No. 20-1074

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

AMGEN INC., AMGEN MANUFACTURING, LIMITED, 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, in No. 1:14-cv-01317-RGA

NON-CONFIDENTIAL REPLY BRIEF FOR PLAINTIFFS-APPELLANTS AMGEN INC., AMGEN MANUFACTURING, LIMITED, AND AMGEN USA, INC.

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 20-1074

Short Case Caption Amgen Inc., et al. v. Sanofi, et al.

Filing Party/Entity Amgen Inc., Amgen Manufacturing, Limited, and Amgen USA, Inc.

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 07/23/2020

Signature: /s/ Jeffrey A. Lamken

Name: Jeffrey A. Lamken

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
Amgen Inc.	None	None
Amgen Manufacturing, Limited	None	Amgen Inc.
Amgen USA, Inc.	None	Amgen Inc.

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☑ Additional pages attached

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☑ None/Not Applicable ☐ Additional pages attached

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

CERTIFICATE OF INTEREST

Appellants Amgen Inc., Amgen Manufacturing, Limited, and Amgen USA, Inc. (collectively "Amgen") state that the following partners or associates have appeared on their behalf before the district court or are expected to appear in this Court:

From **Young Conaway Stargatt & Taylor LLP**: Melanie K. Sharp, James L. Higgins, and Michelle M. Ovanesian.[1]

From **McDermott Will & Emery LLP**: William G. Gaede, III, Sarah C. Columbia, K. Nicole Clouse, Mandy H. Kim, Bhanu K. Sadasivan, David L. Larson, Rebecca Harker Duttry, Eric W. Hagen, Terry W. Ahearn, Shane G. Smith, Michael V. O'Shaughnessy, Esther E. Lin, and Evan Boetticher.[2]

From **Schertler & Onorato, LLP**: Christopher B. Mead.

From **Cravath, Swaine & Moore LLP**: Keith R. Hummel, David N. Greenwald, Lauren A. Moskowitz, Andrei Harasymiak, Geoffrey G. Hu, Sharonmoyee Goswami, and Amal Elbakhar.

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[1] Michelle M. Ovanesian no longer practices with Young Conaway Stargatt & Taylor LLP and is not expected to enter an appearance on behalf of Amgen in this appeal.

[2] Eric W. Hagen, Terry W. Ahearn, Shane G. Smith, Michael V. O'Shaughnessy, Esther E. Lin, and Evan Boetticher no longer practice with McDermott Will & Emery LLP and are not expected to enter appearances on behalf of Amgen in this appeal.

From **Quinn Emanuel Urquhart & Sullivan, LLP**: Lauren N. Martin and Megan Y. Yung.[3]

From **King & Spalding LLP**: Daryl L. Joseffer and Adam M. Conrad.[4]

From **Amgen, Inc.**: Stuart L. Watt, Wendy A. Whiteford, Erica S. Olson, Steven D. Tang, Emily C. Johnson, Dennis J. Smith, and Joshua Mack.[5]

From **MoloLamken LLP**: Jeffrey A. Lamken, Michael G. Pattillo, Jr., Sarah J. Newman, and Sara E. Margolis.[6]

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[3] Megan Y. Yung no longer practices with Quinn Emanuel Urquhart & Sullivan, LLP, and is not expected to enter an appearance on behalf of Amgen in this appeal.

[4] Daryl L. Joseffer and Adam M. Conrad no longer practice with King & Spalding LLP and are not expected to enter appearances on behalf of Amgen in this appeal.

[5] Joshua Mack is no longer employed by Amgen, Inc., and is not expected to enter an appearance on behalf of Amgen in this appeal.

[6] In the prior appeal in this case (No. 17-1480), Christopher R. Healy, Merritt E. McAlister, and Joshua N. Mitchell from King & Spalding LLP appeared before this Court on behalf of Amgen. Those attorneys are not expected to enter appearances on behalf of Amgen in this appeal.

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CONFIDENTIAL MATERIAL OMITTED

Material has been redacted in the Non-Confidential Brief for Plaintiffs-Appellants Amgen Inc., Amgen Manufacturing, Limited, and Amgen USA, Inc. The material omitted from page 32 contains information regarding Amgen's proprietary scientific information, which was covered by the terms of the governing protective order entered by the district court.

