IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER HEALTHCARE LLC,

Plaintiff,

v.

BAXALTA INCORPORATED, BAXALTA US INC., and NEKTAR THERAPEUTICS,

Defendants.

Civil Action No. 1:16-cv-1122-RGA

MEMORANDUM OPINION

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ANDREWS, U.S. DISTRICT JUDGE:

Presently before the Court is the issue of claim construction of multiple terms in U.S. Patent No. 9,364,520 ("the '520 patent"). The Court has considered the Parties' Joint Claim Construction Brief. (D.I. 99). The Court heard oral argument on February 28, 2018. (D.I. 108 ("Tr.")). The parties submitted supplemental briefing at the Court's request. (D.I. 109, 111).

I. BACKGROUND

The patent-in-suit is directed to forms of factor VIII, "a protein necessary for normal blood clotting in response to injury." (D.I. 99 at 1). The '520 patent claims factor VIII conjugates not found in nature, made up of recombinant factor VIII and one or more biocompatible polymers chemically bonded to factor VIII at the protein region known as the "B-domain." (*Id.* at 1, 3). The claimed factor VIII conjugates are formed through a process called PEGylation, which is the conjugation of recombinant factor VIII with polyethylene glycol ("PEG"), a biocompatible polymer. (*Id.* at 5). PEGylation occurs at "one of numerous amino acid sites across" factor VIII. (*Id.* at 6).

II. LEGAL STANDARD

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324) (alteration in original). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v.*

Westview Instruments, Inc., 52 F.3d 967, 977–80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312–13 (citations and internal quotation marks omitted). "[T]he ordinary meaning of a claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a determination of law. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317–19. Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

"A claim construction is persuasive, not because it follows a certain rule, but because it defines terms in the context of the whole patent." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GMBH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (citation omitted).

III. TERMS FOR CONSTRUCTION

Independent claims 1 and 9 of the '520 patent contain all disputed limitations, and are representative. (*Id.* at 1, 3-4). They read as follows:

1. An *isolated polypeptide conjugate comprising*

   a functional factor VIII polypeptide and one or more biocompatible polymers,

   wherein the functional factor VIII polypeptide comprises the amino acid sequence of SEQ ID NO: 4 or an allelic variant thereof and has a B-domain, and

   further wherein the biocompatible polymer comprises *polyalkylene oxide* and is *covalently attached* to the functional factor VIII polypeptide *at the B-domain*.

9. A pharmaceutical composition comprising

   (1) a therapeutically effective amount of a *monopegylated polypeptide conjugate*,

      wherein the *monopegylated polypeptide conjugate* comprises a functional factor VIII polypeptide and one *polyethylene glycol polymer*,

      the functional factor VIII polypeptide comprises the amino acid sequence of SEQ ID NO: 4 or an allelic variant thereof and has a B-domain, and

      the polyethylene glycol is *covalently attached* to the functional factor VIII polypeptide *at the B-domain*; and

   (2) a pharmaceutically acceptable adjuvant.

('520 patent, claims 1, 9) (disputed terms italicized).

A. "an isolated polypeptide conjugate" (claim 1)

1. *Plaintiff's proposed construction:*

   The preamble is not limiting.

   To the extent the preamble is limiting, plain and ordinary meaning: "recombinant polypeptide conjugate"

2. *Defendants' proposed construction*: "a polypeptide conjugate that is not heterogeneous and in which essentially all the molecules have polyalkylene oxide attached at the B-domain"

3. *Court's construction*: "a polypeptide conjugate where conjugation was not random"

"[A]n isolated polypeptide conjugate" appears in the preamble of claim 1. The parties dispute whether the preamble is limiting. (D.I. 99 at 12).

"In general, a preamble limits the invention if it recites essential structure or steps, or if it is 'necessary to give life, meaning, and vitality' to the claim." *Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citing *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999)). "No litmus test defines when a preamble limits claim scope." *Catalina*, 289 F.3d at 808. However, the Federal Circuit has identified "[s]ome guideposts" for determining when a preamble does limit claim scope. *Id.* For example, a preamble might limit claim scope when "Jepson claiming" is used; when there is "dependence on a particular disputed preamble phase for antecedent basis"; "when the preamble is essential to understand limitations or terms in the claim body"; "when reciting additional structure or steps underscored as important by the specification"; and when the preamble contains "statements of intended use or asserted benefits . . . , but only if the applicant clearly and unmistakably relied on those uses or benefits to distinguish prior art." *Id.* at 808-09.

