirudin solution. When more

than one mixing device is used, they may be operated at the same mixing rate or different mixing rates, or a combination thereof. The mixing devices may also be operated at the same periods of time, at different periods of time, or a combination thereof, during the addition of the pH-adjusting solution. Similarly, a mixing device may be used with the addition of the bivalirudin solution to the pH-adjusting solution, or with the addition of the pH-adjusting solution and the bivalirudin solution together.

Moreover, efficient mixing may be achieved through adding the pH-adjusting solution to specific sites within the bivalirudin solution. For instance, the pH-adjusting solution may be added to the surface of the bivalirudin solution or to the bottom of the bivalirudin solution. In the cases wherein a mixing device is used, the pH-adjusting solution may be added to the site of the mixing device, e.g., at the site of the paddles of the paddle mixer or the blades of the homogenizer. The pH-adjusting solution may also be added to more than one site in the bivalirudin solution; for example, the pH-adjusting solution may be added simultaneously at the top of the bivalirudin solution and at the site of the mixing device. Alternatively, the bivalirudin solution may be added to the pH-adjusting solution at specific sites and at more than one site within the pH-adjusting solution, as described above.

Optionally, once the compounding solution is formed, the pH or the final volume of the compounding solution may be adjusted to a specified level before removal of the solvent (see below). The pH or volume can be adjusted using methods known in the art, for instance, the addition of a pH-adjusting solution as described above.

The compounding solution may also be sterilized before the removal of solvent. The compounding solution may undergo aseptic filtration using, for example, a 0.2 μm disposable membrane filter, to sterilize the compounding solution. Techniques of sterilizing the compounding solution are known in the art (see, e.g., Berovic, *Biotechnol. Annu. Rev.* 2005, 11:257-79).

Furthermore, following sterilization, the compounding solution may be aliquotted into containers such as vials, bottles, ampoules, syringes, etc.

3) Removal of Solvent from the Compounding Solution

The compounding process of various embodiments of the invention may comprise removing solvents from the compounding solution in order to produce a pharmaceutical batch(es) or pharmaceutical formulation(s).

Removal of the solvent from the compounding solution may be achieved through lyophilization, which comprises freezing the compounding solution and then reducing the surrounding pressure to allow the frozen solvent/moisture in the material to sublime directly from a solid phase to a gas phase. The lyophilization process may be performed by methods known in the art (see, e.g., Liu, *Pharm. Dev. Technol.* 2006, 11: 3-28; Tang et al., *Pharm. Res.* 2004, 21: 191-200; Nail et al., *Pharm. Biotechnol.* 2002, 14: 281-360; U.S. Pat. Nos. 7,351,431, and 6,821,515, which are incorporated by reference).

For example, the compounding solution may be frozen using such techniques as, but not limited to, mechanical refrigeration, dry ice, and liquid nitrogen. The temperature may be cooled to a range of between about 0° C. and about −80° C., or between about −20° C. and about −55° C. The primary lyophilization step may be characterized by a lowered pressure of between about 0.05 torr and about 10 torr, or between about 1 torr and about 5 torr. The secondary lyophilization step may be characterized by a pressure between about 0.05 torr and about 5 torr, or between about 0.1 torr and about 3 torr. In other instances, only one lyophilization step may be required.

The solvent may also be removed from the compounding solution through other techniques such as spray drying and spray-freeze drying (see, e.g., Lee, *Pharm. Biotechnol.* 2002, 13: 135-58; Maa et al., *Curr. Pharm. Biotechnol.* 2000, 1:283-302), vacuum drying, super critical fluid processing, air drying, or other forms of evaporative drying, as known in the art.

Alternative Compounding Process

In other embodiments, an alternative compounding process for preparing a pharmaceutical batch(es) or a pharmaceutical formulation(s) comprising bivalirudin may comprise (1) preparing a bivalirudin solution, (2) mixing the bivalirudin solution with a pH-adjusting solution, (3) mixing the bivalirudin/pH-adjusting solution with a carrier to form a compounding solution.

The bivalirudin solution may be prepared by mixing bivalirudin in an aqueous or non-aqueous solvent as described above. The resulting bivalirudin solution may be mixed with a pH-adjusting solution as described above, including adding the bivalirudin solution to the pH-adjusting solution, or vice-versa.

The combined bivalirudin/pH-adjusting solution may then be mixed with a carrier such as a bulking agent or stabilizing agent as described above. For example, the carrier may be a sugar such as mannitol. The bivalirudin/pH-adjusting solution and the carrier may be efficiently mixed using methods described in this application.

