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 AND RESPONSE BRIEF OF DEFENDANT-CROSS-APPELLANT HOSPIRA, INC.

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September 26, 2014

FORM 9. Certificate of Interest

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

The Medicines Company v. Hospira, Inc.

No. 14-1469

CERTIFICATE OF INTEREST

Counsel for the (petitioner) (appellant) (respondent) (appellee) (amicus) (name of party) Cross-Appellant certifies the following (use "None" if applicable; use extra sheets if necessary):

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:

Not applicable.

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:

Hospira, Inc. has no parent corporation. The only publicly held company that owns 10% or more of Hospira Inc.'s stock is T. Rowe Price Associates, Inc.

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

May 27, 2014
Date

/s/ Sara T. Horton
Signature of counsel

Sara T. Horton
Printed name of counsel

Please Note: All questions must be answered
cc: All Parties

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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 Administration
"PTO"	United States Patent and Trademark Office
"District Court"	District Court for the District of Delaware
"POSITA"	person of skill in the art
"MB"	Brief of Plaintiff-Apellant The Medicines Company
"BVL"	Ben Venue Laboratories
"A___"	Joint Appendix page number(s)

All emphases in this brief has been added unless otherwise noted.

STATEMENT OF RELATED CASES

Defendant-Cross Appellant Hospira agrees with the Statement of Related Cases provided in the Opening Brief of Plaintiff-Appellant MedCo, in which MedCo lists seven related cases.

In two of these related cases, the district courts construed claim terms from the asserted patents: the *Dr. Reddy*'s court in the District of New Jersey (on January 3, 2013), and the *Mylan* court in the Northern District of Illinois (on August 6, 2012). The District Court in this case was the last court to construe the asserted claims, issuing its claim construction ruling on July 11, 2013.

JURISDICTIONAL STATEMENT

The District Court had subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). This Court has jurisdiction over this cross-appeal under 28 U.S.C. § 1295(a)(1). Hospira filed its timely cross-appeal on May 23, 2014. (A17085-86.)

STATEMENT OF THE ISSUES

1. Whether the District Court correctly construed the asserted claims of the '727 patent to require "efficient mixing," where the claims require process limitations and the intrinsic record establishes that "efficient mixing" is the only alleged invention.

2. Whether the District Court correctly construed "efficient mixing" to require that base be added "slowly and in a controlled manner" and mixed under "high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)," where these

steps are the only criteria in the intrinsic record distinguishing "efficient mixing" from "inefficient mixing."

3. Whether, as the District Court found, Hospira does not infringe any asserted claim because it employs "inefficient mixing" as described in the patents.

4. In addition to affirming that Hospira does not employ "efficient mixing," whether the Court should affirm the District Court's ruling of non-infringement because Hospira's ANDAs do not meet the limitation requiring a "maximum" Asp^9-bivalirudin impurity level of 0.6%.

5. Whether this Court should reverse the District Court's ruling and find the asserted claims invalid under the on-sale bar.

6. Whether the Court should reverse the District Court's ruling and find the asserted claims invalid as obvious.

7. Whether the Court should reverse the District Court's ruling and find the asserted claims indefinite where a POSITA cannot determine whether it infringes the "maximum" limitation of the asserted claims.

STATEMENT OF THE CASE

Preliminary Statement

MedCo's '343 and '727 patents are different from most patents.

The claims of the '343 and '727 patents are not directed to a product, a process or a true product-by-process. The patents claim "batches," but a member

of the public who has made a batch of bivalirudin drug product could not determine infringement simply by analyzing the properties of the batch, how it was made, or both. To determine infringement, one must know the process used to make the batch, the properties of ***all*** batches made by the process, and/or whether the batch in question is representative of ***all*** batches that could be made by that process. There is no dispute that this requirement applies to both patents.

According to MedCo, there are two ways to read the claims, depending on whether they are applied to a batch described in an ANDA or a batch made in an ongoing commercial process. MedCo argues its claims are broad when read on a single batch described in an ANDA, contending that this single batch can always be used to show infringement. Using this broad reading, MedCo argues that it makes no difference that Hospira's ANDAs include a manufacturing specification providing for batches with as much as 1.0% Asp^9-bivalirudin, well in excess of claim requirements.

However, for a batch made in an ongoing commercial process, MedCo argues the claims are to be read narrowly to cover a batch meeting the required 0.6% Asp^9-bivalirudin level ***only if every single batch*** made by the same process that made the accused batch ***also*** meets that impurity level. Thus, even though ***most*** of the 87 commercial batches MedCo made from the 1990s to 2006 met that impurity level, according to MedCo not one of these batches is covered by the

claims because the process that made them also made two batches—with Asp^9-bivalirudin levels of 2.5% and 3.6%, respectively—that were outside the claimed range.

These unusual features of the claims affect almost all issues on appeal. For example, the District Court, following the patents' specification, properly construed the claims to require that base be added to the compounding solution using "efficient mixing." Absent that construction, there would be no way to distinguish the prior art batches of Example 4 from the patented batches of Example 5.

Nature Of The Case, Course Of Proceedings, And Disposition Below

On August 19, 2010, MedCo filed its Complaint against Hospira alleging infringement of the patents-in-suit by virtue of Hospira's submission to the FDA of ANDA Nos. 90-811 and 90-816. (A163.) Hospira seeks approval to market a generic bivalirudin drug product for injection once MedCo's patent covering the bivalirudin drug substance (the molecule itself)—a patent not at issue here—and its corresponding pediatric exclusivity expire on June 15, 2015.

Claim 1 of the '343 patent, the only independent asserted claim of that patent, recites "pharmaceutical batches of a drug product comprising bivalirudin . . . prepared by a compounding process comprising . . . efficiently mixing a pH-adjusting solution with the [bivalirudin] solution . . . wherein the batches have a pH

adjusted by a base . . . and wherein the batches have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%." (A76.)

Claim 1 of the '727 patent, the only independent asserted claim of that patent, recites "pharmaceutical batches of a drug product comprising bivalirudin . . . wherein the batches have a pH adjusted by a base . . . and wherein the batches have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6%." (A60.)

On September 23-25, 2013, the District Court held a bench trial. On March 31, 2014, the District Court issued its Trial Opinion finding all asserted claims not infringed and not invalid. (A3-34.) On April 15, 2014, the District Court issued a Final Judgment. (A1-2.)

MedCo appeals from the District Court's non-infringement ruling, while Hospira cross-appeals from the ruling of no invalidity.

STATEMENT OF FACTS

Below, Hospira describes the development of MedCo's claimed invention, Hospira's ANDAs, the asserted patents, and the present litigation.

I. MEDCO'S ALLEGED INVENTION AND PRE-CRITICAL DATE COMMERCIAL ACTIVITY

A. MedCo's Prior Art Process.

Bivalirudin is a twenty-amino-acid peptide that can serve as an anti-coagulant. (A50, 6:16-19.) In the prior art, it was known that bivalirudin was

prone to an impurity on its ninth amino acid—the aspartate impurity ("Asp^{9}"). (A63, 2:8-14; A14918.)

From the late 1990s to October 2006, BVL manufactured Angiomax®, MedCo's commercial bivalirudin drug product, according to a prior art compounding process. (A16058, 78:8-17; A16120-21, 140:19-141:4.) In this prior art process—described in Example 4 of the patents (*id.*)—after bivalirudin active pharmaceutical ingredient ("API") was dissolved in solution, an operator added a base to increase the pH of the solution to acceptable levels. (A73, 22:32-38.) The operator added this pH-adjusting solution "all at once, or rapidly in multiple portions," and mixed the solution with two paddle mixers running between 400 and 800 rpms. (*Id.*, 22:37-42.) During this compounding process, the Asp^{9}-bivalirudin impurity sometimes formed. (*Id.*, 22:54-61.)

BVL manufactured 87 batches of Angiomax® drug product using this prior art process. (*See id.*, 22:55-65.) Only two batches contained out-of-specification levels of Asp^{9}-bivalirudin. (*See* A16055, 75:9-14; A16062, 82:9-16.)

B. MedCo's Claimed Process.

In an attempt to eliminate these rare occurrences of high levels of Asp^{9}-bivalirudin in MedCo's bivalirudin drug product, MedCo retained Dr. Gary Musso to consult with BVL to modify its compounding process. (A16067-68, 87:6-88:11.) That work resulted in the patents-in-suit. (A16075, 95:7-15.)

In the "new" process to manufacture Angiomax® (described in Example 5 of the patents), just as in the old process of Example 4, after the bivalirudin API was dissolved in solution, an operator added a base to increase the pH of the solution to acceptable levels. (A16109, 129:14-130:11; A74, 23:16-23.) However, in the revised process, a peristaltic pump delivered the pH-adjusting solution "at a controlled rate of 2 L/min." (A74, 23:21-23; *see also* A16659-60, 677:9-678:10.) And instead of using paddle mixers operating between 400 and 800 rpms, the revised process used a high shear mixer (or "homogenizer") operating between 1000 and 1300 rpms and a paddle mixer operating at 300-700 rpms. (A74, 23:21-31; A16132, 152:5-7; A16133, 153:11-14.)

By October 25, 2006, MedCo memorialized this "new" process in its operator manufacturing instructions. (A15102-36; A16597-98, 616:22-617:22; A16662-64, 680:19-682:5.) All batches manufactured since October 25, 2006, were made using the revised process. (A16867-68, 885:18-886:16.) By the critical date for both patents—July 27, 2007—BVL manufactured eleven batches of Angiomax® using this process. (A16678-79, 696:4-697:13.) Each batch was worth about $10 million. (A15986, 6:7-11.) Consequently, before the critical date, MedCo paid BVL to manufacture more than $110 million worth of product using the revised process.

MedCo also validated its revised process before the critical date. The FDA requires process validation to demonstrate that a process consistently works as intended. (A16671-72, 689:3-690:6.) The objectives of MedCo's validation were (1) to "confirm that all in process specifications and critical parameters are maintained during [manufacture]," and (2) "to ensure that the process optimizations indeed minimize the risk of high levels of Asp9." (A14884.)

BVL manufactured three validation batches in 2006 on October 31, November 21, and December 14. (A14959-60; A15210-11; A15452-53; A16838, 856:5-17; A16850, 868:11-20; A16851, 869:9-19.) A MedCo Process Validation Engineer approved the validation on January 18, 2007. (A14962.)

The FDA did not require that MedCo make three validation batches and then discard them, which would have forced MedCo to forego about $30 million in sales. Rather, the validation batches were designated for commercial sale, receiving a "commercial product code" and also being released for "commercial and clinical packaging." (*E.g.*, A14959-60.)

In January and May 2007, MedCo paid BVL $347,500 for the manufacture of the validation batches. (A17177-78, A17183; A16852-53, 870:13-871:16.)

Between December 2006 and the critical date—July 27, 2007—eight more batches were made using the revised mixing process. By the July 27, 2008, filing date of the patents-in-suit, an additional 13 batches were made using the revised

process. These 24 batches are described in Example 5 of the patents-in-suit. (A74, 23:40-52.)

