2020-1074

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING, LIMITED, AMGEN USA, INC.,

Plaintiffs-Appellants,

– v. –

SANOFI, AVENTISUB LLC, fka Aventis Pharmaceuticals Inc., REGENERON PHARMACEUTICALS INC., SANOFI-AVENTIS U.S. LLC,

Defendants-Appellees.

On Appeal from the United States District Court for the District of Delaware in No. 1:14-cv-01317-RGA

BRIEF FOR *AMICUS CURIAE* PFIZER INC. IN SUPPORT OF APPELLEES

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FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Amgen Inc., et al. **v.** Sanofi, et al.

Case No. 20-1074

CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ☐ (appellant) ☐ (respondent) ☐ (appellee) ■ (amicus) ☐ (name of party)

Pfizer Inc.

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Pfizer Inc.	Pfizer Inc.	None

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

None

FORM 9. Certificate of Interest **Form 9**
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5. The title and number of any case known to counsel 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. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

None

6/8/2020
Date

/s/ Amit H. Thakore
Signature of counsel

Please Note: All questions must be answered

Amit H. Thakore
Printed name of counsel

cc: All counsel by ECF

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AMICUS CURIAE'S STATEMENT UNDER RULE 29

Pursuant to Federal Rule of Appellate Procedure Rule 29(a)(4)(E), *amicus curiae* Pfizer Inc. ("Pfizer") confirms that no party's counsel involved in the litigation authored this brief, in whole or in part. Pfizer also confirms that no party or party's counsel, or any other person other than Pfizer, contributed money that was intended to fund preparing or submitting this brief.

Pursuant to Federal Rule of Appellate Procedure 29(a)(2) and Federal Circuit Rule 29(c), Pfizer confirms that all parties have consented to the filing of this amicus brief.

INTEREST OF AMICUS CURIAE

Pfizer is a global pharmaceutical company that discovers, develops, and markets innovative medicines, including monoclonal antibodies. Antibodies comprise an important aspect of current clinical research in numerous therapeutic areas under investigation by Pfizer and other companies. Patents with functional claims that encompass a broad genus of antibodies having no identifiable common structural features threaten the development and commercialization of these products. This appeal provides the Court with an opportunity to clarify the application of the written description and enablement requirements to such functional claims.

The asserted claims of Amgen's patents define a genus of monoclonal antibodies based on their ability to bind to one or two amino acid residues in the sequence of the PCSK9 protein and block binding of PCSK9 to low-density lipoprotein receptor ("LDLR"). The claims do not define any antibody by its structure or amino acid sequence. The claims' reference to amino acids in PCSK9, a well-known antigen neither discovered nor characterized by Amgen, does nothing to cure these fatal defects.

Pfizer has no direct stake in the result of this appeal. In 2016, Pfizer discontinued efforts to commercialize bococizumab, an anti-PCSK9 antibody that was under investigation for the treatment of elevated cholesterol. At present, Pfizer

is not developing a PCSK9 antibody for regulatory approval. Pfizer requests that the Court consider the arguments herein and conclude that Amgen's functionally-defined antibody claims are invalid as a matter of law under 35 U.S.C. § 112.

INTRODUCTION

The enablement and written description requirements of 35 U.S.C. § 112 establish distinct and separate requirements; however, these requirements "often rise and fall together." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010). The fundamental and irredeemable flaw in Amgen's claims, under both the enablement and written description requirement, is their undue breadth. Because Pfizer is focused on the narrow grounds needed to affirm the decision below, and previously submitted an amicus curiae brief on written description (in Appeal 2017-1480), we will address only the enablement requirement here.

The undue breadth of the claims is no accident, but a deliberate strategy designed to capture any and every anti-PCSK9 antibody that a competitor might develop. Having sought and obtained claims of such overreaching scope, Amgen cannot now retreat from or redefine that scope in an effort to salvage the validity of the claims.

The claims at issue are claims 19 and 29 of U.S. Patent No. 8,829,165 ("the '165 patent") and claim 7 of U.S. Patent No. 8,859,741 ("the '741 patent"). Claim 19 depends from claim 1, which reads:

> 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.

Claim 19 modifies claim 1 by requiring that the antibody binds to at least two of the same list of fifteen residues in PCSK9 instead of only one:

> 19. The isolated monoclonal antibody of claim 1 wherein the 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.