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I. SUBSTANTIAL EVIDENCE SHOWED THAT AMGEN'S CLAIMS ARE ENABLED

Having seen ample evidence that Amgen's patents "enable" POSAs "to make and use" the full scope of the claimed invention, 35 U.S.C. § 112(a), the jury properly rejected Sanofi-Regeneron's enablement challenge. The district court erroneously granted JMOL by substituting its own findings of fact for the jury's and finding unpredictability where there is none. At Sanofi-Regeneron's urging, the court improperly attempted to shoehorn this case into the "candidates" analysis of the *Idenix/Wyeth/Enzo* line of cases. Because the facts and law support the jury's enablement verdict—and Sanofi-Regeneron certainly has not shown that every reasonable juror would be compelled to find it disproved enablement by clear-and-convincing evidence—this Court should reverse.

The patents first provide a detailed roadmap that enables POSAs—using routine antibody techniques—to generate and isolate the limited number of distinct antibodies that bind the small sweet spot on PCSK9 and thereby block it from binding LDLR as the claims require. *Wands*, this Court's seminal enablement decision—in the context of this art and these very techniques—confirms that conclusion.

Second, the patents also disclose how to make variants of these antibodies using a prior-art technique called "conservative substitution." As ample evidence

demonstrated, that technique begins with an antibody already known to work (*e.g.*, one generated using mice) and provides for specific substitutions of amino acids of similar charge and size—guided by the patents' Table 1—that reliably produce variants that function just like the original. Hypothesizing "millions" of such variants, Sanofi-Regeneron urges that they ***theoretically*** could lack the ability to bind PCSK9's sweet spot. But it identified ***not one*** example of a variant produced through conservative substitution that lost the ability to bind and block. It offered no proof that occurs with any frequency. It offered only speculation and sound-bites, falling far short of the evidentiary showing necessary for JMOL.

Unlike in *Idenix*/*Wyeth*/*Enzo*, there is no disparity in numbers between the "candidates" that meet the structural limitations of the claims and those that meet the functional requirements. Here, POSAs following the patents' roadmap use proven tools of antibody science to generate the claimed antibodies every time, with minimal experimentation. Like in *Wands*, the transgenic mice and phage display techniques reliably do the work of producing the claimed antibodies. And using conservative substitution predictably results in variants with similar binding to PCSK9 and thus the same function of blocking.

A. Sanofi-Regeneron Failed To Show Any Antibody That Could Not Be Made Using Mice/Phage Display Following the Patents' Roadmap

This Court remanded this case to permit Sanofi-Regeneron to introduce evidence of antibodies, developed after the patents' 2008 priority date, to support its § 112 arguments. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1375 (Fed. Cir. 2017). On retrial, Sanofi-Regeneron made that evidence the centerpiece of its case: It urged that four post-priority-date antibodies—its own Praluent (alirocumab), Merck's 1D05 and AX132, and Pfizer's J16 (collectively, "Competitor Antibodies")—could not be made using the patents' disclosures. SR.Br.14-15.

But the jury rejected that evidence, for good reason: Amgen's Dr. Rees explained, in detailed testimony, how the patents' roadmap produces each Competitor Antibody. Amgen.Br.37-38 (citing Appx3908-3909(757:12-760:21); Appx3918-3919(798:25-799:5)); Appx3909(762:10-20) (roadmap teaches how to make Sanofi-Regeneron's examples). Sanofi-Regeneron nowhere suggests the jury could not credit Dr. Rees's testimony.

Having failed to disprove enablement through the Competitor Antibodies, Sanofi-Regeneron invoked Dr. Boyd's speculation that "[y]ou ***could be*** immunizing mice for a hundred years," and "[t]here ***might be*** kind of an antibody that you didn't come up with." Appx3754(330:18-22) (emphasis added); SR.Br.36, 43-44. But Dr. Boyd neither provided a concrete example of such an antibody, nor opined

one was likely to exist. The jury was not ***required*** to accept, as clear-and-convincing proof, speculation that repeating the same process for a century ***might*** produce a new antibody. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1353 (Fed. Cir. 2003). The district court erred in relying on such speculation to overturn the verdict. *See* Appx23; Amgen.Br.12, 15.[1]

