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

MEMORANDUM OPINION

Pending before the court is Genentech's motion for summary judgment. Genentech moves for summary judgment of 1) invalidity of claims 1–4, 19, and 20 of the '590 patent for lack of written description and enablement, 2) non-infringement under a doctrine-of-equivalents theory, and 3) no willful infringement. For the reasons stated below, the court GRANTS Genentech's motion for summary judgment of invalidity for lack of enablement and need not address Genentech's motion in all other respects.

I. PROCEDURAL HISTORY

On May 4, 2017, Baxalta Inc. and Baxalta GmbH (together, "Baxalta") brought suit against Genentech, Inc. and Chugai Pharmaceutical Co., Ltd., alleging infringement of U.S. Patent No. 7,033,590 ("the '590 patent") by the manufacture, use, sale, offer to sell, and importation of an antibody used to treat hemophilia A and known as emicizumab or ACE910, marketed under the brand name Hemlibra. Compl., ECF No. 1, ¶¶ 37–51. Chugai was subsequently dismissed from

the case. [1] Genentech answered on June 30, denying Baxalta's allegations and counterclaiming for declaratory judgment of noninfringement and invalidity on grounds of lack of enablement and written description support. Answer & Countercl., ECF No. 9, ¶¶ 37–51, 120–49.

On December 14, 2017, Baxalta moved for a preliminary injunction against Genentech. *See* Mot. for Prelim. Inj., ECF No. 41. On August 7, 2018, the court denied Baxalta's motion, finding that it had not proven a likelihood of success with respect to infringement and invalidity, and that even if it had, "given the ample evidence of medical need, the public interest weigh[ed] strongly against issuing a preliminary injunction since Hemlibra has unique medical benefits not available from Baxalta's competing products." Prelim. Inj. Order, ECF No. 262, at 24; *id.* at 28–29.

On December 3, 2018, following a Markman hearing, the court issued a claim construction decision in which it construed the term "antibody" to exclude bispecific antibodies. *See* Claim Construction Order, ECF No. 330, at 22–23. Thereafter, the parties stipulated to non-infringement of the asserted claims under the court's claim construction. *See* Stipulations, ECF Nos. 331–332. The court entered judgment in Genentech's favor on February 1, 2019. *See* Stip. & Final J., ECF No. 337. Baxalta appealed, and on August 27, 2020, the Federal Circuit issued a decision rejecting this court's construction of the terms "antibody" and "antibody fragment," determining that the term antibody included bispecific antibodies, and vacating the judgment of non-infringement and remanding for further proceedings. *See Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1343, 1349 (Fed. Cir. 2020) (construing antibody to mean "an immunoglobulin molecule having a

[1] Chugai is a Japanese company that invented and manufactures the accused product, Hemlibra, in Japan. *See, e.g.*, Yamaguchi Decl., ECF No. 20, ¶¶ 2, 5. Hemlibra is shipped to the United States where it is sold by Genentech. *See id.* ¶¶ 7, 10. The parties stipulated to the dismissal of Chugai as a defendant in this case in June 2018. *See* Stip. & Prop. Order, ECF No. 220; July 2, 2018, Min. Entry.

specific amino acid sequence comprising two heavy chains (H chains) and two light chains (L chains)" and "antibody fragment" to mean "a portion of an antibody"). Upon remand, the case proceeded with fact and expert discovery.

On September 3, 2021, Genentech filed a motion for summary judgment of 1) invalidity of claims 1–4, 19, and 20 of the '590 patent for lack of written description and enablement, 2) non-infringement under a doctrine-of-equivalents theory, and 3) no willful infringement. *See* Opening Br. in Supp. of Genentech's Mot. for Summ. J., ECF No. 416 (Def.'s Mot.), at 1, 15–16. Baxalta thereafter filed its opposition to Genentech's motion, *see* Pl.'s Opp'n to Def.'s Mot. for Summ. J., ECF No. 424 (Pl.'s Opp'n), and Genentech filed its reply on October 15, 2021, *see* Reply Br. in Supp. of Genentech, Inc's Mot. for Summ. J., ECF No. 425. The parties have submitted expert declarations and exhibits, as well as a Joint Stipulation of Fact. *See* Joint Stip. of Fact Regarding Hybridoma Tech. & the Number of Anti-Factor IX/IXa Antibodies Disclosed in the '590 Patent, ECF No. 437 (Joint Stip.). The court heard oral argument on the motion on November 19, 2021. *See* Nov. 22, 2021, Min. Entry.

II. SUMMARY OF DECISION

For the reasons described in detail below, the court finds that Genentech has shown by clear and convincing evidence that the asserted claims of the '590 patent are not enabled. There are millions of candidate antibodies within the genus and a dearth of working examples of those that satisfy the claim limitations. There are only eleven working examples disclosed in the patent. The examples are all murine, monospecific antibodies of the IgG and IgM isotypes, or fragments thereof. The genus of independent claim 1 is functionally and structurally broad. And in many respects there are no examples in the specification for the covered classes of antibodies. For example:

1. Claim 1 covers an antibody that increases the procoagulant activity of Factor IXa by an amount ranging from barely perceptible to an amount capable of use in "a preparation for the treatment of blood coagulation disorders which has particular advantages for factor VIII inhibitor patients." '590 patent, col. 2, ll. 25–28. Claim 1 thus covers an antibody or antibody fragment that increases the procoagulant activity of Factor IXa in the presence of Factor VIII inhibitors.[2] There is no working example of an antibody that increases the procoagulant activity of Factor IXa by more than a marginal amount in the presence of Factor VIII inhibitors. And for the non-inhibitor population, there is no working example of an antibody that increases the procoagulant activity of Factor IXa by an amount capable of moving a patient with a severe hemophilia A condition (comprising over 60% of hemophilia A patients) to a mild condition. Baxalta's expert concedes that the patent's assertions that antibodies of the invention have therapeutic utility is merely "aspirational."
2. Claim 1 covers humanized and chimeric antibodies. There are no working examples of humanized or chimeric antibodies disclosed in the specification.
3. Claim 1 covers bispecific antibodies such as the accused product emicizumab. There are no working examples of bispecific antibodies disclosed in the specification.
4. Claim 1 covers antibodies of the IgE isotype. There are no working examples of IgE antibodies disclosed in the specification.

[2] As discussed below, an "inhibitor patient" is someone who has developed an immune response to traditional Factor VIII replacement therapies.

5. Claim 1 covers antibodies of the IgA isotype. There are no working examples of IgA antibodies disclosed in the specification.

6. Claim 1 covers antibodies of the IgD isotype. There are no working examples of IgD antibodies disclosed in the specification.

7. Claim 1 covers diabodies and dimers, oligomers, and multimers of the claimed antibodies. There are no working examples of diabodies or dimers, oligomers, or multimers of antibodies in the specification.

The specification also provides no guidance as to how to identify which antibodies will satisfy the claim limitations, nor does it describe what structural or other features of the disclosed antibodies cause them to bind to Factor IX/IXa or to increase the procoagulant activity of Factor IXa. The field of antibodies is inherently unpredictable. The only way to practice the teachings of the patent is by trial-and-error; *i.e.*, by screening tens of thousands, if not millions, of candidate antibodies to determine whether they satisfy the limitations of the asserted claims.

The same deficiencies exist as to dependent claims 3–4, 19, and 20, which include the same functional limitations as claim 1 but also specify structural limitations.

This is not adequate enablement under Federal Circuit precedent, including *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), and the cases that have followed, because it requires undue experimentation to practice the full scope of what is claimed.

III. LEGAL STANDARD

A. Summary Judgment

Under Rule 56(a) of the Federal Rules of Civil Procedure, "[t]he court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." The moving party bears the burden of

demonstrating the absence of a genuine issue of material fact. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986). If the moving party has carried its burden, the nonmovant must then "come forward with 'specific facts showing that there is a *genuine issue for trial*.'" *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986) (quoting Fed. R. Civ. P. 56(e)). The court "must draw all reasonable inferences in favor of the nonmoving party, and it may not make credibility determinations or weigh the evidence." *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150 (2000).

B. 35 U.S.C. § 112

One of the statutory conditions for patentability under the Patent Act is adequate disclosure of the invention. Section 112 provides, in pertinent part, that:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112. Section 112 imposes two separate requirements. The first is the written description requirement, found in the first sentence of Section 112, which requires that the specification contain an adequate "written description of the invention." 35 U.S.C. § 112; *see also Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1346 (Fed. Cir. 2010) (en banc) ("[A] separate requirement to describe one's invention is basic to patent law . . . It is part of the *quid pro quo* of a patent; one describes an invention, and, if the law's other requirements are met, one obtains a patent."). The inquiry into written description is a question of fact but it is "amenable to summary judgment in cases where no reasonable fact finder could return a verdict for the non-

moving party." *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1361 (Fed. Cir. 2011) (internal quotation marks and citation omitted).

The second requirement is enablement. "Whether a claim satisfies the enablement requirement of 35 U.S.C. § 112 is a question of law." *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1084 (Fed. Cir. 2021). An enabling disclosure is the "*quid pro quo* of the right to exclude." *J.E.M. Ag Supply, Inc. v. Pioneer Hi–Bred Intern., Inc.*, 534 U.S. 124, 142 (2001). To be enabling, "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)); *see In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) ("[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). Although it is not necessary to disclose every species within a genus, *see In re Angstadt*, 537 F.2d 498, 502–03 (C.C.P.A. 1976), "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed," *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

To be valid, a patent must satisfy both the written description and enablement requirements. *See Ariad*, 598 F.3d at 1351. Because, for the reasons discussed below, the court finds that no reasonable jury could find the full scope of the asserted claims of the '590 patent are enabled, it need not separately address written description, though the claims may also be invalid for lack of written description support.

IV. FACTUAL BACKGROUND

The '590 patent is directed to an antibody or antibody derivative that binds to a protein important for blood coagulation known as Factor IX (or Factor IXa) and increases the procoagulant activity of Factor IXa, for use in treatment of hemophilia A patients, particularly those who have developed Factor VIII inhibitors. '590 patent, col. 2, ll. 25–33. Asserted here are independent claim 1 and dependent claims 2–4, 19 and 20, 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.
>
> 2. The antibody or antibody fragment according to claim 1 that increases the procoagulant activity of Factor IXa in the presence of Factor VIII inhibitors.
>
> 3. The antibody or antibody fragment according to claim 1 wherein the antibody is an IgG, IgM, IgA or IgE antibody.
>
> 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.
>
> 19. The antibody or antibody fragment according to claim 4, wherein the antibody is a humanized antibody.
>
> 20. The antibody or antibody fragment according to claim 2, wherein the antibody is selected from the group consisting of an IgG, IgM, IgA, or IgE antibody.

