No. 20-1074

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING, LTD., and AMGEN USA, INC.,

Plaintiffs-Appellants,

v.

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

Defendants-Appellees.

On Appeal from the United States District Court for the District of Delaware, No. 14-cv-01317, Judge Richard G. Andrews

BRIEF OF DEFENDANTS-APPELLEES (NON-CONFIDENTIAL) (corrected)

George W. Hicks, Jr.
Nathan S. Mammen
C. Alex Shank
KIRKLAND & ELLIS LLP
1301 Pennsylvania Ave., NW
Washington, D.C. 20004
(202) 389-5000

David K. Barr
Daniel L. Reisner
ARNOLD & PORTER KAYE SCHOLER LLP
250 West 55th Street
New York, NY 10019
(212) 836-8000

Matthew M. Wolf
Victoria L. Reines
ARNOLD & PORTER KAYE SCHOLER LLP
601 Massachusetts Ave., NW
Washington, DC 20001
(202) 942-5000

Deborah E. Fishman
ARNOLD & PORTER KAYE SCHOLER LLP
Suite 500
3000 El Camino Real
5 Palo Alto Square
Palo Alto, CA 94306
(650) 319-4500

Counsel for Defendants-Appellees

June 2, 2020

U.S. Patent No. 8,829,165 (Appx411-412)

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.

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.

CERTIFICATE OF INTEREST

Counsel for Appellees Sanofi, Aventisub LLC, sanofi-aventis U.S. LLC, and Regeneron Pharmaceuticals, Inc. certify the following:

1. The full name of every party represented by counsel is:

   Sanofi, Aventisub LLC, sanofi-aventis U.S. LLC, and Regeneron Pharmaceuticals, Inc.

2. The names of the real parties in interest represented by counsel, and not identified in response to Question 3, are:

   Same as above.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the parties represented by counsel are:

   None.

4. The names of all law firms and the partners or associates that appeared for the parties represented by counsel in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

   Wilks, Lukoff & Bracegirdle, LLC: David E. Wilks, Scott B. Czerwonka

   Ashby & Geddes, P.A.: Steven J. Balick, Tiffany Geyer Lydon, Andrew Colin Mayo

   Kirkland & Ellis LLP: Paul D. Clement, Christopher G. Michel*

   Arnold & Porter Kaye Scholer LLP: David Giroux*, Paul Margulies, Michael A. Lynn, Michael H. Sapiro, Krista Carter*, Abigail Langsam, Anne Pearlman*

   Steptoe & Johnson LLP: John J. Molenda, Robert Greenfeld, Jeffrey C. Lee*, Siew Yen Chong*, Vishal C. Gupta, Cassandra Adams*, Richard Praseuth*, Margaret P. Kammerud*, Michael Flynn-O'Brien, Ryann M. Muir, Kiley White*

   McKool Smith: Lauren L. Fornarotto

Akin Gump Strauss Hauer & Feld LLP: Matthew Alan Pearson, Dianne B. Elderkin, Steven D. Maslowski, Matthew G. Hartman, Angela Verrecchio*, Jonathan J. Underwood, Jenna M. Pellecchia, Michael P. Kahn, Michael N. Petegorsky

Regeneron: Arunabha Bhoumik

*formerly

5. The titles and numbers of any cases known to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal are:

None.

Date: June 2, 2020 */s/ Matthew M. Wolf*

TABLE OF CONTENTS

Note re Confidential Material

Material redacted at pages 13-15, 20, and 59-61 of the non-confidential version of this brief, and highlighted in the confidential version, generally relates to Amgen's proprietary scientific information. That information was marked confidential in the proceedings below under the terms of the governing protective order and was not, to counsel's knowledge, revealed in proceedings open to the public.

TABLE OF AUTHORITIES

Cases

Statute

Note: All emphasis is added unless otherwise indicated.

STATEMENT OF RELATED CASES

Pursuant to Fed. Cir. Rule 47.5, Defendants-Appellees Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. (collectively "Sanofi/Regeneron") state that an earlier appeal in this action was previously before this Court. *See Amgen Inc. v. Sanofi*, No. 17-1480, 872 F.3d 1367 (Fed. Cir. 2017) (Prost, C.J., authoring, joined by Taranto and Hughes, JJ.). In that appeal, this Court reversed the district court in part and remanded for a new trial on written description and enablement. This appeal is from that remand trial.

Sanofi/Regeneron are aware of no case pending in this Court or any other court that will directly affect or be directly affected by this Court's decision in this appeal.[1]

[1] Sanofi (initially Aventis) and Regeneron have been full partners in developing the pharmaceutical at issue in this case. Accordingly, for brevity, this brief refers to Sanofi and Regeneron as "Sanofi/Regeneron." Sanofi and Regeneron did not jointly undertake every single activity that this brief attributes to "Sanofi/Regeneron," but the few such instances are immaterial for purposes of this appeal.

INTRODUCTION

This is a patent dispute between innovators who independently developed antibody drugs that reduce low-density lipoprotein ("LDL") cholesterol. The antibodies bind to a protein, PCSK9, thus preventing the destruction of LDL receptors that extract cholesterol from the bloodstream. Sanofi/Regeneron developed Praluent, the first FDA-approved PCSK9 antibody, and Amgen developed Repatha. These antibodies differ in amino acid sequence and where they bind to PCSK9. Both are used to treat tens of thousands of patients.

Sanofi/Regeneron patented Praluent by its amino acid sequence. Amgen likewise initially patented Repatha by its amino acid sequence. But years later, Amgen obtained *additional* patents that broadly claim *all* antibodies that bind to certain amino acids on PCSK9 and block its binding to LDL receptors. Amgen then asserted those patents against Sanofi/Regeneron, arguing that Praluent infringes their broad functional genus claims. A jury found two of Amgen's five asserted claims invalid for lack of sufficient written description—a determination that Amgen does not challenge—and the district court held that, as a matter of law, the remaining three claims are not enabled and thus are invalid.

The district court's enablement ruling was correct. The undisputed evidence showed that (1) Amgen's claims encompass millions of possible antibodies; (2) generating antibodies to bind to a particular location is unpredictable; (3) the

specification's disclosures do not improve a skilled person's ability to discover any of the vast number of antibodies within the claims' scope; and (4) making and using the claims' full scope requires substantial trial-and-error experimentation by randomly generating millions of antibodies or changing the structure of known antibodies and then, for either method, testing them to determine if they satisfy the functional limitation of binding to specified PCSK9 amino acids. Carefully applying the *Wands* factors to this evidence, the district court determined that making and using the claims' full scope requires undue experimentation, rendering the claims not enabled. That ruling follows directly from this Court's recent precedents finding non-enablement in similar circumstances. *See Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149 (Fed. Cir. 2019); *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340 (Fed. Cir. 2019); *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380 (Fed. Cir. 2013).

Tellingly, Amgen barely mentions these decisions, burying them at the end of its brief. Instead, Amgen offers criticisms that are merely an exercise in diversion and distraction. In reality, Amgen has only itself to blame. Having sought and obtained broad functional genus claims in an effort to corner the market on PCSK9 inhibitors, Amgen laid its own invalidity trap: it did not enable the full scope of what it claimed. The fundamental patent bargain is that claims cannot surpass the invention. The district court rightly concluded that Amgen's claims do just that.

The claims are invalid for another reason, too: the patents' written description fails to show that Amgen possessed the vast number of structurally diverse antibodies it claims. As demonstrated by comparing the disclosed antibodies to other antibodies that indisputably fall within the claims' scope, the specification does not disclose species representative of the claimed genus or common structural features that would permit a skilled person to visualize or recognize members of the genus.

Finally, although the undisputed evidence at trial sufficed to establish invalidity, evidence further demonstrating invalidity was improperly excluded, while Amgen's evidence was improperly admitted. Accordingly, should this Court disagree with the district court and conclude that the admitted trial evidence does not support a judgment of invalidity, Sanofi/Regeneron are at least entitled to a new trial.

The Court need not address the written description and evidentiary issues, however, because the district court correctly concluded that the claims are non-enabled and thus invalid. Amgen offers no sound basis for disturbing that judgment, which this Court should affirm.

STATEMENT OF THE ISSUES

I. Whether the district court properly ruled that the asserted claims are invalid because they are not enabled.

II. Whether the claims are also invalid because they lack sufficient written

description.

III. If the claims are not invalid based on the existing trial record, whether a new trial is warranted due to evidentiary errors.

STATEMENT OF THE CASE

A. Development of PCSK9 Antibodies

High LDL cholesterol ("LDL-C") levels can cause heart attacks, strokes, and cardiovascular disease. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1371 (Fed. Cir. 2017). Doctors have long treated high LDL-C with small molecule drugs (statins), but statins can have adverse side effects or be ineffective. *Id.* One alternative treatment is a PCSK9 inhibitor.

PCSK9 is "a naturally occurring protein that binds to and causes the destruction of liver cell receptors … responsible for extracting LDL-C from the bloodstream." *Id.* In the 2000s, academic researchers showed that PCSK9 is involved in regulating cholesterol and suggested that antibodies to PCSK9 could block its activity. Appx3681(189:24-190:17). Building on that knowledge, pharmaceutical companies sought to develop antibodies that could block PCSK9 from binding to LDL receptors ("LDL-Rs"), thereby sparing LDL-Rs from destruction and decreasing LDL-C levels. Appx3681(190:23-191:15); Appx3766(379:1-9).

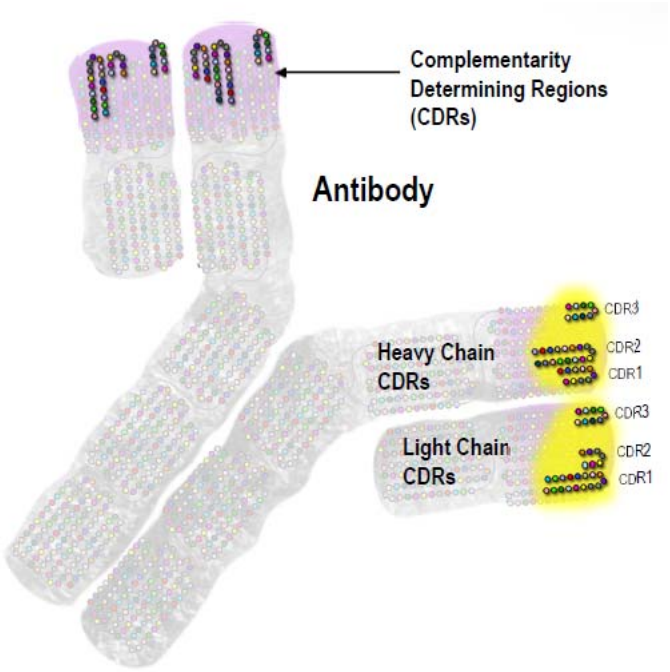
Antibodies are proteins that bind to target molecules (or "antigens") like

PCSK9. Appx3679(184:1-9); Appx3748(306:22-307:10); Appx3693(238:19-239:3); *see AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1290-91 (Fed. Cir. 2014). The region on an antigen to which an antibody binds is an "epitope." Appx3869(599:18-21).

An antibody is comprised of chains of amino acids. Appx3679-3680(184:1-185:1); Appx3748(307:14-22). The amino acid sequence is the antibody's "recipe" or "formula" and constitutes the antibody's "primary structure"; it determines the antibody's three-dimensional structure, which in turn determines the antibody's antigen-binding characteristics, *i.e.*, what the antibody is and does. Appx3914(781:20-24); Appx3783(447:19-448:6); *see also* Appx3748(307:14-22, 308:3-13); *AbbVie*, 759 F.3d at 1301.

An antibody has four "chain[s]" of amino acids (two identical "heavy" and two identical "light"), arranged in a Y-shape. Appx3679(184:1-9). Each chain "consists of a constant region and a variable region." *AbbVie*, 759 F.3d at 1291. The variable region "is the portion of the antibody … that binds to the antigen." *Id.*; Appx3759(349:13-350:10); Appx3679(184:1-15). Each variable region "has three complementarity determining regions ('CDRs')"—CDR1, CDR2, and CDR3—that "interact closely with the epitope of the antigen." *AbbVie*, 759 F.3d at 1291; Appx3680(186:25-187:16). CDRs can vary greatly, which allows antibodies to bind to many different antigens and to the same antigen in different ways. Appx3679-

3680(184:1-187:16). The heavy chain CDR3 is the "most important region of the antibody for determining binding." Appx3680(187:17-188:5); Appx3914-3915(782:21-783:3).



