81 F.4th 1362
United States Court of Appeals, Federal Circuit.

BAXALTA INCORPORATED,
Baxalta GmbH, Plaintiffs-Appellants
v.
GENENTECH, INC., Defendant-Appellee

2022-1461
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Decided: September 20, 2023

Appeal from the United States District Court for the District of Delaware in No. 1:17-cv-00509-TBD, Circuit Judge Timothy B. Dyk.

Attorneys and Law Firms

William R. Peterson, Morgan, Lewis & Bockius LLP, Houston, TX, argued for plaintiffs-appellants. Also represented by Michael J. Abernathy, Christopher John Betti, Maria Doukas, Karon Nicole Fowler, Chicago, IL; Julie S. Goldemberg, Philadelphia, PA.

Eric Alan Stone, Groombridge, Wu, Baughman & Stone LLP, New York, NY, argued for defendant-appellee. Also represented by Nicholas P. Groombridge, Naz Wehrli, Josephine Young.

Before Moore, Chief Judge, Clevenger and Chen, Circuit Judges.

Opinion

Moore, Chief Judge.

***1363** Baxalta Inc. and Baxalta GmbH (collectively, Baxalta) appeal the United States District Court for the District of Delaware's grant of summary judgment that claims 1–4, 19, and 20 of U.S. Patent No. 7,033,590 are invalid for lack of enablement. For the following reasons, we affirm.

BACKGROUND

A

Blood clots are formed through a series of enzymatic activations known as the coagulation cascade. '590 patent at 1:6–10. In a "key step" of the cascade, an enzyme known as activated Factor VIII (Factor VIIIa) complexes with another enzyme known as activated Factor IX (Factor IXa) to activate Factor X. *Id.* at 1:17–19. Hemophilia A is a blood clotting disorder where the activity of Factor VIII is functionally absent, thereby impeding the coagulation cascade and the body's ability to effectively form blood clots. *Id.* at 1:19–27. Historically, Hemophilia A has been treated by intravenously administering Factor VIII. *Id.* at 1:28–30. However, approximately 20–30% of Hemophilia A patients cannot benefit from this traditional treatment because their bodies develop Factor VIII inhibitors (i.e., antibodies against Factor VIII). *Id.* at 1:30–35.

Recognizing these drawbacks, the '590 patent sought to provide alternative means to treat Hemophilia A, particularly in patients who develop Factor VIII inhibitors. *Id.* at 2:22–28. Such preparations comprise antibodies or antibody derivatives that bind to Factor IX/IXa to increase the procoagulant activity of Factor IXa. *Id.* at 2:29–38. These antibodies allow Factor IXa to activate Factor X in the absence of Factor VIII/VIIIa. *Id.* at 1:61–67, 2:39–44. Independent claim 1 is representative and recites:

> 1. An isolated antibody or antibody fragment thereof that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa.

Id. at claim 1.

Antibodies are proteins that bind to antigens (foreign molecules in the body). More specifically, an antibody is a Y-shaped immunoglobulin molecule having a specific amino acid sequence comprising two heavy chains and two light chains. Each chain includes two regions: a variable region and a constant region. The variable region—the amino acid sequence at the tips of the "Y"—is the portion of the chain that varies between antibodies of the same isotype. [1] The variable region contains complementarity-determining regions (CDRs), which are the amino acid sequences primarily responsible for the antibody's binding and functional properties. The remaining constant region is identical across antibodies of the same isotype.

The inventors generated the antibodies claimed in the '590 patent using a prior art method known as the hybridoma technique. *Id.* at 9:62–10:37. This process involves first immunizing mice with human Factor IX/IXa to generate anti-Factor IX/IXa antibody-secreting B-cells. *Id.* The antibody-secreting B-cells are then removed and fused to myeloma cells to create hybridomas that secrete anti-Factor IX/IXa antibodies.