Pharmaceutical Batch(es) or Pharmaceutical Formulation(s) Generated by the Compounding Process

In the characterization of the pharmaceutical batch(es) and pharmaceutical formulation(s) generated by the compounding process, the levels of a parameter determined from the pharmaceutical formulation(s) prepared by a single execution of a compounding process are representative of the entire batch. Moreover, values for impurity levels include those amounts generated by the synthesis of the active pharmaceutical ingredient together with those levels generated by the compounding process.

Each pharmaceutical batch or pharmaceutical formulation prepared by the compounding process may be characterized by an impurity level of Asp^{9}-bivalirudin not exceeding about 1.5%, or not exceeding about 1%, or not exceeding about 0.6%, or not exceeding about 0.4%, or not exceeding about 0.3%.

The pharmaceutical batch(es) or the pharmaceutical formulation(s) prepared by the compounding process may be characterized by a total impurity level not exceeding about 6%, or not exceeding about 3%, or not exceeding about 2%, or not exceeding about 1%, or not exceeding about 0.5%. "Total impurity level" refers to the combined total of all measurable impurities in the pharmaceutical batch(es) or the pharmaceutical formulation(s).

The reconstitution time, i.e., time required to prepare the pharmaceutical batch(es) or the pharmaceutical formulation(s) for use, for the pharmaceutical batch(es) or the pharmaceutical formulation(s) may be characterized by a reconstitution time not exceeding about 180 seconds, or not exceeding about 72 seconds, or not exceeding about 42 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds, or not exceeding about 15 seconds.

Reconstitution time may be determined, for example, by adding 5 mL of water to a unit dosage vial comprising the bivalirudin pharmaceutical formulation. Immediately after adding the appropriate diluent (e.g., water, saline, etc.), a

timer is started. The vial is shaken vigorously, with inversion, for approximately 10 seconds. The vial is viewed to determine if the solid has dissolved. If the solid has not completely dissolved, the vial is shaken for another 10 seconds. These steps are repeated until all the solid dissolves, at which point the time is stopped and recorded.

The pharmaceutical batch(es) or the pharmaceutical formulation(s) prepared by the compounding process may relate to one or more of the characteristics described above.

Collectively, the compounding process of certain embodiments of the invention described herein may consistently generate pharmaceutical batches or pharmaceutical formulations having the same characteristics. As used herein, the use of the terms "consistent" or "consistently" in reference to the compounding process indicates that about 85% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have a specific characteristic, or wherein about 90% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have the characteristic, or about 95% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have the characteristic, or about 99% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have said characteristic, or 100% of the pharmaceutical batch(es) or pharmaceutical formulation(s) have said characteristic.

In various embodiments of the present invention, the pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a maximum impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 1%, or not exceeding about 0.6%, or not exceeding about 0.4%, or not exceeding about 0.3%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) prepared by the compounding process may be characterized by consistently having a mean impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 0.5%, or not exceeding about 0.4%, or not exceeding about 0.3%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a maximum total impurity level not exceeding about 6%, or not exceeding about 3%, or not exceeding about 2%, or not exceeding about 1%, or not exceeding about 0.5%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a mean total impurity level not exceeding about 2%, or not exceeding about 1.3%, or not exceeding about 1.1%, or not exceeding about 0.5%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a maximum largest unknown impurity level not exceeding about 1%, or not exceeding about 0.5%, or not exceeding about 0.4%, or not exceeding about 0.3%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a mean largest unknown impurity level not exceeding about 1.0%, or not exceeding about 0.27%, or not exceeding about 0.25%, or not exceeding about 0.2%.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a maximum reconstitution time not exceeding about 180 seconds, or not exceeding about 72 seconds, or not exceeding about 42 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds.

The pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may be characterized by consistently having a mean reconstitution times not exceeding about 60 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds, or not exceeding about 15 seconds.

Moreover, the pharmaceutical batch(es) or pharmaceutical formulation(s) generated by the compounding process may relate to one or more of the characteristics described above.

Pharmaceutical Batch(es) and Pharmaceutical Formulation(s)

Certain embodiments of the present invention relate to a pharmaceutical batch(es) or pharmaceutical formulation(s) comprising bivalirudin and a pharmaceutically acceptable carrier. The carrier is any component of the pharmaceutical batch(es) or pharmaceutical formulation(s) that, for example, serves as a bulking agent or functions as a stabilizing agent for the active ingredient.

The solvent may comprise carriers such as sugars. For example, the sugar may be a monosaccharide such as glucose or fructose; a disaccharide such as sucrose, maltose, or trehalose; an oligosaccharide; or a polysaccharide. Alternatively, the sugar may be a sugar alcohol, such as sorbitol or mannitol.

A pharmaceutical batch(es) or pharmaceutical formulation(s) may be characterized by an impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 1%, or not exceeding about 0.6%, or not exceeding about 0.4%, or not exceeding about 0.3%.