To find cholesterol-lowering PCSK9 antibodies, Regeneron immunized mice, generated about 1,500 candidate antibodies, narrowed that pool to 35 antibodies for amino acid sequencing, and identified about five antibodies that bound to PCSK9 and blocked PCSK9's binding to LDL-Rs. Appx3766(379:1-15). Regeneron proceeded with clinical development of one antibody, alirocumab, later approved and marketed as Praluent. *See Amgen*, 872 F.3d at 1372. Praluent "targets PCSK9 to prevent it from binding to and destroying" LDL-Rs, permitting the LDL-Rs to "extract LDL-C thereby lowering overall LDL-C levels." *Id.* In 2011, the PTO issued Regeneron a patent that claimed Praluent by its amino acid sequence. *Id.*; *see*

U.S. Patent No. 8,062,640. FDA approved Praluent in July 2015, making Praluent the first PCSK9 antibody marketed in the United States. *Amgen*, 872 F.3d at 1372; Appx3674(163:5-8); Appx3766(379:1-15).

Other pharmaceutical companies also developed PCSK9 antibodies. For example, Merck developed two different antibodies designated 1D05 and AX132. Appx3681(191:9-15). Pfizer developed an antibody designated J16. Appx3681(191:9-15). In the proceedings below and in this brief, Praluent and the antibodies developed by Merck and Pfizer are collectively referred to as the "Competitor Antibodies." Appx9 n.4.

B. Amgen's Development of PCSK9 Antibodies and Related Patent Applications

Amgen, too, developed a PCSK9 antibody. Like Regeneron, Amgen injected PCSK9 into mice, collected about 3,000 candidate antibodies, and screened and tested those candidates for antibodies that bound to PCSK9 and blocked PCSK9's binding to LDL-Rs. Appx3759-3760(351:13-353:1); Appx3797(501:23-504:9); *see Amgen*, 872 F.3d at 1372 (noting the "trial-and-error process [Amgen] used to generate and screen antibodies that bind to PCSK9 and block PCSK9"). This research yielded antibody 21B12, also known as evolocumab and marketed as Repatha. *Amgen*, 872 F.3d at 1371. Like Praluent, Repatha "targets PCSK9 to prevent it from destroying" LDL-Rs. *Id.*

Between August 2007 and August 2008 (including January 2008), Amgen

filed provisional patent applications relating to PCSK9 antibodies; the last became the specification for the patents-in-suit. Appx37; Appx421.[1] The specification described two methods to search for the claimed antibodies, both of which require making new antibodies and testing them to determine if they possess the recited binding and blocking functions. The first method is to randomly generate pools of antibodies by immunizing a mouse, Appx223(51:41-52); Appx234-238(73:35-81:34), or using phage display, Appx224-225(53:27-29, 55:1-5); Appx3909(759:7-17). The second method is to make amino acid substitutions to disclosed antibodies. Appx211(27:26-28:52); Amgen.Br.16-17. The specification's Table 1 provides a list of suggested amino acid substitutions. Appx211-212(28:24-29:10).

Amgen's January 2008 application disclosed amino acid sequences for 26 antibodies that (according to Amgen) bind to PCSK9 and block the binding of LDL-Rs. Appx51-116(Figs. 2A-3JJJ); Appx240(85:9-12, 85:35-43); Appx3800(513:15-22); Appx3868(598:21-23). One disclosed antibody is Repatha, then designated 21B12. Appx90(Fig.3JJ). For two antibodies—21B12 (Repatha) and 31H4—the application disclosed three-dimensional structures showing the PCSK9 residues to which they bind. Appx59(Fig.3E); Appx90(Fig.3JJ); Appx247-249(99:40-103:60).[2]

In 2011, the PTO granted Amgen a patent that claimed antibody 21B12

[1] The patents-in-suit have a priority date of January 9, 2008. *Amgen*, 872 F.3d at 1372.

[2] A "residue" is an amino acid in a protein. Appx3682(195:3-7).

(Repatha) by its amino acid sequence. *See* U.S. Patent No. 8,030,457. Amgen obtained FDA approval for Repatha in August 2015. *Amgen*, 872 F.3d at 1371.

C. The Patents-in-Suit

This case does *not* involve Amgen's patent claiming Repatha by its amino acid sequence. Rather, this case involves two *additional* patents obtained by Amgen three years later—U.S. Patent Nos. 8,829,165 and 8,859,741. In April 2013 and April 2014, Amgen filed the applications that issued as the '165 and '741 patents. Both patents claim priority to the January 2008 provisional application noted above and share a common specification. Appx37; Appx421. Unlike Amgen's earlier '457 patent, these patents do not claim Repatha—or any other antibody—by amino acid sequence. Instead, the relevant claims "cover the entire genus of antibodies that bind to specific amino acid residues on PCSK9 and block PCSK9 from binding to LDL-Rs." *Amgen*, 872 F.3d at 1371-72; *see* Appx411-412(427:46-430:23).

Claim 19 of the '165 patent is representative of the asserted claims. That claim and its corresponding independent claim state:

> 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.
>
> 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.

Appx411-412. Claim 19 thus covers any "isolated monoclonal antibody," regardless of its amino acid sequence, that binds to at least two of fifteen recited PCSK9 residues and "blocks binding of PCSK9 to LDLR."[3]

D. The First Trial and Appeal

In October 2014, mere days after the asserted claims issued, Amgen sued Sanofi/Regeneron, alleging that Praluent infringed the '165 and '741 patents. Sanofi/Regeneron stipulated to infringement of Amgen's broad, functional claims.[4] But Sanofi/Regeneron challenged the claims' validity on, as relevant here, enablement and written description grounds. A jury ruled for Amgen.

On appeal, Sanofi/Regeneron argued, *inter alia*, that the district court erroneously excluded evidence showing that even after Amgen filed its January 2008 priority application, it continued its trial-and-error search for antibodies within the genus. Among other things, Sanofi/Regeneron explicitly identified "Amgen's post-priority-date work to develop an antibody that would bind to the middle of the claimed PCSK9 residues." 17-1480 Corrected.Appellants.Br.33; 17-1480

[3] Claim 29 of the '165 patent recites antibodies that bind to at least two of the fifteen residues; claim 7 of the '741 patent recites antibodies that bind to at least one of two specified residues. Appx412(430:17-23); Appx796(427:36-40, 427:56-57).

[4] It is undisputed that the Competitor Antibodies (including Praluent) fall within the claims' scope. Appx3671(151:5-9); Appx3681(191:9-192:7); Appx3808(546:23-24).

Confidential.Appendix.1230(505:7-507:25), 1387, 1398.[5]

This Court agreed that exclusion of post-priority-date evidence was erroneous and not harmless. *Amgen*, 872 F.3d at 1374-75. The Court explained that "the use of post-priority-date evidence to show that a patent does not disclose a representative number of species of a claimed genus is proper" to show lack of written description. *Id.* at 1375. Additionally, "post-priority-date evidence showing that [Amgen] engaged in lengthy and potentially undue experimentation to enable the full scope of the claims … could have been relevant to determining if the claims were enabled as of the priority date." *Id.* The Court further held that the district court erroneously instructed the jury, and it ordered a new trial on written description and enablement. *Id*. at 1373-79.

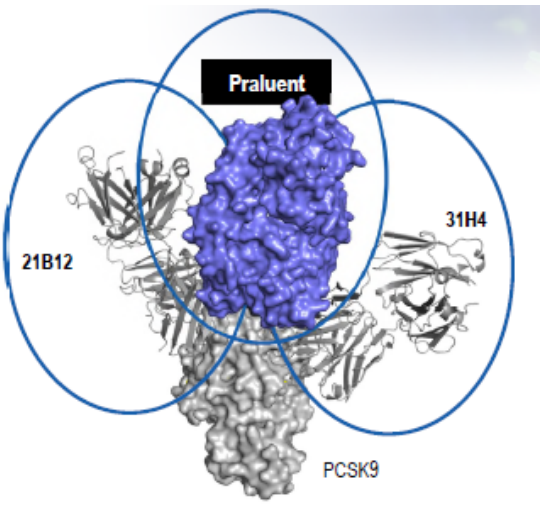
E. The Second Trial

1. Exclusion of Post-Priority-Date Evidence Showing Amgen's Unsuccessful Efforts to Find an EGFa Mimic

Before the second trial, Amgen again sought to exclude some of the very same evidence that Sanofi/Regeneron raised in the first appeal—evidence demonstrating "Amgen's post-priority-date work to develop an antibody that would bind to the middle of the claimed PCSK9 residues." 17-1480 Corrected.Appellants.Br.33. A description of that evidence follows.

[5] Citations to docket entries in *Amgen Inc. v. Sanofi*, Fed. Cir. No. 17-1480 use this format: "17-1480 [document].[page]".

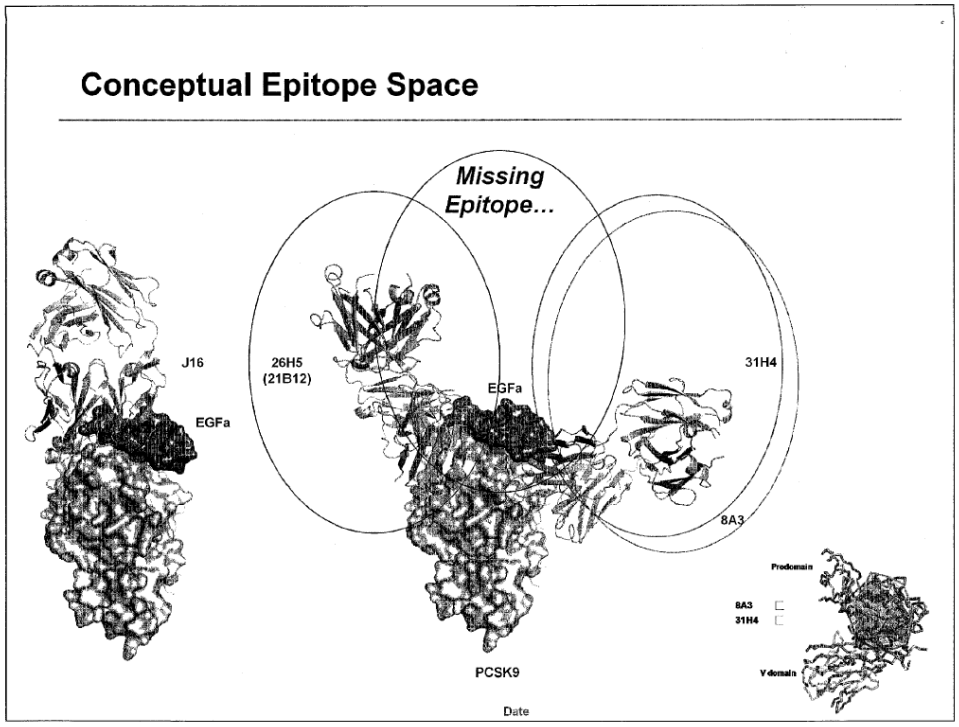
When an LDL-R and PCSK9 interact, the "EGFa domain" of LDL-R binds to all fifteen residues on PCSK9 recited by Amgen's claims. Appx3685(206:18-207:1); Appx3782(444:3-17); Appx4300. Amgen's competitor Merck developed antibodies that mimic the way LDL-R binds to PCSK9. Appx3685(207:2-208:16). Such antibodies are called "EGFa mimics" because they "sit down in this middle area that cover most or nearly all of the same amino acids" on PCSK9 to which the LDL-R binds. Appx3753(327:21-24); Appx3746-3747(300:9-301:23). Pfizer and Sanofi/Regeneron also developed antibodies that bind to most of these residues. Appx3686(209:22-210:5); Appx3782(444:18-24); Appx3783(445:8-13, 445:20-446:5); Appx4377; Appx3747(301:24-302:5). By contrast, Amgen's 21B12 (Repatha) and 31H4 antibodies—the only antibodies for which Amgen disclosed three-dimensional binding data in its January 2008 application—are not EGFa mimics (or so-called "middle binder[s]") because they bind on either side of the recited PCSK9 residues—contacting less than half of them. Appx3782-3783(442:9-445:7); Appx4377; Appx3747(301:24-302:5); Appx3885(663:2-3).



Amgen documents showed that, after 2008, Amgen realized its competitors had discovered these EGFa-mimic, middle-binding PCSK9 antibodies. Appx9674-9675; Appx9703; Appx9705-9706; Appx9708-9710. Amgen scientists acknowledged that, unlike those antibodies, Amgen's antibodies "minimally overlap with the [redacted] on PCSK9," and "none of them sit directly on top of the [redacted] Appx9708. Because Amgen "d[id]n't have any true [redacted] it worked "to find an [redacted] like its competitors. Appx9703; Appx9712; *see also* Appx9714-9715 (stating "[w]e currently do not have an EGFa mimic antibody identified but Pfizer does have one").

