APPEAL NO. 2014-1469, 2014-1504

IN THE
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

PRINCIPAL BRIEF OF DEFENDANT-CROSS-APPELLANT HOSPIRA, INC. IN RESPONSE TO THE COURT'S NOVEMBER 13, 2015 ORDER

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January 11, 2016

CERTIFICATE OF INTEREST

Counsel for Defendant-Cross Appellant Hospira, Inc. certifies the following:

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

Hospira, Inc.

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:

Pfizer, Inc., of which Hospira, Inc. became a subsidiary on September 3, 2015.

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:

Jenner & Block LLP: Bradford P. Lyerla, Aaron A. Barlow, Sara T. Horton, and Jamie K. Lord.

Morris James LLP: Richard K. Herrmann and Mary B. Matterer.

Sutherland Ashbill & Brennan LLP: William F. Long and Tara Stuart (subsequently moved to McKenna Long & Aldridge LLP), and Kristin E. Goran.

January 11, 2016 /s/ Bradford P. Lyerla

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TABLE OF ABBREVIATIONS

"Hospira"	Hospira, Inc.
"MedCo"	The Medicines Company
"'343 patent"	U.S. Patent No. 7,598,343
"'727 patent"	U.S. Patent No. 7,582,727
"patents-in-suit"	U.S. Patent Nos. 7,598,343 and 7,582,727
"ANDA"	Abbreviated New Drug Application
"FDA"	United States Food and Drug Admin-istration
"BVL"	Ben Venue Laboratories
"A___"	Appendix page number(s)

STATEMENT OF RELATED CASES

No other appeal in or from the same civil action in the district court has previously been before this or any other appellate court. The following cases may directly affect or may be directly affected by this court's decision in the pending appeal: (1) *The Medicines Company v. Dr. Reddy's Laboratories Ltd. et al.*, No. 11-2456 (D.N.J.); (2) *The Medicines Company v. Mylan, Inc. et al.*, Nos. 15-1113, 15-1151, & 15-1181 (Fed. Cir.); (3) *The Medicines Company v. Mylan Inc. et al.*, No. 11-1285 (N.D. Ill.); (4) *The Medicines Company v. Apotex Inc. et al.*, No. 13-2801 (D.N.J.); (5) *The Medicines Company v. Aurobindo Pharma Ltd. et al.*, No. 14-2367 (D.N.J.); (6) *The Medicines Company v. Exela Pharma Sciences, LLC et al.*, No. 14-cv-58 (W.D.N.C.); and (7) *The Medicines Company v. Accord Healthcare, Inc. et al.*, No. 14-626 (M.D.N.C.).

JURISDICTIONAL STATEMENT

The district court had subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). The district court entered final judgment on April 15, 2014. MedCo filed a timely notice of appeal on May 9, 2014, and Hospira filed a timely notice of cross-appeal on May 23, 2014. A17083-86. This Court has jurisdiction over MedCo's appeal and Hospira's cross-appeal under 28 U.S.C. § 1295(a)(1). The Court granted rehearing en banc on November 13, 2015.

STATEMENT OF THE ISSUES

1. Do the circumstances presented here constitute a commercial sale under the on-sale bar of 35 U.S.C. § 102(b)?

   a. Was there a sale for the purposes of § 102(b) despite the absence of a transfer of title?

   b. Was the sale commercial in nature for the purposes of § 102(b) or an experimental use?

2. Should this court overrule or revise the principle in *Special Devices, Inc. v. OEA, Inc.*, 270 F.3d 1353 (Fed. Cir. 2001), that there is no "supplier exception" to the on-sale bar of 35 U.S.C. § 102(b)?

INTRODUCTION

The on-sale bar plays a vital role in the patent system. By providing a firm deadline to apply for a patent, triggered by commercial exploitation of the invention, the on-sale bar prevents inventors from substantially extending the statutorily limited period during which they may commercially benefit from their monopoly. An inventor who wishes to commercialize an invention may do so freely and immediately. But once the inventor does so, he or she must apply for a patent within one year or forfeit his or her patent rights.

Here, MedCo commercially exploited its invention extensively prior to the critical date—*i.e.*, one year before it applied for the patents-in-suit. Before that

date, MedCo paid its third-party manufacturer, Ben Venue Laboratories ("BVL"), to make tens of thousands of vials of its bivalirudin product, Angiomax, valued at tens of millions of dollars, using the manufacturing process that is the only novel aspect of those patents. MedCo and BVL treated these activities as commercial in every respect: the batches of Angiomax were given commercial product codes; they were released for commercial and clinical packaging; and they restocked MedCo's long-depleted commercial pipeline of Angiomax. Under settled legal principles, these circumstances triggered the on-sale bar and, accordingly, the asserted claims of the patents-in-suit are invalid.

STATEMENT OF THE CASE

This suit arises from Hospira's submission of ANDA Nos. 90-811 and 90-816. In these ANDAs, Hospira sought approval to market its generic bivalirudin drug products and filed paragraph IV certifications with respect to the patents-in-suit, both of which are listed in the Orange Book as covering Angiomax. On August 19, 2010, MedCo sued Hospira in the U.S. District Court for the District of Delaware (Hon. Richard G. Andrews), alleging infringement of the patents-in-suit. The district court held a bench trial from September 23 to 25, 2013. On March 31,

2014, the court found the asserted claims valid but also not infringed. A3-34.[1] The court entered final judgment on April 15, 2014. A1-2.

MedCo appealed the district court's non-infringement ruling, while Hospira cross-appealed from, among other rulings, the district court's decision that certain pre-critical-date activities did not trigger the on-sale bar of § 102(b). On July 2, 2015, a panel of this Court ruled that MedCo's patents were invalid under § 102(b), without reaching the remainder of the issues presented by the appeals. *See Medicines Co. v. Hospira, Inc.*, 791 F.3d 1368 (Fed. Cir. 2015). On November 13, 2015, this Court granted rehearing en banc.

STATEMENT OF FACTS

I. MEDCO'S CLAIMED INVENTION

A. The Technology at Issue.

Bivalirudin is a peptide that can serve as an anti-coagulant. A50, 6:16-19. MedCo markets a form of bivalirudin in the United States under the trade name Angiomax. A48, col. 1, ll. 52-56. The bivalirudin active pharmaceutical ingredient ("API"), without further processing, is too acidic for health care providers to

[1] Citations in the form "A___" are to the Appendix. After the filing of all en banc briefs, the parties intend to file a Supplemental Joint Appendix containing pages that are cited in those briefs but that were not cited in the parties' panel briefs, and thus were not included in the Joint Appendix previously filed with the Court.

use in humans. A16320, 339:9-19.[2] Consequently, MedCo has prepared its Angiomax product since 1997 by using a compounding process in which it creates a bivalirudin solution; adjusts the solution's pH with a base; and then freeze-dries the solution. A16058, 78:81-7; A16120, 140:19-141:4; A58, col. 21, l. 43-col. 22, l. 28.

MedCo itself does not manufacture Angiomax or any of its raw materials. Instead, since 1997, MedCo has paid BVL to manufacture and deliver commercial quantities of freeze-dried bivalirudin. A16053, 73:2-13. MedCo has an Italian company ship the API to BVL. A16053, 73:20-24. BVL compounds the API with water, sodium hydroxide (the pH-adjusting base noted above), and other common chemicals; loads the resulting solution into vials; freeze-dries the contents of the vials; and ultimately ships them to MedCo's distributor, ICS. A16054, 74:3-17; A58, col. 21, l. 44-col. 22, l. 28. A single batch consists of about 28,000 vials and has a value between $10 million and $20 million. A15986, 6:7-14; A16055-56, 75:15-76:2.

One potential adverse consequence of the compounding process, however, is the production of an impurity called Asp^9. A48, col. 2, ll. 8-9. If high levels of Asp^9 form, the bivalirudin may become unusable. A 16056, 76:13-17. The pa-

[2] To administer the drug, a health care provider must first dissolve it in water. A50, col. 6, ll. 27-34; A16051, 71:11-19; A16328, 347:12-17.

tents-in-suit grew out of BVL's manufacture of two batches with unacceptably high Asp^9 levels—a result that forced MedCo to discard these valuable batches rather than sell them. A16056-57, 76:24-77:6.

BVL made the first of these rejected batches in June 2005. A16055, 75:9-14. Thereafter, MedCo ordered BVL to shut down production of Angiomax for six months while it investigated the problem. A16057, 77:7-21. To address the problem, MedCo implemented changes to the way that the base was added: whereas BVL previously had added the base rapidly or all at once, MedCo now instructed it to add the base in multiple smaller portions. A14403, A16061, 81:10-19.

This change, however, did not solve the problem, for in May 2006 the revised process yielded another batch with unacceptably high levels of Asp^9. A14412; A16062, 82:9-16; A16063, 83:1-4. Once again, MedCo ordered BVL to shut down commercial production of Angiomax. A16066-67, 86:1-87:22.

While production was halted, MedCo determined, in laboratory experiments, that the high Asp^9 levels were caused by inefficient mixing as the base (sodium hydroxide) was added to the bivalirudin solution during the pH-adjusting step, and that a more efficient mixing process would prevent the formation of high levels of Asp^9. A16102, 122:10-20; A16109-110, 129:4-130:11. This experimental work—disclosed in the patents-in-suit as Examples 1, 2, and 3—was conducted at BVL. A16109-110, 129:22-130:1. BVL's invoices identified this work as being for

"product and process development," performance of "pilot studies," and "investigation" of the Asp[9] impurity issue. A17175. In accordance with the results of this experimental work, MedCo documented changes to the compounding process in its "Master Batch Record," the detailed instructions BVL was to follow to manufacture each batch of Angiomax. A15102-24.