A pharmaceutical batch(es) or pharmaceutical formulation(s) may be characterized by a total impurity level not exceeding about 6%, or not exceeding about 3%, or not exceeding about 2%, or not exceeding about 1%, or not exceeding about 0.5

A pharmaceutical batch(es) or pharmaceutical formulation(s) may also be characterized by a reconstitution time not exceeding about 180 seconds, or not exceeding about 72 seconds, or not exceeding about 42 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds, or not exceeding about 15 seconds.

Further, a pharmaceutical batch(es) or pharmaceutical formulation(s) may relate to one or more of the characteristics described above.

A pharmaceutical batch(es) or pharmaceutical formulation(s) may be characterized by a maximum impurity level of Asp^9-bivalirudin not exceeding about 1.5 or not exceeding about 1%, or not exceeding about 0.6%, or not exceeding about 0.4%, or not exceeding about 0.3%. The pharmaceutical batch(es) or pharmaceutical formulation(s) may also be characterized by a mean impurity level of Asp^9-bivalirudin not exceeding about 1.5%, or not exceeding about 0.5%, or not exceeding about 0.4%, or not exceeding about 0.3%.

Moreover, a pharmaceutical batch(es) or formulation(s) may be characterized by a maximum total impurity level not exceeding about 6%, or not exceeding about 3%, or not exceeding about 2%, or not exceeding about 1%, or not exceeding about 0.5%. In addition, the batch(es) may be characterized by a mean total impurity level not exceeding about 2%, or not exceeding about 1.3%, or not exceeding about 1.1%, or not exceeding about 0.5%.

The batch(es) may also be characterized by a maximum largest unknown impurity level not exceeding about 1%, or not exceeding about 0.5%, or not exceeding about 0.4%, or not exceeding about 0.3%. The batch(es) may further be characterized by a mean largest unknown impurity level not

exceeding about 1%, or not exceeding about 0.27%, or not exceeding about 0.25%, or not exceeding about 0.2%.

Yet, the batch(es) may be characterized by a maximum reconstitution time not exceeding about 180 seconds, or not exceeding about 72 seconds, or not exceeding about 42 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds. Also, the batch(es) may be characterized by a mean reconstitution time not exceeding about 60 seconds, or not exceeding about 30 seconds, or not exceeding about 21 seconds, or not exceeding about 15 seconds.

Moreover, the pharmaceutical batch(es) or pharmaceutical formulation(s) may relate to one or more of the characteristics described above.

The pharmaceutical batch(es) or pharmaceutical formulation(s) may be generated by the compounding processes described above. Thus, the batch(es) may be prepared by a compounding process comprising dissolving bivalirudin in a solvent to form a bivalirudin solution, efficiently mixing a pH-adjusting solution with the bivalirudin solution to form a compounding solution, and removing solvents from the compounding solution. This compounding process includes all of the embodiments as described above.

Administering the Pharmaceutical Formulation

Various embodiments of the present invention further relate to a method of administering the pharmaceutical formulation of certain embodiments of the present invention to a subject, which comprises preparing an injectable dosage form, and then delivering the injectable dosage form to the subject parenterally.

The injectable dosage form is prepared by reconstituting the pharmaceutical formulation in a pharmaceutically acceptable vehicle. Methods of reconstituting the pharmaceutical formulation are well known in the art. Pharmaceutically acceptable vehicles are also well known in the art and can include, but are not limited to, water and saline for injection.

As an example, the injectable dosage form may be prepared by adding water to the pharmaceutical formulation and dissolving the pharmaceutical formulation. This solution can then be further diluted in 5% dextrose in water or 0.9% sodium chloride for injection.

Methods of delivering the injectable dosage form parenterally are well known in the art. For example, the injectable dosage form may be delivered intravenously.

The dosage form may be an intravenous bolus dose of between about 0.25 mg/kg and about 1.50 mg/kg, or between about 0.50 mg/kg to about 1.00 mg/kg, or about 0.75 mg/kg. This may be followed by an infusion of between about 1.25 mg/kg/h and about 2.25 mg/kg/h, or about 1.75 mg/kg/h for the duration of the procedure or treatment protocol. Five minutes after the bolus dose is administered, an additional bolus of between about 0.1 mg/kg and about 1.0 mg/kg, or about 0.3 mg/kg, may be given if needed.

The dosage form of various embodiments of the present invention can be indicated for use as an anticoagulant. Also, the dosage form can be used for the prevention and treatment of venous thromboembolic disease. Approved indications include treatment in patients with unstable angina undergoing percutaneous translumnial coronary angioplasty; administration with the provisional use of glycoprotein IIb/IIIa inhibitor for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI); and treatment in patients with, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. Also, the dosage form can be used for the prevention and treatment of venous thromboembolic disease.