C. MedCo's Contract To Sell The Claimed Batches.

On February 27, 2007, MedCo entered into a new "Distribution Agreement" with Integrated Commercialization Solutions, Inc. ("ICS") regarding Angiomax®. (A14674, A14697; A16831-33, 849:6-851:1.) The Distribution Agreement was an offer for sale of Angiomax® made by the patented process. The Distribution Agreement made ICS the "exclusive authorized distributor" of Angiomax® in the U.S., stating that MedCo "shall not sell Product to any person or entity . . . other than Distributor." (A14675, ¶ 2.1.) Under this new "exclusive" Distribution Agreement, "[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." (A14678, ¶ 4.1.) This agreement covered the distribution and ultimate sale of the validation batches described above.

D. Filing And Prosecution Of The Asserted Patents.

On July 27, 2008, MedCo applied for patents covering its revised mixing process. (A47, A62.)

The resulting patents-in-suit, which share a common specification, [1] allegedly address the need for "a compounding process for formulating bivalirudin that consistently generates formulations having low levels of impurities." (A48, 2:19-22.)

The patents highlight the crux of the invention as "efficient mixing." The specification describes mixing the pH-adjusting solution with the bivalirudin solution to accomplish pH-adjustment. The specification often uses permissive language, stating what "may" be done. For example, "[s]olvents ***may include*** aqueous and non-aqueous liquids," "[t]he pH-adjusting solution ***may*** then be mixed . . . ," and "[t]he mixing of the pH-adjusting solution and the bivalirudin solution ***may*** occur under controlled conditions." (A51, 7:63, 8:24, 8:43-44.) But when describing efficient mixing, the patents use mandatory language: "The pH-adjusting solution ***will be efficiently mixed*** with the bivalirudin solution to form the compounding solution." (A51, 8:54-55.)

During the prosecution leading to the asserted patents, the applicants made numerous statements bearing on claim construction.

1. "wherein the batches have a pH adjusted by a base"

The asserted claims did not originally contain the term "wherein the batches have a pH adjusted by a base." During prosecution of the application that became

[1] The patents' paginations are not the same beginning at column 18 because of the placement of certain tables by the Government Printing Office.

the '727 patent—the patent MedCo claims does not include product-by-process claims—the PTO Examiner rejected the claims as anticipated by prior art bivalirudin drug products, noting, "[i]n response to applicant's argument that the references fail to show certain features of applicant's invention," that "the features upon which applicant relies (i.e., compounding process of preparing the pharmaceutical composition) are not recited in the rejected claim(s)." (A6979.)

In response, MedCo filed a declaration from co-inventor Musso explaining that he and his co-inventor, Krishna, "performed detailed investigations on various process parameters that could impact Asp^{9}-bivalirudin levels and lead to batch failures." (A7138, ¶ 13.) Musso stated that they developed a "process improvement strategy to assess the impact of process control wherein the base was added in a controlled (metered) and effectively dispersed (at the bivalirudin precipitate stage) manner." (A7139, ¶ 14.)

The Examiner maintained the rejection (A7208) because the differences between the compounding processes discussed in the declaration were not relevant to any claim limitation. Specifically, the examiner observed that although the mixing conditions of Example 5 differed from the prior art mixing conditions of Example 4, "[t]he claims [as then drafted were] not drawn to the compounding method steps." (A7216.) In response, and at the suggestion of the Examiner, MedCo amended its claims to add "wherein the batches have a pH adjusted by a

base." (A7294; A7423.) After this amendment, the Examiner allowed Claim 1 of the '727 patent. (A7503; *see also* A8296 (amending Claim 1 of '343 patent with same limitation).)

2. "efficient mixing"

During prosecution of both patents, the inventors explained that "Applicants' prior compounding process added the pH-adjusting solution to the bivalirudin solution in an inconsistent manner, at the operator's discretion, resulting in the formation of inconsistent levels of the impurity Asp^9-bivalirudin . . . . In the present invention, various embodiments relate to a less subjective and more consistent process for the mixing of the pH-adjusting solution with the bivalirudin solution." (A6781; A8598.) Further, as mentioned above, inventor Musso submitted a declaration touting the "controlled (metered)" process used to add the pH-adjusting solution. (*See* A45.)

II. HOSPIRA'S ANDA ACTIVITIES

A. Hospira's Exhibit Batch.

In February 2008, before MedCo applied for the patents-in-suit, Hospira manufactured one Exhibit Batch of bivalirudin drug product to support its two ANDAs. (A13940-68; A16160, 180:16-20; A16597, 616:5-11.) In Hospira's process, as in the prior art process, after bivalirudin API was dissolved in solution, base was added to increase the pH to acceptable levels. (A13957-58; A16428, 447:3-8, A16599-600, 618:18-619:8.) Hospira added its base solution in three

equal portions. (A13958.) The first two portions were added "rapidly with about 2-minute mixing time" and the third portion was added "gradually over a period of approximately 10 minutes." (A13958; A16428-29, 447:3-448:13; A16600, 619:9-17.) Hospira's instructions provided no further detail to the operator on adding the portions, leaving that to the operator's discretion. (A16383-84, 402:3-403:13; A16428, 447:9-23.)

Hospira mixed the base into the solution using paddle mixers operating at 560 rpms, falling squarely within the 400-800 rpms range of MedCo's prior art process. (A13958; A16430, 449:9-19.) Hospira did not use a homogenizer or any other kind of high shear mixer. The Exhibit Batch had an Asp^9-bivalirudin level of 0.1-0.2%. (A14276; *see also* A16168-69, 188:15-189:4.)

B. Hospira's ANDAs.

In August 2008, Hospira filed its ANDAs. (*E.g.*, A8698.) For purposes of this case, Hospira's two ANDAs are identical. Hospira's ANDAs disclosed its 45-liter Exhibit Batch and possible scale-up batches. (A13859-61.) Hospira's future commercial batches were disclosed to be between 45 liters and 220 liters. (A13861.)

Hospira does not manufacture bivalirudin API and instead buys it from a supplier. The API supplied to Hospira may have as much as 0.7% Asp^9 impurities, according to Hospira's product specifications. (A14824; A16438-40, 457:3-459:8;

A16603, 622:11-18.) Because of that and inherent manufacturing variability, Hospira allows its compounding process to produce bivalirudin drug product with up to 1.0% Asp^9-bivalirudin. (A16440-41, 459:17-460:20.) That is, Hospira's ANDAs seek approval to place on the market product that has as much as 1.0% Asp^9-bivalirudin. (A14842; A16602-03, 621:24-622:10.)

III. THE INSTANT LITIGATION

A. The Inventors' Testimony.

MedCo's view is that its alleged invention is claimed by neither product, process, nor true product-by-process claims. Whether a batch falls within the scope of the claims cannot be determined solely based on knowledge of product properties and process steps. Rather, all actual or potential batches that could be made must also be analyzed.

The District Court, however, understood the invention to require an efficient mixing step. The inventors have the same understanding and repeatedly testified to that effect. For example, inventor Musso testified that "the claims of the '727 patent . . . require efficient mixing." (A439-40, 21:20-22:16; *see also* A425-26, 21:12-22:4; A429, 96:19-97:12; A426, 23:10-17; A436, 252:7-13; A426, 23:23-24:17; A428, 90:19-91:5.)

B. The District Court's Claim Construction.

In its July 11, 2013, *Markman* decision, the District Court provided express constructions for three claim terms: (1) "pharmaceutical batches;" (2) "wherein

the batches have a pH adjusted by a base;" and (3) "efficient mixing." (A35-46.) The court previously gave the other disputed terms, "maximum" and "about," their plain meaning. (A5501, 4:10-13.)

The claim terms construed by the District Court all relate to the issue discussed above, namely, that the claimed invention is not simply a batch of bivalirudin with improved Asp^9-bivalirudin levels. Rather, whether a batch falls within the scope of the claims requires identifying its manufacturing process and then examining all other batches that are made or could be made by that process.

The disputed claim terms relate to how to identify all batches that must be considered and what aspects of the manufacturing process are relevant.

1. "Pharmaceutical batches" Or "batch"

The first term construed by the District Court was "pharmaceutical batches," which appears in all asserted claims. The District Court construed this term to mean "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." (A36-37.) The District Court based its construction on the fact that the patents' specification "defines 'pharmaceutical batches' as batches made by 'said process.' The antecedent basis of 'said process'

is 'a compounding process of various embodiments of the present invention.'" (A38 (internal citation omitted).)

MedCo does not dispute this construction on appeal.

2. "wherein the batches have a pH adjusted by a base"

Next, the District Court construed the term "wherein the batches have a pH adjusted by a base," which also appears in all asserted claims, to mean "wherein said compounding process requires that a pH-adjusting solution containing a base is added to a bivalirudin solution under efficient mixing conditions." (A39.) The District Court noted that the specification and prosecution history make clear that the claimed invention requires that the pH be adjusted by a base using "efficient mixing":

> The only novel aspect of both the '727 and '343 Patents is the special compounding process aimed at reliably reducing the amount of Asp^9 in "pharmaceutical batches." . . . The specification makes clear that this process is characterized by "efficiently mixing." *See id.* 8:54-55 ("The pH-adjusting solution will be efficiently mixed with the bivalirudin solution to form the compounding solution"); *id.* at 9:3-17.

(A39-40.)

3. "efficient mixing"

Finally, the District Court construed "efficient mixing." The District Court rejected MedCo's argument that the specification defines "efficient mixing" as

"mixing that is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution":

> The Court does not agree that this is definitional language, especially in contrast with other terms in the specification that are clear explicit definitions, set off with quotation marks and accompanied with the language of "as used herein" or "refers to." Further, [MedCo's] proposed construction does not do much to help determine the metes and bounds of the invention. It cannot be any mixing process that results in batches with less than .6% Asp^9. "Efficient mixing" is a distinct step that must be given a meaningful construction. As discussed, it is the compounding process that is the inventive aspect of the patents. Further, construing "efficient mixing" as offered by [MedCo] would give the term a construction that captures all new compounding processes that achieve the same results, even if those methods were truly novel and achieved those results in a superior fashion.

(A43.)

Having rejected MedCo's construction, the District Court proceeded to discern the appropriate meaning of "efficient mixing." It noted that Example 4's "inefficient mixing" lay outside the scope of the claims, and that Example 5 "describes the 'efficient mixing' process." (A44.) The District Court observed that "Example 5 makes clear that addition of the pH-adjusting solution at a constant rate or controlled rate is required, as well as the necessity of high shear mixing." (A45.) The District Court further found that "efficient mixing" required high mixer speeds, with Example 4 "impl[ying] that 'inefficient mixing conditions'

are equivalent to 'slow mixing conditions.'" (A44.) It also reviewed specification statements that were allegedly inconsistent with the implications of Example 4, but held that "[t]he contradiction should be resolved in favor of relying on what the inventor excluded from the scope of the patent," *i.e.*, the conditions of Example 4. (A45.)

Therefore, the District Court construed "efficient mixing" to mean "a pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner, and mixed together by a process comprising high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)." (A42.)

C. MedCo's Calculation Of Hospira's Mixer Speed.

As noted above, Hospira did not mix its Exhibit Batch under "high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)." However, following the District Court's claim construction ruling, MedCo's counsel provided one of its experts, Dr. Stephen Byrn, with a textbook co-authored by Warren McCabe entitled "Unit Operations of Chemical Engineering." (A16262, 282:10-24; A15767-68.) Dr. Byrn used a set of equations from a section in the McCabe book concerning the blending of "miscible liquids"[2] to purportedly convert Hospira's 45-liter Exhibit Batch mixer speed of 560 rpms to a mixer speed for a batch size of

[2] Dr. Byrn formed no opinion as to what Hospira's mixer speed would be if a solid precipitate was present in the bivalirudin solution. (A16259-61, 279:11-281:24.)