In *McRO, Inc. v. Bandai Namco Games America, Inc.*, 959 F.3d 1091 (Fed. Cir. 2020), this Court surveyed its enablement precedent and explained it is the Court's "***usual requirement*** that the challenger ***identify specifics*** that are or may be within the claim ***but are not enabled***." *Id.* at 1104 (emphasis added). "[W]ithout concrete identification" of embodiments "within the claim scope" that are "not enabled," a party's case is "too abstract, too conclusory" to permit JMOL of non-enablement. *Id.* at 1099, 1101. Dr. Boyd's speculation about what "could be," or "might be," is the sort of "abstract assertion" this Court has rejected. *Id.* at 1101. While Sanofi-Regeneron urges that this Court has "never required" parties to

[1] Pfizer speculates that, because the roadmap uses the 21B12 and 31H4 antibodies, it will identify only antibodies "that compete with 21B12 or 31H4." Pfizer.Br.10. But Pfizer, too, fails to identify any antibody that cannot be made following the roadmap. The trial evidence showed that 21B12 and 31H4 are perfect "anchors" because they collectively compete with, and thus identify, antibodies that bind ***anywhere*** on PCSK9's sweet spot. Amgen.Br.12, 15.

identify a concrete embodiment "that could not be produced using" the patent's disclosures, SR.Br.18, 42, *McRO* demonstrates otherwise.

Sanofi-Regeneron blames its loss at trial on the district court's exclusion of certain documents relating to Amgen's post-priority-date research into catabolic antibodies. SR.Br.42-43. As explained below (at 30-34), the court exercised appropriate discretion to prevent jury confusion and a sideshow by excluding documents that "did not actually show" what Sanofi-Regeneron claimed. Appx27.

B. *Wands* Confirms the Jury Could Find Amgen's Patents Enabled

1. *Wands* is not merely this Court's seminal enablement decision. It addressed the same mouse-immunization techniques for antibody production and identification disclosed in Amgen's patents—except that Amgen's patents provide exceptional enhancements and the art has advanced in the 30 years since, making those methods automated, faster, and cheaper. *Wands* confirms that the disclosed techniques do not require undue experimentation. Amgen.Br.34-37.

Sanofi-Regeneron does not defend the district court's attempt to distinguish *Wands* based on the mistaken belief it involved only method claims. Amgen.Br.36. Instead, Sanofi-Regeneron attempts to recharacterize *Wands* as a "narrow" decision addressing only the number of cell lines needed to enable claims. SR.Br.45. But *Wands*' holding was that the disclosed method of making the antibodies using immunized mice—the same method in the patents here—is

not undue experimentation. *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988); Amgen.Br.34-37. The immunization-and-screening process Sanofi-Regeneron now calls "'searching for a needle in a haystack,'" SR.Br.46, is the same process *Wands* holds that "[p]ractitioners of this art are prepared" to perform, 858 F.2d at 740.

2. Sanofi-Regeneron's effort to relitigate individual *Wands* factors similarly falls short. Like the district court, Sanofi-Regeneron does not deny that many factors (mature state of the art, high level of skill, etc.) undisputedly support enablement. Amgen.Br.20; Appx19-20.

Guidance. On the amount of guidance the patents provided, Amgen demonstrated error: The district court's attempt to equate the effort required under the patents' roadmap to that of Dr. Jackson's initial "'research plan,'" Appx21, was simply wrong, Amgen.Br.61-63. Sanofi-Regeneron nowhere defends that incorrect conclusion.

Size of the genus. While the district court concluded that the claims' scope was "vast," Appx16, that issue was hotly contested at trial. Sanofi-Regeneron does not seriously dispute that the jury could have found the number of ***distinct*** antibodies within the genus to be small, numbering around 400. Amgen's experts testified that the claims were "very narrow" and that "the genus of antibodies that bind the sweet spot and block is small." Amgen.Br.20; Appx3883(658:1-5);

Appx3910(763:20-22). Sanofi-Regeneron has no answer to the evidence, including the small number of actual antibodies identified, and Dr. Rees's scientific explanation why the genus is small—that restricted immune response and the sweet spot's tiny size dramatically limit the number of distinct antibodies within the claims. Amgen.Br.40-42; Appx3900(724:20-725:5); Appx3901-3902(730:21-731:3, 732:9-18).[2]