The inventors performed four such hybridoma fusion experiments. *Id.* at 10:11–13. Using routine techniques, the inventors screened the candidate antibodies from the four fusion experiments to determine whether the antibodies bind to Factor IX/IXa and increase procoagulant activity, as ***1364** claimed. *Id.* at 10:39–12:56. The inventors discovered that only 1.6% of the thousands of screened antibodies increased the procoagulant activity of Factor IXa. J.A. 17684. The '590 patent discloses the amino acid sequences of eleven antibodies that bind to Factor IX/IXa and increase the procoagulant activity of Factor IXa. *See* '590 patent at 12:36–49. These disclosed antibodies are all monospecific (i.e., bind to a single antigen) and monoclonal (i.e., produced by a single cell line). The written description of the '590 patent explains that a skilled artisan may use well-known antibody engineering techniques to transform the resulting antibody into different structural formats. *See id.* at 6:15–7:50 (discussing "technically modified antibodies"). For example, scientists can create "bispecific antibodies" by combining a heavy and light chain of one antibody with a heavy and light chain of a different antibody. In bispecific antibodies, unlike monospecific antibodies, each arm binds to a different antigen. *Id.* at 7:32–34. As another example, scientists can create "humanized antibodies" in which animal CDRs are inserted into an otherwise human antibody. *Id.* at 6:49–57.

B

Baxalta sued Genentech, Inc. alleging Genentech's Hemlibra® (emicizumab) product infringes the '590 patent. Emicizumab is a humanized bispecific antibody that binds to Factor IXa with one arm and Factor X with the other arm, thereby mimicking the function of Factor VIIIa. Following the district court's construction of the claim terms "antibody" and "antibody fragment" to exclude bispecific antibodies, the parties stipulated to non-infringement subject to appeal.

On a prior appeal, we held the proper construction of "antibody" was "an immunoglobulin molecule having a specific amino acid sequence comprising two heavy chains (H chains) and two light chains (L chains)," and the proper construction of "antibody fragment" was "a portion of an antibody." *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1345–49 (Fed. Cir. 2020). Because the district court's construction erroneously excluded bispecific antibodies, we vacated the judgment of non-infringement and remanded for further proceedings. *Id.* at 1349. On remand, Genentech moved for summary judgment of, *inter alia*, invalidity of claims 1–4, 19, and 20 for lack of enablement. The district court granted summary judgment. *Baxalta Inc. v. Genentech, Inc.*, 579 F. Supp. 3d 595 (D. Del. 2022). Baxalta appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review summary judgment rulings under the law of the regional circuit, here the Third Circuit. *Junker v. Med. Components, Inc.*, 25 F.4th 1027, 1032 (Fed. Cir. 2022). The Third Circuit reviews the grant of summary judgment de novo. *Melrose, Inc. v. City of Pittsburgh*, 613 F.3d 380, 387 (3d Cir. 2010). Summary judgment is appropriate when, drawing all reasonable inferences in the nonmovant's favor, there is no genuine issue of material fact and the movant is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(a); *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

A patent's specification must describe the invention and "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 ... to make and use the same." 35 U.S.C. § 112(a). As the Supreme Court recently reaffirmed in *Amgen Inc. v. Sanofi*, "the specification must enable the full scope of the invention as defined by its claims," allowing for "a reasonable amount ***1365** of experimentation." 598 U.S. 594, 610–12, 143 S.Ct. 1243, 215 L.Ed.2d 537 (2023). In other words, "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." *MagSil Corp. v. Hitachi Glob.*

Storage Techs., Inc., 687 F.3d 1377, 1380 (Fed. Cir. 2012) (internal quotation marks and citation omitted). Enablement is a question of law based on underlying factual findings. *Id.* "Because patents are presumed valid, lack of enablement must be proven by clear and convincing evidence." *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010).

Baxalta argues summary judgment of invalidity for lack of enablement was improper because, when viewing the evidence in the light most favorable to Baxalta, skilled artisans can obtain the full scope of claimed antibodies without undue experimentation. Specifically, Baxalta argues skilled artisans can make and identify new claimed antibodies (with new variable regions) using the routine hybridoma-and-screening process disclosed in the '590 patent and that such routine screening does not amount to undue experimentation. In light of the Supreme Court's recent decision in *Amgen*, we cannot agree.

