United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING, LIMITED, AMGEN USA, INC.,
Plaintiffs-Appellants

v.

SANOFI, AVENTISUB LLC, FKA AVENTIS PHARMACEUTICALS INC., REGENERON PHARMACEUTICALS INC., SANOFI-AVENTIS U.S. LLC,
Defendants-Appellees

2020-1074

Appeal from the United States District Court for the District of Delaware in Nos. 1:14-cv-01317-RGA, 1:14-cv-01349-RGA, 1:14-cv-01393-RGA, 1:14-cv-01414-RGA, Judge Richard G. Andrews.

Decided: February 11, 2021

JEFFREY A. LAMKEN, MoloLamken LLP, Washington, DC, argued for plaintiffs-appellants. Also represented by SARAH JUSTINE NEWMAN, MICHAEL GREGORY PATTILLO, JR.; SARA MARGOLIS, New York, NY; ERICA S. OLSON, Amgen Inc., Santa Monica, CA; EMILY JOHNSON, STEVEN TANG, STUART WATT, WENDY A. WHITEFORD, Thousand Oaks, CA; KEITH HUMMEL, Cravath Swaine & Moore LLP, New York,

NY; WILLIAM G. GAEDE, III, McDermott, Will & Emery LLP, Menlo Park, CA; CHRISTOPHER B. MEAD, Schertler Onorato & Mead LLP, Washington, DC; JAMES L. HIGGINS, MELANIE K. SHARP, Young, Conaway, Stargatt & Taylor LLP, Wilmington, DE. Plaintiff-appellant Amgen Inc. also represented by SARAH CHAPIN COLUMBIA, McDermott, Will & Emery LLP, Boston, MA; LAUREN MARTIN, Quinn Emanuel Urquhart & Sullivan LLP, Boston, MA.

MATTHEW WOLF, Arnold & Porter Kaye Scholer LLP, Washington, DC, argued for defendants-appellees. Also represented by VICTORIA REINES; DAVID K. BARR, DANIEL REISNER, New York, NY; DEBORAH E. FISHMAN, Palo Alto, CA; GEORGE W. HICKS, JR., NATHAN S. MAMMEN, CALVIN ALEXANDER SHANK, Kirkland & Ellis LLP, Washington, DC. Defendants-appellees Sanofi, Aventisub LLC, Sanofi-Aventis U.S. LLC also represented by STEPHANIE DONAHUE, Sanofi, Bridgewater, NJ. Defendant-appellee Regeneron Pharmaceuticals Inc. also represented by LARRY A. COURY, LYNDA NGUYEN, Regeneron Pharmaceuticals Inc., Tarrytown, NY.

JORGE A. GOLDSTEIN, Sterne Kessler Goldstein & Fox, PLLC, Washington, DC, for amici curiae Bristol-Myers Squibb Company, Merck Sharp & Dohme Corp. Also represented by KRISTINA CAGGIANO KELLY, ELDORA ELLISON, WILLIAM MILLIKEN.

DUANE CHRISTOPHER MARKS, Eli Lilly and Company, Indianapolis, IN, for amicus curiae Eli Lilly and Company. Also represented by TONYA COMBS, MARK STEWART, GILBERT VOY.

AMIT THAKORE, White & Case LLP, New York, NY, for amicus curiae Pfizer Inc. Also represented by DIMITRIOS T. DRIVAS; ELIZABETH K. CHANG, Palo Alto, CA; JEFFREY NEIL MYERS, Pfizer Inc., New York, NY.

STANLEY D. LIANG, Tarrytown, NY, as amicus curiae, pro se.

Before PROST, *Chief Judge*, LOURIE and HUGHES, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Amgen Inc., Amgen Manufacturing, Ltd., and Amgen USA, Inc. (collectively, "Amgen") appeal from a decision of the United States District Court for the District of Delaware granting Judgment as a Matter of Law ("JMOL") of lack of enablement of claims 19 and 29 of U.S. Patent 8,829,165 (the "'165 patent") and claim 7 of U.S. Patent 8,859,741 (the "'741 patent"). *See Amgen Inc. v. Sanofi*, No. CV 14-1317-RGA, 2019 WL 4058927, at *1–2, *13 (D. Del. Aug. 28, 2019) ("*Decision*"). For the reasons set forth below, we affirm.

BACKGROUND

Elevated low-density lipoprotein ("LDL") cholesterol is linked to heart disease. LDL receptors remove LDL cholesterol from the blood stream, thus regulating the amount of circulating LDL cholesterol. The proprotein convertase subtilisin/kexin type 9 ("PCSK9") enzyme regulates LDL receptor degradation. PCSK9 binds to LDL receptors and mediates their degradation, thus decreasing the number of LDL receptors on a cell's surface. Antibodies may bind to and block PCSK9, allowing LDL receptors to continue regulating the amount of circulating LDL cholesterol.

Amgen owns the '165 and '741 patents, which describe antibodies that purportedly bind to the PCSK9 protein and lower LDL levels by blocking PCSK9 from binding to LDL receptors. The '165 and '741 patents share a common written description. *See* Appellants' Br. 10 n.2. The specification discloses amino acid sequences for twenty-six antibodies, including the antibody (designated as "21B12")

with the generic name of evolocumab, marketed by Amgen as Repatha®. *See* '165 patent col. 85 ll. 1–43; Appellants' Br. 11 n.3. As shown for example in Figure 20A of the '165 patent, the specification discloses three-dimensional structures for the antibodies designated 21B12 and 31H4 and shows where those antibodies bind to PCSK9. The '165 and '741 patents claim antibodies that bind to one or more of fifteen amino acids (*i.e.*, "residues") of the PCSK9 protein and block PCSK9 from binding to LDL receptors.

The relevant '165 patent claims are:

> 1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.
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> 19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.
>
> 29. A pharmaceutical composition comprising an isolated monoclonal antibody, wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO: 3 and blocks the binding of PCSK9 to LDLR by at least 80%.

'165 patent col. 427 l. 47–col. 430 l. 23.

The relevant '741 patent claims are:

> 1. An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.
>
> 2. The isolated monoclonal antibody of claim 1, wherein the isolated monoclonal antibody is a neutralizing antibody.
>
> 7. The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope.

'741 patent col. 427 ll. 36–57. The claimed antibodies are defined by their function: binding to a combinations of sites (residues) on the PCSK9 protein, in a range from one residue to all of them; and blocking the PCSK9/LDLR interaction.

This is the second time that these patents have been on appeal in our court. Amgen filed suit against Sanofi, Aventisub LLC, Regeneron Pharmaceuticals Inc., and Sanofi-Aventis U.S. LLC (collectively, "Sanofi") on October 17, 2014, alleging infringement of multiple U.S. patents, including the '165 and '741 patents. *Decision* at *1. Amgen and Sanofi stipulated to infringement of selected claims (including '165 patent claims 19 and 29 and '741 patent claim 7) and tried issues of validity to a jury in March 2016. *Id.* During the trial, the district court granted JMOL of nonobviousness and of no willful infringement. *Id.* At the close of the trial, the jury determined that the patents were not shown to be invalid for lack of enablement and written description. *Id.*

Sanofi appealed to this court. Relevant to the current appeal, we held that the district court erred in its evidentiary rulings and jury instructions regarding Sanofi's defenses that the patents lack written description and enablement, and we remanded for a new trial on those

issues. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1381–82 (Fed. Cir. 2017). We also vacated the permanent injunction. *Id.*

On remand, the parties tried the issues of written description and enablement to the jury. The jury again found that Sanofi failed to prove that the asserted claims were invalid for lack of written description and enablement. Sanofi moved for JMOL and, in the alternative, for a new trial. *Decision* at *1; J.A. 895. The district court granted Sanofi's Motion for JMOL for lack of enablement and denied the motion for lack of written description. *See Decision* at *17; J.A. 35. The court also conditionally denied Sanofi's motion for a new trial. *Id.* Amgen timely appealed, and we have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1). *See* J.A. 909–10.

DISCUSSION

Whether a claim satisfies the enablement requirement of 35 U.S.C. § 112 is a question of law that we review without deference, although the determination may be based on underlying factual findings, which we review for clear error. *See Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014). The statutory basis for the enablement requirement is found in Section 112 of the patent statute, which provides in relevant part that a patent's specification must "enable any person skilled in the art . . . to make and use" the patented invention. 35 U.S.C. § 112(a). The purpose of the enablement requirement is to ensure that the public is told how to carry out the invention, *i.e.*, to make and use it. We have held that such disclosure must be "at least commensurate with the scope of the claims." *Crown Operations Int'l v. Solutia Inc.*, 289 F.3d at 1367, 1378–79 (Fed. Cir. 2002) (citing *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999)).

"To prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence

that a person of ordinary skill in the art would not be able to practice the claimed invention without 'undue experimentation.'" *Alcon Research*, 745 F.3d at 1188 (quoting *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988)). "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Wands*, 858 F.2d at 737. Those factual considerations, which have come to be known as the "*Wands* factors," are:

> (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.

Id.

As we have stated elsewhere, "[a]fter the challenger has put forward evidence that some experimentation is needed to practice the patented claim, the factors set forth in *Wands* then provide the factual considerations that a court may consider when determining whether the amount of that experimentation is either 'undue' or sufficiently routine such that an ordinarily skilled artisan would reasonably be expected to carry it out." *Alcon Research*, 745 F.3d at 1188 (quoting *Wands*, 858 F.2d at 737). Although a specification does not need to "describe how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of the range." *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020) (citing *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003)) (internal citations omitted).

On appeal, Amgen asks us to reverse the district court's decision holding '165 patent claims 19 and 29 and '741 patent claim 7 invalid for lack of enablement. Amgen

contends that, under a proper analysis of the *Wands* factors, the claims at issue were enabled because no undue experimentation is required to obtain antibodies fully within the scope of the claims. Amgen points to expert testimony purportedly showing that a person of skill in the art can 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 argues that the court erred by focusing on the effort required to discover and make every embodiment of the claims, *see* Appellants' Br. 32 (citing *Decision* at *7), while failing to recognize that Sanofi could not identify any antibody that cannot be made by following the specification's teachings. *See* Reply Br. 4–5; *see also McRO*, 959 F.3d at 1104 ("[A] usual requirement [is] that the challenger identify specifics that are or may be within the claim but are not enabled."). Amgen contends that the embodiments in the patent are structurally representative for the purpose of fulfilling the written description requirement, and such evidence is sufficient to indicate a structure/function correlation establishing enablement. *See* Reply Br. 23–24.

Sanofi responds that the district court properly concluded based on the *Wands* factors that the claims are not enabled because they require undue experimentation. As support for its position, Sanofi contends that there are millions of antibody candidates within the scope of the claims, the disclosures do not provide sufficient guidance, antibody generation is unpredictable, and practicing the full scope of the claims requires substantial trial and error. *See* Appellees' Br. 17–18, 56. According to Sanofi, the functionally defined claims cover a vast scope. *See id.* at 34–41. Sanofi argues that Amgen focused on "the number of antibodies actually known to satisfy the claims, when this court's precedents require examining the number of candidates

that must be made and tested to determine whether they satisfy the claimed function." *Id.* at 18.

We begin by considering the *Wands* case itself, which has become the "go to" precedent for guidance on enablement, and which also involved claims relating to antibody technology. The broadest claim in *Wands* "involve[d] immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype." *Wands*, 858 F.2d at 733. The U.S. Patent and Trademark Office Board of Patent Appeals and Interferences had found that undue experimentation would be required for one skilled in the art to make the claimed antibodies used in the methods because "production of high-affinity IgM anti-HBsAg antibodies [was] unpredictable and unreliable." *Id.* at 735. We found, reviewing the facts, that the disclosure adequately taught using hybridoma technology to produce the needed claimed antibodies. *See id.* at 734. We stated that "no evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen," *id.* at 740, and we accordingly held that the specification fully enabled the claimed invention, *see id.* at 736.

Importantly, although *Wands* gave birth to its eponymous factors, *Wands* did not proclaim that all broad claims to antibodies are necessarily enabled. Facts control and, in this court, so does the standard of review. In considering the *Wands* factors, the district court compared the present case to other cases in which we found lack of enablement due to the undue experimentation required to make and use the full scope of the claimed compounds that require a particular structure and functionality. For example, in *Wyeth & Cordis Corp. v. Abbott Laboratories*, we held that claims covering methods of preventing restenosis with compounds having certain functionality requirements were invalid for lack of enablement. *See* 720 F.3d 1380, 1385–86 (Fed. Cir. 2013). Of particular significance, we held that 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. *Id.*

Similarly, in *Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc.*, we found that the claims were similar to those at issue in *Wyeth* in that they required both a particular structure and functionality, and we held that the specification failed to teach one of skill in the art whether the many embodiments of the broad claims would exhibit that required functionality. *See* 928 F.3d 1340, 1345–48 (Fed. Cir. 2019). And, in *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, we affirmed the district court's determination that the claims had both structural and functional limitations, and that undue experimentation would have been required to synthesize and screen the billions of possible compounds because, given a lack of guidance across that full scope, finding functional compounds would be akin to finding a "needle in a haystack." 941 F.3d 1149, 1160–63, 1165 (Fed. Cir. 2019); *see Idenix Pharms. LLC v. Gilead Scis., Inc.*, 2018 WL 922125 (D. Del. Feb. 16, 2018). The district court found that *Wyeth*, *Enzo*, and *Idenix* all support its conclusion that the asserted claims lack enablement. *See Decision* at *9–13.

What emerges from our case law is that the enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim. As we recently explained:

> [C]onducting the *Wands* analysis has routinely involved concrete identification of at least some

> embodiment or embodiments asserted not to be enabled—including what particular products or processes are or may be within the claim, so that breadth is shown concretely and not just as an abstract possibility, and how much experimentation a skilled artisan would have to undertake to make and use those products or processes.