The injectable dosage form may be administered with other drug products such as glycoprotein (GP) IIb/IIIa inhibitor ((see, e.g., Allie et al., *Vasc. Dis. Manage.* 2006, 3: 368-375). Alternatively, the injectable dosage form may be combined with blood thinners including, but not limited to, coumadin, warfarin, and preferably, aspirin.

The invention will now be further described by way of the following non-limiting examples, which further illustrate the invention, and are not intended, nor should they be interpreted to, limit the scope of the invention.

EXAMPLES

Example 1

Generation of High Levels of Asp^9-Bivalirudin

A study was performed in three parts to determine levels of Asp^9-bivalirudin generated in batches prepared by compounding processes having different methods of mixing the pH-adjusting solution with the bivalirudin solution to form a compounding solution. More specifically, the study examined the effects of adding the pH-adjusting solution to the bivalirudin solution in portions with inefficient mixing, the effects of having high levels of pH in the compounding solution, and the effects of high shear mixing of the compounding solution on Asp^9-bivalirudin levels.

In a first part of the study, the bivalirudin solution (~600 mL) comprised bivalirudin at a concentration of ~0.1 mg/mL in a 2.64% w/w mannitol solution. The pH-adjusting solution (233 mL) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution. Asp^9-bivalirudin levels were measured throughout the experiment by high-performance liquid chromatography (HPLC). pH was also measured through the experiment. One measurement of Asp^9-bivalirudin was taken immediately after the bivalirudin solution was formed (baseline).

The pH-adjusting solution was added to the bivalirudin solution in four equal portions over the total duration of about 1 hour at a temperature of 5-8° C., each addition separated by about 15 minutes. The resulting compounding solution was mixed at between 600 rpm and 700 rpm throughout the addition of the first and second portions of the pH-adjusting solution, and the pH and Asp^9-bivalirudin levels were recorded (measurements #1 and #2). During the addition of the third portion, the mixer was turned off and the pH and Asp^9-bivalirudin levels were recorded (measurement #3A). The mixture was then subjected to high shear mixing at 4000 rpm for 30 seconds and the pH and Asp^9-bivalirudin levels were recorded (measurement #3B). During addition of the fourth portion, the mixer was turned off and the levels of pH and Asp^9-bivaluridin were recorded (measurement #4A). Mixing was then continued for, at least, two minutes at 5300 rpm and the pH was and Asp^9-bilvairudun levels were recorded (measurement #4B). The mixing rate was decreased to about 3600 rpm for 1 hour and the pH and Asp^9-bivalirudin levels were recorded (measurement #5). A portion of the material from measurement #4a was allowed to stand for 7 hours and the pH and Asp^9-bivalirudin levels were recorded (measurement #6). The pH and Asp^9-bivalirudin levels are shown in Table 1.

TABLE 1

pH and average Asp^9-bivalirudin levels after addition of pH-adjusting solution in four equal portions with inefficient mixing.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample taken after bivalirudin solution was formed	~2.5	~0.42
#1	Sample taken from compounding solution after addition of first portion of pH-adjusting solution to bivalirudin solution	3.0	—
#2	Sample taken from compounding solution after addition of second portion of pH-adjusting solution to bivalirudin solution	4.2	0.43
#3A	Sample taken from compounding solution after addition of third portion of pH-adjusting solution to bivalirudin solution with no mixing	~6 to 8	0.45
# 3B	Same as #3A, but after mixing	5.0	0.74
#4A	Sample taken from compounding solution after addition of fourth portion of pH-adjusting solution to bivalirudin solution, and after compounding solution sat for 10 minutes with no mixing	~8.5 to 9	0.60
#4B	Same as #4A, but after mixing	6.0 to 6.5	0.57
#5	Same as #4A, but after high speed mixing for 1 hour	5.0	0.71
#6	Same as #4A, but 7 hours later with no mixing	~8.5 to 9	2.05

These results suggest that inefficient mixing of the compounding solution generates Asp^9-bivalirudin. Notably, during the addition of the pH-adjusting solution, a precipitate formed which may contain bivalirudin. Since the level of Asp^9-bivalirudin is based on a % analysis by HPLC of the amount of bivalirudin in solution, the level of Asp^9-bivalirudin appears to increase and decrease during the compounding process.

In a second part of the study, four portions of the final compounding solution from the first part of the study were removed. The pH levels of these portions were adjusted to 8, 9, 10, and 12, respectively, using additional pH-adjusting solution and high shear mixing on a Silverson Laboratory Emulsifier (Model L4RT).