Defendants make two arguments that the preamble is limiting. First, Defendants argue that Plaintiff made "an isolated polypeptide conjugate" an "essential element" of the claims by

amending the preamble during prosecution, and by disparaging "heterogeneous" conjugates in the specification. (D.I. 99 at 16-17). Second, Defendants argue that Plaintiff made a disclaimer by relying on the preamble to distinguish the claimed conjugate over the prior art during prosecution. (*Id.* at 18, 32).

As to Defendants' first argument, Plaintiff added the term "an isolated conjugate" in a claim amendment during prosecution, and relied on three paragraphs from the specification as support. (D.I. 63-1 at p. 515-16). Defendants argue that the paragraphs show "that the claimed conjugate was 'isolated' by having one amino acid available for conjugation, applying the three-step site-directed conjugation method, and yielding a conjugate that was not heterogeneous." (D.I. 99 at 17). However, as Plaintiff notes, this amendment occurred not in response to an art rejection, but during a claim election to proceed with product claims, rather than method claims. (*Id.* at 24 (citing D.I. 62-6 at p. 38)). Furthermore, I agree with Plaintiff that the cited "enabling passages do not invoke the preamble term 'isolated polypeptide conjugate' to distinguish the prior art, much less offer support that such a conjugate was 'isolated' in the way Defendants propose." (*Id.* at 24). Accordingly, I do not find that Plaintiff's action during prosecution made the preamble essential.

Defendants also argue that the '520 patent specification disparages heterogeneous conjugates. (D.I. 99 at 17-18). "[R]epeated derogatory statements . . . reasonably may be viewed as a disavowal of that subject matter from the scope of the [p]atent's claims." *EMC Corp. v. Pure Storage, Inc.*, 77 F. Supp. 3d 402, 412 (D. Del. 2015) (quoting *Chicago Bd. Options Exch., Inc. v. Int'l Sec. Exch., LLC*, 677 F.3d 1361, 1372 (Fed. Cir. 2012)). Defendants argue that statements in the specification make clear that "conjugates" that are "not heterogeneous" are an "essential structural element," meaning the patentee disclaimed heterogeneous conjugates. (D.I. 99 at 17-18). Plaintiff, however, argues that any disparagement in the '520 patent neither amounts to

disclaimer nor makes the preamble essential. (*Id.* at 28). In *EMC Corp.*, argues Plaintiff, "the patent did more than criticize—it expressly distinguished particular prior art methods from the innovation's 'essence.'" (*Id.*). Here, on the other hand, the '520 patent never distinguishes B-domain pegylated conjugate products having any degree of heterogeneity as being excluded. Rather, the patent specification merely states that random PEGylation is "problematic" for factor VIII because it yields "enormous heterogeneity in its product profile," and that "[s]ite-directed attachment also allows for a uniform product rather than the heterogeneous conjugates produced in the art by random polymer coupling." (D.I. 99 at 18; '520 patent at 8:28-30). These statements disparage products with a high degree of heterogeneity. They do not expressly distinguish all prior art products with even the slightest degree of heterogeneity.[1] I agree with Plaintiff that this case is distinguishable from *EMC Corp.* The patent's disclosures do not amount to "clear and unmistakable disclaimer" of heterogeneity, and do not make the preamble essential.

As to Defendants' second argument, Defendants point to several actions by Plaintiff during the prosecution of the '520 patent and its European counterpart (EP 11 153 297), which Defendants argue constitute disclaimer. (D.I. 99 at 19-20).

First, Defendants argue Plaintiff used the "isolated conjugate" limitation to overcome a rejection over U.S. Patent No. 7,199,223 ("Bossard"). (D.I. 99 at 21). In response to the rejection, Plaintiff stated, "The rejection . . . fails in at least four aspects: (1) there is no showing of where Bossard [] teaches an isolated preparation of conjugates having B-domain attachment to a polymer, (2) the alleged showing of B-domain attachment is random PEGylation and does not ensure that attachment occurs at the B-domain; (3) the rejection impermissibly relies upon experimental data from Applicants' own specification as alleged evidence of anticipation; and (4) the Bossard

[1] Defendants' proposed construction indicates that the claims do not cover products with even the slightest degree of heterogeneity.

description is too broad to anticipate the specific conjugates of claims 58 and 60-66." (D.I. 62-13 at p. 23) (underlining in original). Defendants argue that Plaintiff's statements constitute a disclaimer of all polypetide conjugates, unless they are "not heterogeneous." (D.I. 99 at 21).