Some background on antibodies and hemophilia A as well as its prior-art treatment based on the parties' agreed-upon views is necessary.

A. Hemophilia A and Its Prior-Art Treatment

The body stops bleeding by relying on blood coagulation, also known as clotting, which is accomplished through a cascade of reactions between proteins. *See* Sheehan Decl., ECF No. 411,

Ex. 1, Opening Rpt. ¶¶ 23–24 (Sheehan Rpt.); Pl.'s Opp'n, Ex. 8, ECF No. 424-9, Krishnaswamy Rebuttal Rpt. ¶ 25 (Krishnaswamy Rpt.). The individual coagulation proteins are referred to as coagulation "Factors," with respective assigned Roman numerals (*e.g.*, Factor VIII and Factor IX). Sheehan Rpt. ¶ 23; Krishnaswamy Rpt. ¶ 25. These Factors normally circulate in the blood in inactive forms until triggered by a vascular injury, which causes a coagulation cascade. *See* Sheehan Rpt. ¶ 23. Factors in their activated form are identified with an appended "a" (*e.g.*, Factor IXa). *See id.*; Opp'n Br., Ex. 2, Malackowski Opening Rpt. (Malackowski Rpt.), at 20. The relevant steps in the clotting cascade for present purposes are the coming together of Factor VIIIa and Factor IXa. *See* Sheehan Rpt. ¶ 25; Krishnaswamy Rpt. ¶ 26. In a healthy person, activated Factor VIII (Factor VIIIa) "complexes with" activated Factor IX (Factor IXa) and Factor X, causing Factors IXa to activate Factor X to Factor Xa, which is essential for clot formation. *See* Sheehan Rpt. ¶ 25; Krishnaswamy Rpt. ¶ 26.

Hemophilia A is a genetic disorder in which patients lack sufficient functional Factor VIII. Young Decl., ECF No. 414, Rebuttal Report ¶ 14 (Young Decl.); Krishnaswamy Rpt. ¶ 27. This amounts to a roadblock in the clotting cascade, and hemophilia A patients therefore suffer from a reduced ability to form quick and effective blood clots. Without Factor VIII, and without treatment, hemophilia A patients are at risk of bleeding episodes not only from external trauma, but internally into joints and other spaces in the body. Young Decl. ¶ 14. Hemophilia A can be classified as mild, moderate, or severe, depending on the relative level of Factor VIII present. Sheehan Rpt. ¶¶ 31–32; Malackowski Rpt. at 21. There are approximately 23,000–25,000 males with hemophilia A living in the United States. Young Decl. ¶ 16. About half of them have been diagnosed with a severe form of the disorder. *Id.* Females are less likely to have severe

hemophilia A because the genetic mutation associated with hemophilia A is "X-linked recessive." Young Decl. ¶ 15.

Historically, the only treatment for hemophilia A patients was infusion (intravenous) with a Factor VIII replacement, either as needed when bleeding episodes occur (on-demand) or in a preventative matter (prophylaxis). *Id.* ¶ 17; Krishnaswamy Rpt. ¶ 28. The problem with that treatment, however, was that 25–30% of patients with severe hemophilia who were treated with Factor VIII replacement therapies developed an immune response to Factor VIII. Young Decl. ¶ 22; Malackowski Rpt. at 21. This immune response is known as an "inhibitor," and the patients exhibiting this response are known as the "inhibitor population." Young Decl. ¶ 22. As a result, Factor VIII replacement therapy is usually not effective in the inhibitor population. *Id.* ¶ 23; Krishnaswamy Rpt. ¶ 29.

Before the introduction of Hemlibra, the inhibitor population had few effective treatment options. *See* Young Decl. ¶¶ 22–27; Malackowski Rpt. at 21. One option was a therapy called "Immune Tolerance Induction (ITI)." Young Decl. ¶ 24; Malackowski Rpt. at 21. But that treatment is costly, complicated, and prolonged, requiring daily intravenous infusions of high concentrations of Factor VIII over the course of months or even years until the body's immune system begins to tolerate it, if ever. *See* Young Decl. ¶ 24; Malackowski Rpt. at 21.

As of 2018, inhibitor patients could also take one of two "bypass agents" (BPAs), including Baxalta's product FEIBA ("Factor Eight Inhibitor Bypassing Activity"). *See* Young Decl. ¶ 25; Malackowski Rpt. at 21. BPAs work by bypassing the Factor VIII step in the clotting cascade. *See* Young Decl. ¶ 25; Malackowski Rpt. at 21. Like Factor VIII replacement therapy, BPAs can be used in two ways: on-demand when a bleeding episode occurs and/or on a regular schedule as prophylaxis. Young Decl. ¶ 26; Malackowski Rpt. at 25. But they too must be infused, which

may impose a substantial treatment burden on patients and their families. In particular, the infusion can take up to an hour as often as every other day in order to achieve the desired prophylactic effect. *See* Young Decl. ¶ 27; Malackowski Rpt. at 34.

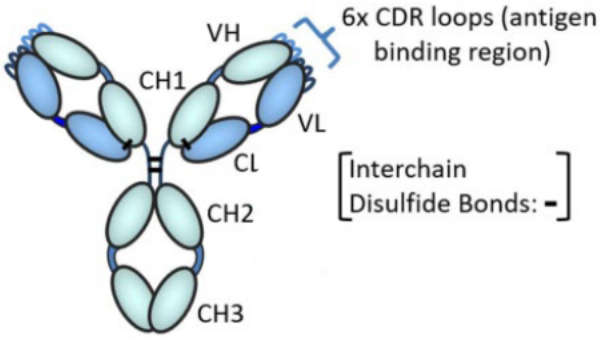
B. Baxalta's Search for an Antibody-Based Hemophilia A Treatment

Recognizing the drawbacks with all the existing treatment options, in 1998, scientists working for Baxalta's predecessor began experimenting with ideas for new, better hemophilia A treatments, particularly for inhibitor patients. Dr. Friedrich Scheiflinger, one of the '590 patent's named inventors, had the idea of using an antibody against Factor IX/IXa to increase the procoagulant activity of Factor IXa even in the absence of Factor VIII. *See* '590 patent, col. 2, ll. 29–44; Cole Decl. vol. 1, Ex. 11, Scheiflinger Dep. Tr. at 98:8–99:20, 101:02–12.

1. Antibody Structure and Genetic Modification

Antibodies are a key component of the immune system. Strohl Decl., ECF No. 413, Ex. 1, Opening Rpt., ¶ 35 (Strohl Rpt.). When confronted with a foreign molecule, or "antigen," the immune system's "B cells" (a type of white blood cell) generate antibodies that attack the antigen by binding to them. *See id.* ¶¶ 35, 41; Garcia Decl., ECF No. 415, Ex. 1, ECF No. 415-1, Opening Rpt. (Garcia Rpt.), ¶ 58. Each unique B-cell produces multiple copies of one specific antibody—meaning, the secreted antibody can bind to only one antigen. Garcia Rpt. ¶ 59. The binding of an antigen to the B-cell surface stimulates the B-cell to divide and mature into identical cells, secreting millions of antibodies into the bloodstream and lymphatic system. *See id.* ¶ 57. An antibody, as that term has been construed in the '590 patent, is "an immunoglobulin molecule having a specific amino acid sequence comprising two heavy chains (H chains) and two light chains (L chains)." *Baxalta*, 972 F.3d at 1349.

Antibodies can be visualized as forming a "Y" shape, with two arms connected by disulfide bonds. Strohl Rpt. ¶ 35. Each arm of the Y shape contains two polypeptides known as the heavy (H) chain and the light (L) chain. *See id.* Each of its heavy and light chains consist of two regions. *See id.* ¶ 36. The portions of the heavy and light chains that vary from antibody to antibody depending on the antigen are called the "variable domains," designated VH and VL, respectively. *Id.* ¶¶ 36–37. Variable regions include (i) complementarity-determining regions ("CDRs"), which are amino acid sequences that play a key role in the antibody's binding to an antigen, and (ii) framework regions, which serve as "scaffolds for the CDRs." *Id.* ¶¶ 36, 39. The remaining portions are called Constant (C) regions of each chain. *See id.* ¶ 36. This is a schematic of an antibody:



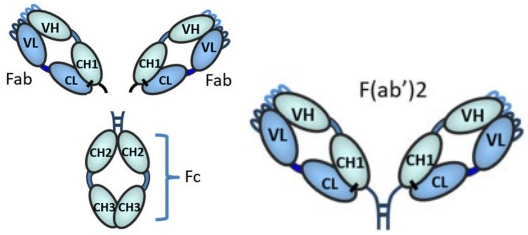
Id. ¶ 35 (Figure 1).

Based on the structure of the constant regions, antibodies are grouped into five classes—IgA, IgD, IgE, IgG, and IgM—each with closely related but different functions. *Id.* ¶ 37.[3] The constant region of all antibodies of the same isotype are identical (*e.g.*, all IgG antibodies have the same constant region and that constant region differs from that of IgA antibodies). *Id.* Because

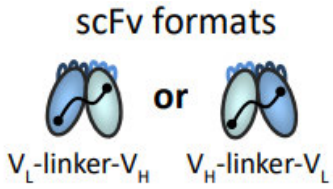
[3] "Ig" stands for immunoglobulin, and each letter signifies the specific class, which may change depending on the stage of the immune response. *See* Marasco Rpt. ¶ 71. The various antibody isotypes "differ from one another in biological properties, functional locations, and ability to deal with different antigens." Marasco Rpt. ¶ 278. IgGs are the most prevalent class, whereas IgDs are the least prevalent. *See* Strohl Rpt. ¶ 37.

each arm of a naturally occurring antibody is identical, each arm targets the same antigen. *Id.* ¶ 38. Naturally occurring antibodies are thus said to be "monospecific." *Id.*

Scientists have developed various genetic engineering techniques for altering natural antibodies to make a wide variety of molecules. Some are of different sizes than natural antibodies, whereas others have different binding specificities or different constant-region functions. For example, scientists have used protein-cleaving enzymes to cut antibodies into "antibody fragments." *Id.* ¶¶ 46–47. These include the Fab, Fc, and F(ab')$_2$ fragments, shown below.

