IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAXALTA INCORPORATED and BAXALTA GMBH,

Plaintiffs,

v.

GENENTECH, INC. and CHUGAI PHARMACEUTICAL CO., LTD.,

Defendants.

Civil Action No. 17-509-TBD

OPINION & ORDER

On May 4, 2017, Baxalta Inc. and Baxalta GmbH (together, "Baxalta") filed suit against Genentech, Inc. and Chugai Pharmaceutical Co., Ltd. alleging infringement of claims 1, 4, 17, and 19 of U.S. Patent No. 7,033,590 patent ("the '590 patent").[1] Chugai was voluntarily dismissed from this lawsuit pursuant to a stipulation of the parties on September 19, 2018. Order Dismissing Chugai, ECF No. 293.

The alleged infringement is the manufacture, use, sale, offer to sell, and importation of an antibody used to treat hemophilia A and known as emicizumab, or ACE910, and marketed under the brand name Hemlibra (hereinafter, "Hemlibra"). Now before this court is the claim construction of six terms of the '590 patent: *antibody*, *antibody fragment*, *bispecific antibody*, *isolated*, *binds Factor IX or Factor IXa and increases*, and *increases the procoagulant activity of Factor IXa*.

[1] Baxalta also initially asserted infringement of claim 15 of the '590 patent, but dropped this claim during the Markman hearing. *See* First Am. Compl. 9, ECF No. 239; Markman Tr. 235:11–13, ECF No. 320.

This court held a Markman hearing on October 16, 2018, and received expert testimony and argument regarding the construction of the six terms. At an earlier preliminary injunction hearing on June 13 and 14, 2018, the court also received testimony and argument on construction of the terms *antibody* and *antibody fragment*.

In terms of the factual record, the court will consider oral testimony given by experts at the Markman hearing, testimony offered at the preliminary injunction hearing, and the deposition testimony and reports and declarations of any of those experts, but the court declines to consider the declarations of experts who have not been subject to cross-examination at either hearing.[2] Whether or not such declarations are considered makes no difference to the constructions adopted by the court here.

BACKGROUND

I. PROCEDURAL HISTORY

On May 4, 2017, Baxalta filed its complaint alleging infringement of the '590 patent. Compl. ¶¶ 37–51, ECF No. 1. On June 30, Genentech answered, denying Baxalta's allegations and counterclaiming for declaratory judgment of noninfringement and invalidity. Answer & Countercl. ¶¶ 37–51, 120–49, ECF No. 9.

On December 14, 2017, Baxalta moved for a preliminary injunction. Mot. Prelim. Inj. 2, ECF No. 41; Prop. Prelim. Inj. Order 1, ECF No. 42-1. After an evidentiary hearing on August

[2] Baxalta initially presented Dr. Anthony A. Kossiakoff's declaration in support of its claim construction positions. *See* Kossiakoff Reb. Decl., ECF No. 126. I postponed the date of this Markman hearing three times and made clear to the parties that the hearing was their opportunity to present expert witness testimony in support of their claim construction positions. *See* May 14, 2018 Minute Entry; Sept. 12, 2018 Oral Order; Sept. 25, 2018 Oral Order. Nonetheless, Baxalta failed to offer testimony from Dr. Kossiakoff at the Markman hearing, and Genentech accordingly objected to reliance on Dr. Kossiakoff's declaration. Markman Tr. 46:1–22, 53:12–54:11. I sustained this objection and do not consider Dr. Kossiakoff's declaration for the purposes of claim construction. Markman Tr. 54:12–55:3. As noted, the Kossiakoff Declaration, even if considered, would make no difference in the outcome.

7, 2018, this court denied Baxalta's preliminary injunction motion. Prelim. Inj. Order at 29, ECF No. 262. In that connection, the court declined to construe *antibody* and *antibody fragment*, concluding that the parties had presented "substantial arguments" on both sides. *Id.* at 13. Baxalta did not appeal the denial of the preliminary injunction. Discovery has been ongoing. Fact discovery is set to close on December 14, 2018, and expert discovery is set to close on April 19, 2019. Stip. & Order Amend. Sched. 1, ECF No. 325.

At the Markman hearing, the parties presented expert testimony and argued construction of six terms: *antibody*, *antibody fragment*, *bispecific antibody*, *isolated*, *binds Factor IX or Factor IXa and increases*, and *increases the procoagulant activity of Factor IXa*. All these terms appear in claims 1 and 4 of the '590 patent, which recite

> 1. An isolated antibody or antibody fragment thereof that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa.
>
> * * *
>
> 4. The antibody or antibody fragment according to claim 1, wherein said antibody or antibody fragment is selected from the group consisting of a monoclonal antibody, a chimeric antibody, a humanized antibody, a single chain antibody, a bispecific antibody, a diabody, and di-, oligo- or multimers thereof.

'590 patent, col. 101, ll. 43–45, 51–56 (underlining added).[3]

[3] Claims 17 and 19 of the '590 patent, also at issue here, are as follows:

> 17. A method of obtaining an antibody that interacts with Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa, comprising the steps of:
> Immunizing an immunocompetent mouse with an antigen selected from the group consisting of FIX, FIXaα, FIXaβ or fragments thereof,
> isolating spleen cells of the immunized mouse,
> producing hybridoma cells,
> screening the hybridoma cell supernatants for an increase in the procoagulant activity of Factor IXa, isolating and purifying the antibody from a supernatant from the hybridoma cells which exhibit an increase in the procoagulant activity of Factor IXa.

II. COAGULATION & HEMOPHILIA A

In general, the term *antibody* is used to describe glycoproteins that are "characterized by their ability to bind both to antigens and to specialized cells or proteins of the immune system." Strohl Decl. ¶ 22, ECF No. 112; *accord* Almagro Decl. ¶ 33, ECF No. 49. Structurally, antibodies are *Y*-shaped, with two arms that are connected by disulfide bonds. Almagro Decl. ¶ 34; Strohl Decl. ¶ 22. Each arm of the *Y* contains two polypeptide chains known as the heavy ("H") chain and the light ("L") chain.[4] Almagro Decl. ¶ 34; Strohl Decl. ¶ 22. The portions of the heavy chain and light chain that are responsible for binding an antigen are called variable domains, V_H and V_L respectively. Almagro Decl. ¶ 34; Strohl Decl. ¶ 23. The remaining portions of the antibody are made up of constant regions. Almagro Decl. ¶ 34; Strohl Decl. ¶ 23.

Within each variable domain, the antigen binding sequence of the antibody is divided into three regions called complementarity-determining regions ("CDRs"). Almagro Decl. ¶ 35; Strohl Decl. ¶ 25. The three CDRs in each variable region—designated CDR1, CDR2, and CDR3—determine the binding specificity of the antibody. Almagro Decl. ¶ 35; Strohl Decl. ¶ 25. The CDR3 region of the heavy chain variable domain is "primarily responsible for antigen binding specificity." Strohl Decl. ¶ 25; *accord* Almagro Decl. ¶ 38.

While the parties agree as to these characteristics of an antibody, they disagree in at least one critical respect. Genentech contends that, as used in the patent, the term *antibody* standing

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* * *

19. The antibody or antibody fragment according to claim **4**, wherein the antibody is a humanized antibody.

'590 patent, col. 103, l. 3–col. 104, l. 6.