Sanofi-Regeneron therefore changes the subject, seeking to apply the "candidates" analysis from *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019), *Wyeth & Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380 (Fed. Cir. 2013), and *Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc.*, 928 F.3d 1340 (Fed. Cir. 2019). Sanofi-Regeneron insists that Amgen, using the disclosed techniques for immunized mice, "collected about ***3,000 candidate antibodies***" that bound somewhere to PCSK9, and "screened and tested ***those candidates***" to find the 384 that block the LDLR well, while Sanofi-Regeneron "generated about ***1,500 candidate antibodies***" (which undoubtedly overlapped with Amgen's). SR.Br.6-7 (emphasis added); *see* Amgen.Br.9 (describing Amgen's research); Appx3918-3919(798:25-799:5). Even if these

[2] Sanofi-Regeneron complains (SR.Br.35 n.12) Amgen "never argued to the jury" that its claims covered only around 400 distinct antibodies. But it never denies the jury could easily reach that number based on the evidence. *See* Amgen.Br.41-42; Appx3902(731:12-732:8) (Dr. Rees counting number of actual antibodies in the genus).

3,000 antibodies were considered "candidates," that number does not approach the "billions," "millions," or even "'tens of thousands'" of candidate compounds the Court found POSAs would have to test in *Idenix*, 941 F.3d at 1157-58, *Wyeth*, 720 F.3d at 1384, and *Enzo*, 928 F.3d at 1349.[3] Sanofi-Regeneron makes no showing that the effort required to isolate the claimed antibodies from such a limited pool—using techniques found enabled in *Wands*, plus 30 years of advances in the art and optimizations for PCSK9 in Amgen's roadmap—involves undue experimentation. Amgen.Br.13-16, 34-37, 60-61.

Despite the small number of antibodies produced pursuant to the roadmap, Sanofi-Regeneron insists (like the district court) that practicing the claims' full scope requires "generating millions of antibodies." SR.Br.2. But it reaches that number ***only*** by purporting to calculate the number of variants that might be produced through conservative substitution. SR.Br.37. The jury could have found Sanofi-Regeneron's "millions" to be artificial: Variants made through conservative substitution—99% identical to the originals—are not distinct antibodies but are considered "'the ***same*** antibody'" as the original. Amgen.Br.17 & n.5

[3] Sanofi-Regeneron's contention that the genus consists of 32,000 antibodies (SR.Br.22 n.6) is a red herring. That is the number of theoretical combinations of 2 or more (out of 15) sweet-spot residues; no expert testified that every combination corresponds to a different antibody. The evidence showed immunized mice/phage display produce ***all*** the distinct antibodies within the claims, and the actual number was around 400. Amgen.Br.32-34, 40-42.

(emphasis added) (quoting Sanofi-Regeneron's Dr. Boyd). And Dr. Rees rejected Sanofi-Regeneron's speculation, testifying that there "certainly" are not "millions." Appx3902(732:7-8); *see generally* Amgen.Br.44-49; pp. 11-13, *infra* (explaining that variants are enabled because they function like the original).

Predictability. Sanofi-Regeneron contends there was "[u]ndisputed evidence" that generating desired antibodies was "highly unpredictable." SR.Br.23. But even the district court acknowledged "conflicting testimony as to the predictability of the art." Appx17. On JMOL, this Court must resolve that conflict in favor of the verdict. *Bio-Tech. Gen. Corp. v. Genentech, Inc.*, 267 F.3d 1325, 1329 (Fed. Cir. 2001). There was ample evidence the patents' roadmap predictably produces the claimed antibodies—using the same techniques found predictable in *Wands*. Amgen.Br.34-37, 52-53.

Sanofi-Regeneron thus changes the test. The invention is not enabled, it says, unless POSAs can ***predict*** "whether a particular antibody sequence would bind" the sweet spot by examining the amino-acid "sequence" in isolation. SR.Br.33.[4] But § 112 requires the specification to teach POSAs "to make and use the claimed invention." *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976). The roadmap does that. The specification does not need to enable methods POSAs do

[4] As discussed *infra*, pp. 11-13, POSAs can predict that variants of working antibodies, made through conservative substitution under Table 1, will work like the original.

not use, like guessing which amino-acid sequences work. Amgen.Br.54-56. Sanofi-Regeneron's Dr. Boyd admitted that antibody scientists do not "sit down and say, I think I'll design an antibody [by] writ[ing] out the amino acid sequence." Appx3683(197:2-3). The jury was entitled to reject Sanofi-Regeneron's argument that predictability is evaluated under a technique POSAs don't use (sequence guessing) rather than ones they do use (mice and phage display).