Plaintiff argues it did not overcome Bossard by eliminating heterogeneity altogether. (*Id.* at 26). Rather, Plaintiff says it overcame Bossard, which "disclosed random [PEG]ylation without regard to location," based on PEGylation being "at the B-domain." (*Id.*). I disagree with Plaintiff that it distinguished Bossard by conjugation being "at the B-domain." Rather, Plaintiff relied on the "isolated polypeptide conjugate" limitation to distinguish Bossard.

In doing so, Plaintiff clearly and unmistakably disclaimed any "polypeptide conjugate where conjugation was random." Plaintiff argued during prosecution of the '520 patent that "Bossard's purification does not teach . . . isolated conjugates," because "[a]ny conjugation [at amines or carboxy sites] is random and does not ensure that attachment occurs at the B-domain." (D.I. 63-1 at p. 960; D.I. 63-1 at p. 902). Plaintiff reiterated that "random conjugation" does not "show[] the claimed conjugates requiring B-domain attachment." (D.I. 63-1 at p. 960-61).

Furthermore, even though the patent specification does not expressly distinguish all prior art products with even the slightest degree of heterogeneity, it does disparage "random conjugation." The patent specification states that random PEGylation is "problematic" for factor VIII because it yields "enormous heterogeneity in its product profile." ('520 patent at 8:28-30).

Accordingly, I find that Plaintiff clearly and mistakably disclaimed any "polypeptide conjugate where conjugation was random." *Purdue Pharma. L.P. v. Endo Pharm. Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006); *RFID Tracker, Ltd. v. Wal-Mart Stores, Inc.*, 342 F. App'x 628, 630 (Fed. Cir. 2009) (citing *N. Am. Container, Inc. v. Plastipak Packaging, Inc.*, 415 F.3d 1335, 1345-46 (Fed. Cir. 2005)) (allowing exclusionary constructions upon finding disclaimer). Even though

"isolated polypeptide conjugate" is a product limitation, and "random conjugation" is a process, "process steps can be treated as part of a product claim if the patentee has made clear that process steps are an essential part of the claimed invention." *Andersen Corp.*, 474 F.3d at 1375.

Second, Defendants argue that Plaintiff made a disclaimer by distinguishing prior art during prosecution of the '520 patent's European counterpart. (D.I. 99 at 19). Plaintiff stated, "[Prior art reference] D6 teaches random PEGylation at any lysine on the [factor VIII] molecule and therefore does not anticipate the presently claimed isolated conjugates in which essentially all the molecules have a polymer attached at the B-domain." (D.I. 67-1 at p. 215). Defendants import Plaintiff's statement into their construction, which specifies that the claimed polypeptide conjugate is one "in which essentially all the molecules have polyalkylene oxide attached at the B-domain." (D.I. 99 at 20).

However, the Federal Circuit "cautions against indiscriminate reliance" on foreign prosecution because "the varying legal and procedural requirements for obtaining patent protection in foreign countries might render consideration of certain types of representations inappropriate for consideration in a claim construction analysis of a United States counterpart." *AIA Eng'g Ltd. v. Magotteaux Int'l S/A*, 657 F.3d 1264, 1279 (Fed. Cir. 2011) (internal quotations omitted). Moreover, Plaintiff's statement strikes me as a statement distinguishing the process claimed in the European patent from a process that teaches random PEGylation using only lysine, rather than a clear and unmistakable disclaimer of all conjugates in which fewer than "essentially all the molecules have polyalkylene oxide attached at the B-domain." Accordingly, I do not find a disclaimer here.

By disclaiming any "polypeptide conjugate where conjugation was random," Plaintiff has made "an isolated polypeptide conjugate" an "essential element of the claims." Therefore, I construe "an isolated polypeptide conjugate" to reflect that disclaimer.