150 liters, which MedCo alleged was the relevant batch size for the asserted claims. (A16211, 231:12-19; A16257, 277:1-5.)

Dr. Byrn calculated that a mixer speed of 560 rpms at 45 liters is equivalent to 1248 rpms at 150 liters. (A16224, 244:6-15.) However, Dr. Byrn all but admitted that he rigged this calculation to guarantee that it would yield a mixer speed above 1000 rpms. For example, Dr. Byrn conceded that he began with the circular assumption that Hospira would desire to achieve "efficient mixing" at the 150-liter batch size. (A16232, 252:11-19.) He also admitted that he used the equations for a different purpose than that set forth by McCabe. (A16263-65, 283:17-285:4.) In addition, he assumed that mixing is complete after just 26.4 seconds in both the 45- and 150-liter batches, deeming irrelevant the fact that Hospira actually mixed its 45-liter batch for 4 hours and 52 minutes. (A16237-38, 257:6-258:18.) He also assumed that Hospira would maintain the same mixer impeller size, *i.e.*, five centimeters, even if it more than tripled the size of its mixing tank. (A16240-41, 260:21-261:18.) He made these assumptions even though he admitted that a mixer speed of 560 rpms achieves the same mixing in a 150-liter batch as in a 45-liter batch if either a longer mixing time or a larger impeller is employed. (A16233-34, 253:13-254:16; A16240-48, 260:21-268:1.)

SUMMARY OF THE ARGUMENT

The Court should affirm the District Court's ruling of non-infringement of all asserted claims.

First, the District Court correctly construed the asserted claims to all require the only inventive aspect of the patents—"efficient mixing"—which in turn entails adding the pH-adjusting solution "slowly and in a controlled manner" and mixing it with the bivalirudin solution under "high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)."

Second, under either the District Court's construction of "efficient mixing" or MedCo's proposed construction, the Court should affirm that Hospira does not "efficiently mix." It utilizes "inefficient mixing": rapid, portion-wise base addition, low-speed mixing, and the sole use of a paddle mixer. The Court should affirm the judgment of non-infringement because all asserted claims require "efficient mixing"—explicitly in the '343 patent and through proper construction of the '727 patent.

This Court should also affirm the ruling of non-infringement on an additional ground because Hospira's ANDAs define a product outside the scope of the claimed maximum Asp^9-bivalirudin levels.

Additionally, the Court should reverse the District Court's ruling that the asserted claims are not invalid.

First, the claims are invalid under the on-sale bar because—prior to the critical date—MedCo bought validation batches from BVL for a commercial purpose, and also because MedCo offered to sell claimed batches to its exclusive distributor, ICS.

Second, the claims are obvious. The only difference between the asserted claims and the prior art is "efficient mixing," and a POSITA seeking to eliminate high Asp^9-bivalirudin levels through routine process optimization would have implemented efficient mixing to do so.

Third, the claims are indefinite. A POSITA cannot determine whether a "batch" infringes the recited "maximum" Asp^9-bivalirudin levels.

ARGUMENT

For the following reasons, this Court should affirm the District Court's judgment of non-infringement and reverse the ruling that the claims are not invalid.

I. THE DISTRICT COURT'S CLAIM CONSTRUCTION IS CORRECT.

MedCo challenges the District Court's claim constructions of (A) "wherein the batches have a pH adjusted by a base," and (B) "efficient mixing." But as shown below, the intrinsic evidence, including the patent specification, makes clear that the District Court's constructions are correct.

A. The District Court's Construction Of "wherein the batches have a pH adjusted by a base" Is Correct.

MedCo first challenges the construction of the "wherein" term in the claims as requiring that the pH-adjusting solution be added with "efficient mixing." The "wherein" term requires that the batches "have a pH adjusted by a base" and the specification unequivocally requires that "[t]he pH-adjusting solution ***will be efficiently mixed*** with the bivalirudin solution . . . ." (A51, 8:54-55.) Thus, the District Court properly construed the claim language to require efficient mixing, as stipulated in the specification.

MedCo raises two challenges, neither of which addresses the intrinsic evidence's requirements to use efficient mixing. *First*, MedCo argues that this construction creates a redundancy in the '343 patent. *Second*, MedCo argues that this construction improperly converts the claims of the '727 patent into product-by-process claims. Both arguments lack merit.

1. The "efficiently mixing" Limitation Of The '343 Patent Is Not Superfluous Under the District Court's Construction.

MedCo argues that because the '343 patent claims contain additional recitations of "efficient mixing," the District Court's conclusion that the pH-adjusting solution must be added using efficient mixing is redundant. (MB 26.) MedCo's argument is meritless.

To begin, it is a red herring. The patents expressly state that the "pH-adjusting solution ***will be*** efficiently mixed." (A51, 8:34.) Accordingly, to the extent the claims require adjusting the pH with a base, the base must be efficiently mixed. That requirement must be found in the claims. MedCo agrees that the '343 patent requires "efficient mixing," so the only issue is whether the '727 patent also requires it. As discussed herein, the intrinsic evidence, in particular the specification, requires that the pH-adjusting solution of the '727 patent be added with efficient mixing, and any alleged redundancy in another patent should not overcome the specification's clear limitation on the invention.

Indeed, the only support MedCo provides for its position is a case involving claim differentiation. *Digital-Vending Servs. Int'l, LLC v. Univ. of Phoenix, Inc.*, 672 F.3d 1270 (Fed. Cir. 2012). In that case, the issue was the meaning of "registration server." Some of the claims in the patent-in-suit that used the term "registration server" stated that it had to be "free of content managed by the architecture," whereas some of the claims did not. This Court held it was error to construe "registration server" to be limited by the "free of content" language because some claims contained that express requirement. However, claim differentiation is only a presumption and is overcome where the intrinsic evidence requires a certain construction, even if that construction renders a claim term superfluous. *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1369-70

(Fed. Cir. 2007) (holding that redundancy in interpreting claims to composites to require pellets or extrudates where other patents required pellets or extrudates did not overcome evidence from specification that composites should be so limited).

In any event, there is no redundancy in the claims of the '343 patent. The two uses of "efficient mixing" in Claim 1 of the '343 patent impose different requirements. The "wherein" clause under the District Court's construction requires that the "pH-adjusting solution containing a base is added to a bivalirudin solution under efficient mixing conditions." However, process steps (i), (ii) and (iii) in Claim 1 of the '343 patent are directed to the handling of the solvents in the compounding process. Step (i) requires dissolving bivalirudin in a solvent. Step (ii) requires "efficiently mixing a pH-adjusting solution . . . wherein the pH-adjusting solution comprises a pH-adjusting solvent." And step (iii) requires removing "the solvent [from step (i)] and pH-adjusting solvent [from step (ii)]." (A76.) Steps (i) and (ii) set up the antecedent basis for step (iii).

Thus, the limitation added by step (ii) is the requirement that when the pH-adjusting solution is efficiently mixed, that solution includes a pH-adjusting solvent. That is not redundant to the additional requirement that the base be mixed efficiently, but is simply providing antecedent basis for the solvents removed in step (iii). Indeed, step (i) also requires the presence of bivalirudin, but that is not

"redundant" to the other parts of the claim that also require the presence of bivalirudin.

In any event, the specification expressly requires that the pH-adjusting solution "will be" efficiently mixed. MedCo's creative claim parsing cannot overcome express requirements stated in the patent specification.

2. The District Court Did Not Improperly Construe Process Limitations Into A Product Claim.

MedCo's second argument is that the District Court's construction allegedly changed the '727 patent's claims from product claims to product-by-process claims. That is incorrect.

a. Whether claims are product-by-process claims depends how they are construed, not *vice-versa*.

MedCo argues that the specification "evidences no intent" to limit the '727 patent claims to "'batch(es)' made using a specific 'efficient mixing' process" because it uses permissive language—the batches "***may*** be generated by the compounding process described above." (MB 31.) However, the claim term at issue is "wherein the batches have a pH adjusted by a base," not "batches." Consequently, the issue is not whether "batches" are limited to batches prepared using a particular compounding process, but whether pH-adjustment requires efficient mixing. On that subject, the specification is clear. The specification does not use the permissive ***may*** language relied on by MedCo, but the mandatory ***will***:

"The pH-adjusting solution ***will be efficiently mixed*** with the bivalirudin solution to form the compounding solution." (A51, 8:54-55.)

Furthermore, whether the claims are product-by-process claims depends on how they are construed, not the other way around. If the claims are construed to require process limitations, then they are necessarily product-by-process claims. MedCo's oft-cited case of *Vanguard Prods. Corp. v. Parker Hannafin Corp.*, 234 F.3d 1370 (Fed. Cir. 2000), does not create a special claim construction rule that one ***first*** determines whether the claims are product claims or product-by-process claims and ***then*** construes them. On the contrary, in *Vanguard*, the Court determined whether the "specification shows that the term was used to describe the product, and not as a designation of a specific manufacturing process." *Id.* at 1372. Here, the specification unequivocally shows that the pH-adjusting solution "will be efficiently mixed" and requires the District Court's construction.

b. The claims of the '727 patent are product-by-process claims.

In any event, as noted by the District Court, the claims of the '727 patent are product-by-process claims. (A40-41.) For example, Claim 1 of the '727 patent already includes the process step of "wherein the batches have a pH adjusted by a base," meaning that it is not a pure product claim. (A40.) MedCo argues that this term is not a process limitation because it "merely describes a property of the claimed batches, *i.e.,* that they have a base-adjusted pH." (MB 16, 32.) But that is

still a process limitation because one cannot analyze a batch without regard to its method of making and determine that its pH was adjusted by a base.

Furthermore, the term "pharmaceutical batches" makes the compounding process step "intrinsic to the claim itself." (A40-41.) No amount of measurements on the properties of a batch will determine whether it falls within the scope of the claims. Rather, the process used to create the batch must be identified and then one must determine whether ***all*** other batches that were made or could be made by that process meet the limitations of the claims.

Consider, for example, a prior art batch with less than 0.6% Asp^9-bivalirudin, of which MedCo concedes there were many. It is impossible to differentiate this prior art batch from a claimed batch "in terms of its properties," as MedCo alleges (MB 30). Both batches have the same sub-0.6% Asp^9-bivalirudin level. Their difference lies only in the processes used to make them and the properties of all other batches made by those processes. Thus, the claims are not product claims.

MedCo also argues that the District Court's construction "eliminates the distinction between the '727 and '343 patents." (MB 28.) However, Claim 1 of the '343 patent contains additional limitations that are not present in the '727 patent. (*Compare* A60, 25:56-64, *with* A76, 27:13-31.) For example, the '343

patent requires extracting solvents in step (iii), which is not required in the '727 patent.

3. MedCo's Proposed Construction Should Be Rejected Because It Lacks Clarity And Is Not Tied To The Alleged Invention.

MedCo advocates that the "wherein" term should have its plain and ordinary meaning or, alternatively, that the Court "may" adopt the construction MedCo successfully pursued in the District of New Jersey, *i.e.*, "during compounding, the pH of the batches is adjusted using a base." (MB 34-35.) This "alternative" construction was also proposed to the District Court, but was rejected. (A39.)

a. MedCo's proposed construction conflicts with the intrinsic evidence and results in functional claiming at the exact point of novelty.