Asserted claim 29 is independent and claims a pharmaceutical composition comprising an antibody as follows:

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

Claim 29, like claim 19, requires binding to at least two PCSK9 residues but adds the requirement of "at least 80%" blocking of PCSK9 binding to LDLR.

Claim 7 of the '741 patent requires binding to only one residue on PCSK9. Claim 7 depends from claim 2, which in turn depends from claim 1. Claims 1, 2 and 7 are as follows:

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

> 7. The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope.

None of the asserted claims contains any structural limitation defining the claimed antibody molecules. Nor do they contain any reference to any of the specific antibodies disclosed in the patent specification, or recite any structural or sequence similarity (whether qualitative, e.g., "conservative," or quantitative, e.g., "80% identity") to the disclosed antibodies. Rather, the claims recite amino acid residues on the *antigen* (PCSK9), which provides no information as to the structure of the claimed antibody.

The claims are of enormous breadth. Any isolated monoclonal antibody (including fragments, per the district court's *Markman* order), having any structure, infringes these claims if it meets the purely functional limitations of binding to PCSK9 and blocking the interaction of PCSK9 with LDLR. All that is required of "binding" or "binds to" is to "interact with [residues] and contributes to the affinity of the PCSK9-antibody interaction." Memorandum Order at 3, *Amgen Inc. v. Sanofi*, No. 14-1317-SLR (D. Del. Oct. 20, 2015), ECF No. 151 (alteration in original).

The disclosure in Amgen's patents does not justify such broad claims. The so-called "roadmap" is no more than an attempt to narrow the claims by imposing process restrictions to preserve their validity. In reality, the "roadmap" is an open-ended research plan for identifying any antibodies that work, *i.e.*, perform the required function. Any antibody that works—irrespective of the process by which

it was discovered—falls within the scope of these claims. The scope of the claims must be the same for both infringement and validity. Amgen cannot now retreat from that broad scope, which was designed to encompass every other competitor through the use of purely functional language, regardless of the degree of difference in the actual antibody molecules.

ARGUMENT

I. THE COURT SHOULD AFFRIM THE DISTRICT COURT'S JUDGMENT ON LACK OF ENABLEMENT

The enablement requirement provides that the patent specification "must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc*., 687 F.3d 1377, 1380 (Fed. Cir. 2012) (internal quotations and citation omitted). To assess enablement, the Court considers several factors, including the breadth of the claim, the predictability of the art, the amount of direction or guidance provided, and the quantity of experimentation required. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Here, the district court considered each of these factors at length and properly concluded, based on the evidence presented at trial, that undue experimentation would be required to practice the full scope of the asserted claims. Appx14-25. This Court should affirm.

A. The Overreaching Breadth of the Claims Supports Lack of Enablement

The claims at issue are directed to a genus of monoclonal antibodies that bind to PCSK9 and block binding of PCSK9 to LDL receptors (LDLR). The claims define the antibody in a purely functional manner by referring to amino acid residues on the PCSK9 antigen and do not recite any structural features or characteristics of the claimed antibody. The district court found that the evidence at trial established that the claims encompass *millions* of distinct antibodies based solely on "conservative" amino acid substitutions described in Table 1 of the patents. Appx16. But the claims are not limited to any particular type of substitution: any amino acid substitution is permissible, in any part of the antibody molecule, as the claims are construed.

Nevertheless, Amgen argues on appeal that the claims are narrow, relying not on the structure of the claimed antibodies but on the claims' recitation of amino acid residues within the so-called "sweet spot" on PCSK9. In doing so, Amgen improperly focuses on the structure of PCSK9 and ignores the broad, functional language of the claims. The limited number of actual PCSK9 antibodies in evidence that meet the claims and the particular methods used by the inventors to produce the antibodies disclosed in the patent do not lend support to the broad scope of the claim. The Court should reject Amgen's arguments and affirm the district court's holding on lack of enablement.