B. "polyalkylene oxide" and "PEG" (claims 1 and 9)

1. *Plaintiff's proposed construction*:

   "polyalkylene oxide": plain and ordinary meaning: "polymer with repeating alkylene oxide units, including polyethylene glycol polymer (PEG)"

   "polyethylene glycol polymer": plain and ordinary meaning: "polymer with repeating ethylene oxide units, including branched, linear, forked, and multifunctional structures or geometries"

2. *Defendants' proposed construction*:

   "polyalkylene oxide": "polyalkylene oxide (such as those recited in col.8 l.41-col.9 l.19) that did not target amines prior to reaction with factor VIII"

   "polyethylene glycol polymer": "polyethylene glycol polymer (such as those recited in col.8 1.62-col.9 1.19) that did not target amines prior to reaction with factor VIII"

3. *Defendants' revised updated construction* (D.I. 111 at p. 2, n.2):

   "polyalkylene oxide": "polyalkylene oxide (such as those recited in col.8 l.41-col.9 l.19) without a functional group that targets amines"

   "polyethylene glycol polymer": "polyethylene glycol polymer (such as those recited in col.8 1.62-col.9 1.19) without a functional group that targets amines"

4. *Court's construction*:

   "polyalkylene oxide": plain and ordinary meaning: "polymer with repeating akylene oxide units, including polyethylene glycol polymer (PEG)"

   "polyethylene glycol polymer": plain and ordinary meaning: "polymer with repeating ethylene oxide units, including branched, linear, forked, and multifunctional structures or geometries"

Defendants ask that I construe the product limitations "polyalkylene oxide" and "PEG" to specify that they are "without a functional group that targets amines." (D.I. 111 at 2 n.2).

In doing so, Defendants ask that I read process limitations into the disputed product limitations. Defendants' proposed constructions focus on how polyalkylene oxide and PEG are used to form the claimed conjugate. They do not focus on the structure of the claimed conjugate itself.

"[P]rocess steps can be treated as part of a product claim if the patentee has made clear that process steps are an essential part of the claimed invention." *Andersen Corp. v. Fiber Composities, LLC*, 474 F.3d 1361, 1375 (Fed. Cir. 2007). Furthermore, a process can limit a claim where "the process is relied on for patentability and validity." *AFG Indus. v. Cardinal IG Co.*, 224 F. App'x 956, 958-59 (Fed. Cir. 2007).

Defendants argue that Plaintiff made a disclaimer that warrants Defendants' proposed constructions.

First, Defendants argue that the specification disparaged the use of polymers that target amines. (D.I. 99 at 41-42). The '520 patent recites that it uses "site-directed attachment." ('520 patent, 8:15-37). Defendants aver that "site-directed attachment" "cannot be achieved on Factor VIII with polymers that target amines." (D.I. 99 at 42). However, the patent's recitation does not amount to "express[] distinguish[ment of] the invention from the prior art based on th[e disputed] feature," which in this case is polyalkylene oxide and PEG. *Retractable Techs., Inc. v. Becton Dickinson Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011). Accordingly, the patent's teachings do not support a finding of disclaimer.

Second, Defendants argue that Plaintiff expressly distinguished prior art on the basis that the '520 patent does not use amine-targeting polymers. (D.I. 99 at 41-44). Plaintiff explained during prosecution that the Bossard reference taught "many polymer attachment sites, such as 'lysine, cysteine, and/or arginine,'" but Bossard's "description does not ensure that attachment

occurs at the B-domain, and does not disclose isolated conjugates with attachment at the B-domain." (D.I. 62-13 at p. 23-24). Plaintiff responds that Defendants' prosecution history disclaimer arguments stem from Plaintiff's response to a rejection directed to whether Bossard disclosed attachment "at the B-domain" at all.[2] (D.I. 99 at 48). Accordingly, I will examine whether Plaintiff disclaimed content when I turn to Term 4, the "at the B-domain" limitation.

Because the patentee did not make clear that these process limitations are an essential part of the claimed invention, I will not read them into these product limitations. Instead, I adopt plain meaning constructions.

Defendants argue that Plaintiff's proposed plain meaning construction for "polyalkylene oxide" is improper for reasons other than its failure to reflect alleged disclaimers. (D.I. 99 at 45-46). Defendants argue that the construction "does not reflect that a polyalkylene oxide or polyethylene glycol polymer must be functionalized in order to react with a Factor VIII molecule," and "recites an inert polymer that could not attach to Factor VIII." (*Id.*). In response, Plaintiff argues, "Defendants ignore that the claims are directed to the end product conjugate (claim 1) or compositions (claim 9), not methods of manufacture of those products." Plaintiff continues, "In the claimed end products, the 'polyalkylene oxide' and 'PEG' are already attached to factor VIII and thus do not require activation." (D.I. 99 at 46-47) (emphasis omitted). Defendants do not respond to Plaintiff's contention in their sur-reply brief. (*See id.* at 49-52). The claimed products are indeed end products. Thus, I agree with Plaintiff that Defendants' objections are irrelevant in the context of the '520 patent. I adopt Plaintiff's proposed plain meaning constructions.