MedCo's proposed constructions fail to follow the requirements for adjusting the pH set forth in the intrinsic evidence. As discussed above, the specification and prosecution histories require that "efficient mixing" be used when the pH is adjusted. The New Jersey decision did not consider whether this claim limitation required "efficient mixing" at all. Consequently, the New Jersey decision failed to address the specification's requirement that the "pH-adjusting solution ***will be efficiently mixed*** with the bivalirudin solution."

Furthermore, stripped of the "efficient mixing" limitation, the claims of the '727 patent recite nothing more than the goal of having a process that would

consistently make batches with impurity levels below 0.6%. Specifically, without the "efficient mixing" limitation, the '727 patent claims batches made by any process as long as the process ***never*** makes a batch with Asp^9-bivalirudin levels more than 0.6%. There is no limitation on the process whatsoever as long as it accomplishes the goal of never resulting in a batch outside the Asp^9-bivalirudin range. Such a construction is incorrect for two reasons. *First*, the process by which the pH-adjusting solution is added is crucial to distinguishing the invention from the prior art, because the prior art included many batches with Asp^9-bivalirudin levels of less than 0.6%, and they were made using base to adjust the pH. *Second*, as discussed next, this construction would render the claims indefinite.

b. Functional claims at the exact point of novelty are indefinite.

Absent the "efficient mixing" limitation, the only point of novelty in the claims of the '727 patent is that the batches be made with a process that never makes a batch with Asp^9-bivalirudin levels greater than 0.6%. Such claims would use functional language—describing the claimed invention by what it accomplishes rather than what it is—at the point of alleged novelty and would therefore run afoul of longstanding Supreme Court authority, recently reaffirmed in *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014) (holding

that claim is indefinite if it fails to inform POSITA of scope of invention with reasonable certainty).

In *Nautilus*, the Court rearticulated the indefiniteness analysis, relying heavily on its own case law. In doing so, the Court cited with approval a number of cases that held claims indefinite because of functional claiming. In fact, the only Supreme Court cases cited in *Nautilus* that invalidated claims did so on those grounds. *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942); *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938). Purely functional claims fail to "appris[e] the public of what is still open to them," leaving a zone of uncertainty for experimentation or future enterprise. *Nautilus*, 134 S. Ct. at 2129.

Nautilus cited *General Electric* for its statement that "[t]he limits of a patent must be known for the protection of the patentee, the encouragement of the inventive genius of others and the assurance that the subject of the patent will be dedicated ultimately to the public." *Id.* at 2129. The last two goals—encouragement of future invention and dedication of the subject matter of the patent to the public—are impossible if claims are purely functional. Functional claims allow no further invention of useful solutions to the problem addressed by the claimed invention. As such, claiming a key feature of the invention in functional terms results in indefiniteness:

> [A] characteristic essential to novelty may not be distinguished from the old art solely by its tendency to remedy the problems in the art met by the patent.

Gen. Elec. Co., 304 U.S. at 371-72. Consequently, *Nautilus* confirmed that functional claims, especially when directed to the key feature of the claims, are indefinite.

Here, MedCo's construction of the pH-adjustment step leads to functional claims because the claims would cover any batch made by a process that never makes a batch having Asp^9-bivalirudin levels of more than 0.6%, no matter how that goal is accomplished. That is improper.

MedCo's prior art process adjusted the pH with base. Consequently, use of that step is insufficient to distinguish an infringing batch from a non-infringing batch. Nor does an impurity level of less than 0.6% allow one to distinguish an infringing batch from a non-infringing batch. Only by knowing that the batch ***is made by a process*** that achieves the goal, by whatever means, of never exceeding the 0.6% impurity level can infringement be determined. Such claims are invalid under *General Electric* and *United Carbon*.

Accordingly, MedCo's alternate claim construction should be rejected.

B. The District Court's Construction Of "Efficient Mixing" Is Correct.

MedCo's second claim construction challenge is on the meaning of "efficient mixing." As shown below, MedCo's arguments are meritless.

1. The District Court Properly Construed "efficient mixing."

The patents' only guidance on the meaning of this term is the contrast between Example 4, which expressly states that it uses "inefficient mixing," and Example 5, which expressly states that it uses "efficient mixing." The mixers in Example 4 are paddle mixers operating at 400-800 rpms, whereas Example 5 uses a homogenizer operating between 1000-1300 rpms "to provide a high shear mixing environment." (A58.) MedCo acknowledges that "Example 4's 'inefficient mixing conditions' do the opposite of the claimed invention." (MB 45.) However, MedCo contends that "the district court's construction went too far" in construing efficient mixing to include certain aspects of Example 5. (MB 46.)[3]

Specifically, MedCo argues that the District Court's construction is contradicted by the part of the specification that allows use of a paddle mixer between 100-1000 rpms. (MB 41-43 (citing A67, 9:34-10:52).) However, that part of the specification, which includes essentially every type of mixing known in the art, does not define the "metes and bounds" of the term "efficient mixing." In fact, it contradicts Example 4—which states unequivocally that mixing at up to 800

[3] In this case, it does not matter whether the entirety of the District Court's construction of "efficient mixing" is correct. As discussed below, Hospira uses a non-high-shear paddle mixer operating at 560 rpms, squarely within the scope of Example 4, which MedCo admits "do[es] the opposite of the claimed invention." Consequently, as long as efficient mixing is not met by the use of paddle mixers at 400-800 rpms as in Example 4, this Court should affirm the non-infringement judgment.

rpms is "inefficient." (A45.) As the District Court noted, "[t]he contradiction should be resolved in favor of relying on what the inventor excluded from the scope of the patent . . . . [T]he public should be able to rely on a patent's statements of exclusion, even if the patent is not entirely consistent as to what is excluded." (*Id.*) MedCo's proposed construction would include within the meaning of "efficient mixing" that which the patents explicitly refer to as "inefficient mixing." (*Id.*)

The specification makes clear that the two critical characteristics of "efficient mixing" are (1) how the pH-adjusting solution is added to the bivalirudin solution, and (2) how the two solutions are mixed together. (*See generally* A52, 9:34-11:9.) Example 5 teaches that the alleged inventive step of efficient mixing is achieved by (1) adding a pH-adjusting solution slowly and in a controlled manner; and (2) mixing the pH-adjusting and bivalirudin solutions under high-shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms). (A43-45.) The District Court's construction does not exclude additional mixing parameters (*see* MB 39-40)—so long as the construction of "efficient mixing" is also met. The remaining patent Examples are consistent with that construction.

2. MedCo's Proposed Construction Conflicts With The Intrinsic Evidence And Reads "efficient mixing" Out Of the Claims.

MedCo contends that "efficient mixing" should be construed to mean "mixing that is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution." This construction suffers from a number of problems.

First, the construction is indefinite. There is no way to determine whether a particular mixing scenario has minimized the Asp^9-bivalirudin levels because another mixing scenario might result in even lower levels. Even the inefficient mixing of Example 4 yielded many batches with less than 0.6% Asp^9-bivalirudin.

Second, MedCo's construction is not supported by the intrinsic evidence. MedCo argues that the specification "defines" the term when it states, "[e]fficient mixing is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution." (A52, 9:34-35.) However, as the District Court noted, this "characterized by" language is not "definitional language, especially in contrast with other terms in the specification that are clear explicit definitions, set off with quotation marks and accompanied by the language of 'as used herein' or 'refers to.'" (A43 (citing 5:24-54); *see also, e.g.,* A66, 8:58-59.) Indeed, the normal meaning of "characterized by" is identifying one, but not all, characteristics of an item and is therefore not definitional.

Furthermore, as noted by the District Court at the *Markman* hearing, construing "efficient mixing" to mean any mixing that results in low levels of Asp^9-bivalirudin reads the phrase out of the claim. (*See* A5558-59, 61:20-62:1.) The claims already require low levels of Asp^9-bivalirudin. If the "efficient mixing" language is met simply by obtaining those low levels, it has no effect on claim scope because that requirement already exists.

3. MedCo's Other Arguments Do Not Support Its Construction.

MedCo's other arguments do not provide support for its proposed construction. *First,* MedCo relies on expert testimony at trial (after the *Markman* hearing) to argue that "high shear mixing" is not defined by mixing speed. (MB 37-38.) However, the claim term here is "efficient mixing" which, as shown by the difference between Examples 4 and 5, at a minimum excludes mixing using a paddle mixer at 400-800 rpms. Furthermore, MedCo failed to present this extrinsic evidence during *Markman* proceedings. Even if it had, the clear intrinsic evidence supports the District Court's construction and, thus, there is no need to analyze any extrinsic evidence. *Phillips v. AWH Corp.,* 415 F.3d 1303, 1317-19 (Fed. Cir. 2005).

Next, MedCo criticizes the District Court for not taking into account "the scale of Example 5." (*See* MB 39-40.) However, MedCo failed to argue that scale was relevant to the construction of the claims until its motion to reconsider the

District Court's claim construction. The District Court reviewed and appropriately rejected this argument. (A5707-08; *see also* A5649.)

Consequently, the District Court's claim constructions should be affirmed.

II. THE COURT SHOULD AFFIRM THE DISTRICT COURT'S JUDGMENT OF NON-INFRINGEMENT.

The District Court held that Hospira does not infringe any asserted claim because it does not employ "efficient mixing." MedCo fails to meet the very high burden of demonstrating that the District Court's ruling was clearly erroneous. *See United States v. United States Gypsum Co.*, 333 U.S. 364, 395 (1948).

As explained below, the Court should affirm the District Court's ruling of non-infringement, regardless of its construction of "efficient mixing," because Hospira utilizes mixing that the patents themselves deem "inefficient." Alternatively, even if this Court declines to hold that Hospira does not employ "efficient mixing," it should affirm the District Court's ruling of non-infringement of all asserted claims because Hospira does not infringe the claim limitation requiring that "the batches have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6% [or, for certain asserted dependent claims, 0.4% or 0.3%]."

A. Hospira Does Not "Efficiently Mix" Its pH-Adjusting Solution With Its Bivalirudin Solution.

The District Court held that Hospira did not infringe the "efficient mixing" limitation for four independent reasons. *First*, Hospira does not add its pH-adjusting solution slowly. *Second*, Hospira does not add the solution in a controlled manner. *Third*, it does not use a high-shear mixer. *Fourth*, it does not employ a mixer speed above 1000 rpms. (A12-17.) MedCo fails to show that any of these findings were clear error. Instead, MedCo relies on mischaracterizations of the District Court's claim construction, a gambit that the District Court already rejected. This Court should do the same.

Even if the Court adopts MedCo's proposed construction of "efficient mixing," the Court should still affirm the District Court's ruling of non-infringement because Hospira uses a type of mixing that even MedCo concedes constitutes "inefficient mixing."

1. Hospira Adds Its pH-Adjusting Solution Rapidly Rather Than Slowly.

As the District Court found, and MedCo does not dispute, Hospira adds its base in three portions, the first two of which are added "rapidly." These two additions defeat MedCo's infringement claim with respect to the "slowly" element.

MedCo argues that because the "third and last portion" of Hospira's pH adjusting solution is added gradually, the "slowly" requirement is satisfied.