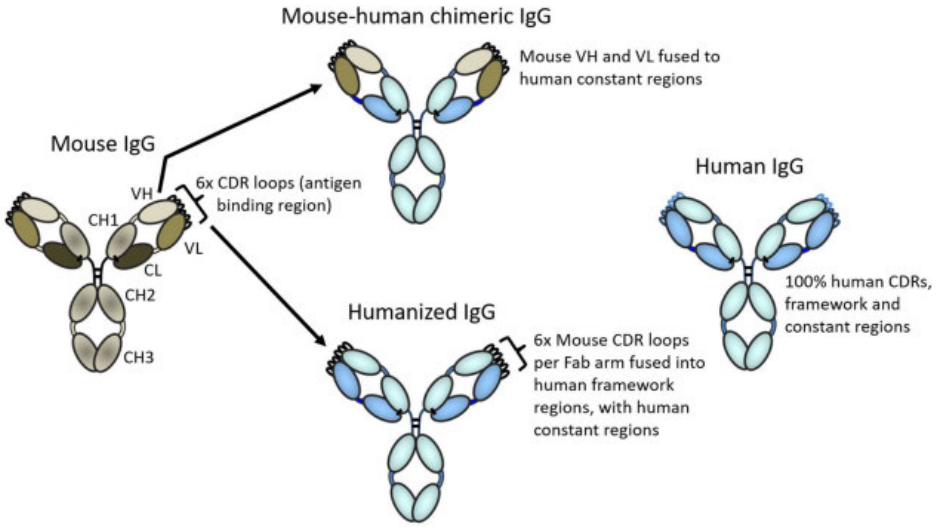


Id. at Figs. 2–3. They have also used recombinant DNA techniques to derive antibody fragments beyond simple enzymatic cleavage of a full-length antibody. One example (depicted below) is a fragment called a single-chain Fv (scFv), which contains the variable region of a heavy chain and the variable region of a light chain, held together by a synthetic string of amino acids. *Id.* ¶ 48.



Id. at Fig. 4.

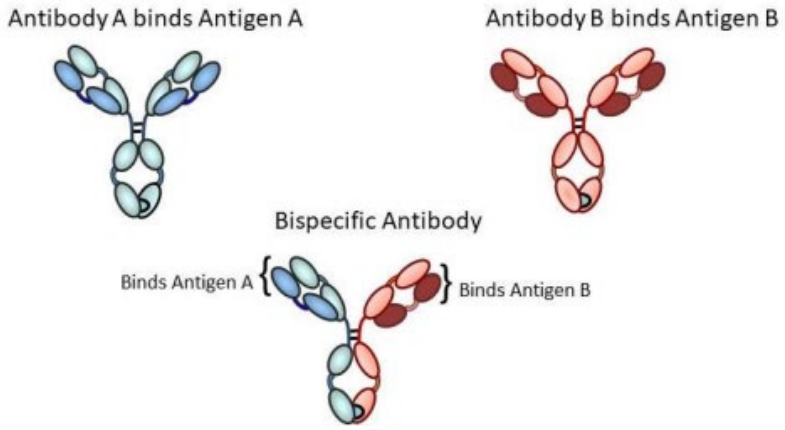
Genetic engineering has also made possible the construction of antibodies that are part animal sequence and part human sequence. *Id.* ¶ 49. These are known as "chimeric" and "humanized" antibodies—as shown below. *Id.*



Id. at Fig. 5. The benefit of humanizing antibodies is that it lessens the chances of an immune response to the antibody. *Id.* ¶ 50. In early efforts to use mouse (or murine) antibodies as therapeutic agents in humans, scientists observed that the human immune system recognized the murine antibody as a foreign substance and made antibodies against it. *Id.* This became known as the "HAMA response," for "human anti-mouse antibody." *Id.* It spurred research to develop a way to engineer antibodies containing more human amino acid sequences and less animal (*e.g.*, murine) sequences. *Id.* ¶ 51.

Initially, scientists used genetic engineering techniques to create "chimeric antibodies" by splicing together genetic material (DNA) encoding the variable regions of animal antibodies (usually murine) with DNA encoding the constant regions of human antibodies. *Id.* ¶¶ 52–53; '590 patent, col. 6, l. 64–col. 7, l. 3. Although successful at first, over time it became clear that humans were developing a HAMA response to the murine sequences in the chimeric antibodies. Strohl Rpt. ¶ 54. To avoid that response, scientists designed "humanized antibodies" wherein non-human CDRs are inserted into an otherwise-human antibody. '590 patent, col. 6, ll. 49–57. In the resulting antibody, the binding affinity is preserved, while adverse human immune reaction is significantly reduced as compared to the original animal antibody. Strohl Rpt. ¶¶ 55–56.

Finally, scientists have created "bispecific antibodies" by pairing the heavy and light chains of an antibody that binds to one antigen with the heavy and light chains of a different antibody that binds to a different antigen. *Id.* ¶ 61. The resulting antibody, depicted below, is thus capable of binding two antigens. *Id.*; '590 patent, col. 7, ll. 32–34.



Strohl Rpt. at Fig. 7.

2. The '590 Patent

Against this backdrop, in 1998, the scientists at Baxalta were experimenting with the idea of using an antibody binding to Factor IX/IXa to increase the procoagulant activity of Factor IXa even in the absence of Factor VIII. '590 patent, col. 2, ll. 29–44. Over the course of approximately four years, they used hybridoma techniques (described below) to create monospecific antibodies that bind to Factor IX or IXa and increase the procoagulant activity of Factor IXa. Cole Decl. vol. 1, ECF No. 409 ("Cole Decl. vol. 1"), Ex. 13, Kerschbaumer Dep. Tr. at 14:325–15:328; '590 patent, col. 7, l. 65–col. 8, l. 1; col. 9, l. 66–col. 10, l. 37; Sheehan Rpt. ¶ 166.

The '590 patent, titled "Factor IX/factor IXa activating antibodies and antibody derivatives," was filed on September 14, 2000, issued on April 25, 2006, and expired in December 2021. *See* Def.'s Mot. at 10. In total, the '590 patent discloses eleven working examples of

antibodies that bind to Factor IX/IXa and increase the procoagulant activity of Factor IXa.[4] Pl.'s Opp'n, Ex. 4, Marasco Rebuttal Rpt., ECF No. 424-5, ¶ 124 (Marasco Rpt.), ¶ 111. To find the eleven examples, the inventors tested tens of thousands of antibodies in assays designed to measure Factor VIII-like activity. *See* '590 patent, col. 10, l. 39–col. 12, l. 56; Joint Stip. ¶ 10. The examples are all murine, monospecific antibodies of the IgG and IgM isotypes, as well as a number of scFv fragments from some of those antibodies, and one Fab fragment. *See* Marasco Dep. Tr. at 102:12–126:04.

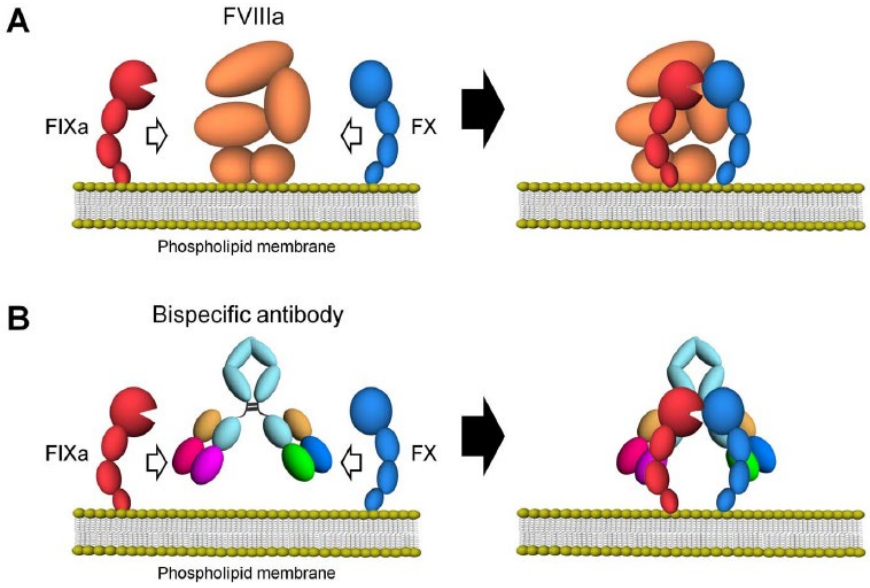
Baxalta's efforts to produce antibodies that bind to Factor IX/IXa and increase the procoagulant activity of Factor IXa continued until 2003. *See* Cole Decl. vol. 1, Ex. 6, Baxalta's Suppl. Resp. to Interrog. 11, at 47. The parties agree that Baxalta has never commercialized an antibody for the treatment of hemophilia A in inhibitor patients consistent with the stated purpose of the '590 patent. *See* Scheiflinger Dep. Tr. at 48:25–49:08; Sheehan Rpt. ¶ 166; Garcia Rpt. ¶ 221; *see also* '590 patent, col. 2, ll. 25–28 ("[I]t is an object of the [] invention to provide a preparation for the treatment of blood coagulation disorders which has particular advantages for factor VIII inhibitor patients[,] . . . through the use of antibodies . . . against factor IX/IXa.").

C. Chugai's Invention of Emicizumab

Around the same time that Baxalta's scientists were experimenting with antibodies capable of binding to Factor IX and increasing the procoagulant activity of Factor IXa, scientists in Japan at Chugai were also working to develop antibody-based treatments for hemophilia A. By at least October 27, 2000, Chugai had the idea of using a humanized bispecific antibody that would bind Factor IXa with one arm and Factor X with the other, holding Factor IXa and Factor X in a position

[4] The parties dispute whether the patent discloses 11 examples, but for the purposes of its motion for summary judgment, Genentech accepts that the specification discloses 11 working examples. *See* Joint Stip. of Fact, ECF No. 437 (Joint Stip.) ¶ 14.

by which Factor IXa would activate Factor X, similar to how Factor VIIIa functions (depicted below). *See* Strohl Rpt. ¶ 115; Cole Decl. vol. 1, Ex. 7 at GNE-01138116 (dated Oct. 27, 2000); *id.*, Ex. 8, Kitazawa Dep. Tr. at 185:01–186:10, 215:20–25; *id.*, Ex. 9 at GNE-01137931; *id.*, Ex. 10 at GNE-01137957.



Sampei et al., *Identification and Multidimensional Optimization of an Asymmetric Bispecific IgG Antibody Mimicking the Function of Factor VIII Cofactor Activity*, PLoS ONE 8(2):1–13 (2013) (Sampei Article), at 2, Fig. 1 (showing (A) Factor VIIIa forming a complex with Factor IXa and supporting the interaction between Factor IXa and Factor X through its binding ability to both factors on the phospholipid membrane, and (B) A bispecific antibody (like emicizumab) binding to Factor IXa and Factor X, promoting the interaction between Factor IXa and Factor X and therefore exerting Factor VIII mimetic activity on the phospholipid membrane.).

Genentech's expert, Dr. William R. Strohl, details the lengthy trial-and-error process through which Chugai's scientists generated tens of thousands of combinations of Factor IX and Factor X antibodies, combining them into bispecific antibodies and testing them in assays. Strohl

Rpt. ¶¶ 202–224.[5] Once the scientists had discovered a candidate worthy of testing in animals and then in humans, they engaged in antibody engineering to refine and optimize the candidate antibody. *Id*. ¶¶ 208–210; Strohl Decl., Ex. 2, ECF No. 413-1, Responsive Report, ¶¶ 61–127 (Strohl Resp.). In total, "it took 10 or more full-time Chugai researchers almost 10 years to construct a therapeutically useful bispecific antibody that binds Factor IX/IXa with one arm and Factor X with the other." Strohl Rpt. ¶ 224.