1. The Claims Are Purely Functional and Encompass an Indeterminate Number of Epitopes and Antibodies

Amgen's patents broadly claim all antibodies that bind to certain residues on the PCSK9 protein. Claims 19 and 29 of the '165 patent each require that the claimed monoclonal antibody binds to "at least two" amino acid residues within a fifteen-amino acid sequence identified as forming the part of the region on PCSK9 that binds to LDLR (the "sweet spot"). Claim 7 of the '741 patent, on the other hand, requires that the antibody binds to residue 237 or 238 of PCSK9. Thus, the asserted claims merely require that the antibody binds to *at most two* of the fifteen residues identified as the critical "sweet spot" region on PCSK9. The claims do ***not*** require that the antibody binds across the entire region. Nor do the claims preclude antibodies that bind to additional residues outside of the claimed region, as long as they bind to one or two residues within the sweet spot. As a result, the claims encompass an indeterminate number of epitopes on PCSK9 comprising as few as one and as many as all fifteen residues that make up the sweet spot. Consequently, there is also an indeterminate number of antibodies with diverse structures and amino acid sequences capable of binding to such epitopes. Even putting the epitope binding region aside, when considering the different classes of antibodies covered by the claims, and the diversity of their structures and functions, the scope of these claims has no bounds. In essence, they preempt any therapeutic antibody that blocks PCSK9.

Amgen's assertion that the patents' specification provides a "detailed roadmap" for making all of the claimed antibodies cannot serve to narrow the scope of the claim. As the district court explained, "the method by which the patented product is made has no effect on the scope of the product claim." Appx15. For example, the third step of the "roadmap" requires performing a binning assay with 31H4 and/or 21B12. Appx21; Amgen Br. 13. Antibodies that "co-bin" with 31H4 or 21B12 will bind to the same or overlapping epitopes on PCSK9 as 31H4 or 21B12. Amgen Br. 15. Thus, any antibodies that are obtained from the "roadmap" will be limited to those that compete with 21B12 or 31H4 for binding to PCSK9. The claims, however, do not recite any such binning requirement and are not limited to antibodies with similar structure (primary, secondary, or tertiary) or function (binding to a subset of residues) as 31H4 or 21B12. Nor are the claims limited to "strong blockers" such as 31H4 and 21B12. Appx15. Non-disclosed antibodies with lesser blocking capabilities, but sufficient to fall within the scope of the claims, may not have the ability to compete with 31H4 and 21B12 in a binning assay and therefore would not be identified using the specification's "detailed roadmap."

2. Conservative Substitutions and Random Mutations Lead to Millions of Candidates

The district court found that by making conservative substitutions just to the twenty-six antibody sequences disclosed in the specification, a person of ordinary skill in the art ("POSA") would obtain millions of distinct antibodies. Appx16.

Conservative substitutions are made by replacing one or two amino acids from the original antibody with other amino acids that have similar characteristics. Amgen Br. 42-43. Table 1 of Amgen's patents discloses "[e]xemplary amino acid substitutions." Amgen Br. 44. Thus, the evidence at trial established that a POSA would obtain millions of potential antibodies within the genus simply by following the patents' teachings. And, as noted further below, the claims are not limited to conservative substitutions, exemplary or not.

Amgen argues that a POSA would initially make only selective, "intelligent" substitutions to identify additional antibodies that bind to PCSK9. Amgen Br. 44. However, the specification provides no information as to which substitutions would be "intelligent" substitutions. Sanofi Br. 37. Moreover, even assuming a POSA would know which substitutions to attempt, there is no dispute that the number of candidates encompassed by the claims extends beyond those made by "intelligent" substitutions. Appx16. As this Court's recent precedent makes clear, the relevant inquiry in assessing the breadth of the claims is the number of possible candidates within the genus. *See, e.g., Idenix Pharms. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1157, 1159, 1162 (Fed. Cir. 2019).

The claims are not limited to antibodies produced by conservative amino acid substitutions. Instead, they encompass any antibody, regardless of its sequence, that binds to one or two residues on PCSK9 and blocks binding to LDLR. Thus, a POSA

could also have produced additional antibodies by making non-conservative, "random" substitutions to the amino acid sequence of a given antibody, resulting in an even greater number of candidates. Appx14-15.

Amgen appears to argue that variants produced by random substitutions would be accounted for by immunizing mice or using phage display to produce antibodies per the patent's "roadmap." Amgen Br. 50. Following these methods, Amgen identified 384 antibodies that blocked the interaction between PCSK9 and LDLR. Appx15. However, it is reasonable to conclude that there are additional embodiments (such as Praluent® and other independently-developed antibodies) that would not be found within the group of antibodies identified by Amgen. Indeed, as the district court correctly noted, "[e]xcept for product-by-process claims or product claims with a process limitation, the method by which the patented process is made has no effect on the scope of the product claim." Appx14-15. Thus, Amgen cannot argue that the claims are narrow based on the specific methods disclosed in the patent to produce PCSK9 antibodies. Antibodies produced by random mutations—which may result in embodiments that could never be discovered through immunization or phage display—are also within the scope of the claims.