Samples of the portion of the compounding solution adjusted to pH 8 were taken immediately, and after about 80 minutes, 300 minutes, and 370 minutes. Samples of the portion of the compounding solution adjusted to pH 9 were taken immediately, after about 80 minutes, and 300 minutes. Further, samples of the portion of the compounding solution adjusted to pH 10 and 12 were taken immediately, after about 80 minutes and 170 minutes. The results of the analyses for levels of Asp^9-bivalirudin in these samples are shown in Table 2.

TABLE 2

Asp^9-bivalirudin levels of portions adjusted to various pH levels.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample measured after bivalirudin solution was formed	5	0.71
#1	Sample measured after pH was adjusted	8	0.71
	Sample measured after ~80 minutes		0.77
	Sample measured after ~300 minutes		1.11
	Sample measured after ~370 minutes		1.26
#2	Sample measured after pH was adjusted	9	0.84
	Sample measured after ~80 minutes		1.07
	Sample measured after ~300 minutes		1.84
#3	Sample measured after pH was adjusted	10	1.24
	Sample measured after ~80 minutes		2.08
	Sample measured after ~170 minutes		2.59
#4	Sample measured after pH was adjusted	12	4.71
	Sample measured after ~80 minutes		8.20
	Sample measured after ~170 minutes		10.95

These results appear to show a relationship between pH, time, and the generation of Asp^9-bivalirudin.

In a third part of the study, the final compounding solution from the first part of the study was placed into a recirculation vessel for use in a recirculation water bath (Precision Model 181) to be subjected to high shear mixing using a Silverson Laboratory Emulsifier (Model L4RT). Prior to this study, it was thought that bivalirudin solutions were unstable to both heat and shear, thus requiring extreme care in handling bivalirudin during the compounding process. Before subjecting the compounding solution to high shear mixing, the level of Asp^9-bivalirudin was recorded (measurement #1). The compounding solution was then subjected to high shear mixing at ~6000 rpm for 30 minutes without use of the recirculation water bath; the temperature of the compounding solution due to the high shear mixing rose to about 36° C. A sample was then measured for Asp^9-bivalirudin level (measurement #2). The mixing speed was then slowed to 5000 rpm for 120 minutes and the temperature was measured at about 33° C., and another sample was analyzed for Asp^9-bivalirudin level (measurement #3). The Asp^9-bivalirudin levels are shown in Table 3.

TABLE 3

Asp^9-bivalirudin levels of the compounding solution undergoing different high shear mixing rates.

Measurement	Sample	Temperature	% Asp^9-bivalirudin
#1	Sample taken from the compounding solution before high shear mixing	RT ~20° C.	0.71
#2	Sample taken from the compounding solution after high shear mixing at 6000 rpm for 30 minutes	36° C.	0.71
#3	Sample as #2, but after mixing rate was reduced to 5000 rpm for 120 minutes	33° C.	0.75

These results also show that, unexpectedly, that bivalirudin is stable to high shear mixing conditions. Also, the tempera-

ture of the compounding solution did not, surprisingly, affect Asp^9-bivalirudin generation in this study.

Example 2

Effects of adding the pH-Adjusting Solution in Two Portions to the Bivalirudin Solution on Asp^9-Bivalirudin Levels

A study was performed to determine levels of Asp^9-bivalirudin generated in compounding solutions prepared by a compounding process involving the addition of the pH-adjusting solution to the bivalirudin solution in two portions.

The bivalirudin solution (~760 mL) comprised bivalirudin at a concentration of 0.050 mg/ml dissolved in a 2.64% w/w mannitol solution. The pH-adjusting solution (233 mL) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution. The experiment was conducted at a temperature of about 8° C.

The pH-adjusting solution was divided into a 75% portion and a 25% portion of the total pH-adjusting solution volume. First, the pH and Asp^9-bivalirudin levels were measured before addition of the pH-adjusting solution (baseline). During addition of the 75% portion, at about 400 rpm, the pH was monitored during mixing until the pH achieved a constant level at which time the Asp^9-bivalirudin level was also measured (measurement #1). A portion of this material was allowed to sit for about 6.5 hours and the amount of Asp^9-bivalirudin was again measured (measurement #2). The 25% portion of the pH-adjusting solution was added about 30 minutes after the last base addition and mixing was continued at 400 rpm. The pH was initially recorded and then both the pH and Asp^9-bivalirudin levels were measured after about 30 minutes of mixing (measurement #3). The pH and Asp^9-bivalirudin levels were again recorded after mixing at 400 rpm overnight (measurement #4). The pH and Asp^9-bivalirudin levels are shown in Table 4.