In October 2012, Amgen scientists prepared a document that showed the binding location of Amgen's antibodies 21B12 and 31H4 (left and right ovals) on PCSK9 compared to Pfizer's middle-binding EGFa mimic, J16. Appx9529; *see also* Appx9528-9535. As Amgen scientists explicitly indicated (see below), Amgen determined that it had a "missing epitope" because it did not have any antibodies

binding to the middle of the recited PCSK9 residues, unlike its competitors' antibodies. Appx5445(¶28); Appx5458-5464(¶¶63-75); Appx9309-9312(¶¶6-8); Appx9528-9535. Amgen's inventors conceded that it would be "tricky to find" a middle-binding EGFa mimic—and, ultimately, they [redacted] *See, e.g.*, Appx9714; *see also* Appx9690; Appx9694-9697; Appx9717-9718; Appx9720; Appx9722-9723; Appx9729-9734.



Sanofi/Regeneron sought to introduce the foregoing evidence as relevant to written description—because it showed that Amgen considered the undisclosed Competitor Antibodies (middle-binding EGFa mimics) materially different from the disclosed antibodies (not EGFa mimics)—and to enablement—because it showed

that Amgen continued to look for such antibodies (EGFa mimics) for years after the priority date but was unsuccessful, despite possessing the 2008 application (and patents-in-suit) that, Amgen now contends, allow a person of skill in the art ("POSA") to make and use the full scope of the claims. *E.g.*, Appx3908(757:12-14). The "missing epitope" document in particular was among the evidence that had previously been excluded and Sanofi/Regeneron had raised before this Court in successfully arguing that exclusion was improper. *See* 17-1480 Confidential.Appendix.1230(505:7-507:25), 1387, 1398; 17-1480 Corrected.Appellants.Br.33 (citing "missing epitope" document); 17-1480 Appellees.Br.34; 17-1480 Appellants.Reply.3. Amgen argued for exclusion because the evidence allegedly related to [redacted] antibody research, a later project to develop a pH-sensitive PCSK9 antibody. Appx5076-5079; Appx9714-9715; Appx9729-9730.

Before trial, the district court excluded the evidence as to enablement but permitted it as to written description. *See* Appx5429-5431. Minutes before trial began, however, Amgen asked the court to prohibit Sanofi/Regeneron from using this evidence in its opening statement addressing written description. Appx3636-3638(10:20-18:23). The court agreed, though it qualified its ruling by stating that it would address each exhibit as offered. Appx3656-3658(92:10-97:5). Nevertheless, when Sanofi/Regeneron sought to introduce one such exhibit, the court sustained

Amgen's objection. Appx3686-3687(211:9-215:16). And when Sanofi/Regeneron twice attempted to use the documents to impeach Amgen's lead inventor, who flatly denied the existence of a "missing epitope," the court again sustained Amgen's objections. Appx3807-3808(542:13-545:10); Appx3869-3870(602:6-606:25).

Meanwhile, over Sanofi/Regeneron's objections, *Amgen* was permitted to use post-priority-date evidence not in the specifications to bolster its written-description arguments. Specifically, for 8 of its 26 antibodies, Amgen introduced data generated years after the priority date (indeed, during this litigation) to argue that the patents disclosed representative species. *See* Appx3884-3885(662:14-664:6); Appx3915(785:17-786:17); Appx3929(841:8-11); Appx3932(853:8-18).

2. Jury Verdict and Post-Trial Decisions

Despite being hamstrung by the evidentiary rulings, Sanofi/Regeneron presented undisputed evidence demonstrating that the asserted claims are not enabled and lack adequate written description, as described in detail *infra*. The jury found claims 7 and 15 of the '165 patent invalid for lack of written description. Amgen has not challenged that verdict. The jury found the three remaining claims adequately described and enabled. Appx3631-3632.

Sanofi/Regeneron moved for judgment as a matter of law that the remaining claims are invalid for lack of enablement and written description. The court heard oral argument and received post-argument submissions. Appx2. The court granted

the motion on enablement and invalidated the remaining claims. Applying the factors of *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), to the undisputed evidence, the court held that, as a matter of law, "undue experimentation would be needed to practice the full scope of the claimed invention." Appx25. The court repeatedly cited this Court's decisions in *Wyeth* and *Enzo*, and the since-affirmed district court decision in *Idenix*, *see* 2018 WL 922125 (D. Del. Feb. 16, 2018) (Stark, C.J.), noting that these cases "support[] [its] conclusions." Appx25. The court denied JMOL on written description, and it denied Sanofi/Regeneron's motion for a new trial based on evidentiary errors. Appx26-34.

SUMMARY OF ARGUMENT

I. As a matter of law, Amgen's patents are not enabled. The undisputed evidence established that making and using the full scope of Amgen's functional genus claims requires undue experimentation under the *Wands* factors. Both parties' witnesses agreed that millions of antibodies could potentially fall within the claims' scope. They agreed that because even small changes to an antibody's amino acid sequence could change an antibody's functionality, a POSA would have to test every generated antibody to determine whether it satisfies the claims' functional limitation by binding to PCSK9 at the specified residues and blocking binding of PCSK9 to LDL-R. And they agreed that testing the vast numbers of antibody candidates generated from methods disclosed in the patent would be such an enormous

undertaking that no scientist would even fathom doing it—even if the methods for generating and testing the antibodies are themselves routine. The patents merely recite an iterative trial-and-error process and are no more enabling than the patents found non-enabled in this Court's recent decisions in *Idenix*, *Enzo*, and *Wyeth*—three precedents that Amgen all but disregards.

Rather than reconcile its patents with precedent, Amgen mischaracterizes the record and the law. Amgen disputes that one cannot know whether an antibody will bind to the claimed PCSK9 residues without testing, but neither the patents' language, its own witnesses' damning testimony, nor Sanofi/Regeneron's witnesses' testimony supports that assertion. Amgen contends that the claims' scope is narrow, but its argument turns 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. Amgen insists that following its patents does not result in millions of candidate antibodies, but that proposition relies on improperly rewriting the specification. Amgen maintains that the techniques for making and testing antibodies are routine and that Sanofi/Regeneron never identified an antibody that could not be produced using its patents, but this Court's precedents have repeatedly found non-enablement notwithstanding the former and have never required the latter. And Amgen accuses the district court of adopting an erroneous enablement standard, but the court

correctly followed the very precedents that Amgen studiously ignores.

II. The judgment can also be affirmed because Amgen's patents lack adequate written description as a matter of law. The patents do not describe species representative of the claimed functional genus: undisputed evidence established that the 26 disclosed antibodies are materially different in both structure and function from other antibodies in the claimed genus, including the Competitor Antibodies. Regardless, given the unpredictability of the art and the need for testing, the specification provides no way of knowing which antibodies fall within the claims' scope. Nor do the patents describe structural features common to the genus. Amgen's witnesses principally identified structural features not of the claimed antibodies, but of the claimed antigen, PCSK9. Amgen's meager showing of structural features purportedly common to the antibodies fails to distinguish species within the genus from those without.

III. If the trial record does not support invalidity, a new trial is nonetheless warranted because key post-priority-date evidence was once again excluded. This Court previously held that post-priority-date evidence could be relevant to show lack of enablement or written description. On remand, Sanofi/Regeneron sought admission of post-priority-date evidence showing just that. Amgen nevertheless obtained exclusion of the evidence, contending that it related to a different research program concerning a later state of the art. But that rationale contradicts this Court's

previous decision, and, regardless, the program required Amgen to *first* possess or make a [redacted] PCSK9 antibody within the claims' scope—which the excluded evidence showed Amgen could not do. Preventing Sanofi/Regeneron from using this evidence was not harmless. All the while, Amgen was improperly allowed to rely on post-priority-date data absent from the specification, under the guise of an "inherency" doctrine inapplicable here.

STANDARD OF REVIEW

This Court "exercise[s] plenary review over a district court's rulings on motions for JMOL." *Idenix*, 941 F.3d at 1153. JMOL "is appropriate where a party has been fully heard on an issue during a jury trial and the court finds that a reasonable jury would not have had a legally sufficient evidentiary basis to find for the party on that issue." *Id.* at 1153-54.

Whether a claim satisfies the enablement requirement is a question of law reviewed de novo, with the factual underpinnings reviewed for substantial evidence. *Id.* at 1154. "Compliance with the written description requirement is a question of fact" reviewed for substantial evidence, "but is amenable to" JMOL "where no reasonable fact finder could return a verdict for the non-moving party." *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1361 (Fed. Cir. 2011).

Denial of a new-trial motion is reviewed "for abuse of discretion." *Seachange Int'l, Inc. v. C-COR Inc.*, 413 F.3d 1361, 1368 (Fed. Cir. 2005).

ARGUMENT

I. Amgen's Claims Are Not Enabled.

A valid patent must "enable any person skilled in the art … to make and use the" claimed invention. 35 U.S.C. § 112 (2006). If "one of ordinary skill in the art could not practice [a claim's] *full scope* without undue experimentation," then the "claim is not enabled." *Idenix*, 941 F.3d at 1154; *accord Trs. of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018). When a specification does not enable a claim's full scope, this Court has not hesitated to hold it invalid as a matter of law. *See, e.g.*, *Idenix*, 941 F.3d at 1153-63; *Enzo*, 928 F.3d at 1345-49; *Wyeth*, 720 F.3d at 1384-86; *Everlight*, 896 F.3d at 1361-65. Amgen's patents fit the mold, and the district court should be affirmed.

A. The *Wands* Factors Establish That Practicing the Full Scope of Amgen's Claims Requires Undue Experimentation, Just As in *Idenix*, *Enzo*, and *Wyeth*.

To determine whether a patent requires "undue experimentation" in order to practice the "full scope" of the claimed invention, this Court considers the *Wands* factors. *E.g.*, *Enzo*, 928 F.3d at 1345-46 (listing factors). After receiving extensive briefing, conducting a lengthy hearing, and considering post-argument submissions, the district court faithfully applied the *Wands* factors to the undisputed evidence and held that no "reasonable factfinder could … fail to find" that "undue experimentation would be needed to practice the full scope of the claimed invention." Appx24-25. That ruling was correct.

Breadth of the claims. Sanofi/Regeneron's Dr. Boyd testified that Amgen's functionally-defined claims "cover … a vast scope of possible antibodies." Appx3750(315:11-23).[6] He explained that under the patents' first approach to generating antibodies, "you could be immunizing mice for a hundred years" and not find all of the claimed antibodies. Appx3751(318:5-13); Appx3754(329:2-331:24); *see also* Appx3896(709:6-18) (Sanofi/Regeneron's Dr. Ravetch observing that "[t]here's no limit to how many you can generate"). Dr. Boyd also explained that, under the patents' second approach to generating antibodies—substituting amino acids according to the patents' Table 1—substituting just two amino acids in a single chain of a single disclosed antibody would produce 97,000 "different antibod[ies]"; doing so for both chains of the 25 other disclosed antibodies would produce "millions," Appx3688(219:9-220:15); Appx3759(349:13-21), and substituting up to one-half of one chain's acids—as taught by the patent, Appx220(46:43-52)—would produce "an astronomically large number," Appx3759(350:13-22).

No Amgen witness was able even to estimate the number of antibodies within the claims' scope. Amgen's Dr. Rees testified he "can't give … a number." Appx3902(732:7-8). Amgen's lead inventor Dr. Jackson "d[id]n't know a specific

[6] The claim language specifies many thousands of combinations: an antibody could satisfy claim 19, for example, by binding to residues S153 and I154; or to S153 and P155; or to S153, I154, and P155; and so forth for all combinations of two or more of the 15 recited residues—about 2^{15}, or over 32,000, combinations. *See* Appx3988-3989(908:25-909:4, 911:7-16).

number." Appx3869(599:6-13). Furthermore, Dr. Rees agreed that the specification "describes substitutions as Dr. Boyd described" (*i.e.*, the Table 1 substitutions), that following those substitutions would generate "millions and millions of antibodies," and that if those "millions of antibodies" were determined to "bind and block," then "of course they would ... fall within the claims." Appx3902(731:12-14, 732:21-733:11); Appx15-16.

Predictability of the art. Undisputed evidence also established that generating antibodies to bind to a particular location on an antigen was (and is) highly unpredictable. Amgen's Dr. Rees admitted that knowing "the amino acid sequence of an antibody" does not "tell you the property of where it binds." Appx3918(797:22-25). Amgen's Dr. Petsko conceded that "[c]hanging a single amino acid in an antibody's sequence can change that antibody's function" and "turn an antibody that actually does bind into an antibody that does not bind"; he further admitted that "small changes in sequence can make big changes in structure and in some cases function," and that POSAs cannot "write down [an antibody's amino acid] sequence" from "the [desired] function." Appx3878(638:8-9); Appx3891(688:21-689:10); Appx3894(699:14-17); *see also* Appx18; Appx3749(309:5-11). And Dr. Mehlin, an Amgen inventor, acknowledged that even "conservative substitutions" are unpredictable: "sometimes what you think is a conservative mutation is not conservative at all … in terms of the protein function."