The resulting antibody, emicizumab, is a humanized bispecific antibody that mimics the function of Factor VIIIa by binding to Factor IXa with one of its arms and to Factor X with the other. Young Decl. ¶ 28; Strohl Resp. ¶ 29. It is the active ingredient in Hemlibra—the first and only FDA-approved product for hemophilia A patients that can be injected under your skin (subcutaneously). Young Decl. ¶ 28; Malackowski Rpt. at 38. Hemlibra has been shown to increase procoagulant activity to about 10% of normal Factor VIII levels. *See* Decl. of Stephanie A. Smith, ECF No. 420, Ex. 1 at ¶ 49 (citing Uchida et al., *A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subject*, Blood 127(13):1633–1641 (2016)); *Id.* at Ex. 2, ¶ 44. This is enough to move a patient from severe hemophilia A (with observed Factor VIII activity less than 1%) to at least a moderate category (with observed factor VIII activity between 1–5%) or even a mild category (with observed factor VIII activity between 5–40%). *See* Smith Decl., Ex. 2, ¶ 44; Krishnaswamy Rpt. ¶ 117 (showing severity classifications).

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[5] The work conducted by Chugai's scientists to discover emicizumab also is documented in literature. *See* Sampei Article; *see also* Sampei et al. (2013) Discussion, *available at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0057479* (explaining that "the lead bispecific antibody was identified from approximately 40,000 different bispecific antibodies" and "[b]ispecific antibodies meeting the criteria for FVIII cofactor activity were extremely rare (<0.3%)").

On November 16, 2017, the FDA approved Hemlibra for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with Factor-VIII inhibitors. Young Decl. ¶ 28. On October 4, 2018, the FDA approved Hemlibra for non-inhibitor patients. *Id.*

V. Enablement Standard

A patent claim is presumed enabled unless proven otherwise by clear and convincing evidence. 35 U.S.C. § 282; *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1318 (Fed. Cir. 2007). The central question for enablement is whether the specification enables the full scope of its claims without undue experimentation. *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003). "Enablement is not precluded where a 'reasonable' amount of routine experimentation is required to practice a claimed invention." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010). To evaluate whether the patent enables a person of ordinary skill in the art to practice the invention without undue experimentation, courts consider a non-exclusive list of items, often referred to as the *Wands* factors: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A court need not consider each of the *Wands* factors, for they "are illustrative, not mandatory." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

VI. Undisputed Facts Relevant to Enablement

The following are undisputed material facts, based on the patent claims, the specification, the court's claim construction order, Genentech's Motion for Summary Judgment, Baxalta's response, and the parties' stipulation dated December 3, 2021:

1. Claim 1 of the '590 patent encompasses any isolated antibody or antibody fragment thereof that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa by any amount. *See* Claim Construction Order at 29.

2. The number of candidate antibodies or antibody fragments within the scope of claim 1 is high, "encompassing millions of different structural formats, binding epitopes, binding affinities, and mechanisms of action." Garcia Rpt. ¶ 215. The specification discloses working examples of only eleven antibodies that satisfy claim 1. *See* Joint Stip. ¶ 14.

3. The structural breadth of claim 1 is illustrated by its dependent claims. The dependent claims show that claim 1 is not specific to any particular isotype of the antibody or antibody fragment and includes antibodies that have been genetically engineered into different structural formats.

    a. Dependent claims 3 and 20, define *Markush* groups[6] and include antibodies of the IgA, IgE, IgG and IgM isotypes that are within the scope of claim 1. Claim 1 also includes the fifth principal isotype, IgD, because claim 1 is not limited by isotype. *See* Def.'s Mot. at 18; Marasco Dep. Tr. at 103:12–104:9. The patent does not disclose working examples of three of these isotypes: IgD, IgA,

[6] "A Markush group lists specified alternatives in a patent claim, typically in the form: a member selected from the group consisting of A, B, and C." *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1372 (Fed. Cir. 2005) (citing to *Manual of Patent Examining Procedure* § 803.2 (2004)).

and IgE. *See* Marasco Dep. Tr. at 102:08–22; 105:06–09; 105:20–106:12. The two isotypes represented by working examples are those that are most commonly present in high proportion in the blood at the early stages of an immune response. Marasco Rpt. ¶ 71; Strohl Rpt. ¶ 37. Using the teachings of the '590 patent, it would be rare to discover antibodies of the IgA and IgE isotypes, as the vast majority of antibodies, 75 percent, exist as IgG and IgM isotypes. It would be rarer still to discover IgD antibodies using the teachings of the '590 patent, since they do not circulate in the bloodstream but are instead bound to the exterior membranes of immune-system cells. *See* Marasco Dep. Tr. at 104:13–105:5.

b. Dependent claims 4 and 19 define *Markush* groups that include various types of antibodies, namely monoclonal antibodies, chimeric antibodies, humanized antibodies, single chain antibodies (such as scFvs), bispecific antibodies, and diabodies, as well as dimers, oligomers, and multimers thereof. The '590 patent does not disclose working examples of seven of the nine structural formats in the *Markush* group of claims 4 and 19: chimeric antibodies, humanized antibodies, bispecific antibodies, diabodies, and dimers, oligomers and multimers thereof. *See* Marasco Dep. Tr. at 124:24–125:12,126:02–04; Scheiflinger Dep. Tr. at 66:16–17.

4. Claim 1 also is functionally broad. An antibody that increases the amount of procoagulant activity by the same amount as Factor VIII does (at least 40%) is within the scope of the asserted claims. *See* Marasco Dep. Tr. at 236:12–18; Cole Decl. vol. 2, ECF No. 410-1, Ex. 20, Krishnaswamy Dep. Tr. at 213:17–214:11. The highest estimated amount by which

any antibody disclosed in the '590 patent increased the procoagulant activity of Factor IXa was by 3.75% (antibody 198/A1)—far less than 40%.[7] *See* Krishnaswamy Rpt. ¶¶ 122–123. The 3.75% would only be capable of moving a patient with hemophilia A classified as severe to a moderate classification, pursuant to the below chart upon which both parties' experts rely.

Factor VIII Activity	**Classification**
< 0.01 IU/mL (< 1% of normal)	Severe
0.01 – 0.05 IU/mL (1%–5% of normal)	Moderate
> 0.05 – < 0.40 IU/mL (>5% – <40% of normal)	Mild

See Krishnaswamy Rpt. ¶¶ 117; Sheehan Rpt. ¶ 99. The specification does not disclose an antibody or antibody fragment that is therapeutically useful for moving someone suffering from a severe case of hemophilia A to a mild case. Patients with severe conditions represent about 60 percent of hemophilia A cases. Malackowski Rpt. at 22.

5. Claim 1 also includes antibodies or antibody fragments that are capable of increasing the procoagulant activity of Factor IXa in the presence of inhibitors (as specified in claim 2). The specification states that the objective of the patent is "to provide a preparation for the treatment of blood coagulation disorders which has particular advantages for factor VIII inhibitor patients." '590 patent, col. 2, ll. 25–28; *id.* at col. 2, ll. 29–45.

6. The '590 patent discloses only one working example of an antibody shown to increase the procoagulant activity of Factor IXa in the presence of Factor VIII inhibitors as required by claim 2 (antibody 193/AD3). *See* Marasco Dep. Tr. at 122:06–11; Marasco Rpt. ¶ 73. The highest amount that the 193/AD3 antibody increased the procoagulant activity of Factor

[7] The 3.75% figure does not appear in the specification; a person of ordinary skill in the art reading the specification could derive it from the information disclosed in Figure 25. *See* Krishnaswamy Rpt. ¶ 123.

IXa by was only 0.3–0.4% equivalent Factor VIII activity—a marginal amount. *See* Sheehan Rpt. ¶ 99; Krishnaswamy Rpt. ¶ 118.

7. In order to treat hemophilia A without a HAMA response, it would be necessary to utilize a humanized, or at least chimeric, antibody. *See* Strohl Rpt. ¶¶ 50–56.[8] There are no working examples of humanized or chimeric antibodies disclosed in the patent specification. *See* Marasco Dep. Tr. at 124:24–125:12,126:02–04; Scheiflinger Dep. Tr. at 66:16–17.

8. The inventors of the '590 patent performed their experimentation for a period of three to four years and never brought to market an antibody within the scope of claim 1 for the treatment of hemophilia A. *See* Scheiflinger Dep. Tr. at 48:25–49:08; Kerschbaumer Dep. Tr. at 14:325–15:328; Sheehan Rpt. ¶ 166.

9. Under the teachings of the '590 patent, arriving at an antibody that binds to Factor IX or IXa and increases the procoagulant activity of Factor IX is a multi-step process, involving experimentation at every critical step. *See infra* ¶¶ 10–27.

10. The level of skill in the art for the '590 patent is high,[9] Pl.'s Opp'n at 28–29 (citing Marasco Rpt. ¶¶ 264–265), and a person of ordinary skill in the art would be familiar with the

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[8] *See also* Morrison, et al., *Chimeric human antibody molecules: mouse antigen- binding domains with human constant region domains*, Proc. Natl. Acad. Sci. USA 81, 6851-55 (1984), *cited in* Marasco Rpt. ¶ 286 n.254.

[9] There is no material difference between the parties' descriptions of the level of skill in the art. *See* Garcia Decl. ¶¶ 52, 53. The court adopts Baxalta's definition for the purposes of this motion. That is, a person of ordinary skill in this art is one who:

> would have had an advanced degree and relevant work experience, either an M.D. and several years' experience practicing in the area of hematology or a Ph.D. in a chemical science- or biological science-related discipline. This person would have a working knowledge of experimental methodologies for detecting the activity of factors in the clotting cascade, measuring blood clotting

technology and techniques discussed in the patent for producing and testing antibodies generally, Marasco Rpt. ¶¶ 264–265. But it would not be possible for a person skilled in the art to predict which antibodies would satisfy the claim limitations without trial-and-error testing. *See* Scheiflinger Dep. Tr. at 92:15–93:3; Marasco Dep. Tr. at 205:04–19; Krishnaswamy Dep. Tr. at 168:09–168:19.

11. There is no guidance or direction in the specification of the '590 patent as to how to identify antibodies that satisfy the claim limitations except by using trial and error. *See* Marasco Dep. Tr. at 205:04–19; Krishnaswamy Dep. Tr. at 168:09–168:19; Scheiflinger Dep. Tr. at 92:15–93:3.