C. "covalently attached" (claims 1 and 9)

1. *Plaintiff's proposed construction*:

[2] Plaintiff argued that the Examiner's reliance on prior art that used amine-targeting polymers did not anticipate the '520 patent claims, stating that "any conjugation" with amines is random and cannot "ensure that attachment occurs at the B-domain." (D.I. 99 at 43; D.I. 63-1 at 960).

Claims 1 and 9, plain and ordinary meaning: "attached with a covalent chemical bond"

2. *Defendants' proposed construction*:

   Claim 1: "chemically bonded by reduction, followed by reductant removal, and treatment with polyalkylene oxide"

   Claim 9: "chemically bonded by reduction, followed by reductant removal, and treatment with polyethylene glycol"

3. *Court's construction*: plain and ordinary meaning

Defendants argue that I should construe "covalently attached" to include additional unclaimed process limitations, namely, "chemically bonded by reduction, followed by reductant removal, and treatment with polyethylene [oxide/glycol]." (D.I. 99 at 52).

"Absent disclaimer or lexicography, the plain meaning of the claim controls." *See Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1369 (Fed. Cir. 2012).

Defendants' proposal is not lexicography, nor do Defendants argue that their proposal is lexicography. Defendants note that the '520 patent discloses only one method for conjugating the claimed conjugates. (D.I. 99 at 56). However, I cannot limit the claims to a single preferred embodiment without more. *Phillips*, 415 F.3d at 1323 ("[W]e have expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment.").

Defendants' proposal does not reflect any disclaimer by Plaintiff. In response to an inherent anticipation rejection by the examiner, Plaintiff made several statements to the PTO to show uncertainty as to whether Bossard's manufacturing process would result in the claimed structure. Namely, Plaintiff stated, (1) "In contrast [to the claimed subject matter], Bossard does not disclose TCEP reduction and subsequent TCEP removal before polymer addition," (2) "Because Appellants' conditions differed from those taught in Bossard, Appellants' specification

does not show the inherent production of B-domain PEGylated full-length factor VIII following the Bossard teachings," and (3) "Appellants' disclosure that PEGylating full-length factor VIII with a malemide reagent requires strong conditions (reduction, denaturation, excess PEG) makes the differences in reaction conditions very important . . . ." (D.I. 63-1 at p. 958). Defendants primarily pin their disclaimer argument on Plaintiff's statement that the disclosed "process" is "very important." (D.I. 99 at 61).

However, Plaintiff's statement that the disclosed "process" is "very important" does not amount to a "clear and unmistakable disclaimer" of all other processes. The examiner questioned whether "the structure taught by the [Bossard] prior art is produced by identical or substantially identical processes." (D.I. 62-14 at p. 33). In response, Plaintiff expressed that Bossard's process would not yield the same product as the '520 patent, and thus does not inherently anticipate the '520 patent. (D.I. 63-1 at p. 957-58). Plaintiff's statement must be understood in this context. Plaintiff did not disavow all processes other than the disclosed process, but rather the process disclosed by Bossard. *See Vanguard Prod. 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.").

Accordingly, the plain meaning of the disputed limitation controls. I do not adopt Plaintiff's proposed plain meaning construction because it does not clarify or add meaning to the disputed limitation. Defendants may not argue that their proposed limitations are required.

D. "at the B-domain" (claims 1 and 9)

1. *Plaintiff's proposed construction*: "selectively at SEQ ID NO: 4 region designated by amino acids 741-1648"

2. *Plaintiff revised proposed construction* (D.I. 109 at p. 2): "attachment at the B-domain such that the resulting conjugate retains functional factor VIII activity"

3. *Defendants' proposed construction*: "at a site that is not any amine or carboxy site in factor VIII and is in the B-domain"

4. *Court's construction*: "attachment at the B-domain such that the resulting conjugate retains functional factor VIII activity"

The parties agree that twenty amino acids exist in the human body. (D.I. 109 at 3; D.I. 111 at 1-2). They further agree that all twenty, including cysteine and amino acids reactive with amine-targeting polymers, exist both inside and outside the B-domain of factor VIII. *Id.*

Defendants aver that "conjugation at a cysteine in full-length Factor VIII ensures PEGylation" "at the B-domain," whereas conjugation at an amine or carboxy site does not. (D.I. 111 at 1-2; D.I. 99 at 51).