[4] Though the basic unit of an antibody is a Y-shaped structure with two L chains and two H chains, certain types of antibodies are more complex and can have up to ten light and ten heavy chains. Markman Tr. 67:4–21.

alone has two heavy chains that are identical and the two light chains that are identical. Genentech Op. Br. 6–8, ECF No. 160; Strohl Decl. ¶ 50. Baxalta, in contrast, argues that the heavy chains are not necessarily identical to one another and the light chains are also not necessarily identical to one another. Baxalta Op. Br. 4–5, ECF No. 158. The resolution of this difference appears to be determinative of infringement.

Hemophilia A and the process of blood coagulation are described at length in the preliminary injunction order. *See* Prelim. Inj. Order 3–4. Relevant here is one particular step of the clotting cascade involving Factor VIIIa and Factor IXa. *See* Aledort Decl. ¶ 13, ECF No. 46. In healthy individuals, Factor VIIIa and Factor IXa form a complex, which allows Factor IXa to activate Factor X. *See id.*; Sheehan Decl. ¶ 36, ECF No. 111. In patients afflicted with hemophilia A, Factor VIII is reduced, defective, or absent. *See* Aledort Decl. ¶ 14; Sheehan Decl. ¶ 42. This hinders the coagulation cascade by limiting the body's ability to activate Factor X. Aledort Decl. ¶ 14; Sheehan Decl. ¶ 42.

Genentech's drug, Hemlibra, is directed to this step of the coagulation cascade and functions by replacing Factor VIIIa. *See* Krishnaswamy Decl. ¶ 61, ECF No. 47. Hemlibra does not have both identical light and identical heavy chains. *See* Strohl Decl. ¶¶ 38, 53; *see also* Krishnaswamy Decl. ¶¶ 55, 60. It is a bispecific antibody. The parties agree that in this patent a *bispecific antibody* has non-identical light chains, or non-identical heavy chains, or both.[5] Markman Tr. 38:5–21, ECF No. 320. One arm of the Hemlibra antibody binds to Factor IX (or IXa) and the other binds to Factor X. *See* Krishnaswamy Decl. ¶¶ 55, 60; Strohl Decl. ¶ 53. By

[5] During the Markman hearing, Dr. Almagro testified that "there were some examples [of bispecific antibodies] before 1999 with identical light chains and identical heavy chains." Markman Tr. 109:16–18, ECF No. 320. Nonetheless, the parties have agreed that the bispecific antibodies in the '590 patent are outside the scope of the column 5 definition of *antibody*. *Id.* 108:11–15, 109:19–110:8 (Almagro testimony).

doing so, Hemlibra allows Factor IX to activate Factor X. *See* Krishnaswamy Decl. ¶ 61, Strohl Decl. ¶¶ 178–79.

ANALYSIS

1. *antibody*

Baxalta's proposed construction: A molecule having a specific amino acid sequence comprising two heavy chains (H chains) and two light chains (L chains).

Genentech's proposed construction: An immunoglobulin molecule, having a specific amino acid sequence that only binds to the antigen that induced its synthesis or very similar antigens, consisting of two identical heavy chains (H chains) and two identical light chains (L chains).

Court's construction: An immunoglobulin molecule, having a specific amino acid sequence that only binds to the antigen that induced its synthesis or very similar antigens, consisting of two identical heavy chains (H chains) and two identical light chains (L chains).

Construing the claims requires resolution of the parties' primary dispute that an *antibody* in the claims is required to have two identical heavy chains and two identical light chains.[6] The parties agree that the requirement that an antibody have two identical heavy chains and two identical light chains would exclude Hemlibra from the scope of the term *antibody*. Prelim. Inj. Tr. 9:15–24, ECF No. 214–15; Markman Tr. 109:23–110:8. Hemlibra is not an *antibody* under Genentech's definition.

a. The Meaning of the Term Antibody *in the Patent as Originally Drafted*

It is clear from the '590 patent's specification that, as originally drafted, the term *antibody* in the claims required identical heavy and identical light chains.

Based on the evidence, I find that the term *antibodies* does not have a single fixed meaning in the art. The word *antibody* can denote different meanings to a person skilled in the

[6] A secondary dispute is whether an antibody must bind only to an antigen that induced its synthesis or very similar antigens. While the broader definition of *antibody* would not imply such a requirement, I find that, since the column 5 definition includes this limitation, it is part of the definition of the term *antibody* in the claims. *See* '590 patent, col. 5, ll. 56–60. It is not clear that this makes any difference with respect to infringement or invalidity.

art depending on the context in which it appears. For example, *antibody* standing alone may connote a different meaning than when it is part of a larger term that defines its structure—e.g., bispecific *antibody*.

The parties agree that the term *antibody* standing alone without other structural terms can have different meanings to those skilled in the art. *See* Markman Tr. 174:21–175:24. One definition is Baxalta's definition (hereinafter the "broader" definition), requiring only a molecule with a specific amino acid sequence and comprising two heavy chains and two light chains. The other definition is Genentech's definition (hereinafter the "narrower" definition), requiring a pair of identical heavy chains and a pair of identical light chains. Baxalta argues that its broader definition should apply because it would have been utilized by persons of ordinary skill in the art. Baxalta Op. Br. 5. But in its opening preliminary injunction brief, Baxalta itself used the narrower definition, stating that "[a]n antibody comprises two identical heavy chains and two identical light chains." Baxalta Op. Prelim. Inj. Br. 13 n.7, ECF No. 42. Similarly, Dr. Almagro, Baxalta's expert, described an antibody in his declaration as "a glycoprotein that has a specific 'Y' shape" that "has two pairs of identical polypeptide chains, which are linked together by disulfide bonds." Almagro Decl. ¶ 34. Genentech's expert agreed that such a definition "represents the plain and ordinary meaning of 'antibody' and is consistent with standard textbook definitions of immunoglobulin molecules dating from prior to the 1999 priority date of the '590 [p]atent." Strohl Cl. Const. Decl. ¶¶ 41–42, ECF No. 161; *accord id.* ¶ 44.

Various references cited on the face of the '590 patent use a similar definition. The Roitt reference describes an antibody as "a unit consisting of two identical light polypeptide chains and two identical heavy polypeptide chains." Ivan Roitt et al., IMMUNOLOGY 72 (5th ed. 1998), Strohl Decl. Ex. F, ECF No. 112-6. And the Harlow and Lane reference says that "[e]ach Y

contains four polypeptides[:] [t]wo identical copies of a polypeptide known as the heavy chain and two identical copies of a polypeptide called the light chain." Ed Harlow & David Lane, ANTIBODIES: A LABORATORY MANUAL 7 (1988), Strohl Decl. Ex. E, ECF No. 112-5. Baxalta does not point to any references cited in the '590 patent that use a broader definition.

Nonetheless the parties agree that Baxalta's broader definition was also known to those skilled in the art. *See* Markman Tr. 172:6–176:6. During the Markman hearing, Dr. Strohl, Genentech's expert testified that the broader definition was a "common language definition." *Id.* at 175:12–13. Baxalta only points to Dr. Strohl's testimony as evidence of the understanding of someone skilled in the art.[7]

In the patent specification, the applicant chose the narrower definition. In relevant part, the summary of the invention provides that

> Antibodies are immunoglobulin molecules having a specific amino acid sequence which only bind to antigens that induce their synthesis (or its immunogen, respectively) or to antigens (or immunogens) which are very similar to the former. Each immunoglobulin molecule consists of two types of polypeptide chains. Each molecule consists of large, identical heavy chains (H chains) and two light, also identical chains (L chains).

