IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAXALTA INC., BAXALTA US INC., and NEKTAR THERAPEUTICS, Plaintiffs, v. BAYER HEALTHCARE LLC, Defendant.	Civil Action No. 1:17-cv-01316-RGA

MEMORANDUM OPINION

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ANDREWS, U.S. DISTRICT JUDGE:

Presently before me is the issue of claim construction of multiple terms in the Bossard family of patents, U.S. Patent Nos. 7,199,223 ("'223 Patent"); 7,863,421 ("'421 Patent"); 8,247,536 ("'536 Patent"); 8,519,102 ("'102 Patent"); 8,618,259 ("'259 Patent"); 8,889,831 ("'831 Patent"); and 9,999,657 ("'657 Patent").[1] (D.I. 136). The Bossard patents share a common specification. (*Id.*).

I have considered the Parties' Joint Claim Construction Brief. (*Id.*). I heard oral argument on June 21, 2019.

I. BACKGROUND

The patents-in-suit relate generally to "conjugates comprising a Factor VIII moiety (i.e., a moiety having Factor VIII activity) and a polymer." ('223 Patent at 1:12-34).

The Parties dispute a term in claim 1 of the '223 Patent:

> 1. A conjugate comprising one, two or three water-soluble polymers covalently attached to a *Factor VIII moiety*, wherein each water-soluble polymer has a nominal average molecular weight in the range of from 6,000 Daltons to 150,000 Daltons and further wherein the conjugate is a 1-mer, 2-mer or 3-mer.

('223 Patent, claim 1 (disputed term italicized)).

The Parties dispute terms that appear in claims 1, 12, 17, and 18 of the '421 Patent. Claim 12 of the '421 Patent is representative:

> 12. A conjugate comprising a water-soluble polymer covalently attached to a *Factor VIII polypeptide* via a thioether linkage, wherein the Factor VIII polypeptide is selected from the group consisting of Factor VIII, Factor VIIIa, Factor VIII:C, Factor VIII:vWF and *B-domain deleted Factor VIII, wherein the Factor VIII polypeptide has been modified to add a cysteine residue* to which the

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[1] Plaintiffs originally sued on one additional patent, U.S. Patent No. 8,143,378 ("'378 Patent"). Plaintiffs advised at the Markman hearing that the '378 Patent is no longer at issue.

water-soluble polymer is covalently attached, and wherein the water-soluble polymer is a poly(alkylene glycol).

('421 Patent, claim 12 (disputed terms italicized)).

The Parties dispute terms that appear in claim 1 of the '536 Patent:

1. A composition that is free from albumin comprising:

a conjugate that comprises one, two or three water-soluble polymers selected from the group consisting of a poly(alkylene glycol), a poly(oxyethylated polyol), a poly(olefinic alcohol), a poly(vinylpyrrolidone), a poly(hydroxyalkylmethacrylamide), a poly(hydroxyalkylmethacrylate), a poly(saccharide), a poly(α-hydroxy acid), a poly(vinyl alcohol), a polyphosphazene, a polyoxazoline, a poly(N-acryloylmorpholine), and combinations thereof, covalently attached to a *Factor VIII polypeptide* selected from the group consisting of Factor VIII, Factor VIIIa, Factor VIII:C, Factor VIII:vWF and *B-domain deleted Factor VIII.*

('536 Patent, claim 1 (disputed terms italicized)).

The Parties dispute terms that appear in claim 1 of the '102 Patent:

1. A conjugate comprising a water-soluble polymer covalently attached to a *Factor VIII polypeptide* via a thiol group of *a cysteine residue that has been added to or substituted in the Factor VIII polypeptide*,

wherein the conjugate comprises an in-vitro activity that is at least 15% of the in-vitro activity of the unconjugated Factor VIII polypeptide,

and wherein the water-soluble polymer is selected from the group consisting of poly(alkylene glycol), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharide), poly(α-hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazoline, poly(N-acryloylmorpholine), and combinations thereof.

('102 Patent, claim 1 (disputed terms italicized)).