Defendants argue that "according to the patent, PEGylation at cysteines can occur only inside the B-domain." (D.I. 111 at 1; '520 patent, 15:16-17) ("A non-mutated [B-domain deleted factor VIII] does not have any available cysteines to react with a PEG[] . . . ."). Defendants explain, "[N]one of the cysteines that exist outside the B-domain can be PEGylated because they form bonds with each other ('form disulfides') 'or are buried within [factor VIII].'" (D.I. 111 at 2 (citing '520 patent, 20:40-45, 15:18-33)).[3] On the other hand, "[i]nside the B-domain, there are four potential cysteines for PEGylation," say Defendants. (D.I. 111 at 2) (citing '520 patent, 15:18-33)).

Plaintiff says Defendants' argument "is based on unpegylated factor VIII starting material," which "ignores that the protein may alter conformation during [PEG]ylation to ultimately obtain an end product with PEG attached at locations that were initially inaccessible."

[3] "In contrast," argue Defendants, "PEGylation will occur both inside and outside the B-domain at sites that could be PEGylated with amine-targeting polymers (lysine, histidine, serine, threonine, and tyrosine)." (D.I. 111 at 1).

(D.I. 99 at 70) (citing '520 patent, 20:40-45). In effect, Plaintiff implies that under certain conditions that occur after the start of PEGylation, PEGylation may occur at cysteines located outside of the B-domain.

Both parties' constructions are silent as to whether conjugation at a cysteine ensures conjugation in the B-domain. I therefore need not determine at this time whether the patent provides such a teaching, and, if so, the effect of such a teaching.[4]

Regardless of whether the patent teaches that PEGylation must occur at cysteines, Plaintiff did not disclaim PEGylation at any amine or carboxy site in factor VIII during prosecution.[5] *See Purdue Pharma. L.P.*, 438 F.3d at 1136; *RFID Tracker, Ltd.*, 342 F. App'x at 630.

In response to an anticipation rejection over Bossard, Plaintiff stated, "[T]he Patent Office's prior arguments relied upon possible conjugation at amines or carboxy sites, which are present not only in the B-domain but in other domains. Any conjugation with these reactive groups is random and does not ensure that attachment occurs at the B-domain." (D.I. 63-1, p. 960).[6] Plaintiff made a similar statement in a different brief in response to the anticipation rejection over Bossard, stating, "[T]he alleged showing of B-domain attachment is random PEGylation and does not ensure that attachment occurs at the B-domain." (*Id.* at 902-03).

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[4] Defendants argue that Plaintiff "distinguish[ed] methods specific to only conjugation at cysteines by emphasizing the importance of the difference in reaction conditions." (D.I. 99 at 51) (emphasis omitted). This assertion does not impact disclaimer. However, I make note of it to demonstrate the relationship between Defendants' various disclaimer arguments. For "covalently attached," Defendants' disclaimer argument relies on these "reaction conditions." *See supra* Section III.C.

[5] Plaintiff notes, "The patent does not say that amino acids with amine and carboxy groups within the B-domain cannot be pegylated in accordance with the invention." (D.I. 99 at 70) (emphasis omitted). However, a patent's silence as to whether an amino acid with amine and carboxy groups within the B-domain can or cannot be PEGylated does not prevent Plaintiff from disclaiming such PEGylation.

[6] I note that Defendants assert, "Bayer's documents characterize conjugates having conjugation at amine and carboxy sites as having a 'heterogeneous product profile.'" (D.I. 99 at 68). This assertion does not impact disclaimer. However, I make note of it to demonstrate the relationship between Defendants' various disclaimer arguments. Defendants makes disclaimer arguments about heterogeneity for three other disputed terms.

Defendants argue that Plaintiff's statements constitute clear and unmistakable disclaimer of conjugation at amines and carboxy sites. I disagree. Plaintiff stated that conjugation at amines and carboxy sites cannot ensure PEGylation at the B-domain—not that conjugation cannot occur at amines and carboxy sites. (D.I. 99 at 70-71).