'590 patent, col. 5, ll. 56–63. The Federal Circuit has recognized that use of the verb "is" may "signify that a patentee is serving as its own lexicographer." *Sinorgchem Co. v. Int'l Trade Comm'n*, 511 F.3d 1132, 1136 (Fed. Cir. 2007) (quoting *Abbott Labs. v. Andrx Pharms., Inc.*, 473 F.3d 1196, 1210 (Fed. Cir. 2007)). The use of the term "are" here is the equivalent of the

[7] Even the expert declaration from Dr. Kossiakoff that Baxalta initially offered in support of its construction, but which I have excluded from consideration, does not elaborate on why a person skilled in the art would have understood the term *antibody* to have the broader meaning offered by Baxalta. *See* Kossiakoff Reb. Decl. ¶¶ 21–52. Dr. Kossiakoff's only statement to this effect is that "a POSITA reviewing the intrinsic record would have understood that the term 'antibody' has a plain and ordinary meaning in the art and would not need to be construed," but that "to the extent a construction is required, it is my opinion that Baxalta's straightforward construction should be adopted." *Id.* ¶ 22.

term "is." Here, the specification unequivocally states what "[a]ntibodies are." '590 patent, col. 5, ll. 56–63. This definition is also clearly defining the term *antibodies* covered by the claims of this patent because the definition immediately follows and immediately precedes references to "the inventive antibodies and antibody derivatives." '590 patent, col. 5, l. 53; *id.* col. 6, l. 1. The fact that the applicants chose to include the narrower definition in the specification over a broader definition confirms that the applicants intended the narrow definition apply to the term *antibody* standing alone.

Baxalta argues that the specification in other places uses the broader definition. Baxalta Op. Br. 6–7. For example, the specification and claims disclose bispecific antibodies, which do not have identical heavy and light chains. *See id.*; '590 patent col. 6, ll. 1–5; *id.* col. 7, ll. 32–35; *id.* col. 101, ll. 51–56 (claim 4). Baxalta also points to the inclusion of IgM antibodies and IgA antibodies in claims 3 and 20 as well as throughout the specification. '590 patent, col. 6, ll. 35–38; *id.* col. 12, ll. 25–26; *id.* col. 14, l. 22–col. 15, l. 4 (Example 4); *id.* col. 30, l. 11–col. 31, l. 10 (Example 13); *id.* col. 101, ll. 49–50 (claim 3); *id.* col. 104, ll. 6–7 (claim 20). IgM and IgA antibodies can have more than two heavy chains and more than two light chains. Markman Tr. 71:11–13, 156:12–159:11. Baxalta thus contends that this limitation of the narrow definition of *antibody* is inappropriate in the context of the '590 patent. Baxalta Op. Br. 6–7. But all these embodiments were initially listed as falling within "antibodies or antibody derivatives." *See, e.g.*, '590 patent, col. 5, l. 51; U.S. Patent App. No. 09/661,992, at 10–11, Strohl Decl. Ex. D, ECF No. 112-4. Thus, as originally drafted, the claims covered antibodies as more broadly defined, but not because they fell within the term *antibody* but because they fell within the term *antibody derivative*.

Under such circumstances, the Federal Circuit has held that the specification's choice of definition governs. *See Sinorgchem*, 511 F.3d at 1136–40 ("Where, as here, multiple embodiments are disclosed, we have previously interpreted claims to exclude embodiments where those embodiments are inconsistent with unambiguous language in the patent's specification or prosecution history."); *Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1300 (Fed. Cir. 2004) (concluding that the scope of the claim terms was controlled by the specification even in the absence of express definitions where applicant admitted to the examiner that the terms had "no accepted meaning in the art" and were "adequately described in the specification"). Indeed, given the specification's clarity, the definition included in column 5 of the '590 patent would govern even if it were contrary to an ordinary meaning of the term. *See Thorner v. Sony Comp. Entmt. Am. LLC*, 669 F.3d 1362, 1365–66 (Fed. Cir. 2012) ("[T]he inventor's written description of the invention, for example, is relevant and controlling insofar as it provides *clear lexicography* . . . ." (alterations and emphasis in original) (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004))).

Before turning to the prosecution history, it is important to ascertain the meaning of the term *antibody derivative* in the patent as initially drafted. The parties agree that *antibody derivative* is not a term that is commonly used in the art. Markman Tr. 119:21–120:3. But Dr. Almagro, Baxalta's expert, admitted during the preliminary injunction hearing, and again during the Markman hearing, that antibodies that have been altered in some significant way are "sometimes . . . called derivatives." Prelim. Inj. Tr. 413:4–15; *accord* Markman Tr. 120:6–11 (Dr. Almagro agreeing with previous testimony that "significant variants" of antibodies are "sometimes . . . called derivatives"). Also in support of this understanding, Dr. Almagro, a person of skill in the art, repeatedly described Hemlibra, a bispecific antibody, as being

"derived" from other antibodies.[8] Almagro Decl. ¶ 54 n. 5, ¶ 87 n. 17; Markman Tr. 122:8–24; *see also id.* 120:6–21 (Dr. Almagro agreeing that "[t]alking in plain English" Hemlibra" is "derived from a Factor IX antibody and a Factor X antibody"). This definition of *antibody derivatives*—an antibody that has been altered in some significant way—is consistent with the specification. First, the specification makes clear that the group consisting of *antibodies* and *antibody derivatives* includes bispecific antibodies and other structures that do not have identical light and heavy chains. Since bispecific antibodies are not within the definition of *antibodies*, they must be within the definition of *antibody derivatives*.

This understanding is further supported by the uses of *antibody derivative* in those places in the patent specification where *antibody derivative* is used separately. *Antibody derivative* is used separately in three instances that inform the interpretation of the term[9]: (1) in Example 10, which is entitled "Structure and Procoagulant Activity of Antibody Derivatives Derived from Anti-FIX/FIXa-antibodies; Subcloning Antibody Variable Domains from Hybridoma Cell Lines," *id.* col. 19, ll. 3–7; (2) in the body of Example 11, where the patent includes in a list of examples of antibody derivatives "scFv, Fab, etc.," *id.* col. 20, l. 36; and (3) again in Example 13, where the patent refers to "antibody derivatives such as Fab, $F(ab)_2$, scFv, etc.," *id.* col. 30, ll. 16–17. *See also* Markman Tr. 13:19–15:6.

These uses make clear that Fab, $F(ab)_2$, and scFv are all antibody derivatives. As Dr. Almagro and Dr. Strohl agree, Fab and $F(ab)_2$ are the sort of canonical *antibody fragments* (a subset of derivatives) that a person of skill in the art would unquestionably have understood as

[8] In a similar vein, Dr. Strohl testified that "a chimeric antibody would be derived and be a derivative." Markman Tr. 172:8–9.