In *Amgen*, the patents claimed all antibodies that (1) bind to specific amino acid residues on a protein known as PCSK9; and (2) block PCSK9 from binding to LDL receptors. 598 U.S. at 602, 143 S.Ct. 1243. The full scope of the claims covered potentially millions of antibodies, but the specification only disclosed the amino acid sequences of twenty-six antibodies that performed the two claimed functions. *Id.* at 612–13, 143 S.Ct. 1243. To make and use the undisclosed claimed antibodies, skilled artisans could either follow the "roadmap" disclosed in the patent or employ a technique known as "conservative substitution." *Id.* at 603, 143 S.Ct. 1243. The roadmap directed skilled artisans to:

> (1) generate a range of antibodies in the lab; (2) test those antibodies to determine whether any bind to PCSK9; (3) test those antibodies that bind to PCSK9 to determine whether any bind to the sweet spot as described in the claims; and (4) test those antibodies that bind to the sweet spot as described in the claims to determine whether any block PCSK9 from binding to LDL receptors.

Id. The conservative substitution technique directed skilled artisans to: "(1) start with an antibody known to perform the described functions; (2) replace select amino acids in the antibody with other amino acids known to have similar properties; and (3) test the resulting antibody to see if it also performs the described functions." *Id.*

The Supreme Court held these methods "amount to little more than two research assignments" and fail to enable the full scope of the claims. *Id.* at 612–15, 143 S.Ct. 1243. The Court reasoned Amgen's roadmap "merely describes step-by-step Amgen's own trial-and-error method for finding functional antibodies—calling on scientists to create a wide range of candidate antibodies and then screen each to see" which practice the claims. *Id.* at 614, 143 S.Ct. 1243. Similarly, the conservative substitution technique simply "requires scientists to make substitutions to the amino acid sequences of antibodies known to work and then test the resulting antibodies to see if they do too—an uncertain prospect given the state of the art." *Id.* Such approaches leave skilled artisans to "engage in 'painstaking experimentation' to see what works," which "is not enablement." *Id.* (quoting *Consol. Elec. Light Co. v. McKeesport Light Co.*, 159 U.S. 465, 475, 16 S.Ct. 75, 40 L.Ed. 221 (1895)). The ***1366** Supreme Court acknowledged, however, that methods like a roadmap or conservative substitution might be sufficient to enable other claims under different circumstances, such as where the patent discloses "a quality common to every functional embodiment." *Id.*; *see also id.* at 611, 143 S.Ct. 1243 ("[I]t may suffice to give an example (or a few examples) if the specification also discloses 'some general quality ... running through' the class that gives it 'a peculiar fitness for the particular purpose.' In some cases, disclosing that general quality may reliably enable a person skilled in the art to make and use all of what is claimed, not merely a subset." (quoting *Consol. Elec. Light Co.*, 159 U.S. at 475, 16 S.Ct. 75)).

The facts of this case are materially indistinguishable from those in *Amgen*. Claim 1 of the '590 patent covers all antibodies that (1) bind to Factor IX/IXa; and (2) increase

the procoagulant activity of Factor IXa.[2] There are *millions* of potential candidate antibodies, J.A. 18754–55 ¶ 22, but the written description discloses the amino acid sequences for only *eleven* antibodies with the two claimed functions. *See* '590 patent at 12:36–49. To obtain the undisclosed but claimed antibodies, the written description directs skilled artisans to: (1) immunize mice with human Factor IX/IXa; (2) form hybridomas from the antibody-secreting spleen cells of those mice; (3) test those antibodies to determine whether they bind to Factor IX/IXa; and (4) test those antibodies that bind to Factor IX/IXa to determine whether any increase procoagulant activity. *Id.* at 9:62–12:56. Just like the roadmap rejected by the Supreme Court in *Amgen*, the '590 patent's roadmap simply directs skilled artisans to engage in the same iterative, trial-and-error process the inventors followed to discover the eleven antibodies they elected to disclose. *See* *Amgen*, 598 U.S. at 613–14, 143 S.Ct. 1243. In both cases, "nothing in the specification [teaches] how to identify any antibodies complying with the claim limitations other than by repeating the same process the inventors used to identify the ... examples disclosed in the specification." *Baxalta*, 579 F. Supp. 3d at 619.