However, the District Court indicated that "slowly" excludes "*any and all* rapid addition" of pH-adjusting solution when it noted that Hospira's request to expressly state that requirement in the claim construction was unnecessary. (A46 ("[T]he proposed requirement excluding any and all rapid addition of the pH-adjusting solution to the bivalirudin solution is ***unnecessary***. . . . The . . . 'not rapidly in multiple portions' limitation[is] therefore ***redundant of the slowly limitation***.").)

Furthermore, contrary to MedCo's argument on appeal, the addition of the third portion is not "the 'critical' step in Hospira's process" that "brings about a significant pH change." (MB 53.) Rather, the significant change occurs with the addition of the first portion, which occurs rapidly. (A16923-24, 941:19-942:16.)

Moreover, even Hospira's third portion is not added "slowly." Hospira gives its operator no instruction on how to add the third portion "gradually over a period of approximately 10 minutes;" the operator adds the portion at his discretion. (A16383-84, 402:3-403:13; A16428, 447:9-23.) Thus, an operator can add some of the third portion rapidly. For example, the operator can pour small amounts of base off-and-on for the first five minutes, then quickly dump one-third of the remaining base solution at minute six, revert back to small pours for the next few minutes, and then empty out the remaining solution in a large, final pour at

minute ten. (*See* A16384, 403:14-24.) This addition, like the addition of the first two portions, would be rapid rather than slow.

2. Hospira Adds Its pH-Adjusting Solution In A Rapid And Discretionary, Rather Than Controlled, Manner.

MedCo's attempts to show clear error in the District Court's finding that Hospira does not add base solution in a "controlled manner" suffer from the same flaws. Namely, MedCo argues that Hospira's "gradual" addition of its third portion is a "controlled" addition. (MB 53-54.) Again, MedCo fails to show clear error in the District Court's ruling.

As the District Court noted in its claim construction ruling and again in its Trial Opinion, the term "controlled" means "constant" and "metered." (*See* A45, A14.) "Controlled" addition removes operator variability to ensure a well-controlled process. (*E.g.*, A16498-99, 517:8-518:3.) Hospira adds none of its portions in such a controlled, or metered, manner.

First, because Hospira's operator adds the first two portions in rapid dumps, there is no controlled rate of addition.

Second, the operator adds the third portion in a discretionary, rather than controlled, manner. The operator can choose to quickly (*i.e.*, rapidly) add a small amount at minute two of ten, much more in a prolonged pour at minute five, and then dump in the rest at minute eight. (*See* A16384, 403:14-24.) Alternatively, the operator could add a small amount each minute. (A16429, 448:14-23.) Because

the possibilities are endless, each operator will add the pH-adjusting solution differently, using a different number of pours at different pouring speeds with a different amount of base in any given pour, separating the pours by different time intervals. (A16384-85, 403:14-404:15; A16429-30, 448:24-449:8.) Even the pours by a single operator during a given compounding process will differ from one another. The discretionary nature of Hospira's base addition renders the step non-"controlled."

3. Hospira Does Not Employ High-Shear Mixing Conditions.

Rather than attempt to show clear error in the District Court's findings that Hospira employs neither a high-shear mixer nor a mixer speed of above 1,000 rpms, MedCo mischaracterizes the District Court's claim constructions. (MB 54-57.)

First, Hospira does not employ "high-shear mixing conditions" because it does not use a high-shear mixer. Hospira uses a convective mixer, *i.e.*, a paddle mixer, which simply pushes material around the mixing tank. (A16430, 449:18-19; A16600-01, 619:18-620:1; A16613, 632:20-23.) MedCo's assertion that "the district court's construction requires 'high shear mixing conditions . . . but not a particular type of mixer" (MB 54) excises "high shear mixing" from the claim construction and contradicts the District Court's ruling that Hospira does not

employ "efficient mixing" because, among other reasons, "Hospira does not use a high shear mixer, but a convective or paddle mixer." (A15.)

"High shear mixing conditions" necessarily require a "high shear mixer," which is a specific type of mixer that utilizes velocity gradients to exert strong forces on a solid or fluid element. (A16646-47, 665:9-666:24.) Even according to the named inventors, a paddle mixer is distinct from a high-shear mixer because it cannot achieve this mechanical shearing effect. (A16133, 153:5-6; A16490, 509:13-19.) Indeed, the District Court found that the patents' discussion of the use of other mixing devices such as paddle mixers to achieve "efficient mixing"—devices that were never actually used for high shear mixing in the patents' Examples—was contradicted by Example 4 and was inconsistent with the overall teaching of the patents. (A44-45.) Thus, Hospira's paddle mixer cannot achieve "high shear mixing conditions."

Second, even if the type of mixer was irrelevant and mixing speed alone was dispositive of high-shear mixing, the District Court correctly found that MedCo failed to prove that Hospira mixes its pH-adjusting solution with the bivalirudin solution at mixer speeds above 1000 rpms. MedCo does not dispute that Hospira mixed its Exhibit Batch at 560 rpms. Therefore, MedCo cannot prove that Hospira infringes the "mixer speeds above 1000 rpms" portion of the Court's construction.

MedCo's argument that Hospira's mixing at 560 rpms for its 45-liter Exhibit Batch literally constitutes mixer speeds above 1000 rpms (specifically, 1248 rpms) is contrary to the claim construction and was rejected by the District Court. MedCo argues that Hospira's mixer speed—used for a 45-liter batch—must first be converted to a mixer speed for a 150-liter batch before it is compared with the asserted claims because "the district court's construction was expressly based on Example 5," which "was based on a batch size of 150 liters." (MB 55.) Essentially, MedCo adds a volume requirement to the Court's construction so that it reads "mixer speeds *at a given batch size that translate to mixer speeds* above 1000 rpms *for a batch size of 150 liters*."

However, the District Court's construction requires a mixer speed above 1000 rpms regardless of batch size. (A15-17.) Hospira uses 560 rpms. Therefore, this Court should therefore affirm that Hospira does not "efficiently mix" when adding its pH-adjusting solution.

Moreover, even if the District Court's construction were conditioned on batch size—such that Hospira's mixer speed at a hypothetical batch size of 150 liters must be determined—this Court should still affirm the District Court's ruling of non-infringement. MedCo argues that mixing "is easier to achieve in a small amount of liquid than in a much larger volume." (MB 56.) It argues that Hospira's mixer speed for its 45-liter Exhibit Batch equates to 1248 rpms for a 150

liter batch, relying on the calculations of its expert, Dr. Byrn. (*Id.*, 57.) However, Dr. Byrn assumed that when Hospira scales up, it will keep impeller size the same, rather than scale the impeller with all other aspects of the process, such as tank size. Accordingly, the District Court found that Dr. Byrn's calculations were based on "flawed assumptions." (A16.) The District Court found that "Hospira will not keep impeller size constant during scale up" (A8), a finding that MedCo does not challenge on appeal. Indeed, MedCo makes no attempt to justify Dr. Byrn's calculations, and, therefore, cannot show that their rejection was clearly erroneous.

4. Hospira's Mixing Is Not Equivalent To "Efficient Mixing."

MedCo also argues that Hospira's mixing is equivalent to "efficient mixing." Below, the District Court rejected the same arguments MedCo presents on appeal for two reasons. *First*, the court noted that MedCo's arguments merely parrot its literal infringement arguments. (A17, *see also* MB 59.) *Second*, the District Court disagreed with MedCo's description of the function of "efficient mixing." (A18.)

On appeal, MedCo fails to address any alleged error in the District Court's equivalents analysis and instead merely repeats the same arguments made below. For that reason alone, the Court should affirm the District Court's judgment on the doctrine of equivalents.

Even if the Court reaches the issue, it should reject MedCo's arguments. MedCo deems the function of "efficient mixing" to be adding the pH-adjusting

solution in a slow, controlled manner. (MB 59-60.) However, the District Court found that Hospira did not perform that function in its analysis of literal infringement. (*See supra* Sections II.A.1-2.)

Furthermore, the District Court found that "the real function of 'efficient mixing' is minimizing precipitate." (A18.) MedCo's only challenge to that is to contend that the District Court is incorrect because "it is not the precipitate itself that causes the formation of the Asp^9 impurity." (MB 58.) However, MedCo's only support is the testimony of its own expert, who stated that it is "not the precipitate itself that leads to the formation of the Asp-9 impurity," but the fact that "some of th[e] base . . . gets trapped within this precipitate." (A16913, 931:8-20.) Thus, the District Court was correct—minimizing precipitate will minimize the chance that base will get trapped within this precipitate, thereby avoiding the Asp^9 impurities.

MedCo cannot dispute that Hospira does not perform this function. Indeed, MedCo's expert conceded that, in Hospira's process, "bivalirudin will precipitate . . . once the first portion of [base] is added." (A16923-24, 941:19-942:16.)

In addition, MedCo's recitation of the alleged way and result of "efficient mixing" merely repeats the requirements for proving literal infringement. Regarding "way," MedCo baldly asserts that Hospira's process is "substantially the same" because its "mixing of a 45-liter batch at 560 rpms is the same as or

equivalent to mixing a 150-liter batch at 1248 rpms." (MB 60.) MedCo cannot meet its burden with respect to the doctrine of equivalents by simply asserting that Hospira's literally different process is "substantially the same." *Texas Instruments Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1567-68 (Fed. Cir. 1996). In any event, as shown above, Hospira does not mix in that manner, and MedCo's arguments to the contrary are without merit. (*See supra* Section II.A.3.)

Finally, MedCo states that the "result" of "efficient mixing" is "reliably minimizing levels of Asp^9-bivalirudin formed in the compounding solution not to exceed about 0.6%." (MB 60.) But this "result" is merely circular and highlights the problems with MedCo's arguments. MedCo ran its "inefficient mixing" process of Example 4 eighty-nine times and most of the time obtained less than 0.6% Asp^9-bivalirudin. Hospira ran its process only once using the same mixing conditions as Example 4 and produced a product with low Asp^9-bivalirudin. But there is no evidence that Hospira's process will never produce a batch with more than 0.6% Asp^9-bivalirudin, and, in fact, Hospira seeks approval for a process specification with up to 1.0% Asp^9-bivalirudin. Simply put, Hospira's inefficient mixing cannot be equivalent to "efficient mixing." *See, e.g.*, *Asyst Techs., Inc. v. Emtrak, Inc.*, 402 F.3d 1188, 1195 (Fed. Cir. 2005); *Moore U.S.A., Inc. v. Standard Register Co.*, 229 F.3d 1091, 1106 (Fed. Cir. 2000).

Thus, this Court should affirm the District Court's holding of non-infringement of all asserted claims.[4]

5. Hospira Does Not Use Mixing That Minimizes Asp^9-Bivalirudin Levels.

Even if the Court adopts MedCo's construction of "efficient mixing," Hospira does not meet this limitation and does not infringe. MedCo's construction cannot encompass the mixing of Example 4, which the patent identifies as "inefficient mixing." Indeed, MedCo agrees that this Court may adopt "the related New Jersey action's construction—'mixing that is characterized by minimizing levels of Asp^9-bivalirudin in the compounding solution and that does not use mixing conditions described in Example 4.'" (MB 47 n.7.) Because Hospira uses the mixing conditions of Example 4, it employs "inefficient" rather than "efficient" mixing.