12. "The only way to know [what antibodies bind as well as function as needed] is to make antibodies and test them." Krishnaswamy Dep. Tr. at 168:20–169:02; Marasco Dep. Tr. at 218:23–219:04.[10] The '590 patent does not describe what structural or other features of the disclosed antibodies cause them to bind to Factor IX/IXa or to increase the procoagulant activity of Factor IXa. *See* Garcia Rpt. ¶ 130; Scheiflinger Dep. Tr. at 91:23–92:3; 97:23–98:02.

> capabilities by a variety of means, or would have general familiarity with basic concepts in immunology, including basic knowledge of methods for making antibodies and using them as therapeutics. This hypothetical person would be teamed with or have access to other highly skilled individuals with advanced degrees (*e.g.*, Ph.Ds.) in other biological disciplines such as immunology or molecular biology who had several years' experience with methods to produce antibodies that bind to antigens of interest.

Id. ¶ 53; Marasco Rpt. ¶ 264.

[10] "Q. . . . [T]he only way that the patent teaches a person of ordinary skill how to tell whether a given antibody to Factor IX or Factor IXa, in fact, increases the procoagulant activity of Factor IXa is to test that antibody in an assay, correct? A. That's what the patent teaches."

13. At step one of the multi-step process for producing antibodies that bind to Factor IX or IXa and increase the procoagulant activity of Factor IXa, the specification discloses how to produce antibodies using one of several methods known in the prior art "(e.g., by conventional hybridoma techniques, or by means of phage display gene libraries, immunoglobulin chain shuffling or humanizing)." '590 patent, col. 7, l. 66–col. 9, l. 10.

14. The antibodies disclosed in the '590 patent were generated using the "hybridoma" technique, as shown in Example 1. *See* Joint Stip. ¶¶ 1, 6; '590 patent, col. 9, l. 66–col. 10, l. 37.

15. In the hybridoma process, mice in groups of one to three are injected with Factor IX or IXa over a period of days. Joint Stip. ¶¶ 3, 7; '590 patent, col. 9, l. 66–col. 10, l. 8.

16. The mouse's immune system responds to the Factor IX injections by producing B-cells in its spleen that secrete antibodies against the human antigen. Joint Stip. ¶ 3. Each B-cell produces only a single antibody. *Id.* It is not possible to predict whether a mouse used to make hybridomas will produce antibodies that satisfy the claim requirements. *See* Scheiflinger Dep. Tr. at 92:15–93:03.

17. Each mouse is then euthanized, and its spleen cells removed. *See* '590 patent, col. 10, l. 8–9; Joint Stip. ¶ 4. In order to enable murine antibodies to survive and to replicate themselves sufficiently for further experimentation, the spleen cells are fused with myeloma (cancer) cells through a process known in the prior art. '590 patent, col. 10, l. 9–11; Joint Stip. ¶ 5. The inventors performed and disclosed in the '590 patent at least four such "fusion" experiments, which they labeled #193, 195, 196, and 198. Joint Stip. ¶ 8 (citing '590 patent, col. 10, ll. 11–13).

18. In each fusion experiment, after the B-cells were fused with the myeloma cells, the resulting hybrid cells, or "hybridomas," were isolated and screened using techniques known in the prior art to determine whether they produce antibodies that bind to the antigen of interest (in this case, Factor IX or IXa). *See* Joint Stip. ¶¶ 5, 9; Garcia Rpt. at 30, Fig. 8; '590 patent, col. 10, ll. 14–31.

19. Not all of the antibodies produced at step one will bind to Factor IX/IXa. Oral Arg. Hr'g Tr., ECF No. 431 (Hr'g Tr.), at 28:16–18; Scheiflinger Dep. Tr. at 92:15–93:3. Around "60% of the hybridoma cell lines screened expressed an FIX-binding antibody." Garcia Decl., Ex. 2, Reply Rpt. ¶ 21 n. 15 (citing Scheiflinger, F. et al., *Enhancement of the enzymatic activity of activated coagulation factor IX by anti-factor IX antibodies*, J. Thromb Haemost 6(2):315–322 (2008)).

20. Once the antibodies are filtered to only those that bind to factor IX/IXa, they must undergo additional screening to determine which among them demonstrate the ability to increase the procoagulant activity of Factor IXa. Garcia Rpt. ¶ 213; Marasco Dep. Tr. at 218:23–219:04.

21. In terms of the method used to measure procoagulant activity, the patent provides that "all the methods used for determining Factor VIII activity may be used." '590 patent, col. 9, ll. 22–25; *see also* Claim Construction Order at 29 (construing "increases the procoagulant activity of Factor IXa" to mean "[t]he 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" (emphasis added)).

22. The specification of the '590 patent recommends the use of a modified version of the commercially available chromogenic test-kit called COATEST VIII:C/4® (COATEST)

for the hybridoma screening step. *See* '590 patent, col. 10, l. 40–col. 12, l. 56. The modified protocols disclosed in the examples of the '590 Patent are significantly different from the recommended protocol for the commercially available COATEST test. Sheehan Rpt. ¶ 150; Krishnaswamy Rpt. ¶¶ 141, 157–161. The modifications that the inventors made to the test were designed to make the test more sensitive. *See* Marasco Dep. Tr. at 219:5–15. They also made the test more complex and time consuming. *See* '590 patent, col. 10, ll. 48–67, col. 15, ll. 44–45; Krishnaswamy Rpt. ¶ 158; Sheehan Rpt. ¶ 150. Whereas the standard COATEST assay takes minutes, the modification disclosed in the patent takes several hours. *See* Sheehan Rpt. ¶ 150, Krishnaswamy Rpt. ¶ 158; '590 patent, col. 10, ll. 48–67, col. 15, ll. 44–45.

23. The inventors of the '590 patent did not use any of the other commonly used methods to screen hybridoma cells for procoagulant activity and did not determine or describe in the specification what modifications would be necessary for those other tests to function. '590 patent, col.9, ll. 22–25; Garcia Rpt. ¶ 220.

24. In an article published by the inventors after the '590 patent was filed, they disclosed that the vast majority of antibodies produced and screened in experiments leading up to the '590 patent (98.4% of them) did not increase the procoagulant activity of Factor IXa by any amount. *See* Cole Decl. vol. 2, Ex. 24, Scheiflinger, et al., *Enhancement of the Enzymatic Activity of Activated Coagulation Factor IX by Anti-Factor IX Antibodies* (Scheiflinger Article), at 320; Marasco Dep. Tr. at 202:18–21 (agreeing that the inventors reported only 1.6% of the antibodies had procoagulant activity); Marasco Rpt. ¶ 262 ("the number [of antibodies] that would activate Factor IXa such that there is an increase in procoagulant activity, is a very, very minor sub-fraction.").

25. Once the inventors discovered antibodies that increased the procoagulant activity of Factor IXa by screening the hybridoma cells using the modified COATEST assay, they then tested one of those antibodies (193/AD3) in aPTT assays to measure clotting time, including in the presence of Factor VIII inhibitors. '590 patent, col. 16, l. 44–col. 17, l. 67; Figures 9, 10A, 10B.

26. There are no examples in the patent of seven of the nine structural formats falling under claim 4 (a chimeric antibody, a humanized antibody, a bispecific antibody, a diabody, or di-, oligo- or multimers thereof). *See* Marasco Dep. Tr. at 102:12–126:04. In order to arrive at those antibody formats from the antibodies produced through the aforementioned steps, it would be necessary for one skilled in the art to genetically modify them. *See supra* § IV.B.1. This was never done, and the patent does not provide specific guidance on how such modification would take place. Although a person skilled in the art would be familiar with the procedures for modifying antibodies using techniques known in the prior art, additional confirmatory testing would have been necessary following modification to ensure that the binding and activating functions of the antibody remained in place. *See* Marasco Rpt. ¶¶ 235, 275; *see also* Garcia Rpt. ¶ 212; Marasco Dep. Tr. at 127:24–128:25.

27. For example, the process for humanizing antibodies was well-known in the art prior to 1999, *see* Marasco Rpt. ¶ 289 n. 258 (citing Strohl Dep. Tr., ECF No. 424-11, at 17:24–18:9), but the process was "not as efficient [] as sometimes presented," Marasco Dep. Tr. at 130:18–19. The process involves selecting "human framework regions . . . from heavy chain and light chain sequences of over 1,000 human sequences each," *id*. at 130:20–22, and "the resulting antibody, despite having the same variable region as the murine antibody, frequently does not have the same effectiveness as the original murine antibody,"

id. at 130:23–131:01. Given this uncertainty, additional screening would be required to confirm whether there had been any degradation in the binding or activating functions of the antibody. *See id.* at 132:10–12; Marasco Rpt. ¶ 275.

28. The accused product, emicizumab, is a bispecific humanized antibody that mimics Factor VIIIa by binding Factor IXa with one arm and Factor X with the other arm. *See* Sampei Article at 1. It took the scientists at Chugai almost 10 years to develop emicizumab. Strohl Rpt. ¶ 224. They underwent a multi-phased, trial-and-error process that involved screening tens of thousands of antibodies and engineering the resulting antibodies for optimization before finding one that was suitable for clinical use. *Id.* ¶¶ 212–224; *see also* Sampei Article at 1–13. "The lead bispecific antibody was identified from approximately 40,000 different bispecific antibodies" and "[b]ispecific antibodies meeting the criteria for FVIII[-like] activity were extremely rare (<0.3%)." Sampei et al. (2013) Discussion, *available at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0057479.*

VII. Application of the *Wands* Factors

Applying the *Wands* factors here, the court finds as a matter of law that undue experimentation would be needed to practice the full scope of the claimed invention. First, with respect to "the quantity of experimentation necessary" (factor 1), Baxalta does not dispute that practicing the teachings of the '590 patent involves a large amount of experimentation. The potential candidates number in the millions. *See supra* § VI ¶ 2. As discussed, the patent teaches a multi-step process, with screening at every critical step to determine antibodies within the scope of the claims. *See id.* ¶¶ 13–27. Turning to factor 2, there is a limited "amount of guidance presented in the patent." *See id.* ¶ 11. There is no guidance or direction as to how to identify antibodies that satisfy the claims' limitations other than by utilizing trial and error. *See id.* This

lack of guidance is compounded by a limited number of "working examples" (factor 3). While the specification of the '590 patent discloses eleven working examples, they are all monospecific murine antibodies or fragments thereof that bind to Factor IX or IXa and increase the procoagulant activity of Factor IXa by a small amount. *See id.* ¶¶ 1–4. It does not disclose working examples of antibodies of the IgE, IgA, or IGD isotypes; of humanized, chimeric, or bispecific antibodies; of diabodies; or of dimers, oligomers or multimers thereof. *See id.* ¶ 3. There also is no working example of an antibody that increases the procoagulant activity of Factor IXa by an amount capable of moving a patient with a severe case of hemophilia A to a mild case. *See id.* ¶ 4. There is not a single example of an antibody that produces procoagulant activity in the presence of Factor VIII inhibitors by more than a marginal amount. *See id.* ¶¶ 4–6.