B. The Transactions at Issue.

In late 2006 and early 2007, MedCo paid BVL $347,500 to manufacture and deliver the first three commercial batches using the revised process. A17177-78; A17183. BVL completed the first such batch on October 31, 2006. A14959. That batch was approximately one-quarter the size of a normal batch and contained 5,746 vials of commercially saleable bivalirudin. A14959; A16055, 75:15-22. On November 21 and December 14, 2006, BVL completed two full-size batches containing 27,594 and 26,918 vials, respectively. A15210; A15452.

The commercial purpose of these activities was unmistakable. In instructing BVL to manufacture these three batches, MedCo put at risk enough API to make some 60,000 vials of Angiomax, worth between $23 million and $45 million. *See* A16055-56, 75:15-76:2 (each batch worth between $10-$20 million.). Consistent with the scale of these activities, MedCo instructed BVL that the resulting product should be "filled for commercial use." A14884. By May 2007, before the critical date, MedCo gave each batch its commercial product code. A14959; A15210;

A15452. And also by that date, the batches were "[r]eleased for commercial and clinical packaging." A14960; A15211; A15453. MedCo itself eventually sold almost all of the vials made in these batches. A14598 (5650 vials of October 2006 batch sold); A14604 (27,480 vials of November 2006 batch sold); A14610 (26,320 vials of December 2006 batch sold).

MedCo also sought to ensure that its revised process complied with FDA regulations regarding process validation. *See generally* 21 C.F.R. § 211.110(a) (providing that "control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product"); Food & Drug Administration, Guideline on General Principles of Process Validation (1987). Accordingly, even as these first three batches began to refill MedCo's depleted commercial product stockpile, they also served the regulatory purpose of generating data to validate the revised process. A14883;

MedCo's contemporaneous documents reflect that, in undertaking to "validate" the revised process, MedCo knew that the process worked. Specifically, the goal of validation was to document what MedCo and BVL already knew from their laboratory-scale experiments:

> Based upon lab scale experiments (PPD Report #06-0130) and evaluation of the potential benefits of these process improvements, it was deemed appropriate to implement them during the manufacturing of three lots of

> Bivalirudin drug product. This *confirmational validation* is intended to *verify and validate* the effectiveness of the process optimization steps associated with the formulation of Part III. This *confirmational validation* is intended to *confirm* the effectiveness of the process optimization steps associated with the formulation of Part III.

A14883 (emphasis added). To similar effect, the objectives of validation were to "confirm" and "ensure" successful operation of the revised process, not to investigate whether it would work:

> The first objective of this study is to *confirm* that all in process specifications and critical parameters are maintained during manufacturing of the product Bivalirudin (50mg/mL; 250mg/vial) with the implementation of the process improvements.
>
> The second objective of this study is to *ensure* that the process optimizations *indeed* minimize the risk of high levels of Asp9 impurity in the final product. Final product testing must meet the current approved specifications for finished product.

A14884. By January 18, 2007, the FDA validation process was complete: all three batches, as expected, were found acceptable. A14962.

With production having been shut down since May 2006, MedCo did not stop with these three batches. Instead, MedCo paid BVL to make another eight full-size, commercial-scale batches by March 30, 2007—still well before the critical date. A16678-79, 696:4-697:13. These additional batches encompassed some 224,000 vials of commercial-grade Angiomax and were worth between $80 million and $160 million. A15986, 6:1-22; A16055-56, 75:15-76:2.

C. MedCo's Patents.

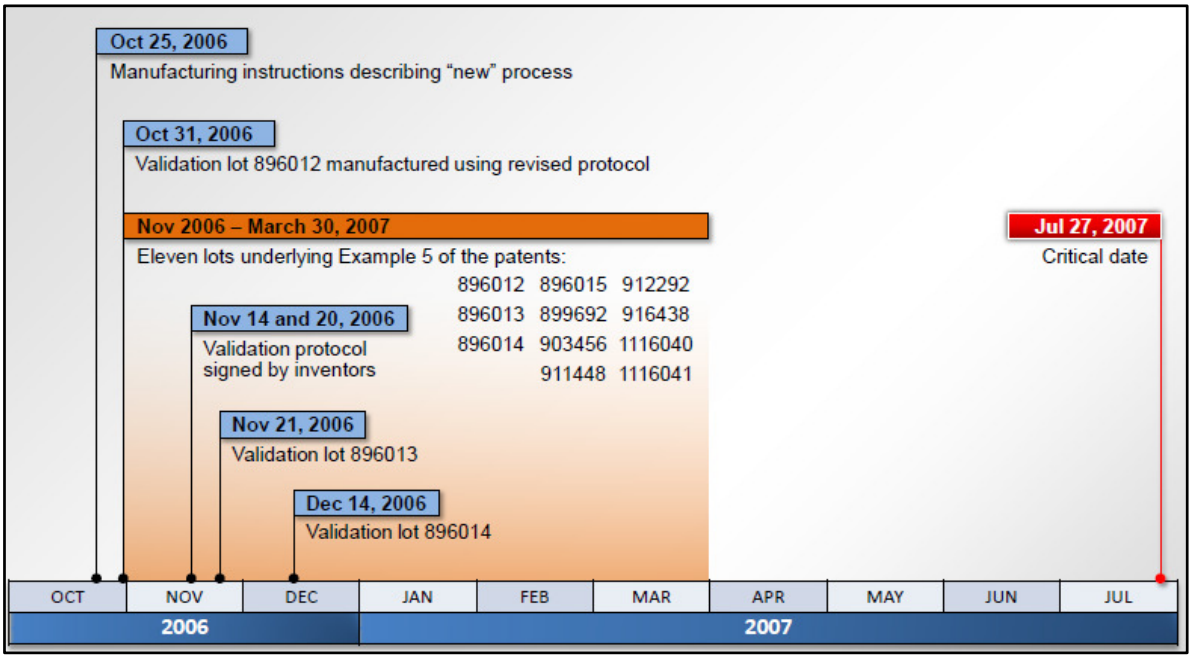
MedCo completed the design of its revised process no later than October 31, 2006, when BVL made MedCo's first commercial-scale batch using that process. A14959; A16663-65, 681:9-683:15. MedCo did not, however, apply for a patent at that point. Nor did it apply for one after the first three commercial-scale batches, or even after the eight additional commercial batches in February and March 2007.

By 2008, however, MedCo was preparing for the end of the exclusivity associated with its patent on the bivalirudin molecule itself. In July 2008, therefore, MedCo applied for patents describing the revised manufacturing process. A47; A62.

Example 4 and the corresponding Table 6 of the patents-in-suit disclose MedCo's prior art process and the 87 resulting batches, dating back to 1997. A58, col. 21, l. 44-col. 22, l. 28; A16120-21, 140:19-141:4; A6781; A7694. These batches, Table 6 reports, had an average Asp^9 level of 0.5%. A58, col. 22, l. 16. Accordingly, MedCo has never disputed that many of these batches had an Asp^9 level below 0.6%—the maximum level recited by the asserted claims of the patents-in-suit. A60, col. 25, ll. 63-64; A76, col. 27, ll. 29-31.

Example 5 and the corresponding Table 7 of the patents-in-suit disclose MedCo's revised process and the resulting batches. A58-59, col. 22, l. 30-col. 24,

l. 35. The differences between Example 4 (the prior art) and Example 5 (the claimed invention) are the conditions for mixing the base (sodium hydroxide) into solution. *See* A58, col. 22, ll. 37-39 (presenting "[t]he effects of adding the pH-adjusting solution to the bivalirudin solution at a constant rate and under efficient mixing condition[s]"). Example 5 discloses that MedCo had made 24 batches with this revised process. A59, col. 23, ll. 1-16. The first of these 24 were the three validation batches and eight additional batches referenced above—all made prior to the critical date, as shown below:



A15898; A16678-79, 696:4-697:9; A58-59, col. 22, l. 30-col. 24, l. 34.

Claim 1 of the '343 patent, which is representative of the claims in that patent, recites:

> 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.

A76, col. 27, ll. 13-31. Claim 1 of the '727 patent, which is representative of the claims in that patent, recites:

> 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.

A60, col. 25, ll. 57-64.

In construing the claims, the district court understood that MedCo's revised process was central to its claimed invention. *First*, the court stressed that, according to the intrinsic record—including the specification's definition of "pharmaceu-

tical batches"—"'pharmaceutical batches' of the invention must be prepared according to the special compounding process" described in the patents. A38 (citing the '343 patent); *see id.* (citing *Anderson Corp. v. Fiber Composites, LLC*, 474 F.3d 1361 (Fed. Cir. 2007), for the proposition that "[w]hen 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"). Indeed, the court reasoned, the patentee "refers to the present invention as an improved compounding process for bivalirudin." *Id.* Referring to the batches of Example 4 and Table 6, the district court elaborated: "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." *Id.*

Second, in connection with "wherein the batches have a pH adjusted by a base," a term used in both patents' claims, the court again observed the centrality of MedCo's revised process to what it claimed to have invented. Construing this term to mean "[w]herein said compounding process requires that a pH-adjusting solution containing a base is added to bivalirudin solution under efficient mixing conditions," the court explained: "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.'" A39; *see* A39-40 (reiterating that "[t]he term 'pharmaceutical batches' is explicitly defined in the specification as resulting

from the compounding process"); A40 n.2 (quoting the patents' discussion of the necessity of "efficient mixing"). It continued: "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 those batches. This was solved by the new compounding process." A41.

II. THE DISTRICT COURT PROCEEDINGS

In the district court, Hospira contested MedCo's allegations of infringement. The mixing process described in Hospira's ANDAs, and used to create Hospira's exhibit batches, uses slow mixing with a simple paddle mixer, just like MedCo's prior art Example 4. For that reason (among others), Hospira argued, the fact that its ANDA exhibit batches had Asp^9 levels below 0.6% did not warrant a finding of infringement. The district court agreed, and held that Hospira did not infringe, either literally or under the doctrine of equivalents. *See* A12-18.