McRO, 959 F.3d at 1100. We then elaborated in a footnote that:

> 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.

Id. at 1100 n.2 (citations omitted).

That reasoning applies here. While functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language. *See, e.g.*, *Wyeth*, 720 F.3d at 1384 (finding that practicing the full scope of the claims would require excessive experimentation); *Enzo*, 928 F.3d at 1345 (finding that the specification failed to teach whether the many embodiments would be both hybridizable and detectable upon hybridization); *Idenix*, 941 F.3d at 1155–56 (finding that the broad functional limitation of having efficacy against hepatitis C virus increased the number of nucleoside candidates that would need to be screened).

Each appealed claim in this case is a composition claim defined, not by structure, but by meeting functional limitations. We agree with the district court's finding that the

specification here did not enable preparation of the full scope of these double-function claims without undue experimentation. *See Decision* at *13. The binding limitation is itself enough here to require undue experimentation.

Turning to the specific *Wands* factors, we agree with the district court that the scope of the claims is broad. While in and of itself this does not close the analysis, the district court properly considered that these claims were indisputably broad. The parties dispute the exact number of embodiments falling within the claims. However, we are not concerned simply with the number of embodiments but also with their *functional* breadth. Regardless of the exact number of embodiments, it is clear that the claims are far broader in functional diversity than the disclosed examples.[1] If the genus is analogized to a plot of land, the disclosed species and guidance "only abide in a corner of the genus." *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299–300 (Fed. Cir. 2014). Further, the use of broad functional claim limitations raises the bar for enablement, a bar that the district court found was not met.

We also agree with the district court that this invention is in an unpredictable field of science with respect to satisfying the full scope of the functional limitations. One of Amgen's expert witnesses admitted that translating an antibody's amino acid "sequence into a known three-dimensional structure is still not possible." J.A. 3910; *see also Decision* at *9. Another of Amgen's experts conceded that "substitutions in the amino acid sequence of an antibody can affect the antibody's function, and testing would be

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[1] For example, there are three claimed residues to which not one disclosed example binds. *See* J.A. 4283; Appellees' Br. 52. And although the claims include antibodies that bind up to sixteen residues, none of Amgen's examples binds more than nine. *See id.*

required to ensure that a substitution does not alter the binding and blocking functions." J.A. 3891; *see also Decision* at *9. And while some need for testing by itself might not indicate a lack of enablement, we note here the conspicuous absence of nonconclusory evidence that the full scope of the broad claims can predictably be generated by the described methods. Instead, we have evidence only that a small subset of examples of antibodies can predictably be generated.

Although the specification provides some guidance, including data regarding certain embodiments, we agree with the district court that "[a]fter considering the disclosed roadmap in light of the unpredictability of the art, any reasonable factfinder would conclude that the patent does not provide significant guidance or direction to a person of ordinary skill in the art for the full scope of the claims." *Decision* at *11. Here, even assuming that the patent's "roadmap" provided guidance for making antibodies with binding properties similar to those of the working examples, no reasonable factfinder could conclude that there was adequate guidance beyond the narrow scope of the working examples that the patent's "roadmap" produced.

As the district court noted, 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.* Either way, we agree with the district court that the required experimentation "would take a substantial amount of time and effort." *Id.* at *12. We do not hold that the effort required to *exhaust* a genus is dispositive. It is appropriate, however, to look at the amount of effort needed to obtain embodiments outside the scope of the disclosed examples and guidance. The functional limitations here

are broad, the disclosed examples and guidance are narrow, and no reasonable jury could conclude under these facts that anything but "substantial time and effort" would be required to reach the full scope of claimed embodiments.

We therefore conclude that, after weighing the *Wands* factors, the court did not err in concluding that undue experimentation would be required to practice the full scope of these claims.

Finally, Amgen is incorrect that the district court's decision is inconsistent with *Wands* or that our affirmance here would overrule *Wands*. *Wands*, as indicated above, does not hold that antibody screening never requires undue experimentation. The holding in *Wands* was based on the facts of that case and the evidence presented there. Here, the evidence showed that the scope of the claims encompasses millions of candidates claimed with respect to multiple specific functions, and that it would be necessary to first generate and then screen each candidate antibody to determine whether it meets the double-function claim limitations. *See Decision* at *7–13. The facts of this case are thus more analogous to those in *Enzo*, *Wyeth*, and *Idenix*, where we concluded a lack of enablement.

CONCLUSION

We have considered Amgen's remaining arguments but find them unpersuasive. For the reasons above, we affirm the district court's determination that the asserted claims are invalid for lack of enablement.

AFFIRMED