The Parties dispute terms that appear in claim 1 of the '259 Patent:

1. A composition that is at least 85% free from albumin, the composition comprising a conjugate comprising a water-soluble polymer covalently attached to a *Factor VIII polypeptide* via a thiol group of *a cysteine residue that has been added to or substituted in the Factor VIII polypeptide*, wherein the water-soluble polymer is selected from the group consisting of poly(alkylene glycol), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone),

poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharide), poly(α-hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazoline, poly(N-acryloylmorpholine), and combinations thereof.

('259 Patent, claim 1 (disputed terms italicized)).

The Parties dispute terms that appear in claim 1 of the '831 Patent:

1. A unit dose of a pharmaceutical composition, the pharmaceutical composition comprising:

(i) a conjugate comprising one, two or three water-soluble polymers, each covalently attached to a *Factor VIII polypeptide* via a thiol group of *a cysteine residue that has been added to or substituted in the Factor VIII polypeptide*, and

(ii) a pharmaceutically acceptable excipient,

wherein the *Factor VIII polypeptide* is present in the unit dose in an amount ranging from 0.001 mg to 100 mg, and further wherein the one, two or three water soluble polymers are selected from the group consisting of poly(alkylene glycol), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharide), poly(a-hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazoline, poly(N-acryloylmorpholine), and combinations of any of the foregoing.

('831 Patent, claim 1 (disputed terms italicized)).

And, the Parties dispute a term which appears in claim 1 of the '657 Patent:

1. A monoPEGylated Factor VIII conjugate comprising a single poly(ethylene glycol) polymer covalently attached to a cysteine residue of a B-domain deleted *Factor VIII polypeptide*, wherein the single poly(ethylene glycol) polymer is branched and has a nominal average molecular weight in a range of about 20,000 daltons to about 85,000 daltons.

('657 Patent, claim 1 (disputed term italicized)).

The Parties agree on a construction for one additional term. (D.I. 136 at 13).

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) (citation 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, 979-80 (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.

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [This 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. "[T]he ordinary meaning of a claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321. "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 on 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 on 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. CONSTRUCTION OF DISPUTED TERMS

1. Factor VIII-Related Claim Terms

The Parties agree that the Factor VIII terms require Factor VIII activity and that the terms cover a native sequence[2] moiety or polypeptide. (D.I. 136 at 21). The Parties dispute, however, whether "Factor VIII polypeptide" and "Factor VIII moiety" should have the same construction. (*Id.* at 14-48). As the terms appear in different patents, with different prosecution histories, I will construe them separately. The Parties also dispute whether those terms cover "muteins"[3] or are limited to native sequence Factor VIII. (*Id.*).

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[2] "Native sequence" refers to the amino acid sequence in naturally occurring Factor VIII proteins. (*See* '223 Patent at 9:38-49).

[3] "Mutein" refers to a protein that is the product of genetic modification. Muteins have an amino acid sequence that is different than their naturally occurring counterparts. The Parties agree there is no single term of art that describes this concept. (D.I. 136 at 22).

a. "Factor VIII moiety"

- *Plaintiffs' Proposed Construction:*
  "a moiety having Factor VIII activity"
- *Defendant's Proposed Construction:*
  "a factor VIII corresponding to a native sequence and having factor VIII activity"
- *Court's Construction:*
  "a moiety having Factor VIII activity"

The specification defines "Factor VIII moiety" as "a moiety having Factor VIII activity." ('223 Patent at 9:4-5). "Where . . . the patentee has clearly defined a claim term, that definition usually is dispositive; it is the single best guide to the meaning of a disputed term." *Jack Guttman, Inc. v. Kopykake Enters., Inc.*, 302 F.3d 1352, 1360 (Fed. Cir. 2002) (cleaned up). Defendant does not directly address the lexicographical definition and, in fact, adopts "having Factor VIII activity" as part of its proposed construction. (D.I. 136 at 21). The lexicographical definition is, on its face, unambiguous. It makes clear that a POSA should determine whether a protein is a Factor VIII moiety by determining whether the protein has Factor VIII activity. The method for undertaking that inquiry is outlined in the specification and is indifferent to the underlying amino acid sequence. ('223 Patent at 9:60-10:15). Thus, the only dispute is whether the applicant disclaimed claim scope during prosecution of the '223 Patent.