Wands did not ask whether POSAs could predict, by looking at amino-acid sequence alone, which antibodies bind the HBsAG antigen as required by the claims there. 858 F.2d at 734. Rather, the Court addressed whether the disclosed "methods" of ***making*** the claimed antibodies were "predictable or reproducible." *Id.* at 739.[5] The district court erred in displacing the jury's supported findings, in disregard of *Wands*. *See* Appx17-18 & n.8.

C. Conservative Substitution Does Not Defeat Enablement

The crux of Sanofi-Regeneron's argument—like the district court's—centers on the patents' additional disclosure that POSAs can use conservative substitutions under Table 1 to make variants of the 26 example antibodies disclosed in the

[5] Sanofi-Regeneron argues *Wands* and other antibody cases are different because "Amgen's claims require binding to ***a specific region*** on an antigen (PCSK9)." SR.Br.33. But identifying the binding site significantly narrows the claim, Appx3900(724:20-725:5); Appx3901-3902(730:21-731:3), and, once demonstrated that an antibody occupying that space will function to block LDLR, makes the teaching more predictable because antibodies that bind the sweet spot ***will*** block LDLR, Appx3876(629:6-18).

patents. Sanofi-Regeneron convinced the court to characterize the variants as "'millions' of candidate[]" antibodies, SR.Br.37-40, that would be unpredictable in their binding to PCSK9 and blocking LDLR—and would thus need to be tested to see if they work, Appx15-16. But the jury had ample grounds for rejecting that theory.

Variants made through conservative substitution predictably bind PCSK9 and block LDLR. The patents teach a technique for producing variants of antibodies known to fall within the claims—*i.e.*, those known to have the three-dimensional structure and biochemical properties to bind the sweet spot and thus block LDLR. Amgen.Br.8-9, 16-17, 20-21, 43-44, 48-49. Sanofi-Regeneron's Dr. Boyd admitted that Amgen's patents "***give[] the rules for generating***" variants through conservative substitution. Appx3688(219:1-8) (emphasis added).[6] As a scientific matter, conservative substitution involves replacing an amino acid with another amino acid with ***highly similar*** structure and biochemical properties, chosen precisely so as ***not*** to defeat the original antibody's binding ability.

[6] Sanofi-Regeneron makes the Hail-Mary contention that there is "no evidence" that "Table 1 substitutions" are "'conservative.'" SR.Br.30 n.9, 39. But neither of its experts contested that POSAs consider those substitutions conservative. The patents disclose that "conservative amino acid substitutions" can be made "without destroying the biological activity." Appx221(48:29-33); *see* Amgen.Br.16-17. Sanofi-Regeneron does not explain what Table 1's "[e]xemplary amino acid substitutions," Appx211, are "exemplary" of if they are not conservative amino-acid substitutions.

Appx211(27:32-39, 27:60-62); Appx221(48:29-33); Appx225(56:13-19). The patents thus explain: "It is ***known*** that ***certain amino acids can be substituted for other amino acids*** . . . and still ***retain a similar biological activity***." Appx211(27:60-62) (emphasis added).[7] Regeneron's own December 2008 patent (cited SR.Br.6-7) agrees: "In general, a conservative amino acid substitution ***will not*** substantially change the functional properties of a protein." U.S. Patent No. 8,062,640, at 12:57-59 (emphasis added). And Dr. Rees testified that, in his experience, substitutions did not defeat an antibody's ability to bind; they yielded variants with "the same properties." Appx3914(780:6-11); Amgen.Br.49.

The fact that variants produced using conservative substitution under Table 1 are 99% identical to the original antibody confirms that POSAs would expect them to bind and block like the original.[8] Sanofi-Regeneron's Dr. Boyd admitted

[7] The patents do not merely say conservative substitutions "'can' result in functional similarity," SR.Br.29; they say it is "known" substitutions can be made "and still retain . . . biological activity," Appx211(27:60-62).