The facts in this case are nearly identical to those in *Idenix*, where this Court found that the specification left a "POSA searching for a needle in a haystack to determine which of the 'large number' of [claimed molecules] falls into the 'small'

group of candidates that effectively treat HCV." *Idenix*, 941 F.3d at 1162. Just like this case, the theoretical number of candidates in *Idenix* was also in the "millions or at least many, many thousands." *Id.* at 1157 (internal quotations and citation omitted). Furthermore, the patentee in *Idenix* attempted to narrow the scope of the claim by arguing that a POSA would not pursue all possible candidate compounds. *Id*. at 1160. However, the Court held that "[t]his factor . . . considers the scope of the claim as written, not just the subset of the claim that a POSA might practice. Idenix does not, and cannot, argue that the scope of the claim is actually limited to this narrow set of candidates." *Id*. at 1162. Likewise, Amgen cannot argue that the scope of the claims in this case is limited to antibodies made by "intelligent substitutions" or to the set of candidates only discoverable through the specification's purportedly "detailed roadmap."

3. Appellees' Evidence of Four Competitor Antibodies Within the Genus *Supports* Non-Enablement

Amgen argues that defendants "mustered only a handful" of antibodies developed by competitors and that this supports Amgen's argument that the genus is narrow. Amgen Br. 42. However, the fact that defendants produced evidence of "only" four competitor antibodies says nothing about the actual size of the genus. If anything, this confirms the time and resources needed to identify and develop antibodies that will be effective as therapeutics. To develop a single drug candidate, an innovator company would have generated thousands of antibodies (as did

Amgen), by immunizing mice or using phage display, and then screened those antibodies for anti-PCSK9 activity. From these antibodies, perhaps a single antibody would have been selected for clinical development. This process alone could take several years.[1] Thus, to argue that evidence of four anti-PCSK9 antibodies developed independently by others is a "paltry showing" ignores the realities of drug development. Amgen Br. 41. Indeed, the district court determined based on the evidence that a person of ordinary skill in the art attempting to obtain a non-disclosed antibody or a variant of an antibody disclosed in the patent would have to do essentially the same amount of work as the inventors of the patents-in-suit. Appx21.

This Court has found, in the context of written description, that evidence of a *single* antibody that is structurally diverse may be sufficient to establish that the claimed genus is broad and that the specification lacks sufficient representative species. *See, e.g., AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299-1300 (Fed. Cir. 2014). The same logic should apply to the Court's analysis of the breadth of the claim in the enablement context where the defendant produces evidence of a competitor antibody having a diverse structure or sequence.

[1] For example, bococizumab was initially identified by Pfizer as a PCSK9 inhibitor in 2008 and developed for several years thereafter before phase III clinical trials were ultimately discontinued in 2016.

Furthermore, when this Court remanded the appeal following the first trial, it held that evidence of post-priority date antibodies is "relevant to the representativeness question" in the context of written description. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017). The Court did not suggest that post-priority date antibodies are required to establish the breadth of the claim for enablement purposes. Rather, the Court indicated that such evidence may be relevant to the *quantity of experimentation* needed to practice the full scope of the claim—a distinct inquiry under *Wands*. The Court should not now conclude that Appellees' evidence of four competitor antibodies, each structurally different from, and recognizing a different set of amino acid residues on PCSK9 than the residues recognized by Amgen's antibodies, somehow supports Amgen's argument that the claims are narrow.

B. The Specification Does Not Provide Sufficient Guidance to Enable the Full Scope of the Claims

The enablement requirement ensures that patentees provide an adequate disclosure of the claimed invention commensurate with the breadth of the claim. Thus, "a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope." *MagSil*, 687 F.3d at 1381. Here, the district court concluded that undue experimentation would be required to produce antibodies within the full scope of the genus, whether by making amino acid substitutions to the antibodies disclosed in the patent or by producing antibodies de novo following the "roadmap"—the two methods disclosed in the patents. Appx24-25. On appeal,

Amgen does not demonstrate that these findings are unsupported by the record or insufficient as a matter of law. This Court should affirm.