There are three hallmarks of Example 4's mixing: (1) addition "all at once, or rapidly in multiple portions;" (2) the use of paddle mixers; and (3) mixer speeds of 400-800 rpms. (A58.) Hospira's mixing shares these very same traits. Its base

[4] MedCo also argues, as part of its literal infringement and doctrine of equivalents contentions, that the lack of formation of a ***dense*** precipitate during Hospira's compounding process evidences the use of efficient mixing. (MB 57-59.) This argument lacks merit. To begin, MedCo did not make this argument in the District Court and, thus, has waived it. In any case, MedCo's expert admitted that Hospira's process forms a precipitate (A16923-24, 941:19-942:16), and the distinction between dense and non-dense precipitates relates to neither the District Court's holdings nor any claim term.

is added in three portions, the first two added rapidly with the third added at the operator's discretion. It uses a paddle mixer. That mixer operates at 560 rpms.

Thus, Hospira uses the mixing of Example 4. Regardless of the construction of "efficient mixing," Hospira does not meet it.

B. Hospira's Batches Have A Maximum Asp^9-Bivalirudin Level Above 0.6%.

Even if the Court does not affirm the ruling of non-infringement of all asserted claims for lack of "efficient mixing," it should affirm on the alternative ground that Hospira does not meet the limitation of all asserted claims that "the batches have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6% [or, for certain dependent claims, 0.4 or 0.3%]." Hospira's ANDAs product specifications seek approval for batches made by a process that yields Asp^9-bivalirudin levels of up to 1.0% and, thus, do not infringe the "maximum" limitation.

The District Court's ruling to the contrary was based on an erroneous reading of this Court's ruling in *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013). In *Sunovion*, the claim recited a compound with "less than 0.25%" of an isomer. *Id.* at 1278. The ANDA sought approval for products having "from 0.0-0.6%." Thus, the ANDA filer sought approval to sell some products falling within the scope of the claim.

Here, a batch with an Asp^9-bivalirudin level of 0.6% or less does not necessarily fall within the scope of the claim. It does so only if every batch made by the same process also falls within the scope of the claim and/or if the batch is representative of the purity level of every potential batch that could be made by the claim. Thus, a batch having an Asp^9-bivalirudin level of 0.1% made by a process that also makes batches with Asp^9-bivalirudin levels of 0.9% does not infringe. Hospira's ANDAs seek approval to make such non-infringing batches.

Thus, here, unlike in *Sunovion*, a process can either make all infringing batches or no infringing batches. The same process cannot make some batches that infringe and some that do not. That was not true in *Sunovion*. There, the ANDA specification of 0.0-0.6% isomer sought approval to make an infringing product—any product with less than 0.25% isomer. Thus, the ANDA in *Sunovion* sought approval to make some products that infringe and some that did not. Here, on the other hand, because Hospira's process will make products having Asp^9-bivalirudin levels with as much as 1.0%, none of the batches can infringe. Accordingly, Hospira's ANDAs do not fall within the asserted claims.

The District Court apparently misread *Sunovion* as mandating a finding of infringement. (A11 ("[I]t is irrelevant that some batches might contain above 0.6% Asp^9-bivalirudin. . . . [T]his argument goes against controlling Federal Circuit case law." (citing *Sunovion*)).) However, rather than support MedCo's infringement

claim, *Sunovion* compels a finding of non-infringement here. The *Sunovion* court noted that "[w]hat [the ANDA applicant] has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur." *Sunovion*, 731 F.3d at 1278. Hospira's ANDAs request approval to market a non-infringing product—batches made by a process that makes up to 1.0% Asp^9-bivalirudin levels.

This Court should affirm the District Court's ruling that Hospira does not infringe because it does not "efficiently mix." Additionally, because Hospira's ANDAs define a product that falls outside the scope of the claimed "maximum" range, this Court should reverse the District Court's holding to the contrary and affirm the judgment of non-infringement on this alternative ground.

* * *

Hospira cross-appeals the District Court's holding that the asserted claims are not invalid. This Court reviews factual findings for clear error, and the ultimate conclusions of law *de novo*. *E.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007).

III. THE ASSERTED CLAIMS ARE INVALID UNDER THE ON-SALE BAR.

The on-sale bar precludes a patent where "the invention was . . . on sale in this country, more than one year prior to the date of the application for patent." 35 U.S.C. § 102(b). It applies where the claimed invention was (1) "ready for

patenting," and (2) "the subject of a commercial offer for sale" prior to the critical date. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 66-68 (1998).

The District Court found the claimed invention was "ready for patenting" prior to the July 27, 2007 critical date based on proof of an enabling disclosure and reduction to practice of the invention. (A22-23.)

However, the District Court found that the invention was not sold or offered for sale prior to the critical date. The District Court erred. Two sets of sales transactions prior to the critical date invalidate the asserted claims here: (1) MedCo's purchase of validation batches from BVL; and (2) its offer to sell claimed batches to its exclusive distributor, ICS.

A. MedCo Paid BVL For The Validation Batches Prior To The Critical Date.

Despite the extensive commercial exploitation of the invention prior to the critical date, the District Court held that there was no "commercial offer for sale." The court agreed with MedCo that its payments to BVL were for manufacturing services rather than for purchase of the batches. The District Court also held that BVL's manufacturing activities were "experimental" and not for commercial purposes.

These conclusions are erroneous. The on-sale bar does not permit "inventors to stockpile commercial embodiments of their patented invention via commercial contracts with suppliers more than a year before they file their patent

application." *Special Devices, Inc. v. OEA, Inc.*, 270 F.3d 1353, 1354 (Fed. Cir. 2001). Here, there is no question that the transactions between MedCo and BVL were commercial. They were the same types of transactions MedCo had engaged in since the inception of its Angiomax® program in the 1990s to have its commercial batches of bivalirudin drug product manufactured. Further, every one of the ***eleven*** pre-critical-date-batches, including the validation batches, was sold to consumers.

The District Court found that the batches were never "sold" to MedCo because "title to the Angiomax always resided with [MedCo.]" (A24.) However, we are aware of no case requiring formal transfer of title for an invention to be "on sale." Here, BVL made the three validation batches and MedCo paid BVL for those batches. Similarly, in *Special Devices*, the manufacturer-supplier made products of the invention solely for the patentee. 270 F.3d at 1354. It would be illogical if the holding of *Special Devices* could be avoided solely by rewriting the supplier agreement to include a legal fiction that "title" to the products vested with the patentee upon their creation.

The on-sale bar is concerned with commercial exploitation, not formal transfer of title. Thus, the on-sale bar has always extended beyond actual sales to require forfeiture of a patent based on commercial exploitation of the invention prior to the critical date. *D.L. Auld Co. v. Chroma Graphics Corp.*, 714 F.2d 1144,

1147 (Fed. Cir. 1983) ("The 'forfeiture' theory expressed in *Metallizing* parallels the statutory scheme of 35 U.S.C. § 102(b), the intent of which 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."). Thus, for example, performing a "patented method for commercial purposes before the critical date constitutes a sale under § 102(b)." *Plumtree Software, Inc. v. Datamize, LLC*, 473 F.3d 1152, 1163 (Fed. Cir. 2006). It makes no difference who held title when MedCo offered to pay and paid BVL to make its eleven pre-critical date batches. This activity constituted commercial exploitation of the invention.

Nor does the District Court's application of the experimental use exception save MedCo's claims. This exception is narrow and limited to circumstances where the primary purpose of the sale was to conduct experimentation. *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1354 (Fed. Cir. 2002) ("The question posed by the experimental use doctrine . . . is not whether the invention was under development, subject to testing, or otherwise still in its experimental stage at the time of the asserted sale. Instead, the question is whether the transaction constituting the sale was 'not incidental to the primary purpose of experimentation.'"). The exception applies only "where the testing was performed to perfect claimed features or . . . to perfect features inherent to the claimed

invention." *Electromotive Div. of Gen. Motors Corp. v. Transp. Sys. Div. of Gen. Elec. Co.*, 417 F.3d 1203, 1211 (Fed. Cir. 2005).

This narrow exception does not apply here. First, the experimental use exception to the on-sale bar is applicable only if the pre-critical date activity "was primarily made for experimentation." *Id.* at 1210. Here, MedCo contends its claims are directed to the batches of bivalirudin drug product produced—not the process. But only the process required validation.[5] Moreover, the manufacture of the validation batches served a commercial purpose independent of any testing objective. The validation batches each had a "commercial product code" and were designated "for commercial and clinical packaging." (A14959-60.)

Significantly, the BVL invoice for the validation batches does not mention any experimental purpose, describing the charge as "to manufacture [the] bivalirudin lot." (A17178.) BVL invoices prepared for experimental work are different. For example, an invoice for work done before manufacturing the validation batches describes BVL's charge as for "product and process

[5] The fact that the batches were for regulatory validation also does not trigger the exception. The purpose of the validation testing was to prove to the FDA that the process met requirements imposed on drug manufacturers. The inventors, and MedCo, clearly had little if any doubt the process would work. They prepared about $23 million worth of product—2 ¼ full batches—expecting success. Indeed, MedCo's internal documents use language indicating that, while MedCo endeavored to prove that its process satisfied FDA requirements, MedCo's engineers were merely "confirm[ing]" that the process worked and not experimenting at all. (A14883.)

development[;] performance of pilot formulation studies to support investigation of Asp[9] impurity." (A17175.) Thus, the validation batches were manufactured for a commercial purpose that was not merely incidental to any experimental purpose. The experimental exception does not apply. *See Allen*, 299 F.3d at 1354.

In addition, the scale of BVL's pre-critical-date activities—11 batches worth at least $110 million—far exceeds the amounts that could be considered non-commercial. *Special Devices* recognized that paying a fabricator to make "a few sample products" may not trigger the on-sale bar. 270 F.3d at 1356. However, where the number of products made is indicative of commercial purposes, courts should conclude that the invention was being commercially exploited. At a minimum, the eight batches made after validation was complete on January 18, 2007, and before the critical date were clearly not experimental.

Finally, the experimental use exception cannot apply to the manufacture of the second and third validation batches because the claimed invention had already been reduced to practice through the manufacture of the first validation batch. The exception provides an avenue to perform experiments leading to reduction to practice; once that is accomplished, its *raison d'être* ceases to exist. *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1299 (Fed. Cir. 2002).

Therefore, MedCo's payment for the manufacture of the validation batches and BVL's continued manufacture of another eight patented batches prior to the

critical date was a commercial activity that invalidates the asserted claims under § 102(b).

B. MedCo Offered For Sale The Claimed Batches To ICS Prior to The Critical Date.

MedCo then offered for sale the claimed invention to its distributor, ICS, before the critical date. This activity also invalidates the asserted claims.

MedCo and ICS entered into a Distribution Agreement effective February 27, 2007, five months before the critical date and after MedCo had changed its manufacturing process to make only the patented batches. (A14674.) Prior to the agreement, ICS had already been a MedCo distributor, but the agreement changed some of the terms, such as giving ICS title to the product. Specifically, ICS wanted to "purchase" Angiomax®. (*Id*.)

ICS was obligated to "place orders for such quantities of [Angiomax®] as are necessary to maintain an appropriate level of inventory based on customers' historical purchase volumes." (A14676, ¶ 3.1.) The Distribution Agreement set forth the payment terms and price that ICS would pay for Angiomax® that it received. (A14678, ¶ 5.1; A14697.) Under the agreement, ICS notified MedCo it needed additional product by submitting a purchase order. (A14676, ¶ 3.1.) A purchase order was deemed accepted by MedCo after two days, and MedCo was then obligated to fill ICS's order within the following two business days. (*Id.*; A14678, ¶ 4.2.) While the agreement provided that MedCo could reject such an

order within two days, this was merely a mechanism to ensure a clear understanding by both parties when shipments would be made. A shipment of a single batch—valued at over $10 million—was a major undertaking and required ICS to have a "secure receiving area" ready to accept the shipment. (A14691, ¶ 2.5.) Indeed, the District Court found "rejecting an order would be unlikely given the parties' course of dealing." (A26 n.13.)

The Distribution Agreement constituted an offer by MedCo to sell to ICS as much Angiomax® as required to maintain inventory levels. Because only batches made according to the "new" process were made after February 2007, the agreement clearly pertained to batches made pursuant to the asserted claims. Furthermore, by the critical date, MedCo had made eleven batches with its "new" process, worth more than $110 million. Sales of Angiomax® represent over 90% of MedCo's revenues (A16050, 70:15-22), and MedCo could not sell ***any*** of the eleven batches in the United States to anyone except ICS.

Despite this evidence, the District Court held that the Distribution Agreement was not an offer to sell Angiomax® because "individual purchase orders were required," and relied on this Court's statement—from *Group One, Ltd. v. Hallmark Cards, Inc.*, 254 F.3d 1041, 1048 (Fed. Cir. 2001)—that "[o]nly an offer which . . . the other party could make into a binding contract by simple

acceptance (assuming consideration), constitutes an offer for sale under § 102(b)." (A25.)

The District Court misapplied these principles. First, the Distribution Agreement is unquestionably "a binding contract" for the sale of Angiomax® from one seller to one buyer at a specified price. 254 F.3d at 1048. Under the terms of the agreement, it would make no sense if all of ICS's orders for Angiomax® were rejected. In fact, in the Distribution Agreement's recitals, MedCo professes that it "desires to sell [Angiomax®] to [ICS]." (A14674.)

In *Group One*, the purported offer to sell was a series of correspondence and the question was whether it rose to the level of a contractual offer. 254 F.3d at 1044. There was no contract at all, much less a binding contract in which one party (MedCo) expressed the "desire[] to sell" and the other party was obligated to purchase enough to maintain inventory levels. *Id.* at 1048.

A contract similar to the one at issue here ran afoul of § 102(b) in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 424 F.3d 1276 (Fed. Cir. 2005). In *Enzo*, the relevant provision that created the on-sale bar was as follows:

> ENZO shall supply to ORTHO and ORTHO shall purchase from ENZO for use in Licensed Products no less than ninety percent (90%) of ORTHO's United States requirements or seventy-five (75%) of ORTHO's worldwide requirements of Active Ingredients; *provided*, however, that ***ENZO shall have this right to supply*** and ***ORTHO shall have this obligation to purchase*** only with regard to Active Ingredients supplied to ORTHO at

> prices and time schedules which are reasonably competitive with those of other sources . . . .

Id. at 1279. This provision—paragraph 2.14—by itself constituted an offer for sale in violation of § 102(b). *Id.* at 1282. The fact that no shipment dates had been determined and the fact that Ortho need not have even ordered all of its product from Enzo did not prevent application of the on-sale bar. *Id.* Nor did the fact that the language in this paragraph implied that Enzo had the right, but not the obligation, to provide product to Ortho mean there was no offer for sale. *Id.*

Like *Enzo*, under the Distribution Agreement here, ICS had an "obligation to purchase" Angiomax®. *See id.* at 1279. Specifically, it was required to order enough Angiomax® to maintain inventory levels. (A14676, ¶ 3.1.) Just as in *Enzo,* under the Distribution Agreement, MedCo had at least "the right to supply" Angiomax® to ICS. In fact, the Distribution Agreement presents a clearer case of a binding offer to sell because, unlike the agreement in *Enzo*, the Distribution Agreement between ICS and MedCo was exclusive. MedCo could not supply Angiomax® to anyone else in the United States.

The *Enzo* court affirmed that paragraph 2.14 "created the necessary contractual obligations on the parties to constitute a commercial offer for sale." 424 F.3d at 1281. The court held that there was "no doubt" that paragraph 2.14 "constitute[d] a binding commitment by the parties to enter into a commercial sale

and purchase relationship." *Id.* at 1282. The Distribution Agreement here was also such a binding commitment.

The Distribution Agreement invalidates the asserted claims because it is an offer to sell an embodiment of the asserted claims. The Agreement went into effect in February 2007. By that time, MedCo admits that Angiomax® was made only by the revised process. (A16867-68, 885:18-886:16.) This admission establishes that the Distribution Agreement covered the claimed invention, *i.e.*, Angiomax® batches made by the revised compounding process. The District Court found accordingly that "[i]n October 2006, the new process was incorporated into a revised Master Batch Record and since then all batches have been made using the new process." (A19.)

In sum, the Distribution Agreement constituted yet another effort by MedCo to commercialize its invention prior to the critical date and invalidates the asserted claims. *See Cardiac Sci., Inc. v. Koninklijke Philips Elecs. N.V.*, 2006 WL 2038625, at *4 (D. Minn. July 19, 2006) (deeming an invalidating offer for sale an exclusive Distribution Agreement, even though the Agreement required the distributor to submit subsequent individual purchase orders for specific sales, because the Agreement "contain[ed] all of the material terms necessary for [the distributor] to purchase" the claimed product, including—like the ICS

Agreement—price, method of delivery, warranty, and method of payment);[6] *see also Atlanta Attachment Co. v. Leggett & Platt, Inc.*, 516 F.3d 1361, 1365 (Fed. Cir. 2008) ("The overriding concern of the on-sale bar is an inventor's attempt to commercialize his invention beyond the statutory term."). If MedCo is permitted to elude the on-sale bar through the routine purchase order mechanism present in the Distribution Agreement, patentees would be able to commercialize their inventions while delaying seeking patent protection simply by inserting provisions that require an extra, though superficial, step in order to complete what would otherwise be an invalidating sale or offer for sale.

The Court should reverse the District Court and hold the asserted claims invalid under the on-sale bar.

IV. THE ASSERTED CLAIMS ARE INVALID AS OBVIOUS.

The Court should similarly find the claims obvious. Obviousness is a question of law that depends on four factual inquiries: (1) scope and content of the prior art; (2) differences between the claims and the prior art; (3) level of ordinary

[6] The District Court acknowledged that, in *Cardiac*, "such a distribution agreement was held to be an invalidating offer for sale." (A26.) However, it held that "*Cardiac* is not binding on this Court, and I therefore decline to follow its reasoning." (*Id.*)

skill in the relevant art;[7] and (4) any objective considerations.[8] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399 (2007).

The District Court correctly found that the "only difference between the claims of the patents and the prior art compounding process is 'efficient mixing.'" (A27.) If this Court adopts MedCo's construction of "efficient mixing," there is no difference between the asserted claims and a host of additional prior art that was not presented at trial. If the Court affirms the District Court's construction, it should reverse the District Court's ruling that the claims are not invalid as obvious for the reasons explained below.

A. The Asserted Claims Are Invalid Because "efficient mixing" Was An Obvious Change To The Prior Art Compounding Process.

The difference between the asserted claims and the prior art is "efficient mixing": (1) the addition of pH-adjusting solution "slowly and in a controlled manner," and (2) its mixing with the bivalirudin solution "under high-shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)." These changes would have been obvious to a POSITA engaging in routine process optimization of the prior art process.

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[7] The District Court held that "there is no dispute that a [POSITA] 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." (A27.)

[8] There are no such considerations that would tend to show non-obviousness here, and the District Court made no findings related to such considerations.

MedCo's prior, "inefficient" process yielded two batches with unacceptable levels of Asp^9-bivalirudin. (A16062, 82:9-16; A16136, 156:16-24.) A POSITA would seek to address this problem to comply with industry requirements that a process yield consistent product. (A16683-84, 701:17-702:8.) He would also be motivated by his ongoing desire to minimize the presence of drug impurities. (*Id.*)

Looking at the problem of high Asp^9-bivalirudin levels, the POSITA would promptly identify the base addition and mixing step as the source of the problem because, as the District Court found, it was generally known that Asp^9-bivalirudin is formed by deamidation of asparagine as base is added to a bivalirudin solution. (A28.) Thus, the POSITA, acting with ordinary creativity, would manipulate this base addition and mixing step to reduce the formation of Asp^9-bivalirudin. *See KSR*, 550 U.S. at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

The base addition and mixing step of the compounding process comprises two variables: (1) adding base to the bivalirudin solution, and (2) mixing the solution. Thus, the POSITA would have two variables to manipulate. (A16695, 713:2-6.)

The District Court clearly erred when it found that there were too many variables at play for a POSITA to find "efficient mixing" obvious—there were only two. In coming to its erroneous conclusion, the District Court relied on a

document authored by Dr. Musso summarizing his initial meeting with BVL, where he listed multiple potential causes for the Asp^9-bivalirudin problem. (A29.) This preliminary listing of possible causes beyond the two key variables listed above does not render the claims non-obvious: Dr. Musso disposed of these potential root causes ***within one day*** of first proposing them. (*Compare* A8680-85 (summarizing July 14, 2006, meeting where variables identified), *with* A17160 (claiming conception date of July 15, 2006).) Moreover, even considering the additional factors, there remain only a finite number of variables to consider. *See KSR*, 550 U.S. at 421; *see also Pfizer*, 480 F.3d at 1363 (holding a universe of fifty-three potential anions is small enough to render obvious the selection of one particular anion).

Regarding the first variable, the addition of pH-adjusting solution "slowly and in a controlled manner": it would have been obvious to a POSITA to add base more slowly and in a controlled manner because doing so removes undesirable human variability. The motivation to limit human variability is clear. Even MedCo admitted this is "a goal for anybody working in the pharmaceutical industry" because it eliminates the potential for human error. (A16142, 162:7-11; A16701-02, 719:12-720:20; A16684-85, 702:22-703:11.) In addition, it would have been obvious to a POSITA to add the pH-adjusting solution in a controlled

way to avoid increasing the pH too rapidly in select spots, as opposed to raising the pH gradually throughout the entire solution. (*See* A16695, 713:9-17.)

Regarding the second variable: it would also have been obvious to the POSITA to employ "high-shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)," to mix the base with the bivalirudin solution. The POSITA would know that base addition causes the formation of a bivalirudin precipitate, which occurs when the base raises the pH of the bivalirudin solution to its isoelectric point at pH 3.6. (A16493-94, 512:21-513:7; A16693-95, 711:17-713:1.) The bivalirudin must be dissolved in solution to be captured in the final drug product. (A16157, 177:3-10; A16435, 454:2-21.) Knowing that the precipitate must be dissolved in order to have a viable product, it would be obvious to the POSITA to increase the mixer speed to break up the solid. (A16696-97, 714:23-715:10.)

High-shear mixers were used extensively in the prior art to break up and dissolve solids of this type. (A16696-98, 714:23-716:14.) Indeed, the District Court found that high-shear mixing was a known method of dispersion in the prior art. (A28.) Further, a POSITA would not have been concerned about using a high-shear mixer with bivalirudin. High-shear mixers were routinely used with peptides similar to bivalirudin in the prior art. (A16698-700, 716:15-718:17.) Hospira's expert testified that he used high shear mixers with peptides thousands

of times—all without incident—before MedCo's alleged invention here. (A16700, 718:1-9).

The District Court found the evidence "in equipoise" as to whether a POSITA would have been dissuaded from using high-shear mixing. (A30.) In particular, the District Court noted testimony proffered by MedCo that high-shear mixing can be undesirable because it can cause foaming. (*Id.*) However, in light of the routine use of high-shear mixing with peptides, a POSITA would at least test whether high-shear mixing would work in the compounding process at issue here. *See Pfizer*, 480 F.3d at 1364 ("[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success . . . .").

Because the difference between the asserted claims and the prior art is "efficient mixing," and a POSITA would have employed "efficient mixing" when faced with the problems of the prior art, the asserted claims are obvious.

B. The Asserted Dependent Claims Are Obvious.

The asserted dependent claims do not provide any alleged novelty aside from "efficient mixing," shown to be obvious above. Therefore, these claims are all obvious as well.

Dependent Claims 2 and 3 of both patents recite maximum levels of 0.4% Asp^9-bivalirudin, and 0.3% Asp^9-bivalirudin, respectively. (A60, Claims 2-3; A76,

Claims 2-3.) These claims are obvious for the same reasons as Claim 1. (A16711-12, 729:21-730:9.) The compounding process of Claim 1—demonstrated above to be obvious—yields batches with less than 0.3% Asp^9-bivalirudin. If it did not, Dependent Claims 2 and 3 would be non-enabled because the patents do not teach any way to achieve lower Asp^9-bivalirudin levels other than through the use of "efficient mixing." *See* 35 U.S.C. § 112 ¶ 1 ("The specification shall contain a written description of the invention . . . to enable any person skilled in the art to which it pertains . . . to make and use the same.").

The other asserted dependent claims recite limitations already known in the prior art process. Therefore, they too are obvious:

- ***Claim 7 (both patents)*** recites batches having a maximum level of another bivalirudin impurity, D-Phe^{12}-bivalirudin, that does not exceed about 2.5%. However, the patents-in-suit admit that the claimed compounding process does not influence the level of D-Phe^{12}-bivalirudin in the final drug product. (A75, 26:1-5.) Thus, to the extent the claimed process yields batches with less than 2.5% D-Phe^{12}-bivalirudin, so too did the prior art compounding process. (A16712-13, 730:10-731:5); *see Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007).

- ***Claim 8 (both patents)*** recites a carrier comprising one or more bulking or stabilizing agents. The prior art process utilized mannitol, which is a bulking agent. (A16713, 731:6-21.)

- ***Claim 9 (both patents)*** recites sugar as the bulking agent. Again, the prior art process used mannitol, which is a sugar. (*Id.*)

- ***Claim 10 (both patents)*** recites the use of mannitol as the bulking agent, as was used in the prior art process. (*Id.*)

- ***Claim 11 ('343 patent) / Claim 17 ('727 patent)*** recites sodium hydroxide as the base used in the pH-adjusting solution. The prior art process also used sodium hydroxide as the base. (A16713-14, 731:22-732:7.)

V. THE ASSERTED CLAIMS ARE INVALID AS INDEFINITE.

The test for definiteness under § 112 ¶ 2 is whether the intrinsic record of the patent informs, with reasonable certainty, a POSITA about the scope of the invention. *Nautilus*, 134 S. Ct. at 2124. Thus, rather than permit a court to construe claims where there is some plausible construction, the test is whether a POSITA would understand which construction is correct. The "reasonable certainty" standard ensures that a patent is "precise enough to afford clear notice of what is claimed, thereby 'apprising the public of what is still open to them.'" *Id.* at 2129. A ruling on indefiniteness is reviewed *de novo*. *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1350 (Fed. Cir. 2010).

The patent claims all include the requirement "wherein the batches have a maximum impurity level of Asp^9-bivalirudin that does not exceed about 0.6% [or 0.4% / 0.3%] as measured by HPLC." "[B]atches" can refer to either a single representative batch or all the batches made by a particular process. The above "wherein" phrase is indefinite unless it has meaning for both types of batches. Otherwise, a POSITA practicing a commercial process making multiple batches would not be able to determine whether the process was truly the patented process. If that process at one point exceeded the maximum of 0.6%, the person would then know the patented process was not being practiced. But before then, there would be uncertainty as to whether the process infringes the "maximum" limitation.

Hospira presented unrebutted evidence that there is no recognized statistical method for determining a statistical significance in comparison of maximum values. (A16542, 561:6-10.) This is common sense. One can always determine the maximum value for a fixed set of measurements, but if the measurements continue into the future, one will never know the maximum until the process stops and no more data will be generated. The maximum can only increase as new measurements are taken.

For example, if you flip a coin and count the numbers of consecutive heads, you will quickly reach the number 2. That will be the maximum number of consecutive heads until you flip heads 3 consecutive times. Then that will be the

maximum—probably for a longer time than 2 was the maximum—until 4 consecutive heads are flipped. However, no maximum will be the permanent and final maximum until you stop flipping the coin.

In the context of these claims, a POSITA running a commercial process for making bivalirudin drug product would never have reasonable certainty as to whether the process infringes until it produces a batch with an impurity level of above 0.6% (for Claim 1 of both patents). At that point, a POSITA would conclude that the process does not infringe. Until that point is reached, however, or the process is permanently discontinued, it is unclear whether the process infringes.

The "reasonable certainty" standard ensures that a patent claim "appris[es] the public of what is still open to them." *Nautilus*, 134 S. Ct. at 2129. A pharmaceutical manufacturer having run even 20 batches where the maximum Asp^9-bivalirudin level was 0.5% would not know with reasonable certainty whether it was infringing, because the 21st batch could have an Asp^9-bivalirudin level of 0.65%.

The unusual nature of the "maximum" limitation leads to nonsensical results. In the above example of the pharmaceutical manufacturer having run 20 batches with Asp^9-bivalirudin levels at 0.5% or less, assume that the 21st batch, run using the same process as the other 20, was the first batch to have an Asp^9-bivalirudin level that exceeded 0.6%. It would be impossible to analyze

infringement of this situation no matter how MedCo argues the claims should be understood.

First, MedCo could argue that the process infringed up to the 20th batch, but suddenly, the day the 21st batch was made, it ceased to infringe. This interpretation makes no sense because then the same process results in infringing products on one day and non-infringing products the next.

Second, MedCo could argue that the process infringes because one of the first 20 batches was "representative" and therefore the entire process infringes, regardless of whether some batches exceed the claimed maximum. That view is inconsistent with the patents' stated goal of providing batches that never exceed 0.6% Asp^9-bivalirudin, and would depend on the happenstance selection of one of the first 20 batches as "representative."

Third, MedCo could argue that until the 21st batch was produced, it was unclear whether the process produced an infringing product—that is, it would be impossible to determine infringement until after more than $200 million in potentially infringing product had been made. That is the epitome of indefiniteness. *See Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003).

Despite the clear indefiniteness of the claims, the District Court ruled against Hospira, holding that because "the batches" ***can*** refer to a single batch, like an

ANDA exhibit batch, the asserted claims are not indefinite because "[w]here the Asp^{9}-bivalirudin levels of a representative batch can be determined, the person of ordinary skill can determine the 'maximum' impurity levels." (A33.) But that ruling is irrelevant to whether the asserted claims ***as a whole*** are indefinite. As an initial matter, the same arguments regarding indefiniteness are applicable to a single "representative batch" as to "all batches." However, the District Court failed to consider that the scope of the claims also includes "all the batches" made by the process. Because indefiniteness is a question of law and the undisputed evidence establishes that a POSITA could not determine with reasonable certainty that "all the batches" of a commercial process meet the maximum Asp^{9}-bivalirudin impurity level, this Court should find the asserted claims indefinite.

MedCo's arguments below to the contrary were unavailing. *First*, MedCo argued that "maximum" could not "include" all the batches because that was rejected during claim construction in favor of the ordinary meaning of "maximum." (A17014.) However, no matter how "maximum" is construed, the claims require that it be applicable to "the batches," which was defined by the District Court, in a construction not appealed by MedCo, as either "a single batch" or "all the batches."

Second, MedCo argued that the claims are not indefinite because they were construed and therefore "amenable to construction" and "not insolubly

ambiguous." (*Id.*) That argument is incorrect under both the Supreme Court's recent *Nautilus* ruling and pre-*Nautilus* law. Simply being able to construe "maximum" as having its ordinary meaning is not enough. A POSITA must be able to "translate the definition into meaningfully precise claim scope." *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1251 (Fed. Cir. 2008). That is not possible here.

Third, MedCo argued that Hospira's expert, Dr. Taylor, based his opinions that a maximum for a statistical process continues to increase over time on "an irrelevant assumption." (A17013-14.) MedCo pointed to Dr. Taylor's use of a standard normal distribution (*i.e.*, a Gaussian distribution) to illustrate his point, whereas the Angiomax® process used by MedCo does not follow a standard normal distribution. However, nothing about Dr. Taylor's opinion was dependent on the particular type of distribution he used for his example. And his testimony that there is no recognized statistical method for determining a statistical significance in comparison of maximum values was unrebutted. (A16542, 561:6-10.)

Because a POSITA could not determine with reasonable certainty that an ongoing commercial process has a "maximum" of 0.6% Asp^9-bivalirudin, the asserted claims are indefinite.

Furthermore, the term "maximum impurity level" makes no sense in the context of a single batch. A single batch has no maximum or minimum impurity level; it has one impurity level. Consequently, the only requirement that makes sense is that the "maximum impurity level" means that the accused process will never make a batch that exceeds the 0.6% Asp^9-bivalirudin level required by the claims. As explained above, under that construction, Hospira does not infringe because its process is approved for making products having impurity levels as high as 1.0%.

Every asserted claim requires that "the batches have a maximum impurity level." This Court should reverse the District Court's decision below that the claims are not invalid for indefiniteness.

CONCLUSION

For the foregoing reasons, on MedCo's appeal, this Court should affirm the District Court's ruling that Hospira does not infringe any asserted claim because it does not "efficiently mix."

Even if the Court rejects the District Court's claim constructions relevant to this issue, then this Court should affirm the judgment of non-infringement on the alternative grounds that (1) Hospira does not "efficiently mix" under MedCo's proposed construction, (2) MedCo's proposed alternative constructions are indefinite under § 112, and (3) Hospira's ANDAs define a product that falls

outside the scope of the claimed "maximum" limitation. Alternatively, this Court should remand for determinations of infringement and invalidity under any new claim constructions.

On Hospira's cross-appeal, this Court should reverse the District Court's ruling that the claimed invention did not violate § 102(b), that the claims are not invalid as obvious under § 103, and that the claims are not indefinite under § 112.

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Respectfully submitted,

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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 16,098 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

September 26, 2014

CERTIFICATE OF SERVICE

I hereby certify that on September 26, 2014, I caused the foregoing **PRINCIPAL BRIEF AND RESPONSE BRIEF OF DEFENDANT-CROSS-APPELLANT HOSPIRA, INC.** 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 parties listed below.

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