[9] The specification also provides that "antibody derivatives may . . . be prepared by means of methods known from the prior art, e.g. by molecular modeling." '590 patent, col. 9, ll. 5–7. This use of *antibody derivative*, however, does not assist in understanding the term.

such. Markman Tr. at 117:7–14 (Dr. Almagro), 155:19–23 (Dr. Strohl). Each of these can be derived from an existing *antibody* as defined in the specification. A Fab comprises "the complete light chain[] paired with the full variable and a portion of the constant domain[] of the heavy chain[]" and can be excised from an existing antibody. *See* Strohl Claim Const. Decl. ¶ 31 & Fig. 2, ECF No. 161; *accord* Markman Tr. 151:18–152:24 (Dr. Strohl). A $F(ab)_2$, comprises "two Fab fragments linked with disulfide bonds" and also "can be generated from an antibody by cleaving off the other portions" to leave the fragment remaining. Markman Tr. 152:25–153:11 (Dr. Strohl); *accord* Strohl Decl. ¶ 32 & Fig. 3. Based on inclusion of Fab and $F(ab)_2$ it is clear that *antibody fragments* are *antibody derivatives*.

But the specification makes clear that an scFv is not an *antibody fragment* using the definition of *antibody* from the specification. Rather, it is called a single-chain variable fragment and is synthetically created by linking with a stretch of synthetic peptide "a truncated fragment comprising only the [variable heavy] domain" of an antibody with a truncated fragment comprising only the variable light region of an antibody. Strohl Claim Const. Decl. ¶ 33 & Fig. 4; *accord* Almagro Decl. ¶ 35; Markman Tr. 60:2–6, 201:17–22. Because of the reference to scFv as an *antibody derivative*, the term *antibody derivative* was clearly meant to include *antibodies* that have been altered in some significant way.

Thus, I find that the term *antibody derivative* was used in the patent to denote *antibodies* within the column 5 definition that had been altered in some significant way. As initially drafted, there was no inconsistency between the dependent claims and the column 5 definition of *antibody*.

***b. The Prosecution History's Exclusion of* Antibody Derivatives *Confirms the Specification's Definition of* Antibody**

During prosecution the Examiner found various categories of derivatives other than antibody fragments not enabled. The applicants disclaimed *antibody derivatives* including bispecific antibodies, except *antibody fragments*.

Initially, the patent specification and the accompanying claims repeatedly referred to "antibodies and antibody derivatives"; the patent did not refer to "antibody fragments." *See* U.S. Patent App. No. 09/661,992, Strohl Decl. Ex. D, ECF No. 112-4. In an office action dated January 2, 2004, the Examiner rejected claims 1–14, 16, 18–19, 23, and 27 of the '590 patent for lack of enablement. Jan. 2, 2004 Rejection, Strohl Decl. Ex. K, at 4, ECF No. 112-11. The Examiner again rejected these claims for near-identical reasons on September 13, 2004. Sept. 13, 2004 Rejection, Strohl Decl. Ex. M, at 2–3, ECF No. 112-13. To respond to those rejections, the term *antibody derivatives* was deleted by an amendment to the claims, and the term *antibody fragment* was added. *Compare* U.S. Patent App. No. 09/661,992 *with* '590 patent.

It is useful to describe how these amendments came about. Considering the prosecution history as a whole, save for the failure to conform the language of certain dependent claims (discussed below), it is apparent that the applicants and the Examiner continued to view the term *antibody* as having its original meaning from the specification, but that antibody derivatives (except antibody fragments) were now excluded from the scope of the claims. As noted, during prosecution, the claims were initially rejected by the Examiner as not enabled. Jan. 2, 2004 Rejection, at 4. The Examiner found enabled certain *antibody derivatives* "wherein the variable region of said antibody derivative comprises" specific portions of certain amino acid sequences (SEQ ID NOs 82, 84, and 86) disclosed in the patent. *Id.* But the Examiner found not enabled *antibody derivatives* comprising different portions of the same amino acid sequences. *Id.*

Among the *antibody derivatives* the Examiner found not enabled were those comprising "chimeric antibodies, humanized antibodies, single chain antibodies, bispecific antibodies, diabodies and di-, oligo- or multimers thereof in claim 4." *Id.* Based on this lack of enablement, the claims were rejected.

Dr. Strohl explained during the Markman hearing that the portions of SEQ ID NOs 82, 84, and 86 found enabled by the Examiner comprised excised portions of already-existing antibodies as defined in the specification, that is, antibody fragments. *See* Markman Tr. 200:5–201:22; *id.* at 203:5–205:16. The portions found not enabled were engineered artificial linker sequences—i.e., human-engineered, synthetic peptides. *Id.* 203:5–205:16; *see also* Strohl Decl. ¶ 30 (discussing the composition of scFvs).

The applicants responded to the Examiner's rejection on July 2, 2004, and argued that the disclosed "antibodies and antibody derivatives" were all enabled because the specification "provides extensive discussion regarding methods of preparing claimed antibodies" and "provides the complete sequence scFvs, variable domains and CDRs, and provides guidance on what regions can be mutated." July 2, 2004 Amendment & Remarks, Strohl Decl. Ex. L, at 12, ECF No. 112-12.

On September 13, 2004, the Examiner again rejected the same claims for lack of enablement in an almost identical manner. Sept. 13, 2004 Rejection, at 2. The primary difference between the first and second rejection was that the Examiner now referred to the enabled portions of the scFvs embodied by SEQ ID NOs 82, 84, and 86 as "antibody fragments" rather than "antibody derivatives." *Id.* The Examiner maintained his rejection of *antibody derivatives* comprising "chimeric antibodies, humanized antibodies, single chain antibodies, bispecific antibodies, diabodies and di-, oligo- or multimers thereof in claim 4." *Id.*

On October 16, 2004, the Examiner conducted a telephonic interview with the applicant. Oct. 16, 2004 Interview Summary, Strohl Decl. Ex. N, ECF No. 112-14. During that interview the Examiner "suggested that the claims be amended to recite antibody fragment thereof to substitute antibody derivative." *Id.* at 1. Thereafter, the applicants amended their claims to implement the changes proposed in the interview by, among other things, revising the claims to recite *antibody fragments* instead of *antibody derivatives*. Dec. 13, 2004 Amendment, Strohl Decl. Ex. O, ECF No. 112-15.

Thus, *antibody derivatives* except for *antibody fragments* were disclaimed from the scope of the claims. As was made clear by the January 2 and September 13 rejections, the Examiner found enabled *antibody fragments*, that is, fragments of antibodies as defined in the specification. By way of example, in the case of the scFvs described by SEQ ID NOs 82, 84, and 86, the Examiner found enabled only the pieces of those scFvs that are naturally occurring—i.e., the V_H and V_L regions—and found not enabled the pieces of scFvs that contained an engineered peptide—i.e., the linker sequence. Moreover, the Examiner maintained his rejection of derivatives comprising, for example, chimeric antibodies, humanized antibodies, and bispecific antibodies. As is the case with an entire scFv, each of these structures, while possibly derived from an *antibody* as defined in column 5 of the specification, would have been understood, in view of the '590 patent, to involve some form of alteration to a naturally occurring antibody. *See* Markman 167:10–168:9 (Dr. Strohl); Prelim. Inj. Tr. 276:10–11 (Dr. Krishnaswamy testifying that "[a]nything you do to the antibody creates a derivative"). Thus, *antibody derivatives* as originally understood—i.e., everything derived from an antibody other than antibody fragments—were disclaimed from the claims, and the narrower *antibody fragments* were claimed

instead. On the face of the prosecution history, it therefore appears that the disclaimer of *antibody derivatives* included *bispecific antibodies*.