1. The "Roadmap" Fails to Enable the Claims

Despite claiming a genus of antibodies in purely functional terms, Amgen's patent discloses only conventional, well-known methods for generating the antibodies, and leaves it to the skilled artisan to undertake undue experimentation to identify other structures that may bind to PCSK9. This is fatal to Amgen's functional antibody claims. If a patentee is to receive such broad claims in the first place, it must provide a disclosure that enhances the knowledge and level of skill in the art so as to enable others to practice the full scope of the claim. *See, e.g., MagSil,* 687 F.3d at 1381 ("The scope of the claims must be less than or equal to the scope of the enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims") (internal citations omitted); *see also Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1353 (Fed. Cir. 2011) (right to exclude cannot "over-reach the scope of [patentee's] contribution to the field of art as described in the patent specification."). Amgen's "roadmap"—by itself and in the context of the state of the art—fails to do so.

The so-called "roadmap" provided in the specification involves (1) immunizing genetically-engineered mice to generate a pool of PCSK9 antibodies;

(2) screening the resulting antibodies using binding assays; (3) identifying antibodies that compete with 21B12 and 31H4 for the PCSK9 binding site using "binning" assays; and (4) confirming whether the antibodies that co-bin with 21B12 or 31H4 block PCSK9's interaction with LDLR. Amgen Br. 14-16; Appx21. Amgen acknowledges that antibody-production techniques such as immunizing transgenic mice were well established in 2008. Amgen Br. 28-29. The same is true of assays that could be used to identify antibodies that bind to a given antigen with high affinity. Appx23. The patents' "roadmap" thus does not advance the art of antibody discovery or improve a POSA's ability to generate and screen antibodies that may fall within the scope of the claims. Appx19-20. Rather, as the district court noted, "the significant similarity between the 'research plan' used by Dr. Jackson and the 'roadmap' disclosed in the patent demonstrates that a person of ordinary skill in the art attempting to obtain a claimed antibody that is not disclosed or is a variant of a disclosed antibody 'would have to do essentially the same amount of work as the inventors of the patents-in-suit.'" Appx21, *citing MorphoSys AG v. Janssen Biotech, Inc*., 358 F.Supp.3d 354, 372 (D. Del. 2019).

On appeal, Amgen argues that the roadmap "starts where the inventors' experiments finished" and enables a POSA to produce the claimed antibodies. Amgen Br. 13, 62. However, even assuming a POSA were to follow the "roadmap," Amgen cannot refute that the POSA would be required to use transgenic mice or

phage display to generate thousands of antibodies—just as Amgen did—and then screen the resulting antibodies for PCSK9 binding. The district court found that "it would be impractical for a person of ordinary skill in the art to generate large pools of antibodies (as the patent's 'roadmap' requires)" even assuming one could do so with "routine techniques and low cost." Appx23-24. There is no basis to reverse on appeal. *See, e.g., Idenix*, 603 F.3d at 1160-1161 (claims held invalid for lack of enablement even where synthesis of claimed compounds "was largely routine").

Amgen also argues on appeal that discovering the region on PCSK9 that binds to LDLR "is the hardest part of antibody science." Amgen Br. 62. However, Amgen's patents are directed to *monoclonal antibodies*—not to PCSK9 or an epitope on PCSK9. As such, they must adequately describe the antibodies and how to make them without undue experimentation. *Ariad*, 598 F.3d at 1344 (Fed. Cir. 2010). Reciting amino acid residues on PCSK9 is a red herring for fact-finders, appearing to confer structural limitations to the claimed antibodies when in fact the claims include no such limitations. In truth, Amgen's extensive characterization of PCSK9 and two antibodies that are strong "edge binders" does not even come close to enabling a POSA to practice the full scope of the claims. Thus, even assuming the inventors in this case identified certain residues on PCSK9 that are important to LDLR binding, Amgen cannot rely on that discovery alone to claim all antibodies that bind to those residues. Such a result would effectively eviscerate the enablement

requirement and allow patentees to preclude other innovators from developing therapeutics that act on the same biologic target or pathway.