Appx3768-3769(388:24-389:8).

Given this unpredictability, Dr. Rees conceded that to determine if generated antibodies actually "bind and block" and thus fall within the claims' scope, "you'd have to test" each of them. Appx3914(779:10-14). Dr. Petsko agreed that to determine an antibody's functionality after changing "a single amino acid," a POSA "would test." Appx3891(688:21-689:10); *see* Appx18. And Dr. Mehlin agreed that "the only way to know" if an antibody resulting from a "conservative mutation" falls within the claims' scope "is to test it." Appx3768-3769(388:24-389:8).

Quantity of experimentation; working examples; amount of direction provided. In light of the uncontested need to test every generated antibody to determine if it falls within the claims, the quantity of experimentation required to make and use the full scope of the claims is substantial, and the specification provides insufficient direction and working examples to aid a POSA's task. Whether one generates pools of random antibodies in mice or with phage display, or makes substitutions to the 26 disclosed antibodies using Table 1—the two disclosed methods for making the claimed antibodies, *see* p.8, *supra*; Amgen.Br.13-17—a POSA must test those resulting antibodies to determine whether they satisfy the functional limitation of binding to PCSK9 residues. *See* Appx20; Appx22. As Amgen's Dr. Rees conceded, testing the "millions" of antibodies generated from such methods is "an enormous amount of work" and not "practical"; indeed, no

"antibody scientist would even contemplate doing" it. Appx3902(733:6-11); Appx3914(780:1-3, 781:10-14). He even admitted that it "wouldn't have been very practical" for Amgen to use its own "roadmap"—Amgen's term for the first method for making the claimed antibodies, Amgen.Br.13-16—to re-make the 26 disclosed antibodies. Appx3916(790:4-19); *see* Appx21.

In short, the undisputed evidence establishes that the "trial-and-error process" that "[t]he patents disclose," *Amgen*, 872 F.3d at 1372, is the antithesis of an enabling disclosure. Because making and using the "full scope" of Amgen's claims requires "undue experimentation," *Idenix*, 941 F.3d at 1154, the district court correctly held that Amgen's patents fail the enablement requirement.[7]

The district court's invalidity ruling adheres closely to three recent decisions from this Court—*Idenix*, *Enzo*, and *Wyeth*—holding that claims covering chemical compounds and their uses were not enabled as a matter of law. In *Idenix*, the claims covered a method of treating hepatitis C by administering a class of compounds that had structural and functional limitations. *Id.* at 1154-56. This Court held that the claims were not enabled after observing, *inter alia*, that there were "'many, many thousands' of candidate compounds"; "[t]esting" or "screening" of each candidate

[7] As the district court noted, the three other *Wands* factors—nature of the invention, state of the art, and relative skill of those in the art—do not materially bear on the analysis. Appx19-20. To the extent Amgen disagrees, Sanofi/Regeneron address its arguments *infra*.

compound was necessary to determine whether it satisfied the claim's functional requirements, given the "unpredictability" of the art; and the specification only "contain[ed] some data showing working examples" and "identif[ied] a 'target' to be the subject of future testing," leaving a POSA to "engage in an iterative, trial-and-error process to practice the claimed invention," even if "synthesis of an individual [compound] was largely routine." *Id.* at 1156-63.

In *Enzo*, the Court likewise held that claims covering compounds meeting functional requirements were not enabled. The Court noted that the "number of possible" compounds within the claims was "at least 'tens of thousands'"; that given "unpredictability in the art," each possible compound "would need to be tested" to determine if it satisfied the functional requirements; and that even if the specification described a working example and taught a POSA "how to create the broad range of labeled polynucleotides covered by" the claims, "undue experimentation" was still required regarding "the many other embodiments of the claims based on the number of possible embodiments and the unpredictability in the art." 928 F.3d at 1346-49.

And in *Wyeth*, this Court held functional claims non-enabled because there were potentially "tens of thousands of candidates"; the art was "unpredictable," since even "minor alterations" to a compound "could impact its" functional properties; and thus it was "necessary to first synthesize and then screen *each* candidate compound" to determine whether it met the functional limitations. 720 F.3d at 1384-

86 (emphasis in original). Accordingly, the specification disclosed "only a starting point for further iterative research," and "practicing the full scope of" the functional claims "would require more than routine experimentation." *Id.* at 1385-86.

The district court's ruling follows inescapably from these precedents. As noted above, at least millions of candidate compounds are within the scope of Amgen's claims. *See Idenix*, 941 F.3d at 1157, 1163 ("many, many thousands"); *Enzo*, 928 F.3d at 1349 ("tens of thousands"); *Wyeth*, 720 F.3d at 1385 (same). Given the unpredictable effect on function of even minor differences in amino acid sequence, there is no way to know whether any one of those candidates would bind to particular PCSK9 residues and block binding of PCSK9 to LDL-R, thereby satisfying the claims, without testing it. *See Idenix*, 941 F.3d at 1159, 1161; *Enzo*, 928 F.3d at 1347, 1348; *Wyeth*, 720 F.3d at 1385. And irrespective of whether producing and testing those candidates involves routine techniques, the working embodiments in the specification are at best a starting point for further "iterative, trial-and-error" exploration. *Idenix*, 941 F.3d at 1159-61; *Enzo*, 928 F.3d at 1347-49; *Wyeth*, 720 F.3d at 1385. Under the *Wands* factors and consistent with *Idenix*, *Enzo*, and *Wyeth*, Amgen's specification therefore fails to enable the claims as a matter of law. *See also MorphoSys AG v. Janssen Biotech, Inc.*, 358 F. Supp. 3d 354, 373 (D. Del. 2019) (Stark, C.J.) (finding functional genus claims to antibodies non-enabled after comparing to *Idenix*, *Enzo*, and *Wyeth*).

B. Amgen's Arguments Are Meritless.

Amgen barely mentions *Idenix* or *Wyeth*—burying them in the final pages of its brief—and does not even cite *Enzo*. And when it finally addresses *Idenix* and *Wyeth*, Amgen makes only a cursory attempt to distinguish them without ever meaningfully confronting the language in them that directs the outcome here. *See* Amgen.Br.67-68. Amgen's studious avoidance of these precedents speaks volumes about the infirmity of its position.[8]

Unable to evade *Idenix*, *Enzo*, and *Wyeth*, Amgen instead advances a fusillade of arguments that mischaracterize the record, the law, or both. Each is unavailing.

1. A POSA Cannot Know That an Antibody Will Bind to the Claimed PCSK9 Residues Without Testing.

Amgen contends that antibodies have predictable properties and need not be tested. Amgen.Br.42-49. But the remarkably uniform statements of Amgen's own witnesses belie this assertion. Amgen's expert Dr. Rees admitted that knowing an antibody's amino acid sequence does not "tell you the property of where it binds," so to determine whether the "millions of antibodies" contemplated by the

[8] Amgen knows that *Idenix* presents an obstacle: before filing its brief here, it filed an amicus brief supporting rehearing *en banc* in *Idenix*. *See* Dkt.85, No. 18-1691. Rehearing was denied. *See* Dkt.95. Having failed to meaningfully argue in its opening brief that *Idenix*, *Enzo*, or *Wyeth* are distinguishable, Amgen is foreclosed from doing so on reply. *See Impax Labs. Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1378 n.3 (Fed. Cir. 2018); *Bohler-Uddeholm Am., Inc. v. Ellwood Grp., Inc.*, 247 F.3d 79, 108 n.15 (3d Cir. 2001).

specification actually bind to the claimed PCSK9 residues, "you'd have to test" every one. Amgen's expert Dr. Petsko agreed that "[c]hanging a single amino acid in an antibody's sequence can change that antibody's function"; thus, the "only way to be sure if that single change affects the antibody's function" is that one "would test." And Amgen's Dr. Mehlin, a named inventor, acknowledged that even a so-called "conservative substitution" can be "not conservative at all … in terms of the protein function," so the "only way to know" whether an antibody meets the claim "is to test it." *See* pp.23-24, *supra*.

Amgen's efforts to downplay these admissions fail. *See* Amgen.Br.46-49, 51, 55-59. Amgen first turns to the patents, contending that antibodies generated by Table 1 substitutions "do not require testing" because they are not "new" and "still bind and block like the original." *Id.* at 46, 56 (capitalization altered). But the cited patent language (at 48-49, 59)—never mentioned to the jury—merely states that POSAs could "predict" which amino acids are important for activity, or which amino acids "can likely be altered" or "can" result in functionally similar antibodies after substitution. Appx221(48:34-42); Appx246(98:27-32). Because changing even one amino acid can have unpredictable functional effects, the fact that a substitution "can" result in functional similarity does not mean it *will*; to confirm the latter requires testing. Amgen.Br.46, 56-58; *see* Appx3768-3769(388:24-389:8); Appx3914(779:10-14); Appx3688-3689(220:16-221:2).

Amgen's attempts to rehabilitate its witnesses' testimony are equally flawed. Amgen contends that when Dr. Petsko testified that "testing would be required" if "a substitution" were made, he "was not addressing *conservative* substitutions or Table 1." Amgen.Br.59 (Amgen's emphasis). But Dr. Petsko could not have been clearer: "[c]hanging" even "a single amino acid in an antibody's sequence can change that antibody's function," so one "would test" any resulting antibodies. Appx3891(688:21-689:10). That statement leaves no room for excluding "conservative" substitutions.[9] Regardless, Dr. Mehlin *did* address "conservative" changes *in haec verba*, testifying that one has "to test" resulting antibodies. Amgen is left to contend that Dr. Mehlin did not make this admission "in the context of Table 1 or the claimed antibodies." Amgen.Br.58-59. But Dr. Mehlin *was reviewing the '165 patent* during that testimony. *See* Appx3768-3769(388:12-389:8). And the most Amgen can say about Dr. Rees is that, on an unrelated project "in the 1980s," he supposedly used "intelligent design of substitutions" to produce antibodies that had "the same properties" as unmodified antibodies. Amgen.Br.57 (quoting Appx3914(779:23-780:11)). That says nothing about the substitutions directed by Table 1—which, Dr. Rees admitted (consistent with Dr. Mehlin), would produce

[9] It bears emphasizing, moreover, that there is no evidence—in the patents or presented by Amgen—that the Table 1 substitutions taught by the patents are "conservative."

antibodies "you'd have to test" to evaluate functionality. *See* pp.23-24, *supra*.[10]

Amgen fares no better in attacking Sanofi/Regeneron's witnesses. According to Amgen, Dr. Boyd asserted that "antibodies with small differences in sequence" are "considered 'the same antibody' that 'bind in the [same] way.'" Amgen.Br.45. But Amgen mischaracterizes the testimony; as Dr. Boyd made clear in the *exact sentence* Amgen cites, he was referring to antibodies with "the *same sequence*." Appx3763(368:9-15). In the very next breath, furthermore, Dr. Boyd doubted whether "it's fully possible for two antibodies with different sequences to bind the same target in exactly the same way." Appx3763(368:19-22). Indeed, just like Amgen's witnesses, Dr. Boyd testified that "making substitutions" results in "new antibodies" that are "different" from the original, and therefore "you would have to test" them because "[s]mall changes have an affect [sic] on how the antibody binds." Appx3759(349:6-7); Appx3688-3689(219:11-15, 220:2-4, 220:20-221:2).