Notably, after the 75% portion of the pH-adjusting solution was added, a large white mass precipitated from the compounding solution and formed a mass at the bottom of the vessel. The addition of the 25% portion did not induce any physical changes in the appearance of the mixture, and there was no additional precipitation. The white mass displayed little change after mixing for 30 minutes after the 25% portion was added, but dissolved after mixing overnight.

TABLE 4

pH and average Asp^9-bivalirudin levels after addition of pH-adjusting solution in two portions of 75% and 25% at 400 rpm.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample taken after bivalirudin solution was formed	1.71	0.42
#1	Sample of the compounding solution taken after addition of 75% portion of the pH-adjusting solution to the bivalirudin solution	Peak at 12.2, then dropped to 8-9	0.44
#2	Same as #1, but after sitting for 6.5 hours with no stirring	—	0.88
#3	Remaining 25% of pH-adjusting solution added	12.4 initially, then dropped to 7.7 after 30 minutes	1.85 (taken from the top) 2.19 (taken from the bottom)
#4	Same as #3, but after mixing overnight	5.0	1.57

These results indicate that addition of the pH-adjusting solution in two portions with inefficient mixing produces high levels of Asp^9-bivalirudin.

Example 3

Effect of Controlled Addition of pH Adjusting Solution at Different Mixing Rates on Asp^9-Bivalirudin Levels

Asp^9-bivalirudin levels were assessed in compounding solutions prepared by a compounding process which comprised adding the pH-adjusting solution at a constant rate to the bivalirudin solution and mixing under high shear conditions.

The bivalirudin solution (675 mL) comprised 64.4 g dissolved in 2.64% w/w mannitol solution. The bivalirudin solution was divided in half for evaluation of adding the pH-adjusting solution at two different mixing rates. The bivalirudin solution was placed in a vessel with a high shear mixer.

The pH-adjusting solution (131.2 mL) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution. The pH-adjusting solution was loaded into a burette, which was connected on the bottom to a tube with a hose. The tube was positioned at the base of the high shear mixer blade inside the mixing vessel containing the bivalirudin solution. A clamp was used to restrict the pH-adjusting solution from passing through the hose.

The speed of the high shear mixer (Silverson Laboratory Emulsifier Model L4RT) was set to either 1500 rpm or 3000 rpm. The clamp on the hose was removed and the pH-adjusting solution was then added to the bivalirudin solution at a controlled, constant rate of approximately 2 L/min.

For the solution mixed at 3000 rpm, addition of approximately 10 mL of the pH-adjusting solution resulted in a pH of the compounding solution of 5.25. The volume of the compounding solution was then adjusted to a final volume of 562.5 mL.

For the compounding solution mixed at 1500 rpm, after the pH-adjusting solution was added, the mixing speed was increased to approximately 4500 rpm for a short period of time to allow faster and complete dissolution, and then reduced to 1500 rpm until the solution was completely dissolved. After complete dissolution, the resulting compounding solution was moved from the vessel to a beaker which contained a stir bar. The solution was adjusted to a target pH of 5.3 using 19 mL of the pH-adjusting solution, and then the volume was adjusted to a final volume of 562.5 mL.

For both mixing conditions, the pH was monitored throughout the addition of the pH-adjusting solution to the bivalirudin solution to form the compounding solution. The level of Asp^9-bivalirudin was measured by HPLC before (baseline) addition of the pH-adjusting solution, after the addition of the pH-adjusting solution (measurement #2), and after the volume of the compounding solution was adjusted to mark (measurement #3). The results of the HPLC analysis are shown in Tables 5a and 5b.

Notably, when the compounding solution was mixed at 3000 rpm, a material precipitated as the pH-adjusting solution was added, first as a milky white dispersion, and then as a semi-transparent aggregate. By the time that all of the pH-adjusting solution was added, most of the precipitated material had dissolved.

Similarly, when the compounding solution was mixed at 1500 rpm, a material also precipitated as the pH-adjusting solution was added, first as a milky white dispersion, and then as a semi-transparent aggregate.

TABLE 5a

pH and average Asp^9-bivalirudin levels before and after addition of pH-adjusting solution at 1500 rpm.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample taken before addition of pH-adjusting solution	~2.5	0.38
#1	Sample taken of the compounding solution after addition of pH-adjusting solution	~6.0	0.31
#2	Sample taken of the compounding solution after compounding solution was adjusted to mark	5.3	0.34

TABLE 5b

pH and average Asp^9-bivalirudin levels before and after addition of pH-adjusting solution at 3000 rpm.

Measurement	Sample	pH	% Asp^9-bivalirudin
Baseline	Sample taken from bivalirudin solution before addition of pH-adjusting solution	~2.5	0.43
#1	Sample taken of the compounding solution after addition of pH-adjusting solution	~5.6	0.41

TABLE 5b-continued

pH and average Asp^9-bivalirudin levels before and after addition of pH-adjusting solution at 3000 rpm.