Courts often consider factors 4 and 7 (the "nature of the invention" and the "predictability or unpredictability" of the art) together. *See, e.g.*, *Alza Corp. v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 655–56 (D. Del. 2009). This area of art is inherently unpredictable. The field of antibodies is itself unpredictable. *See Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1352 (Fed. Cir. 2011) (analogizing finding an appropriate antibody for a particular antigen to searching for a key "on a ring with *a million* keys on it" (internal citations and quotation marks omitted)). That unpredictability is compounded here by the lack of guidance as to how to produce antibodies satisfying the full scope of the claims other than by trial-and-error. *See Fisher*, 427 F.2d at 839 ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.").

Turning to factor 6—the "relative skill of those in the art"—the level of skill would be high, with a POSITA holding "an advanced degree and relevant work experience, either an M.D.

and several years' experience practicing in the area of hematology or a Ph.D. in a chemical science- or biological science-related discipline." *Supra* note 10. Given the "state of the prior art" (factor 5), a POSITA would be familiar with the techniques for producing antibodies using hybridoma or phage display technology and in using the standard chromogenic or aPTT assays used in the trial and error process, *see supra* § VI ¶ 10, but could not predict in advance which antibodies would satisfy the claim limitations, *see id.* ¶ 11.

Finally, turning to factor 8, the undisputed facts show that a reasonable factfinder could only find that the "breadth of the claims" is great. By Baxalta's experts' own admissions, claim 1 covers all antibodies and fragments of any format, isotype or subtype, that bind with any affinity to factor IX/IXa, that achieve procoagulant effect through any mechanism of action, and that demonstrate procoagulant activity ranging from minuscule to therapeutically useful amounts, with or without the presence of Factor VIII inhibitors. *See id.* ¶¶ 1–5.

Decisions of the Federal Circuit applying the *Wands* factors make clear that the claims asserted here are not enabled.

VIII. Enablement of the Full Scope of the Asserted Claims of the '590 Patent

A. Make-and-Screen Nature of Invention

First, where, as here, there are a large number of potential candidates, few working examples disclosed in the patent, and no guidance in the specification as to how to practice the full scope of the invention except to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled. *See Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1155–56 (Fed. Cir. 2019) (finding nonenablement where the claims included the broad functional limitation of having efficacy against hepatitis C virus, which required screening a large number of candidates to identify

compounds that satisfied the limitation); *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1346–47 (Fed. Cir. 2019) (finding nonenablement where the claims required both a particular structure and functionality but the specification failed to teach one of skill in the art whether the many embodiments of the broad claims would exhibit that required functionality); *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385–86 (Fed. Cir. 2013) (finding, due to the large number of possible candidates within the scope of the claims and the specification's corresponding lack of structural guidance, it would have required undue experimentation to synthesize and screen each candidate to determine which compounds in the claimed class exhibited the claimed functionality); *see also McRO*, 959 F.3d at 1100 n.2 ("In cases involving claims that state certain structural requirements and also require performance of some function (*e.g.*, efficacy for a certain purpose), we have explained that undue experimentation can include undue experimentation in identifying, from among the many concretely identified compounds that meet the structural requirements, the compounds that satisfy the functional requirement.").

In this respect, the facts of this case are strikingly similar to the facts of *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080 (Fed. Cir. 2021). There, as here, the claims were directed to a genus that was claimed broadly in terms of functionality. The two patents at issue there were directed to monoclonal antibodies for use in treatment of elevated low-density lipoprotein ("LDL") cholesterol—a leading cause of heart disease. *Amgen*, 987 F.3d at 1082–83. The body removes LDL cholesterol from the blood stream using LDL receptors. *Id.* at 1082. But "PCSK9," a naturally occurring protein, can bind to LDL receptors and cause the receptors to be destroyed, an undesirable result. *Id.* at 1082–83. The antibodies disclosed in Amgen's patents were claimed to prevent the degradation of LDL receptors by binding a specific region of PCSK9. *Id.* at 1083. By binding that specific region, the antibodies block PCSK9 from binding LDL receptors and causing

them to be destroyed. *Id.* The asserted claims thus imposed a functional limitation that the antibodies bind to a specific target.[11] The specification disclosed working examples of 26 antibodies that satisfied the claim limitations. *Id.*

In assessing enablement, the court first explained there are "high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Id.* at 1087. Applying that standard, the court agreed with the district court's finding that the specification did not enable preparation of the full scope of the asserted claims—that the antibodies bind a specific target. *Amgen*, 987 F.3d at 1087. Key to that determination was the court's finding that the "claims [we]re far broader in functional diversity than the disclosed examples," and "the only ways for a person of ordinary skill to discover undisclosed claimed embodiments would be through either 'trial and error, by making changes to the disclosed antibodies and then screening those antibodies for the desired binding and blocking properties,' or else 'by discovering the antibodies *de novo*' according to a randomization-and-screening 'roadmap.'" *Id.* at 1088 (quoting *Amgen Inc. v. Sanofi*, 2019 WL 4058927, at *11 (D. Del. 2019)); *see also Idenix*, 941 F.3d at 1161 ("A specification that requires a [POSITA] to 'engage in an iterative, trial-and-error process to practice the claimed invention' does not provide an enabling disclosure." (quoting *ALZA*, 603 F.3d at 941).

Amgen's reasoning applies with equal force here, where the asserted claims also set forth not one but two functional requirements: that the antibodies bind to a target (Factor IX or IXa) and alter that target's activity (increasing the procoagulant activity of Factor IXa). Marasco Rpt. ¶ 63 (agreeing with Genentech's expert, Dr. K. Christopher Garcia, that the claims include the two functional limitations). Even if the first functional requirement (binding) were enabled, the second

[11] Although the asserted claims also included a functional limitation of "blocking the PCSK9/LDLR interaction," *Amgen*, 987 F.3d at 1083, the court found that "[t]he binding limitation [alone] [wa]s [] enough [] to require undue experimentation," *id.* at 1087.

is not. The record shows that if a person of ordinary skill in the art (POSITA) started with the genus of antibodies and antibody fragments that bind to Factor IX or IXa, only a very tiny percentage of those will meet the claims' functional limitation that the antibody or antibody fragment increase the procoagulant activity of Factor IXa,[12] and the only way to find that small number within the larger whole (of potentially millions of combinations satisfying the structural requirements), given the inherent unpredictability of the art and the lack of guidance in the specification, is by screening tens of thousands (if not more) antibodies or antibody fragments for procoagulant activity. *See supra* § VI ¶¶ 2, 10–24. It is a search for a needle in a haystack.

While Baxalta does not dispute the breadth of the claims, it asserts that only a "very, very minor sub-fraction" of antibodies will satisfy the claim limitations. Pl.'s Opp'n at 12 (quoting Garcia Rpt. ¶ 189). That is true, but this only exemplifies how substantial experimentation is necessary to sift through the broad genus of possible candidates to find the narrow species that satisfy the claim limitation.

The Federal Circuit considered an almost identical theory in *Idenix*, where the court found the claims were invalid for lack of enablement. 941 F.3d at 1161–63. The patent in *Idenix* claimed a method of treatment for the hepatitis C virus (HCV) by using a particular pharmaceutical drug.

[12] Although the results of the '590 patent inventors' experimentation (showing only 1.6% of antibodies screened bound to Factor IX/IXa and increased the procoagulant activity of Factor IXa) are not disclosed in the patent, the court may consider extrinsic evidence of those results to support its finding of non-enablement. *See Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 F. App'x 26, 31 n.3 (Fed. Cir. 2007) ("Although extrinsic evidence cannot be used to supplement a non-enabling specification, such evidence can shed light on whether the specification is itself enabling."); *see also Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984) (considering results of experiments performed by patentee prior to filing the patent); *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1373 (Fed. Cir. 1999) (determining evidence of the patentee's own experimental failures was appropriate to consider).

The patent claimed the drug in a generic manner that included a large number of related compounds. The only independent claim of the patent recited:

> 1. A method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of a purine or pyrimidine β-D-2'-methyl-ribofuranosyl nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester thereof.

Id. at 1155 (quoting U.S. Patent No. 7,608,597).

Of the "billions of potential 2'-methyl-up nucleosides," the specification identified only a small subset (four) compounds as being effective. *Id.* at 1156, 1161. The court thus found that the broad functional limitation of having efficacy against hepatis C virus (HCV) meant that there were a very large number of potential nucleoside candidates and only a few examples that satisfied the claim limitation. *Id.* at 1155–56, 1162. Idenix argued that the claims were not broad because, '[w]hen required to take all of the claim limitations into account, Gilead's witnesses described the claims as embracing only a 'small' number of compounds." *Id.* at 1162.

The court rejected that analysis as "backwards," explaining that "to get from a large number of candidate compounds to a relatively speaking small number of effective compounds . . . leaves a [POSITA] searching for a needle in a haystack to determine which of the 'large number' of . . . [candidate compounds] falls into the 'small' group of candidates that effectively treats HCV." *Id.* "The size disparity between those two groups," the court reasoned, "requires significant experimentation, which weighs against enablement, not for it." *Id.* The same reasoning applies here where the only way to find the very small number of antibodies that meet the claims' broad functional requirements, among millions of possible combinations, is to experiment. That there are few needles in the haystack makes the search harder, not easier.

Baxalta argues that that the experimentation required to practice the full scope of the invention is not undue here because "a POSITA need only engage in *routine* experimentation," as

shown in Examples 1 and 2 of the specification. Pl.'s Opp'n at 22 (emphasis added) (quoting Marasco Rpt. ¶ 214).[13] The same was true in *Amgen*, where expert testimony showed that "a person of skill in the art c[ould] make all antibodies within the scope of the claims by following a roadmap using anchor antibodies and well-known screening techniques as described in the specification or by making conservative amino acid substitutions in the twenty-six examples." *Amgen*, 987 F.3d at 1085. The court nevertheless found the experimentation was undue. *Id.* at 1088.

The Federal Circuit also considered and rejected a similar argument in *Wyeth*. Like Baxalta, Wyeth argued that practicing the full scope of the claims would not require undue experimentation because it "would have required only *routine* experimentation." 720 F.3d at 1384 (emphasis added). The Federal Circuit disagreed, explaining that even taking all of Wyeth's contentions—including that "one of ordinary skill could routinely use the assays disclosed in the specification to determine" which compounds fall within the scope of the claims, the claims were not enabled because "there [we]re still at least tens of thousands of candidates" to screen. *Id.* at 1385.