Amgen similarly twists Dr. Eck's testimony. Amgen.Br.17, 45. His

[10] Throughout trial, as in Amgen's cited testimony, Dr. Rees invoked what he called "intelligent substitutions." *E.g.*, Appx3902(733:2-22). But there is no evidence that his made-for-trial notion of "intelligent substitutions" is equivalent to the substitutions taught by Table 1 or even "conservative substitutions." Unsurprisingly, Dr. Rees was vague regarding the relationship between these concepts. *See* Appx3914(779:21-780:1) (noting that the patent "tells you to make conservative substitutions," but "[a]n antibody scientist would look at that and do what I call intelligent substitution"). And when asked whether the patent "teaches you how to do those intelligent substitutions," he could only nebulously answer that the patent "makes reference to the art that already talks about this." Appx3902(733:12-15).

observation that 12 of the antibodies "disclosed in the patent" share "common structural features" with "some modest variations" was based on disclosure in the patent that the antibodies "bind and block." Appx3788(465:1-5, 467:1-15). That says nothing about the need to test new antibodies that may *not* bind and block, which is necessary precisely because—as Dr. Eck unambiguously testified, consistent with Amgen's witnesses—"even small changes in structure, changing one amino acid … could remove a particular interaction with a claimed amino acid [residue]." Appx3788(466:18-21); *see also* Appx3748(308:6-19); *Wyeth*, 720 F.3d at 1380 (noting that "even minor alterations to the [disclosed] molecule could impact its properties"); *cf. AbbVie*, 759 F.3d at 1301 (characterizing antibody development as "highly unpredictable").[11]

Unable to plausibly dispute the unpredictable effect of changing an antibody's sequence on its binding properties—thereby requiring testing to determine whether generated antibodies fall within the claims—Amgen changes the subject, addressing the purported predictability of *other* aspects of the antibody arts. Thus, Amgen

[11] Amgen accuses the district court of inconsistency because, when analyzing written description, the court remarked that amino acid sequence may not be the "appropriate metric" for comparing disclosed species to the claimed genus. Amgen.Br.54. But the court was merely explaining that, in its view, sequence is not the only metric for assessing "structural similarity." Appx9. That conclusion regarding antibody *structure* does not answer the relevant question of how changes to an antibody's sequence affect its *function—i.e.*, whether and how the modified antibody will bind to the antigen.

argues that the specification's methods of *making* and *screening* antibodies are "quick and routine." Amgen.Br.60; *see also id.* at 54 ("Antibody scientists reliably *produce* antibodies as taught in the patent[.]"). And it contends that practicing those methods would *eventually* produce all of the antibodies satisfying the claims' functional requirements. *See id.* at 33-34, 55. But even if making and screening antibodies were routine, that would not tell a POSA—*before testing*—whether a particular antibody sequence would bind to the claimed PCSK9 residues. As Amgen's witnesses repeatedly acknowledged, testing is required every time.

Amgen's reliance on *Wands*, *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), and *Johns Hopkins University v. CellPro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998), overreads those decisions and misstates the relevant inquiry here. *See* Amgen.Br.56, 61-62. To begin, unlike the claims in those cases, which merely required binding to an antigen, Amgen's claims require binding to *a specific region* on an antigen (PCSK9). It is that particular requirement that implicates the conceded unpredictability of generating antibodies to bind to specific residues (and the need to test such antibodies to determine if they do so). *See* Appx3683(197:2-21) (Dr. Boyd explaining that one cannot "say … I want [an antibody] that binds right up in the top part of the [recited residues]" but instead must "hope that you get [antibodies] that are going to be targeting the areas that you are interested in"). Moreover, in those cases, unlike here, there was no evidence

presented as to the "enormous" amount of work, Appx3902(733:7-11), that would be required to screen the candidate antibodies that could meet the claim limitations. *See, e.g.*, *Wands*, 858 F.2d at 740.

In short, the undisputed evidence established that because even small changes to amino acid sequence can affect an antibody's function, a POSA would have to test every antibody generated through the methods taught by the patents in order to determine if it binds to PCSK9 at the specified residues and thus falls within the claims' scope. This Court has consistently held patents non-enabled in such circumstances. *See Idenix*, 941 F.3d at 1161 (candidate compounds "would need to be tested"); *Enzo*, 928 F.3d at 1348 ("each labeled polynucleotide would need to be tested"); *Wyeth*, 720 F.3d at 1385 (patentee's witness conceding that "until you test [compounds], you really can't tell whether they work or not").

2. The Scope of the Claims is Vast.

a. The Claims Cover Millions of Candidate Antibodies.

Amgen also disputes the claims' vast scope, *see* Amgen.Br.40-42, invoking Dr. Rees's assertion that the claimed genus is "narrow." But neither that statement nor Amgen's other arguments regarding the claims' scope withstands scrutiny.

First and foremost, Dr. Rees's testimony was directed to the number of antibodies *actually known today* to meet the claims' limitations. Amgen reiterates this theme, noting that "the parties identified only a small number of antibodies

meeting the claim limitations"—"around 400 distinct antibodies." Amgen.Br.41-42. But as this Court has repeatedly held—in decisions Amgen disregards—when assessing functional claims, the enablement inquiry begins with the number of possible *candidates* that must be made and tested to determine whether they satisfy the claimed function. *See Idenix*, 941 F.3d at 1157, 1159, 1162 (noting that "at least 'many, many thousands' of *candidate* compounds exist," and "many *candidate* nucleosides would need to be synthesized before they could be screened"); *Enzo*, 928 F.3d at 1346 (noting "the number of *possible* polynucleotides that would fit within the limitations"); *Wyeth*, 720 F.3d at 1385-86 (noting "tens of thousands of *candidates*" of "*potential* rapamycin compounds"). When Dr. Rees was asked about the *potential* number of candidates, he "agree[d]" with Dr. Boyd that following the Table 1 substitutions would produce "millions and millions" of antibodies that could "fall within the claims." Appx3902(731:12-14, 733:2-6).[12]

This critical (and ignored) distinction defeats Amgen's other arguments for "narrow" claim scope. Amgen asserts that the scope is limited because the "sweet spot"—Amgen's name for the list of PCSK9 residues the '165 patent's claims

[12] Notably, Amgen never argued to the jury that the claims only cover "around 400 distinct antibodies." And accepting that argument would mean that "a large part of the asserted claims' scope," which specifies 2^{15} combinations of residues that could be bound by antibodies, "is directed toward inoperative embodiments," which alone establishes non-enablement. *Pharm. Res. v. Roxane Labs., Inc.*, 253 F. App'x 26, 30 (Fed. Cir. 2007); *see also Everlight*, 896 F.3d at 1364 (claims drafted to cover six enumerated permutations not enabled because one permutation was "impossible").

recite—is "a small target." Amgen.Br.40. But even if "only a small group … of antibodies will have the structure" to *actually* "bind that restricted target," *id.*, that does not change the fact that the number of *potential* antibodies over the full scope of the claims that artisans would have to make and test to determine if they meet the functional limitations of the claims remains "millions."

Similarly, Amgen touts its "immunization protocol" as generating only a "restricted group of antibodies." *Id.* at 40-41. But the patents teach other methods of generating antibodies besides immunizing mice—phage display and Table 1 substitutions—and even for mouse-generated antibodies, Dr. Boyd testified without contradiction that "you could be immunizing mice for a hundred years" and not find all of the claimed antibodies. Appx3754(329:2-331:24); *see also* Appx3751(318:5-13). Regardless, the "immunization protocol" that a researcher might use to determine which candidate antibodies actually bind to specific PCSK9 residues is legally irrelevant to determining the breadth of the claim scope. In the enablement inquiry, claim scope depends on "the claim as written, not just the subset of the claim that a POSA might practice" or might find using "common sense, the claims, [the] specification," and research tools not required by the claims themselves. *Idenix*, 941 F.3d at 1162.

b. The Table 1 Substitutions Confirm the Vast Scope.

Amgen disputes that following the substitutions taught in the patents' Table 1 would yield "millions of antibodies that must be tested." Amgen.Br.42; *see id.* at 42-48. Amgen's arguments fail across the board.

Amgen's patents disclose 26 antibodies known to satisfy the claims' limitations. Table 1 of the patents provides a list of amino acids that can be substituted for those in the disclosed antibodies. Appx211-212(28:24-29:10). Sanofi/Regeneron's Dr. Boyd explained that following Table 1 and changing just two amino acids on one chain of one disclosed antibody would result in at least 97,000 "different antibody" candidates; doing so for all 26 disclosed antibodies would result in "millions" of candidates. Amgen's Dr. Rees explicitly agreed with Dr. Boyd on this point. *See* pp.22-23, *supra*.

Amgen first attempts to sidestep all of this by contending that "[n]othing in the patents instructs POSAs to make every possible substitution under Table 1." Instead, POSAs would "make selective, 'intelligent' substitutions," and even then, only to the "CDR region" or "CDR3 loop" of the patents' disclosed antibodies. Amgen.Br.44, 47-48. But the patents themselves say nothing about making "intelligent" substitutions—which, as noted, was a vague, made-for-trial concept that Amgen never actually defined. *See* n.10, *supra*. Likewise, Table 1 does not limit substitutions only to a CDR region. Thus, while Amgen feigns disbelief at Dr.

Boyd's method of calculations, *see* Amgen.Br.43-44, it never actually disputes—nor could it—that Dr. Boyd was "following the rules" in the patent. Appx3688(218:17-220:15). Amgen's attempt to write "intelligent" and "CDR-only" substitutions into the specification based on a POSA's supposed knowledge constitutes "an impermissible end-run around the requirement to enable the full scope of the claim" in the patents themselves. *Idenix*, 941 F.3d at 1159; *see also Enzo*, 928 F.3d at 1348 (explaining that "deficiencies in the description as to enablement cannot be cured … by looking to the knowledge of" a POSA); *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010).[13]

Amgen's quibble with the district court's "invocation of 'random mutations,'" Amgen.Br.49-50 (capitalization altered), fails for similar reasons and misses the point entirely. Below, as here, Amgen argued that the claim scope was narrow "because an antibody scientist would not engage in random mutations to the disclosed antibodies." Appx14. The district court correctly rejected that argument because an "antibody scientist's refusal to engage in random mutations" or any other method to *make* candidate antibodies does not reduce the number of candidate

[13] Amgen argues that Dr. Boyd improperly substituted amino acids "at every position in the heavy chain." Amgen.Br.43 (emphasis omitted). Not so. He made substitutions "in the *variable* part of" the heavy chain, Appx3688(219:18-220:7); Appx3759(349:13-21)—the region "involved in binding the antigen," Appx3759(349:13-350:10); *see AbbVie*, 759 F.3d at 1291.

antibodies that may satisfy the functional claim limitations to begin with. Appx15.[14]

Amgen also contends that "conservative" substitutions "produce virtually identical 'variants' of the reference antibodies," because the resulting amino acid sequences "are more than 99% *identical* to" the sequences of "the original antibody." Amgen.Br.44-45 (Amgen's emphasis). Amgen's "99% identical" assertion is yet another proposition it never presented to the jury, but this contention is flawed regardless. To begin, neither the patents nor Amgen's evidence indicates that the Table 1 substitutions are "conservative." *See* n.9, *supra*. But even assuming that they are conservative, Amgen's assertion assumes that only two amino acids are substituted, Amgen.Br.44-45, which is not a limitation set out in Table 1. More significant, as Amgen's and Sanofi/Regeneron's witnesses uniformly testified, even just one amino acid substitution can drastically affect antibody function, requiring the testing of every variant: "you can replace one amino acid with a different one" to create a variant, "[b]ut it results in you mak[ing] a *different antibody*" that must

[14] Relatedly, that "the patents teach POSAs how to *make*" the Table 1 variants, Amgen.Br.45-46, does not eliminate the need to *test* them. Even if a POSA "could have concluded that synthesis of an individual [antibody] was largely routine," that does not affect the number of "candidates" that need to be tested or enable the claims. *Idenix*, 941 F.3d at 1157, 1160, 1162; *Enzo*, 928 F.3d at 1346, 1349; *Wyeth*, 720 F.3d at 1382, 1385.

be tested. Appx3688-3689(219:11-17, 220:16-221:2).[15]

Amgen argues that "because conservative substitutions can be made to *any* antibody," accepting that Table 1 yields "millions of antibodies" would "render *all* antibody genus claims … invalid." Amgen.Br.46 (Amgen's emphasis). Nonsense. The problems with Amgen's expansive claims and narrow specification are not inherent to all antibody genus patents. Amgen could have sought claims to a genus of antibodies defined by their amino acid *structure*, not merely by their antigen-binding *function*, or to a genus of antibodies defined by a combination of antigen-binding function and structure matching the scope of the invention its specification actually describes and enables. But Amgen sought significantly more than that, and more than what it actually invented and could teach others to predictably make without undue experimentation. Preventing such "inadequate disclosure of an invention and overbroad claiming that might otherwise attempt to cover more than was actually invented" is the *raison d'être* of the "enablement requirement." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012); *see also id.* at 1381-84 (claim to "at least 10%" change in resistance not enabled

[15] Amgen asserts that the new antibody "variant" is "expected to 'still retain a similar biological activity.'" Amgen.Br.44. But Amgen selectively quotes the patent, which states that "certain amino acids can be substituted for other amino acids … and still retain a similar biological activity." Appx211(27:60-62). That says nothing about whether substituting amino acids in disclosed antibodies per Table 1 will necessarily produce antibodies with the same binding properties such that testing is not required.

where inventors achieved only 11.8% change and greater changes were not achieved by others until many years later).

3. Practicing the Full Scope of the Claims Would Require Significant Experimentation.

a. Amgen's Patents Do Not Provide a Roadmap to Practice the Full Scope of the Claimed Inventions Without Significant Experimentation.