The district court's claim construction eliminated the batches of Example 4 as anticipatory because those batches did not use efficient mixing. A58, col. 21, ll. 46-48. Hospira raised other invalidity defenses, however, under § 102(b), § 103, and § 112. As relevant here, Hospira argued that the first three batches of Example 5—which MedCo paid BVL to manufacture prior to the critical date—were invalidating under the on-sale bar of § 102(b).

Applying the two-step inquiry prescribed by *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55 (1998), the district court held that these batches were not invalidating. The court began by holding that the invention was ready for patenting in late 2006. A23. Specifically, the court concluded that MedCo's instructions to BVL on how to make the October 2006 batch and the "validation protocol" signed by the inventors were both enabling disclosures. *Id.* The court also found that the claimed invention was reduced to practice in October 2006 once the first batch was made. *Id.*[3]

Still, the court rejected Hospira's argument that the MedCo-BVL batches were invalidating. A24. The court held that because title to the bivalirudin was always with MedCo, and thus never passed between BVL and MedCo, the transactions at issue did not constitute a "sale." *Id.* The court acknowledged, however, that, "this does not end the inquiry." *Id.* Specifically, the court recognized that, under this Court's decision in *Plumtree Software, Inc. v. Datamize, LLC*, 473 F.3d 1152, 1163 (Fed. Cir. 2006), "performing the patented method for commercial purposes before the critical date constitutes a sale under § 102(b)." *Id.*

[3] Hospira addressed MedCo's ready-for-patenting argument—which urged that the invention actually was not ready for patenting until BVL had made *all* of the batches of Example 5—by showing that BVL had made eleven batches of Angiomax with the revised process prior to the critical date, all at commercial scale and all based on the same new instructions that MedCo had prepared in October 2006. A15898-99.

Nonetheless, the court held that there had been no invalidating sale because the three validation batches purportedly were experimental—an argument that MedCo had never even made, and that Hospira thus had no opportunity to rebut at trial. A25. In support of its sua sponte experimental-use holding, the district court rested solely on the fact that the batches were made in part for the purpose of FDA process validation. *Id.* It took no account of the numerous hallmarks of commercial activity surrounding the transactions between MedCo and BVL. Nor did it acknowledge this Court's holding in *Allen Engineering Corp. v. Bartell Industries, Inc.*, 299 F.3d 1336, 1354 (Fed. Cir. 2002) that, for experimental use to save a patentee from the on-sale bar, experimentation must be the "primary purpose" of the activity at issue, with any commercial purpose merely incidental.[4] And it cited no evidence that the inventors had any doubt that the revised process would work to make commercial-grade vials of low-Asp^{9} bivalirudin.

III. PROCEEDINGS IN THIS COURT

MedCo appealed the district court's non-infringement ruling, as well as certain claim construction rulings. Hospira, in turn, cross-appealed certain of the dis-

[4] The district court also rejected a second on-sale bar argument that Hospira had made—namely, that MedCo had offered batches of Angiomax for sale to its distributor, ICS, prior to the critical date. A26. The district court held that MedCo's agreement with ICS was merely "a contract to enter a contract," and not an invalidating offer for sale. *Id.*

trict court's invalidity rulings, including its holding that the transactions between MedCo and BVL did not trigger the on-sale bar.

After hearing oral argument, the panel held the patents-in-suit invalid under §102(b) by virtue of MedCo's transactions with BVL. The panel acknowledged that "title to the pharmaceutical batches did not change hands" but stressed that this "does not end the inquiry." *Medicines Co.*, 791 F.3d at 1370. Quoting this Court's decision in *D.L. Auld Co. v. Chroma Graphics Corp.*, 714 F.2d 1144 (Fed. Cir. 1983), the panel explained that the on-sale bar's purpose 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." *Medicines Co.*, 791 F.3d at 1370. "To ensure the doctrine is not easily circumvented," the panel continued, "we have found the on-sale bar to apply where the evidence clearly demonstrated that the inventor commercially exploited the invention before the critical date, even if the inventor did not transfer title to the commercial embodiment of the invention." *Id.* at 1370-71; *see id.* at 1371 (noting that "in *D.L. Auld Co.*, we found the on-sale bar to apply where, before the critical date, an inventor sold products made by the patented method").

These principles, the panel held, dictated a result for Hospira here. "We find no principled distinction," the panel explained, "between the commercial sale of products prepared by the patented method at issue in *D.L. Auld Co.* and the com-

mercial sale of services that result in the patented product-by-process here." *Id.* at 1371. On that score, the panel observed that "the sale of the manufacturing services here provided a commercial benefit to the inventor more than one year before a patent application was filed." *Id.* BVL, the panel observed, had "marked the batches with commercial product codes and customer lot numbers" and had sent them to MedCo "for commercial and clinical packaging, consistent with the commercial sale of pharmaceutical drugs." *Id.* Indeed, each batch had a commercial value in excess of $10 million, by MedCo's own admission. *Id.* The panel therefore held that BVL's "sale of services" constituted a commercial sale for purposes of § 102(b). *See id.* (reasoning that "[t]o find otherwise would allow [MedCo] to circumvent the on-sale bar simply because its contracts happened to only cover the processes that produced the patented product-by-process").

The panel also held that the district court had erred in concluding that BVL's batches fell within the experimental-use exception to the on-sale bar. The panel explained: "This is not a situation in which the inventor was unaware that the invention had been reduced to practice, and was experimenting to determine whether that was the case. The batches sold satisfied the claim limitations, and the inventor was well aware that the batches had levels of Asp^9-bivalirudin well below the claimed levels of 0.6%." *Id.* at 1372.

Finally, the panel upheld the district court's conclusion that MedCo's invention was ready for patenting before the critical date, because the BVL batches had reduced the invention to practice. *Id.* Accordingly, the panel held the asserted claims invalid.[5] *Id.* at 1372-73.

MedCo petitioned for panel rehearing and rehearing en banc. On November 13, 2015, the Court granted the petition for rehearing en banc, vacated the panel's decision, and ordered the parties to submit new briefs.

SUMMARY OF ARGUMENT

I. MedCo's transactions with BVL constituted a commercial sale. Prior to the critical date, MedCo paid BVL to manufacture and deliver three batches of Angiomax, using the process that is central to the patents. These batches totaled more than 60,000 vials, with a value well over $20 million. These transactions commercially benefited BVL, which was paid $347,500 for the batches. They also commercially benefited MedCo, which was able to restock its long-depleted commercial pipeline. Indeed, after these first three batches—but still before the critical date—MedCo paid BVL to manufacture another eight batches of Angiomax, these accounting for another 224,000 vials valued at more than $80 million. Under these circumstances, it is plain that both BVL and MedCo commercially exploited the

[5] Because the panel held that the patents were invalid as a result of MedCo's transactions with BVL, it did not reach the parties' remaining arguments, including non-infringement and Hospira's other invalidity arguments.

invention prior to the critical date, and that this commercial exploitation triggered the on-sale bar.

The fact that title to the Angiomax was always with MedCo does not alter this conclusion, for title need not pass in order for there to be a § 102(b) "sale." This Court has never declined to apply the on-sale bar simply because the underlying transaction did not encompass the passage of title to an embodiment of the invention. To the contrary, the Court has applied the on-sale bar even where title passed to something other than the invention itself, or where title did not pass at all. This approach sensibly recognizes that an invention can be commercially exploited regardless of whether title passes to the invention or any of its embodiments. It also recognizes that insisting upon the passage of title would allow inventors to unduly prolong the period during which they can exclusively commercialize their inventions.

Nor is there any basis to conclude that the activities undertaken by BVL and MedCo constituted "experimental use" so as to negate the on-sale bar's application. MedCo did not even argue experimental use below; rather, the district court addressed the issue sua sponte. In all events, there is no basis for a conclusion that MedCo's primary purpose was experimental (as it must be to preclude application of the on-sale bar). MedCo instructed BVL to fill the batches "for commercial use"; BVL released them "for commercial and clinical packaging"; the written pro-

tocol made clear that MedCo and BVL expected the process to work when run at commercial scale; and the sheer scale of these activities belies any experimental purpose. The fact that the first three batches *also* served the purpose of validating the revised process for FDA regulatory purposes cannot overcome the conclusion that their primary purpose was commercial, not experimental. And even if those batches *were* somehow experimental—which they were not—the same cannot be said of the *next* eight batches that MedCo paid BVL to manufacture before the critical date.

II. This Court should not overrule or revise the principle of *Special Devices, Inc. v. OEA, Inc.*, 270 F.3d 1353 (Fed. Cir. 2001), that there is no "supplier exception" to the on-sale bar. That principle is sensible and well-founded. As the Court recognized in *Special Devices*, the text of § 102(b) includes no limitation regarding who must put the invention on sale, or who must purchase it, in order to trigger the bar. Consistent with the statute's categorical approach, this Court has repeatedly declined to weaken the on-sale bar by creating exceptions based on the purchaser's or seller's identity. The principle of *Special Devices* accords with these other decisions. It also accords with the broader principle that any commercial exploitation of an invention will trigger the on-sale bar. And it recognizes that commercially stockpiling an invention—as MedCo did here—can provide an in-

ventor with enormous commercial benefit regardless of whether the inventor makes any sales itself.

Principles of *stare decisis*, moreover, counsel strongly against overruling *Special Devices*. As the Supreme Court recognized just last year, *stare decisis* carries the most force when the precedent at issue concerns the interpretation of a statute—and in patent law, the need for doctrinal stability is particularly acute. *Special Devices*, an interpretation of the Patent Act, has been settled law for fifteen years. It has not proven unworkable, nor have its foundations been undermined. To the contrary, this Court has continued to adhere to the principle that commercial exploitation of an invention triggers the on-sale bar. And Congress, for its part, said nothing about the settled lack of a supplier exception when, in 2011, it substantially revised the Patent Act. Under these circumstances, *stare decisis* applies with full force.