Not surprisingly, the parties agree that *antibody derivatives* were disclaimed from the scope of the '590 patent. Markman Tr. 10:4–21 (parties agreeing with the court that there is "agreement that there was a disclaimer in the prosecution as to derivatives, but there's no agreement as to what a derivative is"). But they disagree on what that term encompasses. *Id.* At the preliminary injunction stage, Baxalta was unable to provide any meaningful guidance as to what, in fact, was disclaimed. Prelim. Inj. Tr. 32:2–23, 33:23–35:15. During the preliminary injunction hearing, Baxalta stated only that while derivatives may very well have been disclaimed during prosecution, the specification and prosecution history "tell[] us very little of the meaning." *Id.* at 33:23–34:5.

At the Markman hearing, Baxalta finally addressed the issue directly, arguing that the disclaimer was very limited and that only two minor embodiments were surrendered, a suggestion not appearing in its earlier briefing. Baxalta's arguments related to two amendments made during prosecution.

The first amendment related to original claims 5 and 6, which read:

> 5. An antibody derivative according to claim 1, wherein said antibody derivative comprises a complement [sic] determining region (CDR) peptide.
>
> 6. An antibody derivative according to claim 5, wherein said CDR peptide is a CDR3 peptide.

U.S. Patent App. No. 09/661,992, at 62. The Examiner rejected these claims as not enabled because the "specification provides no direction or guidance regarding how to produce such antibodies." Jan. 2, 2004 Rejection, at 5. The Examiner explained that because "each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and

affinity which is characteristic of the parent immunoglobulin" "[i]t is unlikely that antibody derivatives as defined by the claims which may contain less than the full complement of CDRs . . . have the required binding function." *Id.* In response, and following an interview with the Examiner in which he requested that the applicants add two dependent claims regarding the CDR3 peptide, Oct. 16, 2004 Interview Summary, the applicants deleted original claims 5 and 6, and added current claims 21 and 22, which are as follows:

> 21. The antibody or antibody fragment of claim **1**, wherein the antibody fragment comprises a CDR3 peptide.
>
> 22. The antibody or antibody fragment of claim **1**, wherein the antibody fragment is a CDR3 peptide.

Dec. 13, 2004 Amendment, at 7 (numbered 30. and 31. in amendment); '590 patent, col. 104, ll. 9–12.

At the Markman hearing Baxalta was unable to explain why these amendments defined the scope of the disclaimer of *antibody derivatives*. Earlier the Examiner had expressed concern that the original claims' reference to CDR1 and CDR2 peptides was not enabled, and Baxalta opined that "the examiner wanted to be assured that that which is critical to antigen binding, the CDR3, was included in the claim," Markman Tr. at 36:5–11. But this sheds no light on the meaning of the term *antibody derivative* or the scope of the disclaimer. All three binding sites (CDR1, CDR2, and CDR3) exist in *antibodies* as defined in the specification and under the broader definition of *antibody*. Referring specifically to the CDR3 binding sites in two dependent claims is perfectly consistent with the narrower definition of *antibody*. In short, while Baxalta agrees that there was a disclaimer of *antibody derivatives* it is unable to show that the term was somehow limited by, or defined by, the addition of the reference to the CDR3 binding site in the dependent claim.

The second amendment on which Baxalta focused was that made to original claim 7, which provided

> 7. An antibody derivative according to claim 6, wherein said CDR3 peptide comprises an amino acid sequence selected from the group consisting of:
> Tyr-Gly-Asn-Ser-Pro-Lys-Gly-Phe-Ala-Tyr;
> Cys-X-X-Tyr-Gly-Asn-Ser-Pro-Lys-Gly-Phe-Ala-Tyr-X-X-Cys
> Wherein
> X may be any desired amino acid;
> Tyr-Gly-Asn-Ser-Pro-Lys-Gly-Phe-Ala-Tyr;
> Asp-Gly-Gly-His-Gly-Tyr-Gly-Ser-Ser-Phe-Asp-Tyr; and
> Phe-Arg-Asn-Arg-Gly-Met-Thr-Ala-Leu-Leu-Lys-Val-Ser-Ser-Cys-Asp.

Strohl Decl. Ex. D, at 2–3. The claim language on its face does not identify a specific amino acid, or set of amino acids, that can be substituted for the variable "X," and provides only that "X may be any desired amino acid." *Id.* The Examiner rejected this claim as not enabled because he reasoned that "it is unpredictable if any functional activity will be shared by two antibodies having less than 100% identity over their CDR3 region." Jan. 2, 2004 Rejection, at 5; *accord* Sept. 13, 2004 Rejection, at 3. Again following an interview with the Examiner in which "the antibody derivative and CDR3 peptide" were discussed, Oct. 16, 2004 Interview Summary, the applicants amended claim 7 (now claim 5) to address the Examiner's concern with variability in the CDR3. Claim 5 now provides

> 5. A CDR3 peptide of the antibody or antibody fragment according to claim 1 consisting of an amino acid sequence selected from the group consisting of:
> Tyr-Gly-Asn-Ser-Pro-Lys-Gly-Phe-Ala-Tyr (SEQ ID NO:5); and
> Asp-Gly-Gly-His-Gly-Tyr-Gly-Ser-Ser-Phe-Asp-Tyr (SEQ ID NO:6).

Dec. 13, 2004 Amendment, at 4–5; '590 patent, col. 101, ll. 57–63.

During the Markman hearing Baxalta argued that this amendment disclaimed "antibody derivatives comprising CDR3 peptides with variable or random amino acids as originally claimed in 7." Markman Tr. at 36:21–37:9. But again, as was the case with the other amendment, this amendment sheds no light on the meaning of the disclaimed *antibody*

derivatives. It is entirely possible that there are *antibodies* and *antibody fragments*, as those terms are defined by the court, that contain a CDR3 region comprising what was claimed in both original claim 7 and amended claim 7. The specification and amended claims are perfectly consistent with the specification's definition of *antibody*.

Given Baxalta's failure to offer a plausible alternative definition of the disclaimer, the court concludes that the obvious definition—a disclaimer of antibodies altered in some significant way—should govern.

c. The Language of the Dependent Claims as Issued Does Not Require That the Term* Antibodies *Standing Alone be Defined to Include Bispecific Antibodies

Baxalta's primary argument is that adopting the narrow construction of *antibodies* is impermissible because, after the reference to *antibody derivatives* was deleted during prosecution, certain dependent claims covered structures that would be excluded under the narrower construction of the term *antibody*. In other words, Baxalta argues that including such dependent claims after the amendment (which deleted *antibody derivatives* from the claims) effectively redefines the term *antibody*. The language of the allowed claims is set forth above. Baxalta points, for example, to dependent claim 4, which claims "[a]n antibody or antibody fragment according to claim 1, wherein said antibody or antibody fragment is selected from a group consisting of a monoclonal antibody, a chimeric antibody, a humanized antibody, a single chain antibody, a bispecific antibody, a diabody, and di-, oligo-, or multimers thereof." '590 patent, col. 101, ll. 51–56. Baxalta contends that under the narrower construction of *antibody*, the humanized antibodies, chimeric antibodies, and bispecific antibodies of claims 4 and 19 would be excluded from the scope of the claims, as would the IgM and IgA antibodies of claims 3 and 20, and the artificial linker sequences of claims 7, 9, and 11. Baxalta Op. Br. 4–5; Baxalta Supp. Ltr. 1–3, ECF No. 202; Markman Tr. at 40:8–45:2 (citing Strohl Dep. Tr., Dadush Decl.