Amgen contends that its patents provide a "roadmap" for "using … two antibodies to make the full scope" of candidate antibodies using purportedly "predictable," "quick," and "routine" methods that enable the claims. Amgen.Br.33; *see id.* at 37-38, 51-53, 60-63. In reality, however, Amgen's patents provide no more of "a starting point" and "direction for further research" than did the patent in *Idenix*, and require just as much "significant experimentation" to make and use the full scope of the claims. 941 F.3d at 1160, 1162.

In *Idenix*, the claims covered "billions of potential 2'-methyl-up nucleosides" for treating hepatitis C. *Id.* at 1156. Idenix argued that its specification was enabling because it "identifie[d] the 'key' modification (2'-methyl-up)," "contain[ed] 'working examples of active 2'-methyl-up ribonucleosides that were tested," and "provide[d] [sufficient] guidance because a POSA would understand NS5B to be the 'target' enzyme or would understand that the modified nucleoside must have" a certain structure to treat hepatitis C. *Id.* at 1160. "[S]ynthesis of an individual nucleoside" was also "largely routine." *Id.* This Court nonetheless held that the

specification provided at best a "starting point" or "direction for further research," which did not enable the claims. *Id.* To be enabling, the specification needed not just "an identification of" the purported "key" 2'-methyl-up modification, but also "identification of which 2'-methyl-up nucleosides will effectively treat HCV," which required "[t]esting" and "screening." *Id.* at 1158-60, 1163. Accordingly, the patent exceeded the "'limits on permissible experimentation.'" *Id.* at 1163 (quoting *Wyeth*, 720 F.3d at 1386).

The failings of Amgen's patents are nearly identical. As in *Idenix*, they identify "working examples" of compounds falling within the claims "that were tested," a "target" to bind to (PCSK9 residues), and purportedly "routine" methods for making additional compounds. *Id.* at 1160, 1163; Appx16. But because Amgen's patents, like that in *Idenix*, lack any "identification of which [compounds] will effectively" bind the target, they are not enabled. *Idenix*, 941 F.3d at 1160. Indeed, when asked how he would make antibodies satisfying the claims, Amgen's Dr. Petsko did not even think to use Amgen's vaunted "roadmap"; instead, he testified that "one might be able to conceive a research plan that would allow you to" make such antibodies. Appx3892-3893(692:1-15, 694:23-695:4).

Amgen repeatedly asserts that Sanofi/Regeneron "failed to identify a single, actual antibody that could not be produced quickly and easily using the patents' roadmap." Amgen.Br.2; *see also id.* at 25, 27, 31, 37-38. That accusation requires

chutzpah: Sanofi/Regeneron *did* identify such antibodies, but Amgen fervently (and successfully) sought to *exclude* that evidence. *See* pp.59-63, *infra*. Regardless, the undisputed evidence that Sanofi/Regeneron *did* introduce is readily sufficient to find the patents non-enabled as a matter of law, just as in *Idenix*, *Enzo*, and *Wyeth*. None of those cases remotely implies the evidentiary requirement Amgen now manufactures, and Amgen cites no case so holding.[16]

Amgen's repeated contention that "POSAs following [its] roadmap 'would be certain to make all of the claim's antibodies,'" Amgen.Br.34 (quoting Appx3909(762:14-20)); *see also id.* at 26, 37, 38, 53, 55, is likewise belied by the same improperly excluded evidence; regardless, Amgen ignores the relevant inquiry. Even if a POSA could find every antibody that binds to the claimed residues using Amgen's purported "roadmap," that does not answer whether the required experimentation would be "significant." *Idenix*, 941 F.3d at 1162. Someone instructed to use the routine method of digging for gold might eventually find all the gold in the world, but not without extraordinary trial-and-error efforts; so too here. *See* Appx9830(96:3-9). Indeed, Dr. Rees never said how long it would take to identify the full scope of antibodies, much less refuted Dr. Boyd's testimony that even following the patents' "roadmap," "[y]ou could be immunizing mice for a

[16] The same reasoning disposes of Amgen's related assertion that Sanofi/Regeneron "identified not one conservative substitution that destroyed the claimed biological activity." Amgen.Br.22-23; *see also id.* at 3, 49, 59.

hundred years" looking for antibodies and not know when the search is complete. Appx3751(318:5-13); Appx3754(329:2-331:24).[17]

Amgen's remaining arguments fail for the same reasons the patentees' arguments failed in *Idenix*, *Enzo*, and *Wyeth*. Amgen contends, *inter alia*, that "the disclosed methods" for obtaining claimed antibodies were "predictable," the specification "enables any mode of making and using the invention," Dr. Jackson "discover[ed]" the "anchor antibodies" that are the basis for Amgen's "roadmap," and that "confirmatory processes" for testing whether an antibody binds to the claimed PCSK9 residues are "quick and routine." Amgen.Br.52, 55, 60, 62-63. *Idenix*, *Enzo*, and *Wyeth* rejected these arguments. In those cases, this Court accepted that generating or screening compounds for the claimed functionalities "was largely routine" and achievable "in relatively short order." *Idenix*, 603 F.3d at 1160-61; *see Enzo*, 928 F.3d at 1346 (assuming "specification teaches one of skill in the art how to create the broad range of [compounds] covered by the claims"); *Wyeth*, 720 F.3d at 1385 (assuming POSAs "could routinely use the assays disclosed in the specification to determine [functional] effects in candidate compounds"). Yet the Court held those facts were insufficient to enable the claims as a matter of law.

[17] Amgen mischaracterizes Dr. Ravetch's testimony, *see* Amgen.Br.53; he merely said that, using known techniques, "it's inevitable you're going to get" *an* antibody that satisfies the claims, Appx3897(711:7-11)—not "the antibodies" throughout the full claim scope.

The district court's adherence to those cases is not error, much less "obvious error." Amgen.Br.61.[18]

b. *Wands* Does Not Establish That All Antibody Claims Are Enabled.

Affirming here would not "overrule *Wands*." *Id.* at 37; *see* Bristol-Myers.Br.6, 11-13. According to Amgen, *Wands* settled whether "the antibody arts [a]re predictable," whether "the steps for making [and screening] antibodies [require] undue experimentation," and that patents reciting those steps enable antibody claims. Amgen.Br.35, 37, 51. But Amgen massively overreads *Wands*, which is fully consistent with non-enablement here.

In *Wands*, this Court reversed because the PTO's "interpretation of the data" led "to the absurd conclusion that the more [cell lines] an applicant makes and saves without testing, the less predictable the applicant's results become." 858 F.2d at 739-40. That narrow basis for reversal has no application here. The decision below did not hold (and Sanofi/Regeneron do not argue) that Amgen's specification requires undue experimentation based on Amgen's failure to further screen

[18] Amgen frequently contends that the district court "repeatedly acknowledged conflicting evidence, but reweighed the evidence for itself." Amgen.Br.1; *see also id.* at 20, 23, 31, 51. In fact, the district court only once deemed testimony "conflicting," Appx17, and it explained that the purported "conflict[]" was immaterial if not illusory because "there is no testimony from any expert that the structure-function relationship would eliminate" the undisputed "need for testing newly-created antibodies to determine whether they had the functions of blocking and binding," Appx19.

promising PCSK9 candidate antibodies. Moreover, whereas in *Wands* "[n]o evidence was presented by either party on how many [cell lines] would be viewed by those in the art as requiring undue experimentation to screen," *id.* at 740, here Amgen's expert admitted that screening "millions of antibodies" would be an "enormous amount of work" that no "antibody scientist would even contemplate doing," Appx3902(733:10-11); Appx3914(781:10-14).

Wands also did not hold that a patent is enabling merely because it describes how to "obtain antibodies that 'satisf[y] all of the claim limitations.'" Amgen.Br.36. Even after *Wands*, this Court has held that describing how to *make* claimed compounds is insufficient; a specification is not enabling when a POSA could not predict whether undisclosed compounds would satisfy the functional limitations without testing. *See Idenix*, 941 F.3d at 1157, 1160, 1162; *Enzo*, 928 F.3d at 1346, 1349; *Wyeth*, 720 F.3d at 1382, 1385. That description fits Amgen's patents to a tee. Amgen's patents "leave[] a POSA searching for a needle in a haystack to determine which of the 'large number' of" antibody candidates "falls into the 'small' group of candidates that" bind to the claimed PCSK9 residues. *Idenix*, 941 F.3d at 1162.

C. The District Court Properly Applied the Requirement That a Patent Must Enable Its Claims' "Full Scope."

Amgen last contends that the district court "adopt[ed] an enablement standard that is contrary to precedent" because "it considered the experimentation required to 'discover[]' and make '*every antibody* within the scope of the claims.'"

Amgen.Br.63-64 (quoting Appx15) (Amgen's emphasis). But Amgen concedes, as it must, that the district court applied "this Court's requirement that the specification teach POSAs 'how to make and use the *full scope* of the claimed invention without undue experimentation.'" *Id.* (quoting Appx11) (Amgen's emphasis). That requirement is "part of the *quid pro quo* of the patent bargain." *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

Amgen's criticism instead depends on distorting the district court's decision. Amgen's entire argument turns on a handful of words in the court's assessment of the claims' full scope—the "breadth of the claims." Appx14-15 (capitalization altered). In *that* context, the court observed, Amgen could not limit the claims' scope by excluding antibodies made by random mutations, as not "every antibody" within the scope of the claims could be discovered through "intelligent substitutions"; rather, there could be antibodies within the claims "that could only be discovered by performing a random mutation." Appx15. For that reason among others, the court rejected Amgen's assertion "that the claimed genus is … 'narrow.'" Appx15.

Amgen thus disputes a strawman, not the district court's actual reasoning, when it argues "that the 'full scope of the claimed invention' standard does *not* require the patent to 'describe how to make and use every possible variant.'" Amgen.Br.64 (quoting *AK Steel*, 344 F.3d at 1244) (Amgen's emphasis). The district court never required Amgen's patents to describe making every possible

antibody within the genus to satisfy the enablement requirement.

There is no conflict between the district court's analysis and the cases cited by Amgen. Those cases recognize that determining the full scope of a claim is necessary for assessing whether the patent has enabled that full scope. In *Minerals Separation v. Hyde*, the Supreme Court understood all "variation of treatment" for "different ores" to be "within the scope of the claims." 242 U.S. 261, 270 (1916). In *AK Steel*, this Court understood the "full scope of the claimed invention" to include all embodiments in the claimed "range." 344 F.3d at 1244. Amgen's other cases hold similarly.[19] Moreover, this Court has recognized, without exception, *Wands*'s requirement that patents "teach those skilled in the art how to make and use the *full scope* of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993) (citing *Wands*); *see Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1360 (Fed. Cir. 2007); *Idenix*, 941 F.3d at 1154, 1156 n.3, 1159, 1162-63; *Wyeth*, 720 F.3d at 1384-85; *AK Steel*, 344 F.3d at 1244; *Angstadt*, 537 F.2d at 502; *Moore*, 439 F.2d at 1236; *Halleck*, 422 F.2d at 914 (similar); *cf. Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d

[19] *See Wands*, 858 F.2d at 736 (all "high-affinity IgM monoclonal antibodies"); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) (operative and "inoperative" combinations); *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976) ("every catalyst which will work" and "not work"); *In re Moore*, 439 F.2d 1232, 1236 (C.C.P.A. 1971) (all "recited alkyl adamantanes"); *In re Halleck*, 422 F.2d 911, 914 (C.C.P.A. 1970) (all "proportions," which "may vary for a specific agent and specific animal").

629, 661 (E.D. Tex. 2017) ("full scope").[20]

The district court's judgment is thus fully consistent with the Supreme Court's and this Court's precedent, including recent controlling decisions. On the undisputed evidence and as a matter of law, a POSA "could not practice the[] full scope" of Amgen's claims "without undue experimentation." *Idenix*, 941 F.3d at 1154 (quoting *Wyeth*, 720 F.3d at 1384). Amgen's claims are not enabled, and a reasonable jury could not have found otherwise. The Court should affirm.