The '223 Patent's prosecution history does not establish disclaimer such that the lexicographic definition of "Factor VIII moiety" no longer controls. "[A] patentee may limit the meaning of a claim term by making a clear and unmistakable disavowal of scope during prosecution." *Purdue Pharma L.P. v. Endo Pharm. Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006) (citation omitted). Defendant argues that, because the applicant removed "variants" from the claims in response to a written description rejection, the applicant disclaimed muteins. (D.I. 136 at 25-27).

The basis for the written description rejection, and subsequent amendments, is ambiguous. Claim 14 of the '223 Patent's original application claimed:

> The composition of claim 3, wherein the Factor VIII moiety is selected from the group consisting of Factor VIII, Factor VIIIa, Factor VIII:C, Factor VIII:vWF, B-domain deleted Factor VIII, and biologically active fragments, deletion variants, substitution variants or addition variants of any of the foregoing.

('223 Patent File History: Application (Feb. 26, 2004) at 72 (D.I. 83-2 at BAXJIVI0000076)). The examiner rejected that claim for lack of written description:

> The claim is drawn to biologically active fragments of Factor VIII. The claim does not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claim is drawn to a genus of polypeptides that is defined by an unclear functional relationship to Factor VIII. . . . In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be characteristics of the claimed genus are not described. [sic] The only adequately described species is Factor VIII and no active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

('223 Patent File History: Office Action (Dec. 23, 2004) at 3-5 (D.I. 83-5 at BAXJIVI0000670-72)). The applicant responded to that rejection by removing the phrase "biologically active fragments." ('223 Patent File History: Response to Office Action (March 23, 2005) at 12 (D.I. 83-5 at BAXJIVI0000709)). The examiner did not accept that revision as sufficient and issued a final rejection:

> Applicants' argument has not been found persuasive because the following phrases still remain in the claim: "deletion variants, substitution variants or addition variants of any of the for[e]going", as indicated previously in the Office action mailed December 23, 2004 the applicants have not provided a written description for the mentioned variants.

('223 Patent File History: Final Office Action (June 16, 2005) at 3-4 (D.I. 84-3 at BAXJIVI0001259-60)). The applicant ultimately removed "deletion variants, substitution variants or addition variants of any of the foregoing" from the claim without prejudice. ('223

Patent File History: Response to Final Office Action (August 16, 2005) at 11 (D.I. 84-3 at BAXJIVI0001279)).

This history is "amenable to multiple reasonable interpretations," and is, therefore, not sufficient to show disclaimer. *Avid Tech., Inc. v. Harmonic, Inc.*, 812 F.3d 1040, 1045 (Fed. Cir. 2016). It is not clear whether the examiner's rejection was based on a lack of specification support for the potential sequences of the claimed variants or based on a lack of clarity in the claim as to whether the variants must have a certain activity. It is possible that the examiner was concerned only with potential variants with non-Factor VIII activity. Moreover, the applicant's rationale for removing the "variants" language is not present in the prosecution history, rendering it difficult to find an intent to disclaim claim scope. Thus, I do not find that the applicant disavowed non-native sequence Factor VIII during prosecution.

Accordingly, I will construe "Factor VIII moiety" according to its lexicographical definition: "a moiety having Factor VIII activity."

b. "Factor VIII polypeptide"

- *Plaintiffs' Proposed Construction:*

  "a Factor VIII protein, such as that described in column 9 line 38 to column 11 line 27"

- *Defendant's Proposed Construction:*

  "a factor VIII corresponding to a native sequence and having factor VIII activity"

- *Court's Construction:*

  Plain and ordinary meaning: "protein having Factor VIII activity"

The specification does not provide a lexicographic definition for "Factor VIII polypeptide." Thus, the term must be construed using the usual tools of claim construction.

Defendant argues that, based on the teachings of the specification, a POSA would not understand "Factor VIII polypeptide" to cover "Factor VIII muteins." It relies heavily on its

expert for support of this position. (D.I. 136 at 22-25). Defendant's expert opines that the specification discloses only chemical methods of modifying the Factor VIII. (D.I. 146, Tab 2 at ¶ 74). He further concludes that a person of skill in the art would not have understood the words used in the specification ("modified" and "substituted") to encompass genetic modification. (*Id.*).