Ex. 1, ECF. No. 234-2 at 99:23–100:13; Prelim. Inj. Tr. 61:4–7). Baxalta insists that "[i]t is axiomatic that a dependent claim cannot be broader than the claim from which it depends." *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012); *see also* Baxalta Op. Br. 4–5; Baxalta Supp. Ltr. 1–3. It reasons that the independent claims, such as claim 1, must encompass *bispecific antibodies* and that the term *antibody* must therefore include *bispecific antibodies*.

I do not find Baxalta's argument persuasive. To be sure, Baxalta is correct, and Genentech agrees, that at least dependent claims 4 and 19 are inconsistent with the narrower definition of the term *antibody*.[10] *See* Markman Tr. 143:2–19 (Genentech admission that claims 4 and 19[11] are inconsistent with the column 5 definition of *antibody*). The Federal Circuit has recognized that adopting a construction that excludes dependent claims from the patent scope is disfavored. *See AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1242 (Fed. Cir. 2003) ("Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend."). But the court has also made clear that this rule of construction does not govern where the independent claims on their face are of more limited scope. *See Enzo Biochem Inc. v. Applera Corp.*, 780 F.3d 1149, 1156–57 (Fed. Cir.

[10] Other dependent claims alleged by Baxalta to be inconsistent with the narrower definition of *antibody* may well be consistent with that definition. For example, even though IgM and IgA antibodies can have more than two identical light chains and two identical heavy chains, they can also be understood as being composed of several monomers that have the structure identified in column 5. *See* Markman Tr. 112:15–23 (Dr. Almagro agreeing that "an IgM is a pentamer of a module that has two identical heavy chains and two identical light chains" and "that module meets the definition in column 5"); *id.* 114:17–23 (Dr. Almagro admitting that "some IgMs circulate as monomers in serum"); *id.* 155:24–159:11 (Dr. Strohl confirming that IgM and IgA antibodies sometimes contain two identical light chains and two identical heavy chains).

[11] It is apparent from context that Genentech's counsel misspoke when he named claim 9, rather than claim 19, as being inconsistent with the column 5 definition.

2015) (claim differentiation rejected as reason to broaden scope of independent claim contrary to its plain meaning). That is the case here, for the reasons disclosed above.

In such situations, where the scope of the independent claims is clear, the Federal Circuit has held that the failure of a patentee to conform dependent claims to the scope of the independent claims results in invalidation of the inconsistent claims rather than an expansion of the independent claim. *See Regents Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1375–76 (Fed. Cir. 2008); *Seachange Int'l, Inc. v. C-COR, Inc.*, 413 F.3d 1361, 1369–75 (Fed. Cir. 2005); *N. Am. Vaccine, Inc. v. Am. Cyanamid Co.*, 7 F.3d 1571, 1577–78 (Fed. Cir. 1993). For instance, in *Dakocytomation*, the Federal Circuit rejected the appellants' argument that the district court's claim construction, which excluded repetitive sequences, was "incorrect in light of certain dependent claims requir[ing] inclusion of repetitive sequences." 517 F.3d at 1375. The court explained that, although there exists a presumption that dependent claims have narrower scope than the independent claims from which they depend, "[p]resumptions are rebuttable." *Id.* Thus, "while it is true that dependent claims can aid in interpreting the scope of claims from which they depend, they are only an aid to interpretation and are not conclusive." *Id.* (quoting *N. Am. Vaccine*, 7 F.3d at 1577 (brackets omitted)). The Federal Circuit emphasized that a contrary construction "dictated by the written description or the prosecution history" could overcome the presumption. *Id.* (quoting *Seachange*, 413 F.3d at 1369).

I conclude that the presumption that the independent claim here is broader than the dependent claim has been rebutted. The retention of inconsistent language in the dependent claims does not suggest that the interpretation of independent claims should depart from the original meaning of the term *antibody* as provided in column 5 of the '590 patent. *See Dakocytomation*, 517 F.3d at 1375–76 ("Here . . . the prosecution history overcomes the

presumption; the correct construction of 'heterogeneous mixture' is one that excludes repetitive sequences, notwithstanding the presence of certain dependent claims that do not exclude them."); *Seachange*, 413 F.3d at 1375 ("The presumption attendant to claim differentiation doctrine is rebutted. The phrase 'network for data communications' is limited to networks in which every processor system is connected to every other processor system via direct, point-to-point, two-way channel interconnections."); *N. Am. Vaccine*, 7 F.3d at 1577–78 (rejecting construction of independent claim based on scope of dependent claims because "[t]he dependent claim tail cannot wag the independent claim dog"). While the result of the court's construction is that certain embodiments in the specification are no longer covered by the claims, this is not uncommon in disclaimer situations.

Finally, even with the narrowing amendment to delete *antibody derivative*, the narrower definition of *antibody* does not exclude any disclosed embodiments actually made by the inventors from the scope of the claims. As Genentech established through its expert, Dr. Strohl's testimony, which I credit, and through cross-examination of Dr. Almagro, the patent does not disclose that the inventors of the '590 patent ever made a bispecific antibody, a humanized antibody, or a chimeric antibody. Markman Tr. at 110:12–20 (Dr. Almagro regarding humanized and bispecific antibodies); *id.* at 179:23–180:25 (Dr. Strohl testifying that Example 13 of the '590 patent is prophetic and therefore does not show that the inventors created a chimeric antibody within the scope of the claims). Rather, as Dr. Almagro admitted, "all of the antibodies that Baxalta made in performing the experiments set forth in [the '590] patent would fall within the definition of column 5." Markman Tr. 105:15–21.

Based on the foregoing, I conclude that the term *antibody* means an immunoglobulin molecule, having a specific amino acid sequence that only binds to the antigen that induced its

synthesis or very similar antigens, consisting of two identical heavy chains (H chains) and two identical light chains (L chains). Baxalta concedes that Hemlibra does not infringe the '590 patent under the court's construction of *antibody*. Prelim. Inj. Tr. 9:15–24.

2. ***antibody fragment***

Baxalta's proposed construction: A portion of a molecule having a specific amino acid sequence comprising two heavy chains (H chains) and two light chains (L chains).

Genentech's proposed construction: A fragment of an antibody which partially or completely lacks the constant region; the term "antibody fragment" excludes all other forms of antibody derivatives.

Court's construction: A fragment of an antibody which partially or completely lacks the constant region; the term "antibody fragment" excludes bispecific antibodies.

Though substitution of the word *fragments* for *derivatives* preserved the applicant's claim to derivatives that are fragments, there is no assertion here that the term *fragments* included bispecific antibodies, or expanded the defined meaning of the term *antibody*. Nor is there any contention that Hemlibra is a fragment. "[T]here is no dispute between the parties that [Hemlibra], the accused product, is not a fragment. It's a full-length antibody." Prelim. Inj. Tr. 79:10–15; *accord* Markman Tr. 122:13–21 (Dr. Almagro agreeing that Hemlibra "is a bispecific antibody," "not a Fab" and "not a fragment"). And as Baxalta conceded during the preliminary injunction hearing, "the inclusion of the word 'fragment' wouldn't expand the meaning of the term 'antibody.'" Prelim. Inj. Tr. 35:23–36:2.

Baxalta argues that under the court's definition of *antibody* any piece of an antibody can be considered an *antibody fragment*. Genentech argues instead that the term *antibody fragment* includes only "the sort of canonical antibody fragments that [a person of skill] talks about when [that person] talks about a fragment." Markman Tr. 11:11–12. In light of the prosecution

history, Genentech contends that this sort of antibody fragment comprises a portion of an antibody which partially or completely lacks its constant region.

The specification expressly states that "antibody fragments . . . partially or completely lack the constant region." '590 patent, col. 6, ll. 20–21. The examples of fragments listed in the specification—"Fv, Fab, Fab' [and] $F(ab)'_2$"—all support this limitation. *Id.*; *see also supra* at 11–12.

In summary, the court rejects Baxalta's proposed construction of *antibody fragment*. The Baxalta definition is unduly broad because it would include something as small as three amino acids, which Dr. Almagro agreed would not be understood by a person skilled in the art to constitute an *antibody fragment*. When asked if you "cut the last three amino acids off the constant region" and ask an antibody scientist in 1993 whether that is an antibody fragment, Dr. Almagro agreed that "[s]he'd say 'No, that's three amino acids.'" Markman Tr. 117:19–118:4.

Therefore, the court finds that *antibody fragment* comprises a fragment of an antibody which partially or completely lacks the constant region; the term "antibody fragment" excludes bispecific antibodies.

3. ***bispecific antibody***

Baxalta's proposed construction: An antibody that is a macromolecular, heterobifunctional cross-linker having two different binding specificities within one single molecule.

Genentech's proposed construction: An antibody derivative that is an artificially engineered, macromolecular, heterobifunctional cross-linker having two different binding specificities within one single molecule; a bispecific antibody does not consist of two identical heavy chains and two identical light chains.

Court's construction: An artificially engineered, macromolecular, heterobifunctional cross-linker having two different binding specificities within one single molecule; a bispecific antibody does not consist of two identical heavy chains and two identical light chains.

The parties agree a *bispecific antibody* in the patent is a macromolecular, heterobifunctional cross-linker having two binding specificities within one single molecule, and does not consist of two identical heavy chains and two identical light chains.[12] Markman Tr. 38:5–16. The court construes the term *bispecific antibody* consistent with the parties' agreement. Therefore, a *bispecific antibody* is an artificially engineered, macromolecular, heterobifunctional cross-linker having two different binding specificities within one single molecule; a *bispecific antibody* does not consist of two identical heavy chains and two identical light chains.

4. ***isolated***

Baxalta's proposed construction: Essentially free from other antibodies or antibody fragments that do not bind Factor IX or Factor IXa.

Genentech's proposed construction: Free of molecularly non-identical antibodies or antibody fragments; all antibody molecules or antibody fragment molecules in the claimed composition are identical.

Court's construction: All antibody molecules or antibody fragment molecules in the claimed composition have identical amino acid sequences except for any post-translational modifications.

Construction of *isolated* appears to be relevant to the question of patent validity. As to the term *isolated*, the parties dispute the degree to which antibodies or antibody fragments that are *isolated* must be identical. The specification provides no apparent guidance as to the meaning of the term. *Isolated* is only used twice in the body of the specification, and neither reference illuminates what it means for an *antibody* or *antibody fragment* to be *isolated*. *See*

[12] Although Dr. Almagro agreed that bispecific antibodies generally "don't have two identical heavy chains and two identical light chains," he noted that "[t]here are some recent examples" to the contrary. Markman Tr. 108:11–15. Genentech clarified, and Dr. Almagro confirmed, that the recent examples Dr. Almagro referenced are bispecific antibodies developed by Genentech that "in fact, have identical chains." *Id.* 108:16–20. But the patent's reference to *bispecific antibodies* does not include these antibodies with identical chains.

'590 patent, col. 32, l. 37–38 ("clones were isolated"); *id.* col. 32, ll. 57–58 ("the gene of the 198/B1 scFv was isolated from the plasmid").

The prosecution history is also unhelpful. The Examiner added the term *isolated* to the claims during prosecution but neither explained why the change was made, nor why the change was necessary for allowance. *See* Dec. 21, 2004 Interview Summary, Cole Decl. Ex. 2, ECF No. 162-1; Notice of Allowance and Fees Due, U.S. Patent Appl. No. 09/661,992 (P.T.O. Dec. 29, 2004), ECF 202-1. Genentech argues that the term *isolated* was added to claim 1 of the '590 patent alongside the "inventors' efforts to subclone mixed populations of hybridomas 'to obtain homogenous [sic] cell populations.'" Genentech Op. Br. 14 (quoting '590 patent, col. 11, l. 53). Because such subcloning was performed until each hybridoma population "produce[d] the same FIX/FIXa binding antibody," '590 Patent, col. 12 l. 19–21, Genentech contends that antibodies or antibody fragments which are *isolated* must be identical.

The sole expert testimony regarding this term comes from Genentech's expert, Dr. Strohl. Dr. Strohl explained that *isolated* in context of the specification's description of dilution subcloning would be understood to limit the antibodies and antibody fragments of claim 1 to those that have an "identical amino acid sequence" but not necessarily an identical glycosylation pattern. Strohl Claim Const. Decl. ¶¶ 124–27. Dr. Strohl also admitted that slight differences in the amino acid sequences of antibodies may arise due to a process called post-translational modification. Strohl Dep. Tr. 168:4–20, ECF No. 159-1.

Baxalta offers no testimony, evidence, or argument to the contrary. Based on the content of the specification, Baxalta contends only that the term *isolated* cannot require identicalness because such a construction ignores the contrast between the terms *isolated* and *purified* in the claims and specification of the patent. Baxalta Resp. Br. 2–4, ECF No. 234 (citing '590 Patent,

cl. 17; *id.* col. 9 ll. 11–15; *id.* col. 13, ll. 16–58). Baxalta argues that because the patent discusses "purifying" an antibody after it is "isolated," antibodies that are *isolated* cannot all possibly be identical, because were that the case, purification would be unnecessary. *Id.* I disagree with this understanding of the patent. Purification is meaningful even under Genentech's interpretation since the reference to purification in the patent describes a solution containing antibodies and the cells from which they are derived (hybridomas), and purification eliminates those cells from the final product. *See, e.g.*, '590 patent, col. 13, ll. 16–42.

Baxalta further points to a case, *Morphosys AG v. Janssen Biotech, Inc.*, No. 16-221-LPS, 2017 WL 4769368, at *4 (D. Del. Oct. 23, 2017), in which *isolated* was construed to mean "essentially free from antibodies that do not bind to CD38." The court's construction in *Morphosys* is not relevant, as the case dealt with an entirely different patent. *See Monsanto Co. v. Bayer Bioscience N.V.*, 363 F.3d 1235, 1244 (Fed. Cir. 2004) (stating that "similar terms can have different meanings in different patents depending on the specifics of each patent").

Thus, Genentech's construction most clearly corresponds to how *isolated* was used in the patent, taking into account the caveats raised by Dr. Strohl regarding glycosylation and post-translational modification. Accordingly, I find that the term *isolated* requires that all antibody molecules or antibody fragment molecules in the claimed composition have identical amino acid sequences except for any post-translational modifications.

5. ***binds Factor IX or Factor IXa and increases***

Baxalta's proposed construction: "and" has its plain and ordinary meaning.

Genentech's proposed construction: The increase in procoagulant activity of Factor IXa is caused only by the binding of the antibody or antibody fragment to Factor IX/IXa.

Court's construction: Binding to Factor IX need not be the sole cause of the increase in procoagulant activity.

This court's construction of *binds Factor IX or Factor IXa and increases* appears to be relevant to infringement. As to this term, the parties dispute only the degree of causation required between the binding of the inventive antibodies or antibody fragments to Factor IX/IXa and the resultant increase in procoagulant activity. Genentech contends that the increase in procoagulant activity must be caused only by the binding of the inventive antibodies or antibody fragments with Factor IX/IXa. Genentech Op. Br. 17–19. Baxalta, on the other hand, argues that sole causation is not required. Baxalta Op. Br. at 14–15.

Genentech cites various portions of the specification in support of its construction. The abstract provides "[a]n antibody or antibody derivative against factor IX/activated factor IX (FIXa) which increases the procoagulant activity of FIXa." '590 patent, Abstract. The title of the patent is "Factor IX/Factor IXa Activating Antibodies and Antibody Derivatives." *Id.* col. 1. The Summary of the Invention states that the "object of the present invention to provide a preparation for the treatment of blood coagulation disorders" is "achieved through the use of antibodies or antibody derivatives against factor IX/factor IXa which have factor VIIIa-cofactor activity or factor IXa-activating activity and lead to an increase in the procoagulant activity of factor IXa." *Id.* col. 2, ll. 25–33. The specification states that "hybridomas are selected with a view to the fact that the antibodies and antibody derivatives in the supernatants of the hybridoma cells bind to factor IX/factor IXa and cause an increase of the procoagulant activity of factor IXa." *Id.* col. 8, ll. 18–21. Though these portions of the specification certainly imply that binding to Factor IX/IXa plays a role in causing an increase in procoagulant activity, they do not suggest *sole* causation as Genentech contends.

Because nothing in the intrinsic record suggests otherwise, I find this term unambiguous and conclude that *and* in the term *binds Factor IX or Factor IXa and increases* means that binding to Factor IX need not be the sole cause of the increase in procoagulant activity.

6. ***the procoagulant activity of Factor IXa* and *increases the procoagulant activity of Factor IXa***

Baxalta's proposed construction: The rate of clot formation promoted by Factor IXa.

Genentech's proposed construction: The ability of Factor IXa to activate Factor X to Factor Xa by any amount as determined by any assay used to measure Factor VIII-like activity.

Court's construction: The ability of Factor IXa to activate Factor X to Factor Xa by any amount as determined by any assay used to measure Factor VIII-like activity.

The court's construction of this term appears to be relevant to the question of patent validity. The parties' final dispute relates to the term *increases the procoagulant activity of Factor IXa*. This construction raises the question of how the patent claims instruct a person of skill in the art to measure the procoagulant effect of the inventive antibodies and antibody fragments. Baxalta proposes a construction that limits the assessment of procoagulant activity to tests that measure the rate of clot formation—e.g., by use of Activated Partial Thromboplastin Time ("aPTT") assays, Baxalta Op. Br. at 16–19. Genentech, on the other hand, argues that any prior art test for measuring Factor VIII-like activity, including clotting-time and chromogenic assays, can be used—e.g., aPTT assays and chromogenic assays like COATEST VIII(C) and Immunochrom, Genentech Op. Br. at 16; Markman Tr. 223:6–15; *id.* at 224:14–17.

I conclude that the specification provides clear guidance that any prior art assay that can measure Factor VIII-like activity may be used. The patent twice expressly states that any method for determining Factor VIII-like activity may be used to measure procoagulant activity: In column 8 the patent provides that "[t]he increase in the procoagulant activity may, e.g., be

proven by assaying methods as known from the prior art for the measurement of factor VIII-like activity, e.g. chromogenic assays." '590 patent, col. 8, ll. 21–25. And in column 9 the patent states

> The following methods may be used as the test methods to show that the antibodies and antibody derivatives of the present invention bind to factor IX/factor IXa, increase the procoagulant activity of factor IXa or have factor VIII-like activity: the one step coagulation test . . . or the chromogenic tests, such as COATEST VIII:C® (Chromogenix) or Immunochrom (IMMUNO). In principle, all the methods used for determining factor VIII activity may be used.

Id. at col. 9, ll. 14–23. The patent reiterates this point in Example 5, where the specification states that "[f]actor VIII activity is usually determined with a chromogenic assay and/or an APTT-based clotting assay" and that "[b]oth types of assays rely on FVIIIa/FIXa-mediated factor Xa generation." *Id.* col. 15, ll. 10–13.

There is no support for Baxalta's contrary position that only clotting-time assays are permissible. Baxalta's primary argument is that the '590 patent in certain places refers to clotting time assays alone as a measure of procoagulant activity. For example, Baxalta points to column 17 of the patent, which states that "[t]here is a clear dose-dependent reduction of the clotting time in samples supplemented with antibody 193/AD3" and that such "results imply that [the] antibody . . . is procoagulant in the presence of FIXa." *Id.* col. 17, ll. 35–38. Baxalta also notes that column 29 of the patent states that a particular peptide "becomes procoagulant as indicated by the reduced clotting time" and that column 23 similarly states that certain peptides "did not give any reduction in the clotting time indicating that they lack procoagulant activity." *Id.* at col. 29, ll. 36–40; *id.* at col. 23, l. 66–col. 24, l. 2. The patent's reference to the use of clotting-time assays to measure procoagulant activity hardly excludes other possible methods of measurement, particularly where other parts of the specification state that "assaying methods as known from the prior art" may be used. *Id.* at col. 8, l. 21–25.

Baxalta also relies on the statement in column 9 of the patent that the inventive antibodies and antibody fragments "increase the procoagulant activity of factor IXa or have factor VIII-like activity." *Id.* at col. 9, ll. 17–18. It contends that the use of "or" implies a distinction between procoagulant activity and Factor VIII-like activity. Baxalta Resp. Br. at 8–12. Baxalta argues that Example 9 illustrates the same distinction. *See* '590 patent, col. 18, ll. 22–67. It follows, says Baxalta, that the term "procoagulant activity" and "factor VIII-like activity" are mutually exclusive, so that the chromogenic assay used to determine factor VIII-like activity cannot be used to determine procoagulant activity. The premise of this argument is simply incorrect. Procoagulant activity and Factor VIII-like activity are not distinct terms, but rather are overlapping.

Accordingly, I conclude that the term *increases the procoagulant activity of Factor IXa* means the ability of Factor IXa to activate Factor X to Factor Xa by any amount as determined by any assay used to measure Factor VIII-like activity.

IT IS SO ORDERED this 3 day of December, 2018.

Honorable Timothy B. Dyk
United States Circuit Judge, sitting by designation