The same reasoning dooms Baxalta's routine experimentation arguments here. There is no guidance or direction in the specification of the '590 patent as to how to distinguish antibodies that bind to Factor IXa and increase the procoagulant activity of Factor IXa from those that do not. *Supra* ¶ 10. And "there is no genuine dispute that it would be necessary to first synthesize and then screen *each* candidate compound using the assays disclosed in the specification to determine

[13] Baxalta also points to its expert's statement that "'[t]he specification instructs a POSITA to use well-known, inexpensive, and efficient means of producing an antibody or fragment thereof that binds to Factor IX or Factor IXa and identifying those that increase the procoagulant activity of Factor IXa,' [and] it would not require 'substantial time and effort' to make and use the claimed invention." Pl.'s Opp'n at 22 (quoting Marasco Rpt. ¶ 241).

whether it has" procoagulant effect, and until you screen the antibodies, "you can't tell whether they work or not." *Wyeth*, 720 F.3d at 1385.

Finally, while acknowledging that "a POSITA would need to screen for procoagulant activity," Pl.'s Opp'n at 22 (citing Marasco Dep. Tr. at 204:01–205:19), Baxalta argues that the requisite experimentation is nevertheless not undue because "POSITAs would 'feel confident that they could [utilize the teaching of the patent to produce] antibodies [] that have procoagulant return,'" *id.* (quoting Marasco Dep. Tr. at 209:02–09). Baxalta quotes one of its experts' testimony that there is a "'profound[]' difference between (i) making antibodies that bind to Factor IX/IXa and screening them for procoagulant activity, and (ii) starting from scratch or through trial and error." *Id.* at 22 (quoting Marasco Dep. Tr. at 206:07–13); *see also* Marasco Dep. Tr. at 206:14–19 ("A. . . . It's no longer an unknown of maybe I'll find them."). But this was also true in the *Idenix*, *Enzo*, *Wyeth* and *Amgen* cases, where the inventors had identified a small number of compounds within the scope of the claims and the court found the claims were not enabled given the breadth of the claims and the lack of sufficient guidance in the specifications.[14] There is nothing in the specification teaching how to identify any antibodies complying with the claim limitations other than by repeating the same process the inventors used to identify the eleven examples disclosed in the specification.

[14] Baxalta also attempts to distinguish *Amgen* on the basis that the claims there specified the amino acids (or residues) on PCSK9 to which the antibodies must bind. Pl.'s Opp'n at 32 (citing *Amgen*, 987 F.3d at 1087 n.1 ("For example, there are three claimed residues to which not one disclosed example binds."). Baxalta maintains "[t]here is no similar unpredictability or lack of enablement in the" asserted claims in this case because they "merely require binding to Factor IX/IXa and do not require binding to specific residues." Pl.'s Opp'n at 32. The court disagrees. Here, similar to *Amgen*, there are various categories of antibodies that are identified in the claims that are not represented by working examples.

B. Broad Functional Scope

Second, the patent claims in this case, even more so than those in *Amgen* (which focused only on the binding requirement), cover a wide range of functionality in terms of procoagulant activity and that range is not represented by working examples**.** The Federal Circuit's cases make clear that where, as here, "a range is claimed, there must be reasonable enablement of the scope of the range." *See Amgen*, 987 F.3d at 1085 (quoting *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020)); *see also MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012) (claims not enabled where the patentee argued for a broad scope despite meager results achieved by the inventors). By Baxalta's own admission, the patent covers everything from a barely perceptible amount of procoagulant activity at the bottom end to an amount that would be created by Factor VIII itself (at least 40%) at the upper end. *See* Marasco Dep. Tr. at 236:12–18;[15] Krishnaswamy Dep. Tr. at 213:17–214:11;[16] *see also supra* § VI ¶ 4.

The Federal Circuit's decision in *MagSil* is instructive. There, a patentee asserted infringement of a claim directed to a device used in computer hard drive disks that required a "change in resistance by at least 10%" between two electrodes on the device. 687 F.3d at 1379–80. The background section of the patent explained that past efforts to "produce an adequate level of change in the [ ] resistance" had achieved only a 2.7% change. *Id.* at 1379. The Federal Circuit found the claims were not enabled. In relevant part, the court observed that the patent specification "only disclose[d] enough information to achieve an 11.8% resistive change," even

[15] "Q. So if an antibody binds Factor IX or IXa and increases the procoagulant activity of Factor IXa by as much as Factor VIII does, that antibody is within the scope of the claim, correct? A. . . . yeah, I think it's within the scope of the claim."

[16] "Q. . . . [I]f it turned out that . . . there were an antibody that mirrored the activity of factor VIII itself, such an antibody would still be covered by these claims if it met the other limitations; correct? A. I would agree with that statement, yes."

though the claims were construed to cover resistive changes "from 10% up to infinity." *Id.* at 1383. The Federal Circuit further stated, "[t]he record contains no showing that the knowledge of [a skilled] artisan would permit, at the time of filing, achievement of the modern values above 600% without undue experimentation." *Id.* at 1384. "Indeed," the court observed," it had taken "nearly twelve years of experimentation to actually reach those [modern] values." *Id.* The same problem exists here.

Just as it took twelve years after the filing of the patent in *Magsil* for others to reach a 604% change in resistance, here, it took scientists at Chugai almost 10 years to discover the accused product emicizumab, which increases procoagulant activity by 10%. *See supra* § VI ¶ 28; Kitazawa Dep. Tr. at 241:12–20. The highest amount that any antibody disclosed in the specification is estimated to have increased the procoagulant activity of Factor IXa is by 3.75% of normal Factor VIII levels. *See supra* § VI ¶ 4. Both are far short of normal Factor VIII levels (at least 40%). *See id.* Although agreeing that an antibody that increases procoagulant activity by the same amount as would a normal level of Factor VIII would be within the scope of the claims, *see* Marasco Dep. Tr. at 236:12–18, Baxalta's expert concedes "it would be difficult or indeed impossible to create" an antibody that increases the procoagulant activity by such an amount, Krishnaswamy Dep. Tr. at 212:18–213:7. A specification cannot adequately enable something that is admittedly impossible to accomplish. *See, e.g.*, *Tr. of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362 (Fed. Cir. 2018) ("We can safely conclude that the specification does not enable what the experts agree is physically impossible."). But even as to the compounds within the realm of possibility, there is no enablement.

The stated object of the invention is "to provide a preparation for the treatment of blood coagulation disorders . . . ." '590 patent, col. 2, ll. 25–28; *see also id.* at col. 9, ll. 25–36 ("The

present antibodies . . . are suitable for therapeutic use . . . ."). And the primary utility disclosed in the '590 patent for antibodies and antibody fragments that "increase[] the procoagulant activity of Factor IXa" is a therapeutic one. *See id.* col. 1, ll. 32–35; *id.*, col. 2, ll. 22–33; *id.*, col. 2, ll. 39–44; *id.*, col. 9, ll. 25–36; *id.*, col. 9, ll. 50–61.[17] But as discussed, the highest amount by which any antibody disclosed in the specification is estimated to have increased the procoagulant activity of Factor IXa (3.75%), would only be capable of moving a patient with hemophilia A classified as severe to a moderate classification. *See supra* § VI ¶ 4. It would not be capable of moving a patient with severe hemophilia to a mild classification. Although the experts debate whether such a small amount of procoagulant activity could be therapeutically useful for some patients, *see, e.g.*, Krishnaswamy Rpt. ¶¶ 115–118; Sheehan Rebuttal Rpt. ¶¶ 40–63, Baxalta acknowledges in the 20 years since the '590 patent was filed, it has never brought to market a product embodying the '590 patent's invention, *see* Scheiflinger Dep. Tr. 48:25–49:11 ("no company has ever brought to market a monospecific antibody to Factor IXa to treat hemophilia"); *see also* Hr'g Tr. at 55:09–12 (counsel for Baxalta agreeing that none of the eleven examples in the patent were "developed into a therapeutic product").

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[17] After discussing the therapeutic utility of the claimed subject matter, the specification proposes other uses for the disclosed antibodies and antibody fragments, which only require that they bind to factor IX/IXa (not increase the procoagulant activity of factor IXa):

> Moreover, the antibodies and antibody derivatives according to the invention may also be used for industrial applications, e.g. for the purification of factor IX/factor IXa by means of affinity chromatography, or as a component of detection methods (e.g. ELISA assays), or as an agent for identification of and interaction with functional domains of a target protein.

'590 patent, col. 9, ll. 50–56. Even if true that a stated purpose of the patent was the use of antibodies in industrial applications, that can hardly be used to show the enablement of what is clearly the primary purpose of the patent and indisputably covered by the claims—the treatment of hemophilia A.

What is more, the patent also claims therapeutic effectiveness in the presence of Factor VIII inhibitors (claim 2), necessary for the treatment of inhibitor patients. The only antibody that was subjected to the aPTT and measured in the presence of Factor VIII inhibitors was 193/AD3, *see supra* § VI ¶ 25, for which Baxalta's expert concedes the specification lacks "[]sufficient information to accurately estimate the relevant rates of Factor Xa generation" in the chromogenic assay, Krishnaswamy Rpt. ¶ 122. Genentech's expert estimated, based on Figure 6A in the patent, that 193/AD3 (the only antibody tested in the presence of Factor VIII inhibitors) increases the level of procoagulant activity only at about 0.3–0.4% equivalent of Factor VIII activity, a marginal amount. *See supra* § VI ¶ 6.

Baxalta's expert now concedes that the patent's assertions that antibodies of the invention have therapeutic utility was merely "aspirational," Krishnaswamy Dep. Tr. at 42:05–45:14, and agrees that there is "not enough information conveyed in the patent to tell whether an antibody such as [198/A1] would have activity sufficient for clinical use," *id.* at 185:23–186:05.

Baxalta's only response to *MagSil* is that it is "factually inapposite" because it pertains only to claims to "a marginal improvement to a known quality," Pl.'s Opp'n at 34, and that a lower enablement standard should somehow apply to claims covering subject matters with previously unknown qualities, as Baxalta contends is the case here, *id.*; *see also* Hr'g Tr. 57:20–58:1–2.[18] Baxalta cites no caselaw for such a proposition, and the court does not read *MagSil* to be cabined in such a way. In *Plant Genetic Systems*, the Federal Circuit made clear that the enablement requirement is the same regardless of whether marginal or major advances are the subject of a

[18] "[The court]: There's no upper limit? [Counsel for Baxalta]: No, Your Honor, . . . this is not a quality that was known in advance."

patent. 315 F.3d at 1339–40 (rejecting as "not supported by precedents" an argument that a patent was entitled to a lower enablement requirement for a "pioneering" patent).