Defendant's proposed constructions amount to a request that I read a process limitation into the claims. "[A] 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 to the process by which it was made." *Vanguard Prod. Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000). "However, process steps can be treated as part of a product claim if the patentee has made clear that the process steps are an essential part of the claimed invention." *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1375 (Fed. Cir. 2007). It is undisputed that the specification anticipates post-translational modification of Factor VIII using organic chemistry techniques. (D.I. 136 at 23-24). That is, the patents anticipate pegylating chemically modified, non-native sequence Factor VIII. (*See* '421 Patent, claim 12 (claiming a pegylated Factor VIII with a non-native sequence cysteine residue)). Thus, non-native sequence proteins are clearly within the scope of the claims. And, as there is no evidence that the patentee represented the process described in the patent as essential to making the final product, the process is not a limitation.

Although I agree with Plaintiffs that the claim is not limited to native sequence proteins, I do not find their proposed 124-line construction helpful. The portion of the specification identified by Plaintiffs is consistent with understanding "Factor VIII polypeptide" in terms of its

activity. ('223 Patent at 9:38-11:27). Accordingly, I will construe "Factor VIII polypeptide" as having its plain and ordinary meaning, which is a protein having Factor VIII activity.

2. "B-domain deleted Factor VIII"

a. *Plaintiffs' proposed construction*:

"part or all of the B-domain is deleted"

b. *Defendant's proposed construction*:

"factor VIII protein having SEQ ID NO: 1 with a deletion corresponding to at least 581 amino acids within the region between Arg^{759} and Ser^{1709} and has factor VIII activity"

c. *Court's construction*:

Plain and ordinary meaning: "part or all of the B-domain is deleted"

The Parties do not dispute that "B-domain deleted Factor VIII" was a known term of art and understood by a POSA at the time of filing. (D.I. 136 at 54-55). The Parties disagree, however, whether the specification defines, or merely provides an example of, a B-domain deleted Factor VIII. (*Id.* at 49-59). Defendant's argument is based on a single paragraph of the specification:

> **Nonlimiting examples of Factor VIII moieties include** the following: Factor VIII; Factor VIIIa; Factor VIII:C; Factor VIII:vWF; **B-domain deleted Factor VIII (and other truncated versions of Factor VIII)**; hybrid proteins, such as those described in U.S. Pat. No. 6,158,888; glycosylated proteins having Factor VIII activity, such as those described in U.S. Patent Application Publication No. US2003/0077752; and peptide mimetics having Factor VIII activity. **Preferred truncated Factor VIII versions (encompassed by the term "B-domain deleted Factor VIII) corresponds to a protein having the amino acid sequence of human Factor VIII (SEQ. ID. NO. 1) having a deletion corresponding to at least 581 amino acids within the region between Arg^{759} and Ser^{1709}**, more preferably wherein the deletion corresponds to one of the region between Pro^{1000} and Asp^{1582}, the region between Thr^{778} and Pro^{1659}, and the region between Thr^{778} and Glu^{1694}.

('223 Patent at 10:16-31 (emphasis added)). Defendant argues that the "encompassed" parenthetical indicates an intent to define "B-domain deleted factor VIII." (D.I. 136 at 58-59). I do not find Defendant's argument persuasive. The quoted paragraph, which begins with

"nonlimiting" and follows that up closely with "preferred," is not lexicography. A clearly exemplary paragraph, with a significant amount of hedging, cannot support a finding of intent to redefine a well-known term. Accordingly, I will construe "B-domain deleted Factor VIII" as having its plain and ordinary meaning, which is part or all of the B-domain is deleted.