Measurement	Sample	pH	% Asp^9-bivalirudin
#2	Sample taken of the compounding solution after compounding solution was adjusted to mark	5.25	0.40

These results indicate that there were no changes in Asp^9-bivalirudin levels before and after the addition of the pH-adjusting solution at a constant rate, and under high shear mixing conditions. Moreover, it was surprising that bivalirudin was not susceptible to degradation by high shear mixing even up to 4500 rpm, even though many peptides are susceptible to degradation by high shear mixing or by high temperatures.

Example 4

Effects of Rapidly Adding pH Adjusting Solution to the Bivalirudin Solution Under Inefficient Mixing Conditions—Large Scale Study

The effects of rapidly adding the pH-adjusting solution to the bivalirudin solution under slow mixing conditions were studied. Multiple batches were generated by the same method.

The bivalirudin solution (~110 L) comprised bivalirudin at a concentration of 0.050 mg/ml dissolved in a 2.64% w/w mannitol solution. The pH-adjusting solution (~40 L) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution.

The pH-adjusting solution was added to the bivalirudin solution 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. Both paddle mixers operated at a rate of between about 400 and about 800 rpm. When the pH-adjusting solution was added to the bivalirudin solution, a large amount of a material precipitated. The precipitated material eventually dissolved after continued mixing. After the pH-adjusting solution was completely added and mixed, the compounding solution was sterile filtered and lyophilized, and the lyophilizate was analyzed by HPLC for impurity levels.

This study analyzed impurity levels and reconstitution times of the lyophilizate of 89 batches. Results from the study are displayed in Table 6 (note that not all of the samples were analyzed for each characteristic).

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

According to these results, the batches displayed a maximum level of Asp^9-bivalirudin of 3.6%, while the mean level

of Asp^9-bivalirudin was 0.5%. Furthermore, the standard deviations relative to the means were larger. These results suggest that the characteristics of the batches generated by this process may be variable.

Example 5

Effects of Adding pH Adjusting Solution at a Constant Rate and Under Efficient Mixing Conditions—Large Scale Study

The effects of adding the pH-adjusting solution to the bivalirudin solution at a constant rate and under efficient mixing condition were studied. Multiple batches were generated by the same method.

The bivalirudin solution (~110 L) comprised bivalirudin at a concentration of 0.050 mg/ml dissolved in a 2.64% w/w mannitol solution. The pH-adjusting solution (~40 L) comprised 0.5 N sodium hydroxide in a 2.64% w/w mannitol solution.

The pH-adjusting solution was added to the bivalirudin solution at a controlled rate of 2 L/min using a peristaltic pump. A homogenizer was used to provide a high shear mixing environment (between about 1000 rpm and 1300 rpm) within the bivalirudin solution as the pH-adjusting solution was added. A feed tube extended from the peristaltic pump to an inlet in the homogenizer, so that the pH-adjusting solution was added to the bivalirudin solution at a site adjacent to the blades of the homogenizer. Simultaneously, a paddle mixer was used for mixing (mixing rate of between about 300 rpm and 700 rpm) near the surface of the bivalirudin solution. As the pH-adjusting solution was added, a small amount of material precipitated which later dissolved. After the pH-adjusting solution was completely added, the compounding solution was sterile filtered and lyophilized, and the lyophilizate was analyzed by HPLC for impurity levels.

In this study, which prepared 25 batches, analysis of impurity levels and reconstitution times for the lyophilizate are shown in Table 7.

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

The results of one batch was not included in the data presented in Table 7, as the method used to generate the batch was not compliant with the protocol established for this study.

Comparison of the batches of Example 5 to the batches of Example 4 revealed that the batches of Example 5 displayed significantly lower mean levels of Asp^9-bivalirudin, total impurities, and largest unknown impurity. The batches of Example 5 also showed smaller standard deviations relative to the means for levels of Asp^9-bivalirudin, total impurities, and largest unknown impurity. Together, these results suggest that the process demonstrated in Example 5 produced batches generally and consistently having lower levels of impurities than the process of Example 4.

In addition, the batches of Example 5 displayed significantly shorter mean reconstitution times, and smaller standard deviations relative to the mean, as compared to the batches of Example 4. These results suggest that the process of Example 5 generated batches generally and consistently having shorter reconstitution times than the batches generated by the process of Example 4.

A comparison between the batches generated in Example 4 and Example 5 is shown in Table 8 which assesses the mean values of the characteristics of the batches, and Table 9, which examines the maximum values of the characteristics of the batches:

TABLE 8

Comparison of mean values of the characteristics of the batches generated by the compounding process of Example 4 and the characteristics of the batches generated by the compounding process of Example 5 ($p < 0.05$).