II. Amgen's Claims Lack Adequate Written Description.

Amgen's patents also fail, as a matter of law, to adequately describe the claimed genus of antibodies. *See, e.g.*, *Idenix*, 941 F.3d at 1165. To satisfy written description, "a patentee must convey in its disclosure that it 'had possession of the claimed subject matter as of the filing date.'" *Amgen*, 872 F.3d at 1373. The risk of inadequate written description is "especially acute with genus claims that," as here, "use functional language to define the boundaries of a claimed genus," because they

[20] Amgen's remaining cases are inapposite. In *Mowry v. Whitney*, the defendant argued that following the specification would destroy the claimed wheels *every time*, whatever the claims' scope. 81 U.S. 620, 644 (1871). *Wood v. Underhill* held only that the lower court erred in taking enablement from the jury. Even then, it observed that where, as here, "the qualities of" claimed materials "differ so widely … that the [claimed] improvement cannot be used with any advantage … without first ascertaining by experiment" what materials achieve a desired function, "then the invention is not patentable." 46 U.S. (5 How.) 1, 6-7 (1847). In *Johns Hopkins*, this Court rejected arguments based on a "technique [not] disclosed in the specification" and for failure to "produce[] evidence concerning the level of skill of [certain] individuals." 152 F.3d at 1360.

"may simply claim a desired result … without describing species that achieve that result." *Ariad Pharms, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1349 (Fed. Cir. 2010) (en banc). To show possession of such claims, a patent must allow a POSA to "'visualize or recognize' the members of the genus" by disclosing either "a representative number of species falling within the scope of the genus" or "structural features common to the members of the genus." *Amgen*, 872 F.3d at 1373 (quoting *Ariad*, 598 F.3d at 1350). Amgen's patents come up short.

A. Amgen's Patents Do Not Describe Species Representative of the Claimed Genus.

To satisfy the "representative species" test, a patentee must "show that [it] has truly invented the *genus*, *i.e.*, that [it] has conceived and described sufficient representative species encompassing *the breadth of the genus*." *AbbVie*, 759 F.3d at 1300. An adequate written description allows a POSA to visualize or recognize the identity of the members of the genus. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

Amgen claims a genus of antibodies that bind to at least one or two of sixteen specified PCSK9 residues and block LDL-R from binding to PCSK9. Appx411-412; Appx796. But Amgen's 26 disclosed antibodies do not represent the undisclosed Competitor Antibodies that indisputably fall within Amgen's claims—much less the millions of other antibodies potentially covered by the claims. That is no surprise, for in light of the unpredictability of the art and the need for testing, the

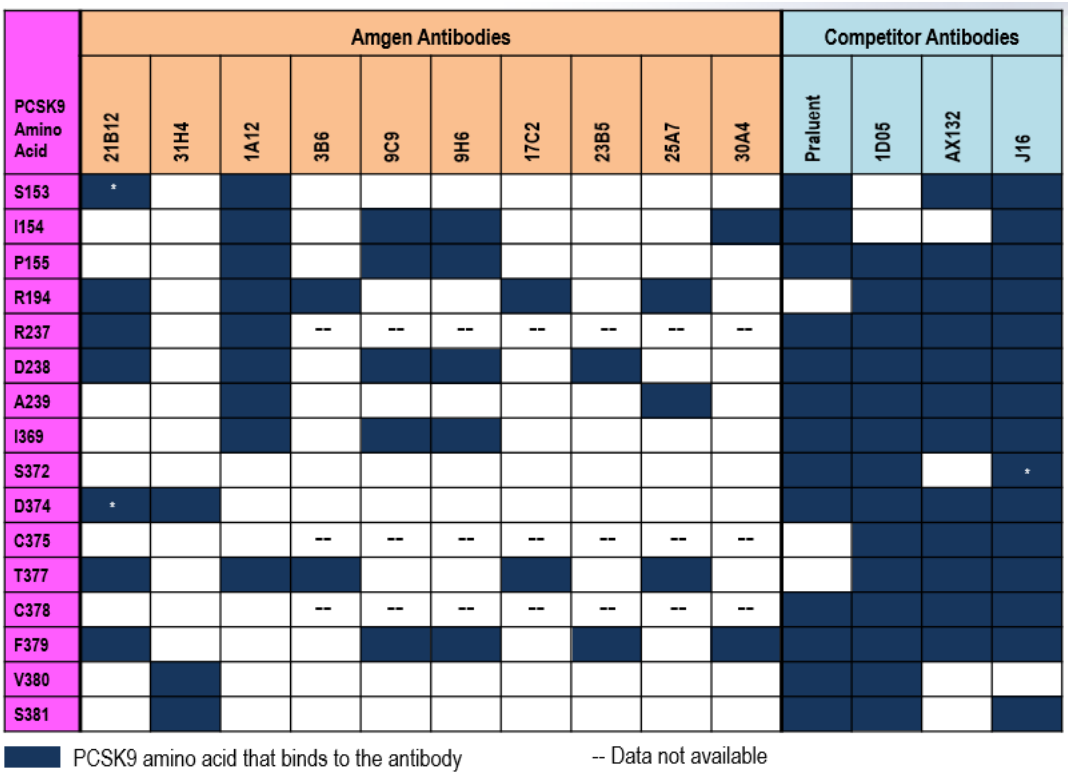
specification provides no way of knowing which antibodies fall within the claims' scope.

To begin with, the disclosed antibodies are not representative of the structural diversity of the claimed genus. *AbbVie*, 759 F.3d at 1301. Dr. Boyd compared the amino acid sequences—*i.e.*, the "primary structure," Appx3748(307:16-22)—of the disclosed antibodies with the Competitor Antibodies, and concluded that the disclosed species "[a]re not representative" of the breadth of the genus. Appx3692(236:5-11). Specifically, he determined that none of Amgen's disclosed antibodies is at least 80% identical in amino acid sequence to any Competitor Antibody (where 80% sequence identity is the typical minimum threshold for similarity in the field). Appx3691-3692(230:22-236:9); Appx3748(305:11-25); *see also* Appx3692(236:9-11) (disclosed antibodies are "not representative" because "[t]hey don't look anything like the competitor antibodies in terms of their sequences").

Furthermore, Amgen's disclosed antibodies do not represent the range of claimed antibodies, which are defined (in the claims) by where they bind to PCSK9. The claims cover antibodies that bind to many combinations of the sixteen residues (locations).[21] But Amgen's specification only discloses antibodies that bind to just

[21] The '165 patent's claims recite fifteen residues on PCSK9 (the so-called "sweet spot") and the '741 patent's claim recites one additional PCSK9 residue.

a few of those combinations. As the following table shows, the Competitor Antibodies bind to PCSK9 at markedly different residues and different combinations of residues than Amgen's disclosed antibodies:



PCSK9 Amino Acid	Amgen Antibodies										Competitor Antibodies			
	21B12	31H4	1A12	3B6	9C9	9H6	17C2	23B5	25A7	30A4	Praluent	1D05	AX132	J16
S153	*		■								■		■	■
I154			■		■	■				■	■			■
P155			■		■	■					■	■	■	■
R194	■		■	■			■		■			■	■	■
R237	■		■	--	--	--	--	--	--	--	■	■	■	■
D238	■		■		■	■		■			■	■	■	■
A239			■						■		■	■	■	■
I369			■		■	■					■	■	■	■
S372											■	■		*
D374	*	■									■	■	■	■
C375				--	--	--	--	--	--	--		■	■	■
T377	■		■	■			■		■			■	■	■
C378				--	--	--	--	--	--	--	■	■	■	■
F379	■				■	■		■		■	■	■	■	■
V380		■									■	■		
S381		■									■	■		■

■ PCSK9 amino acid that binds to the antibody -- Data not available

Appx4283. Among other striking differences, *not one* of Amgen's disclosed antibodies binds to three of the sixteen PCSK9 residues specified in the claims: S372, C375, and C378. Yet three Competitor Antibodies bind to both S372 and S375, and all four bind to C378. Appx4283; Appx3776(420:12-20); Appx3777(421:1-5). Additionally, while Amgen's claims encompass antibodies that bind up to 16 PCSK9 residues, none of Amgen's disclosed antibodies binds to more than *9* residues. Yet *all* of the Competitor Antibodies bind to at least *12* residues. Finally, Pfizer's and Merck's antibodies are EGFa mimics that "s[i]t right

on top of PCSK9," Appx3685-3686(206:18-210:5). By contrast, Amgen's patents do not "identif[y] an antibody like that." Appx3754(332:7-11). Amgen's claims also encompass countless additional combinations of residues that could be bound. When somebody else invents those antibodies, Amgen's claims will cover them, "preempt[ing] the future before it has arrived." *Ariad*, 598 F.3d at 1353-54. Because its "specification only describes a part of [the claimed] genus," Amgen's claims are invalid as a matter of law for lack of sufficient written description. *AbbVie*, 759 F.3d at 1299.

At trial, Amgen did not dispute any of the foregoing. Instead, it merely attempted to undermine the sequence comparison between Amgen's disclosed 9H6 antibody and Praluent. Appx10; Appx3764-3765(372:10-374:24). This is legally insufficient because Amgen made no attempt to dispute the sequence comparisons that Dr. Boyd performed demonstrating the differences between the *three other* Competitor Antibodies and Amgen's disclosed antibodies. Thus, its patents fail to "at least describe some species representative of antibodies that are structurally similar to" species within the claim scope. *AbbVie*, 759 F.3d at 1301; *see also Idenix*, 941 F.3d at 1165 ("representative examples" must "support a claim on a structurally similar genus"). Amgen's failure to challenge this evidence is by itself dispositive.

Even as to Praluent, Amgen's argument—that "there was testimony of 80% [sequence] *similarity* between" the relevant portions of 9H6 and Praluent—fails.

Appx10; Appx3764-3765(372:10-374:24). Dr. Boyd testified without challenge that the correct metric for comparison is sequence *identity*—not sequence *similarity*. Appx3765(373:1-374:24) (discussing Appx4065); *see also* Appx3692(235:8-21); Appx3747-3748(304:19-305:18). "Similarity," unlike identity, fails to account for differences in sequence length, which "is really … important." Appx3765(373:10-14); *see also* Appx3765(373:1-374:11). Dr. Boyd compared the most relevant portions of the Praluent and 9H6 amino acid sequences (the CDR3 regions) and concluded that they "are not the same length," which means the antibodies are "quite different from each other." Appx3765(373:10-14). These sequence differences cause Praluent and 9H6 to bind to PCSK9 differently, as shown in the table above.

Amgen also argued that "three-dimensional structure," rather than "amino acid sequence," is the appropriate metric for measuring representativeness. Appx9. But that contention ignores Amgen's own admission that amino acid sequence defines an antibody's structure. Appx3914(781:20-24); *see also* Appx3748(307:14-22); Appx3783(447:19-448:6). Moreover, both sides' experts agreed that differences in amino acid sequences can result in different binding characteristics, Appx3878(638:2-5); Appx3783(447:19-448:9); Appx3783-3784(448:10-449:19), and these differences indisputably resulted in entirely different binding locations, as indicated above. And Amgen presented no evidence of "similarity in the three-dimensional structure" of its disclosed antibodies and Competitor Antibodies.

Appx9. Nor can Amgen dispute that whatever evidence of three-dimensional structure may exist, it does not allow POSAs to "visualize or recognize the members of the genus," *Idenix*, 941 F.3d at 1164, because a POSA still must test an antibody to see if it falls within the claimed genus.

Indeed, the unpredictability of the art provides an independent basis for concluding that the patents do not sufficiently describe representative species, separate and apart from the dissimilarity of the disclosed antibodies and the Competitor Antibodies. This Court has consistently held that "[a] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated." *In re Alonso*, 545 F.3d 1015, 1020 (Fed. Cir. 2008); *accord Boston Sci.*, 647 F.3d at 1364-67; *Eli Lilly*, 119 F.3d at 1568. And this Court has repeatedly invalidated patents for lack of written description when there is "no evidence to show whether one of skill in the art could make predictable changes to the described antibodies to arrive at other types of antibodies" within the genus. *AbbVie*, 759 F.3d at 1301; *see also Ariad*, 598 F.3d at 1354 (field of invention was "particularly unpredictable"); *Alonso*, 545 F.3d at 1020. Most recently, in *Idenix*, the Court held that a patent lacked adequate written description because the specification "fails to provide sufficient blaze marks to direct a POSA to the specific subset of" species satisfying the claims' functional

requirements. 941 F.3d at 1164. The specification "deprived" a POSA of "meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result" as the disclosed species. *Id.*

So too here. The undisputed evidence showed that the art is unpredictable, the claims' scope is vast, changing even a single amino acid of an antibody can alter its function, and, thus, every generated antibody must be tested to determine if it falls within the claims' scope. *See* pp.21-27, *supra*. Accordingly, this is precisely the sort of situation where a patentee cannot "claim a genus after only describing a limited number of species," because there is "unpredictability in the results obtained from species other than those specifically enumerated" in the patents. *Alonso*, 545 F.3d at 1020. Given that even a slight difference in amino acid sequence can have substantial effects on antibody function, Amgen's patents lack "meaningful guidance into what" antibodies beyond the 26 disclosed antibodies "would provide the same result" as those disclosed antibodies. *Idenix*, 941 F.3d at 1164. In short, the patents do not permit a POSA to "'visualize or recognize' the members of the genus." *Amgen*, 872 F.3d at 1373.