2. Amino Acid Substitutions to Disclosed Antibodies Also Requires Undue Experimentation

Amgen's patents contemplate making amino acid substitutions to the antibody sequences identified in the patent to produce additional variants that may fall within the scope of the claims. Appx15-16. The evidence at trial indicated that if a POSA were to make only two amino acid substitutions to a single antibody according to Table 1 of the patents, this would produce 97,000 different antibodies, and if a POSA were to make similar substitutions for all twenty-six antibody sequences disclosed in the patents, the result would be millions of antibodies. Appx15-16; Sanofi Br. 22. Significantly, the court found that "[e]ven for the suggested substitutions in the patent ('165 patent, table 1), a person of ordinary skill in the art would still be required to test the newly-generated antibody to see if it meets the functional limitations of the claim." Appx20. Accordingly, the court concluded that "[this] trial-and-error process of amino acid substitution[s]" constituted undue experimentation. Appx24.

The district court's analysis is in line with this Court's recent precedent. For example, in *Idenix*, the Court held that broad genus claims covering a class of compounds were not enabled where testing was necessary to determine whether each compound within the genus would satisfy the functional requirements of the claims.

Idenix, 941 F.3d at 1156. Similarly, in *Enzo Life Scis., Inc. v. Roche Molecular Sys.,* 928 F.3d 1340, 1346 (Fed. Cir. 2019), the Court held that the genus claims at issue were not enabled because each possible embodiment within the claimed genus would need to be tested. Finally, in *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013), the Court held that the functional claims at issue were invalid where it would be necessary to synthesize and screen each candidate compound. Following this precedent, the district court held that Amgen's functional antibody claims encompassing millions of possible variants lack enablement as well. Appx24-25.

On appeal, Amgen argues that variants produced by these so-called "conservative" substitutions would *not* need to be tested to see if they still bind to the sweet spot, because "conservative substitutions predictably produces variants that retain the structure of the original antibody and thus its claimed binding and blocking." Amgen Br. 57. However, in addressing this issue, the district court cited Amgen's own expert, who testified that testing would be required. Appx18. Furthermore, taking Amgen at its word, this means that each of the millions of variants produced by conservative substitutions will satisfy the claims, since they are only "minor" variants of antibodies that are known to fall within the scope of the claims. Amgen Br. 43. This is directly at odds with Amgen's contention that the claimed genus is "narrow" (perhaps as small as 400 antibodies). Amgen Br. 2, 21,

42. The only logical conclusion—and the one that the district court made—is that many, but not all, of these variants will likely retain the binding properties of the original antibody, and the only way a POSA could ascertain this would be to test each antibody. Appx16, Appx18.

The district court also addressed variants produced by non-conservative or "random" substitutions, and found that a POSA could only discover such variants through trial and error by making changes to the disclosed antibodies and then screening them, or by discovering the antibodies de novo (*e.g.*, by immunizing mice). Appx22. Under either scenario, a POSA would be required to engage in extensive experimentation (at least as much as what the inventors did) to identify these antibodies. Indeed, as recent as 2019, scientists described the exploration of mutations to improve antibody affinity as "an extremely time-consuming and laborious process." Maryam Tabasinezhad et al., *Trends in Therapeutic Antibody Affinity Maturation: From in-vitro Towards Next-Generation Sequencing Approaches*, 212 IMMUNOLOGY LETTERS 106, Abstract (2019), https://www.sciencedirect.com/science/article/abs/pii/S0165247819302706.

On appeal, Amgen suggests that any such antibodies would be obtained through the patent's "roadmap." Amgen Br. 50. However, as discussed above, the roadmap produced only 384 antibodies that were identified as blocking the interaction between PCSK9 and LDLR. According to Amgen, this is because the

immunization protocol disclosed in the specification produced a restricted group of antibodies that bind to the antigen. Amgen Br. 41. Thus, not all of the antibodies within the claimed genus—including each of the competitor antibodies—would be produced by following Amgen's protocol, and Amgen certainly produced no evidence to the contrary.