Moreover, it is undisputed the '590 patent contains no disclosures—such as "a quality common to every functional embodiment," *Amgen*, 598 U.S. at 614, 143 S.Ct. 1243—that would allow a skilled artisan to predict which antibodies will perform the claimed functions. The patent does not disclose any common structural (or other) feature delineating which antibodies will bind to Factor IX/IXa and increase procoagulant activity from those that will not. Nor does the patent describe why the eleven disclosed antibodies perform the claimed functions, or why the other screened antibodies do not. The only guidance the patent provides is "to create a wide range of candidate antibodies and then screen each to see which happen to bind" to Factor IX/IXa and increase procoagulant activity. *Id.* *Amgen* makes clear that such an instruction, without more, is not enough to enable the broad functional genus claims at issue here. *Id.* at 614–15, 143 S.Ct. 1243 ("[T]he ... problem we see [is that] Amgen offers persons skilled in ***1367** the art little more than advice to engage in 'trial and error.' ").

In an attempt to distinguish *Amgen*, Baxalta argues the hybridoma-and-screening process disclosed in the '590 patent does not require trial and error but instead predictably and reliably generates new claimed antibodies every time it is performed. Even accepting as true that skilled artisans will generate at least one claimed antibody each time they follow the disclosed process, this does not take the process out of the realm of the trial-and-error approaches rejected in *Amgen*.[3] *Amgen* made clear that § 112(a) requires inventors to enable the "full scope" of the claimed invention without unreasonable experimentation. *Id.* at 610–12, 143 S.Ct. 1243. Here, it is undisputed that to practice the full scope of the claimed invention, skilled artisans must make candidate antibodies and screen them to determine which ones perform the claimed functions. *See* J.A. 16451, 17340–41 (Baxalta's experts testifying the only way for skilled artisans to identify a new embodiment of the genus "is to make antibodies and test them"). This is the definition of trial and error and leaves the public no better equipped to make and use the claimed antibodies than the inventors were when they set out to discover the antibodies over which they now have an exclusive right. Under *Amgen*, such random trial-and-error discovery, without more, constitutes unreasonable experimentation that falls outside the bounds required by § 112(a). 598 U.S. at 613–15, 143 S.Ct. 1243.

Finally, Baxalta argues the district court's enablement determination is inconsistent with *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). We do not agree. We have previously explained the factual distinction between *Wands* and *Amgen*. *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1085–86 (Fed. Cir. 2021). The facts of this case are more analogous to—and are, in fact, indistinguishable from—those in *Amgen*. We do not interpret *Amgen* to have disturbed our prior enablement case law, including *Wands* and its factors.[4]

In light of the foregoing, we hold the '590 patent fails to teach skilled artisans how to make and use the full scope of claimed antibodies without unreasonable experimentation. We therefore affirm the district court's grant of summary judgment that claims 1–4, 19, and 20 are not enabled.

CONCLUSION

We have considered the parties' remaining arguments and find them unpersuasive. For the reasons given above, we affirm the district court's grant of summary judgment.

AFFIRMED

All Citations

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Footnotes

1 Antibodies are grouped into five classes known as “isotypes”: IgA, IgD, IgE, IgG, and IgM. “Ig” stands for immunoglobulin, and the following letter specifies the class.

2 The parties do not raise distinct arguments with respect to dependent claims 2–4, 19, and 20. Rather, the parties agree that practicing the challenged claims requires two steps: (1) obtaining new antibodies with new variable regions that bind to Factor IX/IXa and increase procoagulant activity; and (2) engineering these variable regions into the isotypes and formats recited in the dependent claims. Because, as discussed *infra*, we hold it requires unreasonable experimentation to practice the first step, we need not consider whether it would require unreasonable experimentation to practice the second step.

3 Indeed, the same was apparently true in *Amgen*. *See* Brief for Petitioners at 49, *Amgen*, 598 U.S. 594 (No. 21-757) (“It was undisputed that, by following the patents' roadmap, skilled artisans can generate other claimed antibodies *every time*.”). Yet, the Supreme Court still held Amgen's roadmap required trial and error. *See* *Amgen*, 598 U.S. at 614–15, 143 S.Ct. 1243.

4 At oral argument, both parties agreed the Supreme Court did not disturb the *Wands* factors. Oral Arg. at 00:40–1:16, 30:31–31:15, *available at* https://cafc.uscourts.gov/home/oral-argument/listen-to-oral-arguments. We see no meaningful difference between *Wands*' “undue experimentation” and *Amgen*'s “[un]reasonable experimentation” standards.