That the '590 patent discloses a starting point for further research by disclosing a monospecific murine antibody that binds to Factor IX or IXa and increases the procoagulant activity of Factor IXa by a small amount is not sufficient enablement. *See Wyeth*, 720 F.3d at 1386 (determining that the specification provided "only a starting point for further iterative research in an unpredictable and poorly understood field"); *Storer v. Clark*, 860 F.3d 1340, 1350 (Fed. Cir. 2017) ("The specification need not recite textbook science, but it must be more than an invitation for further research.").

C. Structural Scope

Third, it is established that a claim is not enabled if it is structurally broad and there are insufficient working examples and guidance to enable the full scope of the structural limitations. *See, e.g.*, *Idenix*, 941 F.3d at 1157–58. Here, claims 2–4 and 19–20 are necessarily within the scope of claim 1 because they are dependent claims. It is undisputed that the '590 patent provides no working examples of two of the four *Markush*-group members in claims 3 and 20 (IgE and IgA), nor does the specification provide any guidance as to how one skilled in the art would alter the process disclosed in the patent or engineer antibodies to arrive at those isotypes. In fact, Baxalta's expert testified that it would be exceedingly rare to discover antibodies of those isotypes for which there are no working examples. *See supra* § VI ¶ 3(a). Although the specification states that a class switch "may also be caused in a directed manner by means of genetic engineering methods" known in the prior art, '590 patent, col. 6, ll. 41–45, the inventors of the '590 patent did not perform such engineering or provide any specific guidance beyond reference to what was known in the prior art.

Nor are there any working examples of seven of the nine members of the *Markush* group in claim 4—"a chimeric antibody, a humanized antibody, . . . , a bispecific antibody, a diabody, and di-, oligo- or multimers thereof." *See supra* § VI ¶ 3(b). Although a POSITA would have a general understanding of the process for modifying an antibody into these various formats, there is no specific direction as to the structure (*e.g.*, to what antigen the second arm of a bispecific antibody should bind),[19] and no assurance that, once the modifications are made, the antibody will retain the same functional qualities much less that making it bispecific would enhance its properties. *See id.* ¶ 26.

Of particular significance is the absence of any working examples of a humanized antibody (claim 19). While there are references to humanized antibodies in the list of antibody types known in the art, '590 patent col. 6, ll. 15–19, 49–63, and a reference to prior-art humanization techniques, *see id.* at col. 7, l. 66–col. 8, l.4, the inventors never created a humanized antibody, provided no guidance in the specification as to how to create a humanized antibody that would exhibit the claimed function, and never determined whether humanizing an antibody (that would otherwise satisfy the claim limitations) would preserve its claimed procoagulant function, *see supra* § VI ¶ 27*;* Marasco Dep. Tr. at 120:13–20, 125:24–126:04. And because there is no way to predict whether, after humanization, an antibody or antibody fragment will retain its ability to bind to factor IX/IXa and increase the procoagulant activity of factor IXa, additional screening would be

[19] Although Baxalta's expert opines that "a POSITA would know to identify a second binding specificity for the bispecific form of the claimed invention," Pl.'s Opp'n, Ex. 12, ECF No. 424-13, Chang Rpt. ¶ 81, and that a "natural choice for a second binding specificity would be one of the two proteins associated with Factor IXa in the coagulation cascade: Factor VIII or Factor X," *id.* at ¶ 82, an inventor of the '590 patent admitted that, at the time of filing, they had not thought of or disclosed which antigens a bispecific antibody would bind, *see* Kerschbaumer Dep. Tr. at 19:459–461, and another Baxalta expert conceded that additional confirmatory testing would be necessary following modification of an antibody into a different format to ensure that the binding and activating functions of the antibody remained in place, Marasco Dep. Tr. at 127:24–128:25.

necessary after modification of the antibody. *See supra* § VI ¶ 27; Garcia Rpt. ¶¶ 84–85, 167. Baxalta's expert Dr. Marasco wrote in a patent of his own, and confirmed at his deposition, that "humanizing an antibody is not as efficient a process as sometimes presented," and that after humanization an antibody "frequently does not have the same effectiveness as the original murine antibody." Marasco Dep. Tr. at 130:02–131:07.

D. Dependent Claims

So far, the court has been focused on claim 1, but the dependent claims fare no better. If anything, it is even clearer that the dependent claims are invalid given the dearth of working examples for the vast majority of what they claim as a matter of structure, as discussed *supra* § VIII.C. And the functional limitations of claim 1 apply equally to the dependent claims because they each claim the antibody or antibody fragment according to claim 1 and do not narrow the functional limitations of claim 1 in any way. *Alcon Rsch., Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("[B]ecause a dependent claim narrows the claim from which it depends, it must 'incorporate . . . all the limitations of the claim to which it refers.'" (quotation omitted)). Accordingly, given the limited working examples for the structural limitations of the asserted dependent claims—including no working examples of antibodies that satisfy claim 19 (humanized antibodies), only examples of two of the four isotypes listed in claims 3 and 20, and no working examples of seven of the nine structural formats listed in claim 4—combined with the broad scope of the functional limitations under claim 1 and the lack of guidance in the specification, no reasonable jury could find the dependent claims are enabled.

E. Nonenablement of Emicizumab

Finally, it is significant that the patent does not remotely enable the accused antibody, emicizumab, which must fall within the scope of the claims to establish an infringement claim.

Emicizumab increases the procoagulant effect by approximately 10%[20]—an amount that has proven capable of reducing bleeding episodes in inhibitor patients by a clinically significant amount. *See* Smith Decl. ¶¶ 44, 49; Malackowski Rpt. at 34, 36 . Yet, as discussed, the patent does not disclose an antibody that has procoagulant activity anywhere near that amount. None of the 11 disclosed antibodies in the specification increase the procoagulant activity of factor IXa more than 3.75%, and it is unknown whether that example would perform the same in the presence of Factor VIII inhibitors. *See supra* § VI ¶¶ 4, 6.

Moreover, key to emicizumab's therapeutic effectiveness is its structure as a bispecific humanized antibody, *see* Sampei Article at 2, and as discussed, there is no working example of either a bispecific or humanized antibody in the specification of the '590 patent, let alone an antibody that is both. Two inventors of the '590 patent, Scheiflinger and Kerschbaumer, admitted they did not make a bispecific antibody, *see* Scheiflinger Dep. Tr. at 68:08–19; Kerschbaumer Tr. at 18:429–434, and Baxalta's expert, Dr. Krishnaswamy, conceded that the patent's "language" about antibodies of the invention have therapeutic utility was merely "aspirational," Krishnaswamy Dep. Tr. at 42:05–45:14. Significantly, it took Chugai over ten years of multi-phased experimentation and the screening of tens of thousands of candidate compounds to discover emicizumab. *See supra* § VI ¶ 28.

Although Baxalta concedes that emicizumab is within the scope of the claims, it now argues that the court should not be concerned with the lack of enablement of emicizumab because

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[20] Baxalta's expert disputes the accuracy of this 10 percent figure, *see* Krishnaswamy Rpt ¶ 112, but that opinion is based on testing of emicizumab at a diluted concentration level and says nothing of the concentration level used in the treatment of hemophilia A. Moreover, the literature relied on by the same expert states that emicizumab at the treatment concentration level is "assumed to be equivalent to that of . . . 10% FVIII." Uchida et al., *A first-in-human phase 1 study of ACE910, a novel factor VIII–mimetic bispecific antibody, in healthy subjects*, Blood 127(13):1633–1641 (2016) (cited as Ex. E in Krishnaswamy Rpt).

the high coagulant effect of emicizumab may be due to the fact that it is bispecific and binds Factor X with the other arm, whereas the asserted claims involve the arm that binds Factor IX. *See* Hr'g Tr. at 50:20–51:05. In that event, Baxalta suggests maybe a compound is not within the scope of the claims if the procoagulant effect is only caused by a bispecific antibody's arm that binds to Factor X. *See id.* at 52:03–19.[21] This convoluted argument, offered for the first time at the Summary Judgment hearing, does nothing to show enablement. Baxalta convinced the Federal Circuit that bispecific antibodies are within the scope of the claims. It cannot now prevail by arguing that one bispecific antibody is perhaps not within the scope of the claims if its procoagulant activity results from its bispecific nature.

Past decisions have advised that patents should be awarded to the true inventor and that the enablement requirement serves an important purpose in this respect. *See Amgen Inc. v. Sanofi, Aventisub LLC*, 850 F. App'x 794, 796 (Fed. Cir. 2021) (denying rehearing en banc) ("One should not gain exclusivity over claimed subject matter without disclosing how to make and use it. And if one considers that one has invented a group of compositions defined by a genus but does not know enough to fully enable that genus, one would suppress innovation if one were able to claim such a broad genus, not enhance it."); *see also J.E.M. Ag Supply*, 534 U.S. at 142 (identifying an enabling disclosure as the "*quid pro quo* of the right to exclude" (quoting *Kewanee Oil Co. v.*

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[21] Counsel: "The claimed invention is about the bispecific antibody with the arm that binds Factor 9, 9A and that arm that exhibits the procoagulant activity on Factor 9, 9A, and it's not necessary to enable or to fully describe even the portions of the . . . composition that are not part of the claim."

Court: "[S]o there would be no infringement here if Hemlibra procoagulant activity resulted from the Factor 10 binding and not from the fact that it binds, the other chain binds to Factor 9A?"

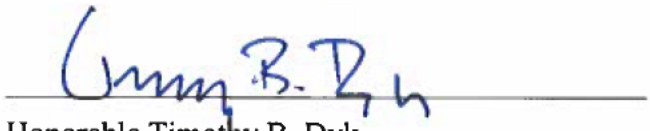
Counsel: "If the only procoagulant activity [] came from the binding of Factor 10 and there was no procoagulant activity as a result of the Factor [IX/IXA] arm, my understanding is that there would be no infringement."

Bicron Corp., 416 U.S. 470, 484 (1974)); *McRO*, 959 F.3d at 1099–100 ("The requirement of enablement . . . enforces the essential '*quid pro quo* of the patent bargain.'" (quoting *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003)).

That is, the enablement requirement ensures that the entity that does the hard work to invent a useful compound is the recipient of the patent, not some earlier inventor who may have conceived of such a therapy or made the first step in research, but did not enable its ultimate production. *See Genentech*, 108 F.3d at 1366 ("Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."); *see also Wyeth*, 720 F.3d at 1386 (finding that disclosing "only a starting point for further iterative research in an unpredictable and poorly understood field" does not constitute sufficient enablement). That is the situation here. The court cannot allow Baxalta to provide a starting point for further research and then claim "someone else's solution to the problem." *Genentech*, 108 F.3d at 1366.

CONCLUSION

For the foregoing reasons, the court GRANTS Genentech's motion for summary judgment of invalidity for lack of enablement and DENIES as moot Genentech's motion for summary judgment in all other respects.



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