	Batches of Example 4 Mean ± SD	Batches of Example 5 Mean ± SD	% change*	p
Asp^9-bivalirudin (%)	0.5 ± 0.4	0.3 ± 0.1	−40%	<0.0003
Total impurities (%)	1.4 ± 0.5	1.0 ± 0.4	−29%	<0.004
Largest unknown impurity (%)	0.3 ± 0.1	0.2 ± 0.1	−33%	0.03
Reconstitution time (seconds)	30 ± 12	18 ± 6	−40%	<0.000001

*% change = 100 × [(mean value from Example 5 batches) − (mean value from Example 4 batches)]/(mean value from Example 4 batches)

TABLE 9

Comparison of maximum values of the characteristics of the batches generated by the compounding process of Example 4 and the characteristics of the batches generated by the compounding process of Example 5 ($p < 0.05$).

	Batches of Example 4 Maximum	Batches of Example 5 Maximum	% change*
Asp^9-bivalirudin (% w/w)	3.6	0.6	−83%
Total impurities (% w/w)	3.0	2.0	−33%
Largest unknown impurity (% w/w)	0.5	0.3	−40%
Reconstitution time (seconds)	72	42	−42%

*% change = 100 × [(maximum value from Example 5 batches) − (maximum value from Example 4 batches)]/(maximum value from Example 4 batches)

As shown in Table 8, the levels of Asp^9-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution time are all significantly less in the batches made by the process of Example 5 as compared to the batches made by the process of Example 4. Further, Table 9 shows that the maximum values for the levels of Asp^9-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution

time are also greatly less in the batches made by the process of Example 5 as compared to the batches made by the process of Example 4

Example 6

Generation of D-Phe[12]-Bivalirudin in Stored Bivalirudin Pharmaceutical Formulations

The bivalirudin pharmaceutical formulations prepared in Examples 1-3 were stored in refrigerated conditions and then evaluated by HPLC to compare the level of D-Phe[12]-bivaliru-din impurities among the different formulation methods. The results show that the levels of D-Phe[12]-bivliarudin were similar across each formulation method, which indicated that the methods did not influence the generation of D-Phe[12]-bivliarudin.

Having thus described in detail embodiments of the present invention, it is to be understood that the invention defined by the above paragraphs is not to be limited to particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit or scope of the present invention.

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What is claimed is:

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, 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.

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.

4. The pharmaceutical batches of claim 1, wherein the batches have a maximum total impurity level that does not exceed about 2% as measured by HPLC.

5. The pharmaceutical batches of claim 4, wherein the maximum total impurity level does not exceed about 1% as measured by HPLC.

6. The pharmaceutical batches of claim 5, wherein the maximum total impurity level does not exceed about 0.5% 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.

11. The pharmaceutical batches of claim 1, wherein the base is sodium hydroxide.

12. 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 reconstitution time that does not exceed about 42 seconds and a maximum total impurity level that does not exceed about 2% as measured by HPLC.

13. The pharmaceutical batches of claim 12, wherein the maximum reconstitution time does not exceed about 30 seconds.

14. The pharmaceutical batches of claim 13, wherein the maximum reconstitution time does not exceed about 21 seconds.

15. The pharmaceutical batches of claim 12, wherein the pharmaceutically acceptable carrier comprises one or more of a bulking agent or a stabilizing agent.

16. The pharmaceutical batches of claim 15, wherein the bulking agent is a sugar.

17. The pharmaceutical batches of claim 16, wherein the sugar is mannitol.

18. The pharmaceutical batches of claim 12, wherein the base is sodium hydroxide.

19. Pharmaceutical batches of a drug product comprising bivalirudin (SEQ ID NO: 1) and mannitol 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 sodium hydroxide, said pH is about 5-6 when reconstituted in an aqueous solution for injection, and wherein the batches have a maximum reconstitution time that does not exceed about 42 seconds and a maximum total impurity level that does not exceed about 2% as measured by HPLC.

20. The pharmaceutical batches of claim 19, wherein the batches have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6% as measured by HPLC.

* * * * *

United States Court of Appeals for the Federal Circuit

CERTIFICATE OF SERVICE

I, Richard F. Kurz, being duly sworn according to law and being over the age of 18, upon my oath depose and say that Counsel for Plaintiff-Appellant authorized me to electronically file the foregoing Brief of Plaintiff-Appellant The Medicines Company with the Clerk of Court using the CM/ECF System, which will send notice of such filing to the following registered CM/ECF users:

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August 13, 2014

By: /s/ Richard F. Kurz

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CERTIFICATE OF COMPLIANCE

Undersigned counsel certifies that:

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Date: August 13, 2014

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