3. The Facts in *Wands* are Distinguishable

Amgen and its *amici* argue that this Court's holding in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), requires a finding of enablement in this case. *Wands* involved immunoassay methods for detecting hepatitis B virus particles by using monoclonal antibodies having a high affinity to the hepatitis B antigen. The sole issue on appeal was whether undue experimentation was required to produce high-affinity monoclonal antibodies used in the claimed methods. *Id.* at 736. The patent application at issue in *Wands* was filed in 1980 and discussed methods for making monoclonal antibodies by immunizing mice with an antigen and generating hybridomas that secreted antibodies against that antigen—the same technology described in Amgen's "detailed roadmap." *Id*. at 737-738. These animal hybridoma techniques were the only methods available at the time for producing the monoclonal antibodies in the patent application at issue. Thus, the Court found that the functionally-defined antibodies in the patent application's method claims were enabled based on the traditional animal hybridoma techniques disclosed in the

application. *Id*. at 740.

The facts and claims here are significantly different. Unlike in *Wands*, a POSA may obtain the claimed antibodies through methods beyond animal hybridoma techniques (e.g., conservative and non-conservative mutations). The district court considered this and properly found that Amgen's patent specification does not enable the claimed genus, which may include millions of potential anti-PCSK9 antibodies that satisfy the functional limitations of the claims. Moreover, when *Wands* was decided in 1988, functionally-defined genus claims may have been justifiable due to the difficulties in characterizing the structure or precise amino acid sequence of antibodies. However, by 2008, researchers had readily available techniques for identifying the crystal structure and amino acid sequence of antibodies. Amgen itself relied on such techniques to identify the crystal structure of 21B12 and 31H4, and in fact claimed these antibodies in other related patents not at issue in this case. Sanofi Br. 8-9. Thus, the only purpose of the asserted claims is to capture later-discovered competitor antibodies that inhibit PCSK9. The facts in *Wands* are too different to compel a finding of enablement in this case.

II. THE COURT SHOULD APPLY THE LAW CONSISTENTLY FOR SMALL MOLECULES AND LARGE MOLECULES

This Court has consistently held that broad, functional claims that encompass a large genus of small molecules are invalid for lack of written description and/or lack of enablement where the specification does not adequately describe or enable

the full scope of the claim. The rationale for the holdings in those cases is no less relevant where the claims at issue cover large molecules, such as proteins or antibodies. Patentees should not be able to use broad functional claims that encompass diverse species to unfairly "preempt the future before it has arrived," merely because they are claiming biologic drugs rather than small molecules. *Ariad*, 598 F.3d at 1353 (citation omitted).

This Court's recent decision in *Idenix* illustrates the importance of the enablement requirement where patentees attempt to claim a genus of molecules that achieve a certain function. In *Idenix*, the Court held that claims directed to anti-HCV nucleoside compounds were invalid for lack of enablement where the claims encompassed at least thousands of molecules and testing was necessary to determine whether any such compounds satisfied the claims. *Idenix*, 941 F.3d at 962. Underlying the Court's holding was the fact that a POSA would not be able to predict *ex ante* which particular candidate compounds within the genus would be effective and which would not, due to the unpredictability associated with each potential chemical substitution or modification. *Id*. at 1159-1161. This is equally true for large molecules such as antibodies, where changing one or more amino acids can have a dramatic effect on the three-dimensional structure and function of the antibody. The enablement requirement must therefore be applied to ensure that

genus claims do not overreach beyond the inventors' contribution and the level of predictability in the art.

Furthermore, the field of antibody engineering is continuously expanding with new technologies to discover antibodies that are unseen through traditional antibody engineering methods. Antibodies designed using such technologies may have sequences resulting in improved affinity that may never be discovered through traditional antibody engineering methods. If patentees are permitted to claim antibodies in a purely functional manner, as Amgen did in this case, such antibodies may nevertheless be captured by patents that fail to teach others how to arrive at such optimized antibodies.

Pfizer does not object to an innovator claiming what it has made, or claiming a genus based on disclosure of representative species, or claiming a composition of matter by a structural definition that permits reasoned and predictable variation. However, the only purpose of the asserted functional claims here is to preempt competition as broadly as possible and well beyond the actual contribution of the inventors. If such claims are to be granted in the first place, and subsequently upheld in litigation, they must be subject to the same rigorous scrutiny that has been applied to functionally-defined small molecule claims.

CONCLUSION

The Court should affirm the district court's decision below that Appellants

have not satisfied the enablement requirement with respect to the asserted claims of U.S. Patent Nos. 8,829,165 and 8,859,741.

June 8, 2020

Respectfully submitted,

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Form 30
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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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