STANDARD OF REVIEW

This Court reviews the district court's factual findings for clear error and its ultimate conclusions of law de novo. *Electromotive Div. of Gen. Motors Corp. v. Transp. Sys. Div. of Gen. Elec. Co.*, 417 F.3d 1203, 1209-10 (Fed. Cir. 2005). In particular, "[w]hether an invention was on sale within the meaning of § 102(b) is a question of law that [is] review[ed] de novo based upon underlying facts, which [are] review[ed] for clear error." *Id.*; *see id.* at 1210 (explaining that whether an

invention is the subject of commercial use under the first prong of *Pfaff* is a "legal question"). A district court's conclusion that a use was experimental, thereby negating the on-sale bar, is also reviewed de novo. *See Petrolite Corp. v. Baker Hughes, Inc.*, 96 F.3d 1423, 1426 (Fed. Cir. 1996) ("Experimental use is a question of law to be analyzed based on the totality of the surrounding circumstances.").

ARGUMENT

I. THE CIRCUMSTANCES HERE CONSTITUTED A COMMERCIAL SALE.

The on-sale bar serves two important policies. First, the bar limits the duration of the period when a patentee can derive commercial benefit from the exclusivity associated with his or her invention. *See, e.g.*, *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998) (explaining that "§ 102 of the Patent Act serves as a limiting provision, both excluding ideas that are in the public domain from patent protection and confining the duration of the monopoly to the statutory term"); *UMC Elecs. Co. v. United States*, 816 F.2d 647, 652 (Fed. Cir. 1987) (noting the policy of preventing an inventor "from commercially exploiting the exclusivity of his invention substantially beyond the statutorily authorized" period); *Ferag AG v. Quipp, Inc.*, 45 F.3d 1562, 1565-67 (Fed. Cir. 1995) (stressing "the policy of preventing inventors from exploiting the commercial value of their inventions while deferring the beginning of the statutory term"). Were it not for the on-sale bar, an inventor could extend his or her monopoly simply by delaying the application

date—even while deriving commercial benefit for the entire period of delay. *See City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 137 (1877) ("[A]n inventor acquires an undue advantage over the public by delaying to take out a patent, inasmuch as he thereby preserves the monopoly to himself for a longer period than is allowed by the policy of the law . . . . Any attempt to use [the invention] for a profit, and not by way of experiment, for a longer period . . . before the application, would deprive the inventor of his right to a patent.").

Second, the on-sale bar incentivizes speedy disclosure of an invention to the public. *See, e.g.*, *Pfaff*, 525 U.S. at 63 (stressing that "the patent system represents a carefully crafted bargain that encourages both the creation *and the public disclosure* of new and useful advances in technology, in return for an exclusive monopoly for a limited period of time" (emphasis added)). By establishing a one-year window to apply for a patent, the on-sale bar ensures that once the inventor begins to commercialize the invention, the process of disclosing the invention will commence within one year—laying the groundwork for future innovation.

The Patent Act does not elaborate on what it means for an invention to be "on sale." This Court and the Supreme Court, however, have held that the invention must have been the subject of a commercial sale (or offer for sale) prior to the critical date, and it must have been ready for patenting. *See, e,g.*, *Plumtree Software, Inc. v. Datamize, LLC* 473 F.3d 1152, 1161 (Fed. Cir. 2006); *Pfaff*, 525 U.S.

at 67-68. In articulating this two-pronged inquiry, *Pfaff* did not directly address the meaning of "commercial sale" or "commercial offer for sale."[6] Immediately after announcing the now-familiar two-part test, however, it favorably quoted Judge Hand's decision in *Metallizing Engineering Co. v. Kenyon Bearing & Auto Parts Co.*, 153 F.2d 516 (2d Cir. 1946): "[I]t is a condition upon an inventor's right to a patent that he *shall not exploit his discovery competitively* after it is ready for patenting." *Pfaff*, 525 U.S. at 68 (quoting *Metallizing*, 153 F.2d at 520) (emphasis added).

Consistent with *Pfaff*, *Metallizing*, and the policies set forth above, this Court has given the on-sale bar broad scope. The touchstone of whether an invention was "on sale," the Court has repeatedly stressed, is commercial exploitation of the invention. *See, e.g.*, *STX, LLC v. Brine, Inc.*, 211 F.3d 588, 590 (Fed. Cir. 2000) ("The overriding concern of the on-sale bar is an inventor's attempt to commercialize his invention beyond the statutory term."). Thus, it has long been clear that transactions exploiting the invention for commercial purposes are sufficient to trigger the bar. *See, e,g., Plumtree,* 473 F.3d at 1163 (explaining that "[p]erforming the steps of the patented method for a commercial purpose is clearly an attempt to profit from the commercial use of an invention" and therefore trig-

[6] The issue presented in *Pfaff* was not what sorts of transactions trigger the bar but, instead, whether the bar can be triggered in the absence of reduction to practice. *See* 525 U.S. at 57.

gers § 102(b)); *In re Kollar*, 286 F.3d 1326, 1333 (Fed. Cir. 2002) (explaining that "performing the [patented] process itself for consideration would trigger the application of § 102(b)"); *id.* (explaining that "a sale by the patentee or a licensee of the patent of a product made by the claimed process would constitute . . . a sale because that party is commercializing the patented process in the same sense as would occur when the sale of a tangible patented item takes place").

It is also well-settled that the commercial benefit triggering the bar may flow from any commercialization of the invention, regardless of whether an embodiment of the invention is itself sold. Thus, in *D.L. Auld Co. v. Chroma Graphics Corp.*, the Court held that the sale of *products* made with the patented *process* triggered the bar. *See* 714 F.2d 1144, 1147 (Fed. Cir. 1983). It explained: "If Auld produced an emblem by the method of the invention and offered that emblem for sale before the critical date, the right to a patent on the method must be declared forfeited." *Id.*; *see Scaltech, Inc. v. Retec/Tetra, LLC*, 269 F.3d 1321, 1328 (Fed. Cir. 2001) (applying the bar where "the process itself was not offered for sale but only offered to be used by the patentee").

Both this Court and the Supreme Court have taken a broad view, moreover, of *whose* sales (or offers to sell) may trigger the on-sale bar. Sales by third parties are sufficient to trigger the bar. *See, e.g.*, *In re Caveney*, 761 F.2d 671, 675 (Fed. Cir. 1985); *Zacharin v. United States*, 213 F.3d 1366, 1371 (Fed. Cir. 2000). That

is so, the Supreme Court has held, even if the underlying sale takes place without the inventor's consent. *See The Driven-Well Cases*, 123 U.S. 267, 275 (1887). This Court has reaffirmed as much. *See Evans Cooling Sys. Inc. v. Gen. Motors Corp.*, 125 F.3d 1448, 1453-54 (Fed. Cir. 1997). And in *Special Devices, Inc. v. OEA, Inc.*, 270 F.3d 1353 (Fed. Cir. 2001), this Court rejected the argument that the on-sale bar is subject to a "supplier exception" under which sales by a supplier to the inventor do not trigger the bar. *See id.* at 1355-56 (explaining that "neither statutory text[] nor precedent" supports a supplier exception). As the Court explained in *Special Devices*: "If such an exception is to be created, Congress, not this Court, must create it." *Id.* at 1357; *see also Brasseler U.S.A. I, L.P. v. Stryker Sales Corp.*, 182 F.3d 888, 890 (Fed. Cir. 1999) (applying on-sale bar despite allegation that buyer and seller were joint developers of the invention).

Despite its breadth, the on-sale bar leaves ample room for an inventor to perfect his or her invention. As the Supreme Court explained in *Pfaff*: "[A]n inventor who seeks to perfect his discovery may conduct extensive testing without losing his right to obtain a patent for his invention—even if such testing occurs in the public eye." 525 U.S. at 64; *see id.* ("The law has long recognized the distinction between inventions put to experimental use and products sold commercially."). Thus, if an inventor's activities qualify for this "experimental use" exception, the on-sale bar does not apply. *See, e.g.*, *Allen Engineering Corp. v. Bartell Industries*,

Inc., 299 F.3d 1336, 1354 (Fed. Cir. 2002); *see also Brasseler*, 182 F.3d at 890-91 (envisioning that the bar might not apply where an inventor orders "a few sample products" from a supplier); *Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1361-62 (Fed. Cir. 2010) (noting that "[i]nventors can request another entity's services in *developing* products embodying the invention without triggering the on-sale bar" (emphasis added)). To fall within that exception, however, it is not enough for those activities to have some experimental benefit. Rather, their "primary purpose" must be experimental. *See Allen Eng'g*, 299 F.3d at 1354.

A. The Transactions Between MedCo and BVL Triggered The On-Sale Bar.

Under the standards set forth above, the transactions between MedCo and BVL constituted a commercial sale for purposes of the on-sale bar.[7] Prior to the critical date, MedCo paid BVL $347,500 to perform the process that is the subject of the patents. A17177-78; A17183. In return, MedCo received vast commercial quantities of Angiomax—three batches totaling more than 60,000 vials. A14959; A15210; A15452. MedCo specifically requested that these batches be "filled for commercial use." A14884. Each batch was given a commercial product code and

[7] In addition, the invention was ready for patenting, as required by the second prong of the inquiry prescribed by *Pfaff*: the invention was reduced to practice at the time when MedCo documented the manufacturing protocol, and certainly no later than the time when BVL successfully produced the first batch using the revised process. A23; A14959-60; A15102-36; A16662-73.

was "[r]eleased for commercial and clinical packaging." A14959-60; A15210-11; A15452-53. Collectively, these batches were valued at well over $20 million. A14959; A15210; A15452 (batches contained 5746, 27,594, and 26,918 vials, respectively); A16055-56, 75:15-76:2 (a batch of about 28,000 vials is worth $10 to $20 million). And MedCo then had BVL manufacture eight *more* commercial batches valued at $10-20 million each, all before the critical date. A16055-56, 75:15-76:2, A16678-79, 696:4-697:13.

These activities easily encompassed a commercial sale for purposes of the on-sale bar. MedCo paid BVL to produce vast amounts of commercially saleable embodiments of the invention. And this arrangement constituted commercial exploitation from the standpoint of both companies. BVL received hundreds of thousands of dollars in exchange for performing MedCo's revised process and providing MedCo with commercial-scale quantities of Angiomax. MedCo, meanwhile, derived a massive commercial benefit from the transactions: whereas it had previously shut down production because of failed batches, *see* A16057, 77:7-21; A16066-67, 86:1-12, 87:19-22, it now was able to fully restock its commercial pipeline with Angiomax whose impurity levels were acceptably low. *See, e.g.*, *Special Devices*, 270 F.3d at 1357 (explaining that there is "no reason why sales [by a supplier to an inventor] for the purpose of commercial stockpiling of an invention . . . should merit different treatment" from other sales). With both parties

commercially exploiting the invention prior to the critical date, it was necessarily "on sale" within the meaning of § 102(b). *See Plumtree*, 473 F.3d at 1163; *In re Kollar*, 286 F.3d at 1333; *D.L. Auld*, 714 F.2d at 1147; *Scaltech*, 269 F.3d at 1328; *Metallizing*, 153 F.2d at 520.

B. The Fact That Title Did Not Pass Cannot Save MedCo From The On-Sale Bar.

As explained above, MedCo's transactions with BVL bore all the hallmarks of commercial activity. MedCo arranged for BVL to be given large quantities of extremely valuable API; paid BVL hundreds of thousands of dollars to manufacture Angiomax using the process that the district court recognized was integral to the patents; and received tens of millions of dollars of commercially saleable Angiomax produced with that process.

In light of the foregoing, it is immaterial whether title to the API and Angiomax ever passed between BVL and MedCo. To begin with, the case law has long made clear that the passage of title to an invention's embodiment is *not* necessary for the on-sale bar to be triggered. As noted above, *Pfaff* did not define what constitutes a "commercial sale" or a "commercial offer for sale"; it did, however, invoke Judge Hand's statement that an inventor "shall not exploit his discovery competitively" once it is ready for patenting—a broad formulation that contains no requirement that title pass. *Pfaff*, 525 U.S. at 67-68 (quoting *Metallizing*, 153 F.2d at 520) (internal quotation marks omitted). This Court's case law likewise has de-

clined to insist upon the passage of title. In *D.L. Auld*, for instance, the Court considered the validity of a patent on a manufacturing process. It held that the inventor had forfeited its rights by using that process to manufacture products, then selling the products—even though title never passed to any embodiment of the invention itself. *See* 714 F.2d at 1147. The Court explained: "If Auld produced an emblem by the method of the invention and offered that emblem for sale before the critical date, the right to a patent on the method must be declared forfeited." *Id.* In *Scaltech*, the Court again declined to require the passage of title to the invention or its embodiment. *See* 269 F.3d at 1328 (applying the bar where "the process itself was not offered for sale but only offered to be used by the patentee"). And in *Plumtree*, the Court once more confirmed that title need not pass: "[P]erforming the patented method for commercial purposes before the critical date constitutes a sale under § 102(b)." 473 F.3d at 1163; *see In re Kollar*, 286 F.3d at 1333 (stressing that "performing the process itself for consideration" would trigger the on-sale bar); *Minton v. Nat'l Ass'n of Secs. Dealers, Inc.*, 336 F.3d 1373, 1377 (Fed. Cir. 2003) (applying on-sale bar to lease of computer program).

To be sure, the above-cited cases involve patented processes or methods. But there is no sensible reason for a different rule to apply to patented processes than to other inventions. This Court has repeatedly explained that the on-sale bar is designed to prevent inventors from unduly prolonging the period during which

they can exclusively commercialize their inventions. *See STX*, 211 F.3d at 590; *Plumtree*, 473 F.3d at 1163; *Kollar*, 286 F.3d at 1333; *see also Metallizing*, 153 F.2d at 520. Commercialization of a product, even where title does not pass, implicates those concerns no less than does commercialization of a process. Notably, MedCo's briefs have cited no case declining to apply the on-sale bar simply because title has not passed.

Here, moreover, the relevant transactions between MedCo and BVL are economically equivalent to ones in which title *would* pass. MedCo paid BVL $347,500 characterized as a manufacturing charge, and had its own supplier provide the API to BVL. A16053, 73:202-4; A17177-78; A17183. Just as easily, BVL could have purchased the API from that same supplier (taking title to the API), then charged MedCo an amount equivalent to that cost plus the $347,500. This case, in which title remained with MedCo, differs economically from that hypothetical scenario only in that MedCo paid the API's cost directly to the supplier, instead of BVL paying it and then passing it along to MedCo as part of the drug price. Whether the on-sale bar applies should not depend on differences that do not alter a transaction's basic economics. *Cf. Group One, Ltd. v. Hallmark Cards, Inc.*, 254 F.3d 1041, 1049 n.2 (Fed. Cir. 2001) ("[A] sale of an interest that entitles the purchaser to possession and use of the machine, unrelated to any patent present or future, could be couched as a 'license'; such labeling would not prevent the

transaction from triggering the on-sale bar, all other requirements being met."); *In re Kollar*, 286 F.3d at 1330 n.3; *Quanta Computer, Inc. v. LG Elecs., Inc.*, 553 U.S. 617, 628-29 (2008) (stating, for purposes of patent exhaustion, that "[o]ur precedents do not differentiate transactions involving embodiments of patented methods or processes from those involving patented apparatuses or materials," and rejecting a rule in which "[p]atentees seeking to avoid patent exhaustion could simply draft their patent claims to describe a method rather than an apparatus").

That is particularly true here, for the asserted claims have process limitations. As the district court observed, there is "nothing novel here about the product alone," because the specification itself shows that "pharmaceutical batches containing less than .6% Asp^9 existed in the prior art." A41. MedCo's innovation, if any, consisted solely of a process to more reliably manufacture batches with those low levels of impurity. *See id.* ("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.").[8] And it is that very process that, according to MedCo's own "manufacturing services" characterization of the transaction, MedCo paid BVL to perform prior to the

[8] Even under MedCo's own proposed construction, moreover, the claims contain process limitations. *See* A39 (reciting MedCo's proposal that "Wherein the batches have a pH adjusted by a base" be given its plain and ordinary meaning or, alternatively, be construed to mean that "[d]uring compounding, the pH of the batches is adjusted using a base").

critical date. Where a manufacturer is paid to practice a claim's process limitations—and particularly where those limitations are exactly what distinguishes the invention from the prior art—it is particularly inapt to suggest that the on-sale bar can be avoided on the technicality that title did not pass.

Insisting upon passage of title would not be sound policy, either. Even a few months of pharmaceutical exclusivity can be worth hundreds of millions of dollars, creating overwhelming incentives to delay a patent's expiration date—and MedCo's proposed rule would give inventors a road map to do so. Under that rule, an inventor could readily skirt the bar by recharacterizing a transaction as a mere "manufacturing contract" under which title never passes—even where, in economic substance, the transaction constitutes a highly lucrative commercial exploitation of the invention. That result could severely undermine the on-sale bar's goal of "preventing inventors from exploiting the commercial value of their inventions while deferring the beginning of the statutory term." *Ferag*, 45 F.3d at 1566; *see UMC Elecs.*, 816 F.2d at 652; *Pfaff*, 525 U.S. at 64-65.

Nonetheless, in its rehearing petition, MedCo argued—for the first time—that the on-sale bar was not triggered because the Uniform Commercial Code's definition of "sale" requires the passage of title. That argument is meritless. This Court has never held that the on-sale bar encompasses only those transactions that are "sales" within the meaning of the UCC. To the contrary, as described above,

the Court has repeatedly stressed that the bar broadly encompasses commercial exploitation of the invention, and has applied the bar even where no goods have been "sold" as a matter of commercial law. *See supra* pp. 25-26, 30-32. And the Court has rejected approaches that turn on a transaction's form, rather than its substance. *See Group One*, 254 F.3d at 1049 n.2; *In re Kollar*, 286 F.3d at 1330 n.3; *cf. Quanta*, 553 U.S. at 628-29. There is no reason why form should prevail here.

The one case that MedCo has cited in support of its UCC argument cannot bear the necessary weight. *See Group One*, 254 F.3d at 1047. In *Group One*, the Court considered whether certain communications between the patentee and a potential purchaser were sufficiently definite to constitute an "offer for sale." The Court explained that "[a]s a general proposition" it would look to the UCC "to define whether, as in this case, a communication or series of communications rises to the level of a commercial offer for sale." *Id.* Even as to the limited question before it, the Court declined to ascribe talismanic significance to the UCC. *See id.* at 1047-48 (characterizing the UCC as a "*useful, though not authoritative,* source in determining the ordinary commercial meaning of terms used by the parties" (emphasis added; internal quotation marks omitted)); *see also Scaltech*, 269 F.3d at 1328 (characterizing the UCC as "an important relevant source of general contract law" for purposes of that determination, and citing *Group One*). And *Group One* said nothing about a title-passage requirement for purposes of the on-sale bar, or

about using the UCC to determine whether particular *consummated* transactions (as opposed to putative offers for sale) trigger the bar.[9]

C. The Experimental-Use Exception Does Not Apply Here.

In the district court, MedCo never argued experimental use. Instead, the issue was raised for the first time by the court itself in its post-trial decision. There, the court held—sua sponte—that the transactions at issue satisfied the experimental-use exception because they were used to satisfy the FDA's process validation requirements. A24. Under long-settled law restricting the scope of the experimental-use exception, the district court was wrong.

The experimental-use exception applies in only a narrow set of circumstances. It is not enough for the patentee's activities to have had some experimental character, however defined. *See Allen Eng'g*, 299 F.3d at 1354 ("[T]he question . . . is not whether the invention was under development, subject to testing, or oth-

[9] This Court's on-sale bar cases concerning the effect of a license do not counsel in favor of MedCo's rule, either. The Court has held that a patentee's grant of a license to practice an invention, even in exchange for consideration, does not trigger the bar. *See, e.g.*, *In re Kollar*, 286 F.3d at 1330-31; *see also Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1217 (Fed. Cir. 1998); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1267 (Fed. Cir. 1986). These decisions, however, rest on the idea that a mere sale of the "right to commercialize" an invention should not be equated with commercialization of the invention itself. *See, e.g.*, *In re Kollar*, 286 F.3d at 1330 (stressing the absence of any "indication that a product of the claimed process was actually offered for sale"). Here, the transactions between MedCo and BVL, in which MedCo paid BVL to manufacture large amounts of Angiomax using its revised process, amounted to actual commercialization of the invention—not just the transfer of a right to commercialize.

erwise still in its experimental stage at the time of the asserted sale." (internal quotation marks omitted)). Rather, experimentation must have been the "primary purpose" of those activities. *Id.* (quotation marks omitted); *see Electromotive*, 417 F.3d at 1210 (activities must have ben "primarily . . . for experimentation"). The sale, by contrast, must have been purely "incidental" to that experimental purpose. *Id.*; *see Pfaff*, 525 U.S. at 64 (noting "the distinction between inventions put to experimental use and products sold commercially"). Insisting that the experimental purpose be "primary"—and that the commercial purpose be "incidental"— makes good sense, given the ease with which a patentee can assert *some* manner in which the invention was still being refined or tested. In all events, a patentee must demonstrate experimental use with evidence, not conclusory recitations of an experimental purpose. *See, e.g.*, *Lisle Corp. v. A.J. Mfg. Co.*, 398 F.3d 1306, 1316 (Fed. Cir. 2005).

MedCo failed to make the required showing. Indeed, MedCo did not even *argue* that the experimental-use exception applied here—an omission difficult to square with the notion that the record actually supports such a determination. And the record below contains not a shred of evidence that the purpose of the batches was to determine whether the invention "work[ed] for its intended purpose"—as is required for the exception to apply. *RCA Corp. v. Data Gen. Corp.*, 887 F.2d 1056, 1061 (Fed. Cir. 1989); *see City of Elizabeth*, 97 U.S. at 137 (no on-sale bar

"when the delay is occasioned by a *bona fide* effort . . . to ascertain whether it will answer the purpose intended").

It is unsurprising that MedCo did not attempt to demonstrate experimental use, for the record overwhelmingly demonstrated the contrary—*i.e.*, that MedCo knew the process worked as intended, and that the transactions' commercial purpose was far more than "incidental." *Allen Eng'g*, 299 F.3d at 1354. *First*, the manufacturing protocol (approved by MedCo and BVL) announced the commercial purpose of BVL's manufacturing. That protocol unequivocally proclaimed: "The solution *will be filled for commercial use*." A14884 (emphasis added). That statement alone disposes of any notion that MedCo's purpose was experimental. Consistent with that statement, the batches were each given a commercial product code and were "[r]eleased for commercial and clinical packaging." A14959-60; A15210-11; A15452-53.

Second, the same manufacturing protocol demonstrated that MedCo expected the process to succeed in minimizing the risk of Asp^9 impurity. One objective, the protocol stated, was "to *confirm* that all in process specifications and critical parameters are maintained during the manufacturing of the product . . . with the implementation of the process improvements." A14884 (emphasis added); *see id.* (noting objective "to ensure that the process optimizations *indeed* minimize the risk of high levels of Asp9 impurity in the final product" (emphasis added); *id.*

("The satisfactory test results . . . will successfully support the process improvements of the formulation manufacturing process . . . "); *id.* at 14883 (lots "will be utilized as an effectiveness *verification* of the process improvements" (emphasis added)). Like MedCo's statement that the solution "will be filled for commercial use," this is not the language of experimentation. Indeed, the protocol stated that the necessary experiments had *already* been conducted. *See* A14883 ("*Based upon lab experiments* . . . and evaluation of the potential benefits of these process improvements, it was deemed appropriate to implement them during the manufacturing of three lots of Bivalirudin drug product." (emphasis added)).

Third, the sheer scale of BVL's batch manufacturing belies any assertion that these activities were experimental. *See S. Snow Mfg. Co. v. SnoWizard Holdings, Inc.*, 567 F. App'x 945, 951 n.2 (Fed. Cir. 2014), *cert. denied*, 135 S. Ct. 1416 (2015) (rejecting experimental-use argument because of scale of purchases). In the first three batches alone, BVL manufactured 60,000 vials of Angiomax, valued at more than $20 million. A14959; A15210; A15452; A16055-56, 75:15-76:2. Manufacturing at that scale cannot plausibly be deemed experimental. What is more, MedCo had previously shut down production, and developed its revised process, because of the great expense associated with discarding commercial batches for unacceptably high levels of impurity. A15986; A16057, 77:7-21; A16066-67,

86:1-12, 87:19-22. Calling the new commercial-scale batches "experimental" would illogically treat MedCo as suddenly willing to risk that same expense.

Fourth, BVL and MedCo communicated about the batches in a manner inconsistent with an experimental purpose. BVL's invoices did not mention experimentation. Instead, they described each of the invoiced amounts (which totaled $347,500) as "Charge to manufacture Bivalirudin lot." A17177-78, A17183. When BVL *had* undertaken work of an experimental character, by contrast, it invoiced MedCo for "product and process development" and "performance of pilot formulation studies to support investigation of Asp9 impurity." A17175 (capitalization removed).

Fifth, even if the primary purpose underlying the first batch was experimental, that purpose cannot have persisted for subsequent batches. The experimental-use exception allows an inventor to perform experiments targeted towards reducing the invention to practice. But once the invention has in fact been reduced to practice, the exception cannot apply. *See RCA*, 887 F.2d at 1061 ("[E]xperimental use, which means perfecting or completing an invention to the point of determining that it will work for its intended purpose, ends with an actual reduction to practice."). Here, even assuming that the first batch was experimental—which it was not—its successful manufacture necessarily amounted to a

reduction to practice. Subsequent batches therefore could not fall within the exception. *See id.*

Finally, even if all of the first three batches somehow were experimental—and they were not—the experimental-use exception still would not save MedCo from the on-sale bar. MedCo and BVL did not stop with these three batches. Instead, MedCo paid BVL to manufacture eight *more* commercial batches of Angiomax using the revised process—all before the critical date. 16678-79, 696:4-697:13. As implausible as it is to conclude that the first three batches were experimental, it is even less plausible to suppose that eight *more* batches were experimental—especially after the first three batches yielded acceptably low levels of Asp[9] impurity.[10]

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[10] MedCo has previously claimed that Hospira waived this argument by failing to present it to the district court. *See* MedCo Panel Reply Br. 36. That contention, however, ignores the course of proceedings below. MedCo never argued experimental use in the district court—presumably because it realized that the facts could not support the exception. Only in its post-trial decision did the district court raise the experimental-use issue sua sponte, holding that the three validation batches were experimental. A24.

Because MedCo never argued experimental use in the first place, Hospira had no need to argue that anything more than the first three batches triggered the on-sale bar. That is so even though the record contained evidence of all eleven batches. A16678-79. Had MedCo (or the district court) raised the issue earlier with respect to the first three batches, Hospira not only would have argued that the first three batches were not experimental, but also would have included the last eight batches in its on-sale argument. It would make little sense to hold that Hospira has waived an argument by failing to make it at a time when it was unnecessary.

Nonetheless, and in the face of all of this evidence, the district court concluded that the transactions at issue satisfied the experimental-use exception because one purpose of BVL's and MedCo's activities was to satisfy FDA process validation requirements. A24. The district court's reasoning cannot be sustained.

To begin with, the record contains no evidence that the process validation undertaken here was experimental. The manufacturing protocol suggests just the opposite. It describes the process validation here as "*confirmational* validation" that was "intended to verify and validate the effectiveness of the process optimization steps" A14883 (emphasis added). Calling this undertaking "confirmational" is inconsistent with the idea that MedCo and BVL actually were seeking to determine whether the revised process worked as intended. *See RCA*, 887 F.2d at 1061.

Nor is there any basis for a conclusion that "process validation" is inherently experimental. Such a conclusion finds no support in the FDA's regulations. Those regulations provide only that "control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." 21 C.F.R. § 211.110(a). The regulations do not characterize process validation as "experimental." Nor do they otherwise purport to relate to the experimental-use exception—or, for that matter, to any criteria for patentability. *See id.*; *see also* Food & Drug Administration, *Guideline on General*

Principles of Process Validation 6 (1987) ("Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics").[11]

In any event, even assuming that the process validation here had some experimental character—which it did not—it cannot overcome the overwhelmingly commercial character of the activities at issue. Again, MedCo expected the process to succeed; it directed that that the solution be "filled for commercial use"; the batches were treated like other batches; the scale of manufacturing was vast; and the three validation batches were followed by eight *more* batches. *See supra* pp. 38-41. Under these circumstances, any experimental purpose cannot plausibly be characterized as the "primary purpose" of MedCo's and BVL's activities, and thus cannot defeat the on-sale bar.

II. THE COURT SHOULD NOT OVERTURN OR REVISE *SPECIAL DEVICES*.

As explained above, this Court's decision in *Special Devices* compels rejection of MedCo's argument that, because the sales here were made *to* the inventor, they did not trigger the on-sale bar. In granting en banc review, however, the Court

[11] The fact that process validation can be characterized as a form of "testing" likewise does not mean that it is "experimental." *Every* batch of pharmaceutical product must be "tested" before it is made available for sale, *see* 21 C.F.R. § 211.110(a)—but that does not turn it into an experimental batch.

has asked whether *Special Devices* should be overruled or revised. Hospira respectfully submits that the answer is no. *Special Devices* was rightly decided, and principles of *stare decisis* underscore that the decision should be left intact.

A. The Holding Of *Special Devices* Is Sound.

In *Special Devices*, this Court considered whether to create an exception to the on-sale bar. At issue was whether an inventor-supplier relationship should be granted special status, so that commercial sales between those parties would not trigger the bar. *See* 270 F.3d at 1355. The panel declined to create such an exception. *Id.* That decision was correct in all respects.

To begin with, the text of § 102(b) cannot accommodate a supplier exception to the on-sale bar. That text states categorically that if "the invention was . . . on sale in this country" prior to the critical date, the patent will be invalid. *See* 35 U.S.C. § 102(b) (2010).[12] As *Special Devices* explained, Section 102(b)'s text includes no limitation regarding who must put the invention on sale, or who must purchase it, in order to trigger the on-sale bar. *See* 270 F.3d at 1355 (explaining that "the text of section 102(b) itself makes no room for a 'supplier' exception"). The Court reasoned: "By phrasing the statutory bar in the passive voice, Congress

[12] Congress amended 35 U.S.C. § 102 in 2011 as part of the America Invents Act ("AIA"). Unless otherwise noted, citations to § 102 in this brief are to the pre-AIA version of the section, for that is the version that applies here. *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 35, 125 Stat. 284, 341 (2011).

indicated that it does not matter who places the invention 'on sale'; it only matters that someone—inventor, supplier or other third party—placed it on sale." *Id.*

Particularly since a supplier exception has no basis in the statutory text, there is no reason for the judiciary to create one. The *Special Devices* Court recognized as much. It explained: "If such an exception is to be created, Congress, not this court, must create it." *Id.* at 1357.

This Court's precedent provides no more basis for a supplier exception than does the statutory text. Instead, *Special Devices* is just one of a long line of decisions rejecting efforts to weaken the on-sale bar by excepting certain transactions based on the identity of the buyer or seller. In *Buildex Inc. v. Kason Industries, Inc*,, 849 F.2d 1461, 1466 (Fed. Cir. 1988), for example, this Court refused to create an exception for sales made by a supplier to a party with whom it worked to develop the invention. In *Ferag*, the Court refused to create an exception for sales made by a supplier to an inventor— even though the inventor company partially *owned* the supplier. *See* 45 F.3d at 1565-67. And in *Brasseler*, the Court refused to create an exception for sales between joint developers of an invention. *See* 182 F.3d at 890. It reached this conclusion even though the co-inventor/purchaser "retained control over the manufacturing of the patented invention" by the co-inventor/supplier. *Id.* Thus, the *Special Devices* decision was—and remains—hardly remarkable. It simply clarified what other cases had already determined: "it

does not matter who places the invention 'on sale'; it only matters that someone—inventor, supplier or other third party—placed it on sale." *Special Devices*, 270 F.3d at 1355.

More generally, a judicially created supplier exception would undermine the purpose of the on-sale bar. *See id.* at 1357. As the Supreme Court has explained, "the patent system represents a carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in technology, in return for an exclusive monopoly for a limited period of time." *Pfaff*, 525 U.S. at 63. The on-sale bar plays a critical role in maintaining this balance: "Congress was concerned with encouraging inventors to file for a patent as soon as possible and, at the same time, prevent[ing] the commercial exploitation of an invention as a trade secret for more than 1 year." *Gould Inc. v. United States*, 579 F.2d 571, 580 (Ct. Cl. 1978); *see also, e.g.*, *Ferag*, 45 F.3d at 1566 (describing "the policy of preventing inventors from exploiting the commercial value of their inventions while deferring the beginning of the statutory term" as "[f]oremost" among the motivations for the on-sale bar); *D.L. Auld*, 714 F.2d at 1147 (explaining that the intent of the on-sale bar "is to preclude attempts by the inventor . . . to profit from commercial use of an invention for more than a year before an application for a patent is filed").

A supplier exception, as *Special Devices* explained, would improperly permit an inventor to commercially stockpile his invention (as MedCo did here) without starting the clock to apply for a patent. *See* 270 F.3d at 1357 (explaining that there is "no reason why sales [by a supplier to an inventor] for the purpose of commercial stockpiling of an invention . . . should merit different treatment" from other sales). The facts of that case vividly illustrate this point: There, the inventor purchased 20,000 commercial units of its invention from a supplier before the critical date. *Id.* at 1355. The "sheer number of units purchased" and the commercial purpose of that sale led the Court to conclude the obvious: "the invention was commercially exploited before the critical filing date." *Id.* at 1356; *see also Biogen, Inc. v. Schering AG*, 954 F. Supp. 391, 396-97 (D. Mass. 1996) (holding that a manufacturer's spending $24 million to stockpile and prepare to market a drug product made the manufacturer subject to suit even before FDA approval).

This case illustrates the point just as vividly. Before the critical date, BVL supplied MedCo with eleven commercial batches of Angiomax made with the revised process. A16678-79, 696:4-697:13. These batches, each valued at more than $10 million, accounted for vast numbers of commercially saleable doses. A15986; A16055-56, 75:15-76:2; A14959; A15210; A15452. By the time of the critical date, therefore, the transactions at issue gave MedCo a fully stocked commercial pipeline with a commercial value exceeding $100 million—manifesting

commercial exploitation of the sort that should start the clock to apply for a patent. Indeed, MedCo's replenishment of its long-depleted commercial pipeline gave it a *further* commercial benefit before the critical date: Confident that it would be able to fill orders for Angiomax well into the future, in February 2007 MedCo entered into a new exclusive distribution agreement with ICS. A14674-700. That agreement envisioned that ICS would order enough Angiomax to maintain appropriate levels of inventory, and that MedCo would make commercially reasonable efforts to fill ICS's orders promptly. A14676-78. Without a fully stocked commercial pipeline, it is difficult to imagine MedCo entering into this agreement.

The absence of a "supplier exception" is far from harsh. Even without such an exception, inventors maintain significant flexibility to engage in non-commercial purchases of embodiments of their inventions without starting the one-year grace period. This Court has long recognized the important distinction between the commercial exploitation of an invention, on one hand, and transactions in which "an individual inventor takes a design to a fabricator and pays for . . . a few sample products," on the other. *Brasseler*, 182 F.3d at 891. Here, however, MedCo plainly was not transacting for "a few sample products" before the critical date. Rather, as discussed above, MedCo transacted with BVL to obtain tens of millions of dollars of commercially saleable Angiomax—transactions that amounted to commercial exploitation under any reasonable understanding of the term.

In a similar vein, the absence of a "supplier exception" does not mean that using another entity's services to perfect the invention will start the one-year grace period of § 102(b). In such instances, the experimental use exception could apply. *See, e.g.*, *EZ Dock v. Schafer Sys., Inc.*, 276 F.3d 1347, 1351-52 (Fed. Cir. 2002). But that is not the case here; as detailed at length above, MedCo's primary purpose in its transactions with BVL, the basis for applying the on-sale bar here, was commercial, not experimental. *See supra* pp. 38-41.

Nor is there merit to MedCo's argument that the lack of a supplier exception unfairly disadvantages smaller companies that lack in-house manufacturing capacity. Pet. for Reh'g 3. Whatever the legal significance of large-scale in-house manufacturing, the on-sale bar does not prohibit any transactions between an inventor and its supplier, nor does it restrict inventors and suppliers from structuring their businesses as they wish. The bar merely requires the inventor to file a patent application—even a provisional one—within a year of the commercial exploitation of the invention. *See Special Devices*, 270 F.3d at 1355 (explaining that inventors can simply "protect themselves in these circumstances by taking 'prompt action' and filing a patent application within the one-year deadline" (quoting *Evans Cooling Sys.*, 125 F.3d at 1453) (internal quotation marks omitted)). That is not an onerous requirement at all. And enforcing the requirement as to inventor-supplier transactions is entirely consistent with the purpose of the bar: to "encourag[e] in-

ventors to file for a patent as soon as possible." *Gould*, 579 F.2d at 580. Doing away with the principle of *Special Devices*, by contrast, would merely impose additional costs on the public.

B. *Stare Decisis* Requires Adherence To The Principle Of *Special Devices*.

As explained above, the rule of *Special Devices* is the right one. Bedrock principles of *stare decisis*, moreover, require adherence to the Court's settled precedent—especially where, as here, the precedent is a statutory decision that Congress has declined to overrule.

"*Stare decisis*—in English, the idea that today's Court should stand by yesterday's decisions—is 'a foundation stone of the rule of law.'" *Kimble v. Marvel Entertainment, LLC*, 135 S. Ct. 2401, 2409 (2015) (quoting *Michigan v. Bay Mills Indian Cmty.*, 134 S. Ct. 2024, 2036 (2014)). "The doctrine rests on the idea . . . that it is usually 'more important that the applicable rule be settled than that it be settled right.'" *Id.* (quoting *Burnet v. Coronado Oil & Gas Co.*, 285 U.S. 393, 406 (1932) (Brandeis, J., dissenting)); *see also id.* ("[A]n argument that we got something wrong—even a good argument to that effect—cannot by itself justify scrapping settled precedent.").

The need for doctrinal stability is particularly important in patent law. The Supreme Court made this point clear less than a year ago in *Kimble*. *See* 135 S. Ct. at 2410 (explaining that property law—including patents—is a context in which

"considerations favoring *stare decisis* are 'at their acme'" because "parties are especially likely to rely on such precedents when ordering their affairs").

Under the doctrine of *stare decisis*, there must be "special justification" to overrule binding precedent. *Dickerson v. United States*, 530 U.S. 428, 443 (2000); *Halliburton Co. v. Erica P. John Fund, Inc.*, 134 S. Ct. 2398, 2407 (2014). Mere disagreement with that precedent is not enough. Departure from precedent may be proper when "subsequent cases have undermined [its] doctrinal underpinnings," when applying the precedent has proved "unworkable," or when "a considerable body of new experience" requires revisiting and changing the law. *Dickerson*, 530 U.S. at 443; *J.R. Sand & Gravel Co. v. United States*, 552 U.S. 130, 139 (2008); *Pearson v. Callahan*, 555 U.S. 223, 234 (2009).

Here, *Special Devices* has been the law for nearly fifteen years. *See Robert Bosch, LLC v. Pylon Mfg. Corp.*, 719 F.3d 1305, 1316 (Fed. Cir. 2013) (en banc) (stressing that "[p]anel opinions are . . . opinions of the court" and form the precedent of this Circuit); *id.* (explaining that panel decisions "represent[] the established law of the circuit, [and] a due regard for the value of stability in the law requires that [there be] good and sufficient reason to reject it at this later date" (quoting *United States v. Bailey*, 36 F.3d 106, 110 (D.C. Cir. 1994) (en banc)). In the absence of any "special justification," therefore, the Court must adhere to that decision.

No "special justification" exists here. *First*, the decision in *Special Devices* is doctrinally sound and consistent with the broader swath of case law regarding the on-sale bar. As described above, when the Court in *Special Devices* declined to create a "supplier exception" to the on-sale bar, it was hardly breaking new ground. Rather, that decision was just one in a long line of cases declining to create exceptions to the bar based on the identity of the buyer or the seller. *See supra* pp. 26-27. Overruling *Special Devices* would not amount to eliminating a lone aberrant precedent; rather, it would call into question a line of cases dating back decades.

Subsequent decisions, meanwhile, have not called *Special Devices* into question. *Compare Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1293 (Fed. Cir. 2009) (en banc) (overruling a case that had been undermined by a later Supreme Court decision). To the contrary, this Court has expressly relied upon the lack of a supplier exception after *Special Devices*. *See Hamilton Beach Brands, Inc. v. Sunbeam Prods., Inc.*, 726 F.3d 1370, 1375 (Fed. Cir. 2013) (explaining that because "there is no 'supplier exception' to the on-sale bar[,] . . . it is of no consequence that the 'commercial offer for sale' at issue in this case was made by Hamilton Beach's own supplier and was made to Hamilton Beach itself."). More generally, the Court has reiterated the broad principle from which *Special Devices* flows: that the on-sale bar precludes "an attempt to profit from the commercial use of an in-

vention" for more than a year before a patent application is filed. *Plumtree*, 473 F.3d at 1163.

Second, the *Special Devices* rule has not proven unworkable or difficult to administer. *Compare Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1289 (Fed. Cir. 2011) (en banc) (revising standards where prior doctrine had "plagued not only the courts but also the entire patent system"); *TiVo Inc. v. EchoStar Corp.*, 646 F.3d 869, 881 (Fed. Cir. 2011) (en banc) (overruling prior decision that had "confuse[d]" two distinct legal inquiries and proved to be "unworkable" in the lower courts). The decision in *Special Devices* articulated a simple, bright-line rule: the on-sale bar contains no exception for sales by a supplier to the inventor. 270 F.3d at 1357. That holding, as discussed above, is consistent with a long line of cases rejecting other exceptions based on the identity of the buyer or seller. Lower courts, for their part, have not expressed frustration, confusion, or dismay in applying the simple rule that there is no supplier exception to the on-sale bar. Instead, they have easily applied this straightforward rule to each case's specific facts. *See Myers v. Master Lock Co.*, No. 06-cv-619, 2008 WL 2168977, at *4 (D. Colo. May 22, 2008); *PGH Techs., LLC v. TimeMed Labeling Sys., Inc.*, No. 3:05-cv-1091, 2006 WL 2670967, at *9 (M.D. Tenn. Sept. 18, 2006); *see also Fisher-Price, Inc. v. Safety 1st, Inc.*, No. 01-civ-51, 2002 WL 1307333, at *11 (D. Del. June 14, 2002). And the clear rule articulated by *Special Devices*—that the

on-sale bar applies to transactions with suppliers—undoubtedly has guided inventors in deciding when to apply for patents in the first instance. The workability of *Special Device*'s holding, in short, counsels against overturning the decision.[13]

Third, the fact that *Special Devices* is a statutory decision only underscores the inappropriateness of overruling or revising it. That is because the doctrine of *stare decisis* has particular importance where the precedent at issue is statutory. This presumption that the courts will adhere to prior rulings has "special force" for precedents that resolve statutory questions, because "Congress remains free to alter what we have done." *J.R. Sand & Gravel Co.*, 552 U.S. at 139 (internal quotation marks omitted); *Robert Bosch, LLC*, 719 F.3d at 1316. The Supreme Court reiterated this point less than a year ago—and in a case involving the Patent Act, no less. *See Kimble*, 135 S. Ct. 2409 (explaining that all judicial decisions interpreting a statute, "in whatever way reasoned, effectively become part of the statutory scheme, subject (just like the rest) to congressional change"). "Absent special justification," the Supreme Court emphasized, statutory rulings "are balls tossed into Congress's court, for acceptance or not as that branch elects." *Id.* So too here: The fact that *Special Devices* is a statutory ruling counsels strongly in favor of adhering to principles of *stare decisis*.

[13] Further, new experience has done nothing to undermine *Special Devices*. There is no reason to think, for instance, that applying for a patent within one year has become any more difficult than it was when *Special Devices* was decided.

That conclusion is only bolstered by the fact that Congress *has* extensively revised the Patent Act, including § 102, since *Special Devices* was decided. In so acting, Congress modified the text of the on-sale bar—but it did not revise the statute further to create an exception for sales between suppliers and inventors.[14] *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 102, 125 Stat. 284, 285-86 (2011); *Kimble*, 135 S. Ct. at 2410 (reasoning that "Congress's continual reworking of the patent laws . . . further supports leaving the decision in place"). Particularly where Congress has declined to overrule *Special Devices*, this Court should not do so itself.

Finally, overruling *Special Devices* would give an undeserved windfall to MedCo, at the public's expense. In 2006 and 2007, when MedCo undertook the transactions at issue here, *Special Devices* was settled law. MedCo therefore should have exercised diligence and applied for patents within one year. It did not. Overruling *Special Devices* would effectively reward Medco for ignoring settled law and sleeping on its rights.

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[14] Until 2011, the statutory text provided that a patent could issue unless "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b) (2010). The statute now provides that a patent may issue unless "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention," except if the "disclosure [was] made 1 year or less before the effective filing date of a clamed invention." 35 U.S.C. §§ 102(a)(1), (b)(1) (2012).

CONCLUSION

For the foregoing reasons, the district court's decision that MedCo's transactions with BVL did not trigger the on-sale bar should be reversed. In the event that the en banc court holds otherwise, it should remand to the panel for consideration of the remaining issues raised by MedCo's appeal and Hospira's cross-appeal.

January 11, 2016

Respectfully submitted,

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January 11, 2016

ADDENDUM

ADDENDUM

Final Judgment, Docket No. 829 (Apr. 15, 2014) A1-2

Trial Opinion, Docket No. 827 (Mar. 31, 2014)..... A3-34

U.S. Patent No. 7,582,727..... A47-61

U.S. Patent No. 7,598,343..... A62-76

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

~~[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).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

II. ANTICIPATION

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

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

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

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

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

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

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

A. Legal Standard

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

B. Findings of Fact

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

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

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

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

C. Conclusions of Law

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

III. OBVIOUSNESS

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

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

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

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

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

A. Legal Standard

Under 35 U.S.C. § 103(a) a patent "may not be obtained… if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." Obviousness is a question of law that depends on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the relevant art; and (4) any objective considerations such as commercial success, long felt but unsolved need, and the failure of others. *Transocean Offshore*

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

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

B. Findings of Fact

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

C. Conclusions of Law

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

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

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

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

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

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

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

IV. 35 U.S.C. § 112

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

A. Legal Standard

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

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

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

B. Conclusions of Law

i. The Asserted Claims Satisfy the Written Description Requirement

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

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

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

ii. The Asserted Claims Are Enabled and Not Indefinite

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

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

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

V. CONCLUSION

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

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

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**

(75) Inventors: **Gopal Krishna**, Parsippany, NJ (US); **Gary Musso**, Parsippany, NJ (US)

(73) Assignee: **The Medicinces 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.

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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-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.

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Glu Glu Tyr Leu
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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.

* * * * *

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(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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(*) 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.

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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-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]-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.

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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, 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.

* * * * *

CERTIFICATE OF SERVICE

I hereby certify that on January 11, 2016, I caused the foregoing Principal Brief of Defendant-Cross-Appellant Hospira, Inc. in Response to the Court's November 13, 2015 Order to be electronically filed with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the CM/ECF system, which also caused a copy of the foregoing to be delivered by electronic means to the counsel of record listed below.

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/s/ Bradford P. Lyerla

CERTIFICATE OF COMPLIANCE

I hereby certify that:

1. This Brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because this Brief contains 13,540 words, excluding the parts of the Brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This Brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this Brief has been prepared in a proportionately spaced typeface using Microsoft Office Word 2007 in Times New Roman, Font Size 14.

/s/ Bradford P. Lyerla