In the absence of disclaimer, I adopt Plaintiff's revised proposed construction, "attachment at the B-domain such that the resulting conjugate retains functional factor VIII activity." Defendants do not contest the substance of this construction. Rather, Defendants argue only that it should be narrowed due to disclaimer. (D.I. 111).

Plaintiff states, "The patent does not provide information regarding whether PEGylation could occur at the remaining 14 amino acids . . . ." (D.I. 111 at 2). Accordingly, my construction is silent as to these amino acids.

E. "monopegylated polypeptide conjugate" (claim 9)

1. *Plaintiff's proposed construction*:

   Plain and ordinary meaning, "a polypeptide with one polyethylene glycol polymer (PEG) attached"

2. *Defendants' proposed construction:* "a polypeptide conjugate that is not heterogeneous and having only one PEG attached at only one site"

3. *Court's construction*:

   Plain and ordinary meaning, "a polypeptide with one polyethylene glycol polymer (PEG) attached"

The parties agree that "monopegylated polypeptide conjugate" refers to the attachment of one PEG. However, they disagree as to whether it should be further construed as (1) having the one PEG be "attached at only one site," and (2) being "not heterogeneous." (D.I. 99 at 72).

As to the first point of disagreement, Plaintiff argued during prosecution that "monopegylation means that only one site on the polypeptide is the site for polymer

conjugation." (D.I. 63-1 at p. 911). Defendants thus argue that Plaintiff "expressly defined the term monoPEGylated as having only one polyethylene glycol attached per Factor VIII molecule at only one location." (D.I. 99 at 74). Defendants say, "Attaching PEG at the same location on every Factor VIII molecule reduces heterogeneity, and creates a 'defined' product." (*Id.* at 78). However, Plaintiff says "this [statement] refers to the fact that because there is only one PEG attached to the factor VIII (i.e., it is 'monopegylated'), it is expected to have only one point of attachment at the B-domain; not that it must be at the same position within the B-domain in every conjugate." (*Id.* at 77).[7] Plaintiff's argument during prosecution could reasonably lead to either party's interpretation. Therefore, it is less than clear, and is not a disclaimer. I agree that with Plaintiff that its argument does not mean that monopegylation necessitates attachment at the same site in every conjugate.

Defendants also argue that Plaintiff "distinguished the prior art PEGylation methods for failing to yield non-heterogeneous monoPEGylated conjugates during prosecution of the parent patent to the '520 patent," U.S. Patent No. 7,632,921. (*Id.* at 74). Plaintiff argued, "even if mono-PEGylation occurs using the [prior art] Rostin technique, the mono-PEGylation is likely to occur on multiple different lysine sites and thus would be a heterogeneous monoPEGylated product that would result in yield loss when purified . . . ." (D.I. 66-1 at p. 724). As a result, Defendants argue that Plaintiff disclaimed products where PEG is not attached "at only one site." (D.I. 99 at 75). However, the parent patent claims cover "muteins" having "genetically engineering attachment sites at specific amino acid positions." (*Id.* at 77-78). The parties agree that "muteins" are outside the scope of the '520 patent. (*Id.*). Accordingly, I find Defendants'

[7] Plaintiff also argues that "[a]s a matter of science, it is not possible to achieve 100% [PEG]ylation at the same exact amino acid position in any protein product." (D.I. 99 at 77). However, in light of the intrinsic record, I need not evaluate this argument.

disclaimer argument to be, at best, unpersuasive. Plaintiff did not clearly disclaim attachment "at only one site." I will not include "attached at only one site" in my construction.

As to the second point of disagreement, Defendants argue that Plaintiff disclaimed heterogeneous conjugates. (D.I. 99 at 75). The parties agree that the issues here are the same as the issues for Term 1 ("an isolated polypeptide conjugate"). (*Id.* at 76-77). In the briefing on that term, Plaintiff argues it did not overcome Bossard by eliminating heterogeneity altogether. (*Id.* at 26). Rather, Plaintiff says, it overcame Bossard, which "disclosed random [PEG]ylation without regard to location," based on PEGylation being "at the B-domain." (*Id.*). As I found previously, I agree with Plaintiff as to how it distinguished Bossard. Thus, while the distinguishing of Bossard results in disclaimer, it is disclaimer relating to the construction of "at the B-domain" (see Term 4) and not disclaimer relating to heterogeneity.

I adopt Plaintiff's proposed plain meaning construction.

IV. CONCLUSION

Within five days the parties shall submit a proposed order consistent with this Memorandum Opinion.