B. Amgen's Patents Do Not Describe Structural Features Common to Members of the Claimed Genus.

The undisputed evidence also established that Amgen's patents fail to sufficiently describe "structural features common to the members of the [claimed] genus so that one of skill in the art can 'visualize or recognize' the members of the

genus." *Id.* Amgen's patents do not describe any common structural feature of the claimed antibodies. And Amgen never identified any structure-function correlation, in either its specification or the art, that would allow a POSA to "visualize or recognize" whether an undisclosed antibody falls within the claims' scope.

Adequate written description requires patents to "distinguish the genus from other materials." *Ariad*, 598 F.3d at 1350. But Sanofi/Regeneron's Dr. Eck could not "find … anywhere in the patent where" Amgen "point[ed] to a structural element that makes things inside or outside the claims." Appx3789(470:13-16); *see also* Appx3781(440:17-23). Similarly, Dr. Boyd testified that Amgen did not "identify any common structural features" allowing a POSA to distinguish "a PCSK9 binding antibody… from all the other antibodies." Appx3748(306:22-307:10).

No Amgen witness testified otherwise. Instead, Amgen's witnesses focused on (1) structural features of the *antigen* (PCSK9), not the claimed *antibodies*, and (2) purported features neither disclosed by the patents nor capable of "distinguish[ing]" claimed species "from other materials." *Ariad*, 598 F.3d at 1350.

For example, when asked to identify the "common structural feature" of the claimed antibodies, Amgen's Dr. Rees focused on the "sweet spot"—residues on PCSK9 itself—stating that "the common structural feature is that antibodies that bind *across the sweet spot* here must have complementary features that enable them to bind *across that sweet spot*." Appx3912(772:18-23). Likewise, Dr. Petsko

testified that "if you know the *structure of the sweet spot* like this, you … would know that antibodies that have a shape that's complimentary [sic] to the *structure of the sweet spot* … will bind." Appx3880(645:4-9); *see also* Appx3895(705:23-706:5). But one cannot "claim antibodies by describing something that is not the invention, *i.e.*, the antigen." *Amgen*, 872 F.3d at 1378.

Amgen also attempted to provide a structure-function correlation by pointing to a so-called "greasy patch" on the antibodies. *See* Appx3880-3881(645:20-647:9). But because "almost all antibodies have a greasy spot on their tips," Appx3920(804:16-22); Appx3749(309:16-310:1), then even if the patent disclosed this structural feature (and it does not), this characteristic does not "distinguish the genus from other materials." *Ariad*, 598 F.3d at 1350. The only way to determine whether an antibody with a "greasy patch" is within the claim and thus "distinguish[ed]" from other materials is to test it. This fails to provide a description supporting Amgen's genus claims.

Last, Amgen asserted that it identified common structural features by *ex post* comparing the three-dimensional structures of its 1A12 antibody and the Competitor Antibodies. *See* Appx3912-3913(772:24-775:17); Appx3916(787:23-789:18); Appx4143-4144. This is a red herring (and factually inaccurate). Neither Amgen's patents nor the art discloses this purported comparison—nor could they, since the Competitor Antibodies postdate Amgen's priority date. *See* Appx3916(788:19-

789:18); Appx3785(455:14-15). A comparison that "relies on knowledge that a POSA did not have at the priority date of the patents" cannot discharge Amgen's written description obligation. *MorphoSys*, 358 F. Supp. 3d at 367.

III. If The Invalidity Judgment Is Not Affirmed, A New Trial Is Required On The Remaining Claims Because of Evidentiary Errors.

Even if the Court concluded that the record evidence does not support invalidity as a matter of law, it should remand for a new trial because key post-priority-date evidence demonstrating lack of enablement and written description was once again improperly excluded, while Amgen was improperly permitted to introduce its own post-priority-date evidence.

In previously ordering a new trial, this Court explained that post-priority-date evidence "is proper" for "show[ing] that a patent does not disclose a representative number of species of a claimed genus," and that post-priority-date evidence "showing that [Amgen] engaged in lengthy and potentially undue experimentation to enable the full scope of the claims" could be "relevant to determining if the claims were enabled as of the priority date." *Amgen*, 872 F.3d at 1375. Those were precisely the reasons that, on remand, Sanofi/Regeneron sought to introduce evidence of Amgen's unsuccessful post-priority-date efforts to discover [redacted] antibodies, which indisputably fall within the claims' scope. Appx3685(207:12-208:3). The excluded evidence showed that years after the priority date, Amgen considered such antibodies different from its existing

antibodies, and that it could not find such antibodies either among its existing antibodies or make them by following the methods disclosed in its patents. *See* pp.11-15, *supra* (describing evidence). Particularly "[g]iven the low threshold for relevancy, it is clear that th[is] evidence was relevant" to establishing that, as of the priority date, Amgen did not possess antibodies representative of the claims' full scope or enable the claims' full scope. *OddzOn Prods., Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1407 (Fed. Cir. 1997).[22]

Amgen nevertheless convinced the district court to exclude this evidence as irrelevant and confusing by arguing that because Amgen's effort to find [redacted] was associated with work to develop a so-called [redacted] or [redacted], PCSK9 antibody, it concerned a later state of the art. Appx5076-5079; Appx5429-5430; Appx3813(568:3-5). But that argument twice fails. First, as before, Sanofi/Regeneron "were not offering post-priority-date evidence to show that [Amgen's] claimed genus is not enabled because of a change in the state of the art." *Amgen*, 872 F.3d at 1375.

Second, even if Amgen were trying to find a [redacted] PCSK9 antibody, Amgen's scientists acknowledged that creating a [redacted] antibody required them "to *start with* a fully human [redacted] antibody *and then* engineer [redacted]

[22] Indeed, this evidence included some of the *very same evidence* that was previously excluded and that Sanofi/Regeneron cited in the previous appeal. *See* p.15, *supra*.

into it." Appx9714; Appx3810(555:6-10). That is, Amgen's program required it *first* to have a [redacted] antibody" within the scope of the claims. But as the excluded evidence shows, Amgen did not possess one—demonstrating lack of written description—and *could not make one*, despite having in hand the specification of the patents-in-suit—demonstrating lack of enablement. *See, e.g.*, *MagSil*, 687 F.3d at 1381-84. Amgen's invocation of its [redacted] program, therefore, does not diminish the unquestionable relevance of the excluded evidence. Nor is that relevance "substantially outweighed" by the possibility of juror confusion, Fed. R. Evid. 403, particularly since the jury could have received a limiting instruction, *see United States v. Morris*, 79 F.3d 409, 412 (5th Cir. 1996) (noting that "courts often rely on limiting instructions to resolve problems under Rule 403").[23]

Excluding this evidence was not harmless. Sanofi/Regeneron were barred from introducing this evidence affirmatively and to impeach Amgen's witnesses, who—contrary to the excluded documents—flatly denied there was ever a "missing epitope" and asserted that Amgen possessed "middle binders." Appx3686-

[23] Notably, in the previous appeal, Amgen argued that because the "purpose" of its [redacted] program was "to develop a pH-sensitive antibody," excluding the post-priority-date evidence was proper. 17-1480 Appellees.Br.40 n.3. This Court nevertheless reversed. *See Smith Int'l, Inc. v. Hughes Tool Co.*, 759 F.2d 1572, 1577 (Fed. Cir. 1985) (observing that law-of-the-case doctrine forecloses arguments "decided by necessary implication").

3687(210:23-215:16); Appx3869-3870(602:20-603:1); Appx9528-9535; Appx3881(650:23-25); Appx3884-3885(660:1-661:1, 662:24-663:1); Appx9708-9710; Appx9725-9727; *compare also* Appx3908(757:23-758:6) (Amgen's Dr. Rees testifying that Praluent "could well have been in the . . . patent"), *with* Appx9674-9675 (Amgen stating in excluded document that "we … did not get [the antibody in Praluent] from PCSK9 #1"). Indeed, Amgen now accuses Sanofi/Regeneron of not "identify[ing] a single, actual antibody that could not be produced quickly and easily using the patents' roadmap," but that is *exactly* what the excluded evidence showed. *See* pp.42-43, *supra*.[24] Furthermore, when Sanofi/Regeneron *were* able to present evidence that Amgen could not make antibodies covered by certain claims, the jury found those claims *invalid*. *See* Appx3806(538:7-540:21); Appx3670(146:11-16) (Dr. Jackson's concessions regarding claims 7 and 15 of '165 patent); Appx3631-3632 (finding claims 7 and 15 invalid). Had the jury seen the excluded evidence showing that Amgen never possessed and could not make antibodies within the other claims, it would have likely invalidated those claims as well.

Making matters worse, *Amgen* was permitted to use post-priority-date data absent from its patents' specification to bolster its written description arguments.

[24] To be clear, while the evidence is relevant to showing lack of enablement and written description, and its exclusion not harmless, it is not *necessary* to proving invalidity as a matter of law, and its exclusion does not undermine JMOL for Sanofi/Regeneron.

Over Sanofi/Regeneron's objection, Amgen introduced data generated years after the priority date for 8 of its 26 antibodies, including experiments performed during this litigation. Appx3884-3885(662:14-664:6); Appx3915(785:13-786:17); Appx3929(841:8-11); Appx3932(853:8-18); Appx5408-5409; Appx5412; Appx5431-5432. Amgen's experts relied on this post-priority-date data to conclude that those 8 antibodies bind to the recited residues and thus fall within the claims. *See, e.g.*, Appx3884-3885(662:14-664:6). But written description is judged as of the priority date. *Amgen*, 872 F.3d at 1375. Amgen sought to evade this requirement by invoking the principle of "inherency," but for that doctrine to apply, "the missing descriptive matter *must necessarily be present* in the … specification such that" a POSA "would recognize such a disclosure." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998). That does not begin to describe the data that Amgen invoked; were it otherwise, a POSA would recognize whether a disclosed antibody is within the claim scope without doing any post-priority-date testing.

CONCLUSION

The Court should affirm the judgment or, alternatively, grant Defendants a new trial.

Respectfully submitted,

/s/ Matthew M. Wolf
Matthew M. Wolf

George W. Hicks, Jr.
Nathan S. Mammen
C. Alex Shank
KIRKLAND & ELLIS LLP
1301 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
(202) 389-5000

Deborah E. Fishman
ARNOLD & PORTER KAYE SCHOLER LLP
Suite 500
3000 El Camino Real
5 Palo Alto Square
Palo Alto, CA 94306
(650) 319-4500

Matthew M. Wolf
Victoria L. Reines
ARNOLD & PORTER KAYE SCHOLER LLP
601 Massachusetts Ave., NW
Washington, DC 20001
(202) 942-5000

David K. Barr
Daniel L. Reisner
ARNOLD & PORTER KAYE SCHOLER LLP
250 West 55th Street
New York, NY 10019
(212) 836-8000

Attorneys for Defendants-Appellees Sanofi, Aventisub LLC, Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC

CERTIFICATE OF SERVICE

On June 2, 2020, the non-confidential version of this brief was submitted to the Court by CM/ECF, and thereby served on all parties. The confidential version was filed with the Court by ECF, two copies were sent by FedEx to principal counsel for Defendants-Appellees at the address below, and electronic courtesy copies were sent to counsel for Defendants-Appellees at jlamken@mololamken.com.

Jeffrey A. Lamken
MOLOLAMKEN LLP
Suite 500
600 New Hampshire Ave., NW
Washington, DC 20037

Dated: June 2, 2020

/s/ C. Alex Shank
C. Alex Shank
KIRKLAND & ELLIS LLP
1301 Pennsylvania Ave., NW
Washington, DC 20004
(202) 389-5000

Attorney for Defendants-Appellees Sanofi, Aventisub LLC, Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC

CERTIFICATE OF COMPLIANCE

I certify that the foregoing Defendants-Appellees' Brief:

1. Complies with the type-volume limitation of Fed. Cir. R. 32(a). This brief contains 13,994 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b). Microsoft Word was used to calculate the word count.

2. Complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). This brief has been prepared in a proportionally-spaced typeface using Microsoft Word in 14-point Times New Roman type style.

3. Complies with the word limit of Fed. Cir. R. 28(d) and contains 10 unique words marked as confidential in the confidential version of this brief and redacted in the non-confidential version.

Dated: June 2, 2020

/s/ Matthew M. Wolf

Matthew M. Wolf
ARNOLD & PORTER KAYE SCHOLER LLP
601 Massachusetts Ave., NW
Washington, DC 20001
(202) 942-5000

Attorney for Defendants-Appellees Sanofi, Aventisub LLC, Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC