IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

CLAIM CONSTRUCTION

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July 11, 2013
Wilmington, Delaware

Richard G. Andrews

ANDREWS, UNITED STATES DISTRICT JUDGE:

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

The disputed terms follow.

(1) "Pharmaceutical batches"

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

	representative of all commercial batches and wherein the levels of impurities and reconstitution time in a single batch represent levels for all potential batches made by said process.

The parties dispute the construction of "pharmaceutical batches" as used in both of the patents. The term is used in claim 1 of the '343 Patent as follows:

> 1. Pharmaceutical batches of a drug product comprising bivalirudin (SEQ ID NO:1) and a pharmaceutically acceptable carrier, for use as an anticoagulant in a subject in need thereof, said batches prepared by a compounding process comprising...

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

> As used here, "batch" or "pharmaceutical batch" refers to material produced by a single execution of a compounding process of various embodiments of the present invention. "Batches" or "pharmaceutical batches" as defined herein may include a single batch, wherein the single batch is representative of all commercial batches (see generally, Manual of Policies and Procedures, Center for Drug Evaluation and Research, MAPP 5225.1, Guidance on the Packaging of Test Batches at 1), and wherein the levels of, for example, Asp^9-bivalirudin, total impurities, and largest unknown impurity, and the reconstitution time represent levels for all potential batches made by said process. "Batches" may also include all batches prepared by a same compounding process.

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

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

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

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

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

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

> 1. Pharmaceutical batches of a drug product comprising bivalirudin (SEQ ID NO:1) and a pharmaceutically acceptable carrier for use as an anticoagulant in a subject in need thereof, wherein the batches have a pH adjusted by a base, said pH is about 5-6 when reconstituted in an aqueous solution for injection, and wherein the batches have a maximum impurity level of Asp^9–bivalirudin that does not exceed about .6% as measured by HPLC.

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

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

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

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

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

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

`727 Patent at 9:03-17.

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

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

3. "Efficient mixing"

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

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

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

> 1. Pharmaceutical batches of a drug product comprising bivalirudin (SEQ ID NO:1) and a pharmaceutically acceptable carrier, for use as an anticoagulant in a subject in need thereof, said batches prepared by a compounding process comprising:
>
> (i) dissolving bivalirudin in a solvent to form a first solution;
> (ii) efficiently mixing a pH-adjusting solution with the first solution to form a second solution, wherein the pH adjusting solution comprises a pH-adjusting solution solvent; and
> (iii) removing the solvent and pH-adjusting solution solvent from the second solution;
>
> wherein the batches have a pH adjusted by a base, said pH is about 5-6 when reconstituted in an aqueous solution for injection, and wherein the batches have a maximum impurity level of Asp^9 –bivalirudin that does not exceed about .6% as measured by HPLC.

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

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

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

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

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

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

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

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

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

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

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

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

proposed construction states that the mixing occurs both "under high shear mixing conditions" and "not solely under slow mixing conditions[.]" If the mixing requires high shear mixing conditions, then by definition it does not occur "solely under slow mixing conditions." The "not solely under slow mixing conditions" is therefore redundant. Second, the proposed requirement excluding any and all rapid addition of the pH-adjusting solution to the bivalirudin solution is unnecessary. Example 4 of the patent does show generally that rapid addition of the pH-adjusting solution is inconsistent with "efficient mixing." That is why "slowly" is appropriate. The "not rapidly all at once" and "not rapidly in multiple portions" limitations are therefore redundant of the "slowly" limitation. For these reasons, the Court construes "efficient mixing" as "A pH-adjusting solution is added to a bivalirudin solution slowly and in a controlled manner, and mixed together by a process comprising high shear mixing conditions (*i.e.*, mixer speeds above 1000 rpms)."