3. The Cysteine-Residue Related Claim Terms

a. "wherein the Factor VIII polypeptide has been modified to add a cysteine residue"

- *Plaintiffs' Proposed Construction:*

  Plain and Ordinary Meaning: "wherein the Factor VIII polypeptide has been modified to add a cysteine residue by exemplary methods known in the art"

- *Defendant's Proposed Construction:*

  "addition of a cysteine after the factor VIII polypeptide is expressed"

- *Court's Construction:*

  Plain and ordinary meaning: "wherein the Factor VIII polypeptide has a non-native sequence cysteine residue"

b. "a cysteine residue that has been added to or substituted in the Factor VIII polypeptide"

- *Plaintiffs' Proposed Construction*:

  Plain and ordinary meaning: "a cysteine residue that has been added or substituted in the Factor VIII polypeptide by exemplary methods known in the art"

- *Defendant's Proposed Construction:*

  "addition or substitution of a cysteine after the factor VIII polypeptide is expressed"

- *Court's Construction:*

  Plain and ordinary meaning: "a non-native sequence cysteine residue in the Factor VIII polypeptide"

The Parties agree that these terms cover post-translational modification by organic chemistry techniques. The Parties dispute, however, whether the cysteine-residue claim terms require addition of the cysteine only after the Factor VIII protein has been expressed. (D.I. 136 at 59-67). The construction of this term is closely tied to the construction of the Factor VIII terms. As I discuss above, (1) the applicant did not disclaim muteins and (2) it is not appropriate to import a process limitation into these claims. Thus, I will construe these terms to reflect the importance of the final product, and the irrelevance of the process used to arrive at the product.[4] Accordingly, I will construe "wherein the Factor VIII polypeptide has been modified to add a cysteine residue" as having its plain and ordinary meaning, "wherein the Factor VIII polypeptide has a non-native sequence cysteine residue," and "a cysteine residue that has been added to or substituted in the Factor VIII polypeptide" as having its plain and ordinary meaning, "a non-native sequence cysteine residue in the Factor VIII polypeptide."

4. "wherein the conjugate comprises an in-vitro activity that is at least 15% of the in-vitro activity of the unconjugated Factor VIII polypeptide"

a. *Plaintiffs' Proposed Construction:*

"wherein the conjugate retains an in-vitro activity that is at least 15% relative to that of the unmodified parent Factor VIII polypeptide"

b. *Defendant's Proposed Construction:*

"wherein the conjugate retains an in-vitro activity that is at least 15% relative to that of the unpegylated form of the same polypeptide"

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[4] I note that much of Defendant's briefing on these terms, and the Factor VIII terms, reads like an enablement argument: "Muteins are excluded from the scope of these claims not because of when or how they are made, but because they cannot be made as a matter of science using the disclosure in the Bossard Patents." (D.I. 136 at 66).

c. *Court's Construction:*

"wherein the conjugate retains an in-vitro activity that is at least 15% relative to that of the unpegylated form of the same polypeptide"

The Parties agree that the claims require at least 15% of the in-vitro activity of something. They disagree, however, as to what that something is. (D.I. 136 at 67-80). That is, they disagree on the appropriate point of comparison.

The plain and ordinary meaning of the claims support Defendant's position that the in-vitro activity must be relative to the activity of the unpegylated form of the same polypeptide. The relevant portion of the claim recites:

> A conjugate comprising a water-soluble polymer covalently attached to a Factor VIII polypeptide via a thiol group of a cysteine residue that has been added to or substituted in the Factor VIII polypeptide,
>
> > wherein the conjugate comprises an in-vitro activity that is at least 15% of the in-vitro activity of the unconjugated Factor VIII polypeptide . . .

('102 Patent, claim 1). The first clause describes "*a* Factor VIII polypeptide." The second clause references back to that same polypeptide by claiming "at least 15% of the in-vitro activity of *the* unconjugated Factor VIII polypeptide." The use of the word "the" indicates that the applicant intended the reader to understand she was referring to the unconjugated Factor VIII polypeptide mentioned earlier in the claim.

As the interpretation of this term primarily turns on grammar, the specification, prosecution history, and extrinsic record do not shed additional light on its meaning. Thus, I will construe "wherein the conjugate comprises an in-vitro activity that is at least 15% of the in-vitro activity of the unconjugated Factor VIII polypeptide" as "wherein the conjugate retains an in-vitro activity that is at least 15% relative to that of the unpegylated form of the same polypeptide."

IV. CONCLUSION

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