[8] Sanofi-Regeneron faults Amgen for "assum[ing] that only two amino acids are substituted, which is not a limitation set out in Table 1." SR.Br.39 (citation omitted). But Dr. Boyd never suggested POSAs would make more than two substitutions "following the rules" in Table 1. Appx3688(219:21-25); Appx3919(802:12-23). That is the only testimony Sanofi-Regeneron presented to the jury about the number of Table 1 substitutions, and it is the evidence the court cited below. Appx15-16. Sanofi-Regeneron protests that the patents disclose "substituting up to one-half of one chain's acids." SR.Br.22. But those disclosures, never argued by Sanofi-Regeneron, address an unrelated technique of replacing entire antibody "sections" from Table 2 (*e.g.*, CDRs already known to bind)—not substitution of

that variants with such similar sequences should be considered "the ***same*** antibody" that "bind in the [same] way." Appx3763(368:6-15) (emphasis added). Sanofi-Regeneron attempts to recharacterize that testimony as saying "'the ***same sequence***'" will bind the same way. SR.Br.31. But Dr. Boyd said more, testifying that "another antibody that's very, very close in its sequence"—and conservative substitutions certainly are—would "bind in the [same] way." Appx3763(368:6-15).

Sanofi-Regeneron's Dr. Eck confirmed that such similar antibodies—and ones less similar—are "'essentially copies'" that "'are likely to interact with PCSK9 in the same way.'" Amgen.Br.45 (discussing Appx3788(465:9-20, 467:7-15)). Sanofi-Regeneron argues that his testimony concerns only antibodies known to bind and block. SR.Br.31-32. But conservative substitutions are targeted changes to antibodies known to bind and block; those changes thus yield "essentially copies" of the original that "interact with PCSK9 in the same way."

The vast majority of Dr. Boyd's proposed changes are outside the binding region. Sanofi-Regeneron's "millions" calculation mostly involves substitutions in regions outside the CDR3 loop, which—the experts agreed—is what determines the antibody's binding properties. Amgen.Br.47-49. Sanofi-Regeneron defends

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individual amino acids using Table 1. Appx220(46:44-64); Appx3902(732:23-733:1).

including irrelevant changes because "Table 1 does not limit substitutions only to a CDR region." SR.Br.37-38. But Sanofi-Regeneron cannot explain how changes outside CDR3—the area "most important" for binding, Appx3911(767:24-768:2)—create unpredictability in binding. And even within the CDR3 region, because substitutions are like-for-like, the variants similarly bind PCSK9 regardless. *See* Appx221(48:29-33); Appx225(56:29-32).

Sanofi-Regeneron provides no example of a conservative variant losing the ability to bind PCSK9. Despite having years to prepare its case, Sanofi-Regeneron never identified even ***one*** Table 1 substitution that caused an antibody to lose binding to PCSK9's sweet spot. The failure to identify any concrete example itself defeats JMOL on enablement. *See McRO*, 959 F.3d at 1104.

Enablement does not require exclusion of hypothetical outliers. Moreover, enablement does not require POSAs to perform every possible substitution and test them to "'specifically exclude'" hypothetical outliers that do ***not*** work. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). It is only when "the number of inoperative combinations becomes significant"—as in *Idenix*/*Wyeth*/*Enzo*, pp. 17-18, *infra*—that it "in effect forces" POSAs "to experiment unduly in order to practice the claimed invention." *Atlas Powder*, 750 F.2d at 1576. Here, Sanofi-Regeneron offered no proof showing ***any*** variants made by conservative substitution lost binding, much less a sufficiently

significant number as to prevent POSAs from making and using the invention without undue experimentation.

Sanofi-Regeneron's soundbites fall short of requiring JMOL. Besides Dr. Boyd's speculation, all Sanofi-Regeneron offers is an assemblage of disconnected soundbites from Amgen witnesses that, at most, suggest there hypothetically ***might*** be amino-acid changes that can affect function. *See* SR.Br.23-24, 28-29. Sanofi-Regeneron invokes Dr. Petsko's supposed admission that, because "'[c]hanging a single amino acid in an antibody's sequence'" could theoretically change that antibody's function, the "'only way ***to be sure*** if that single change affects the antibody's function'" is to "'test.'" SR.Br.29 (brackets in original) (emphasis added). But patent law long ago rejected a certainty requirement, ***refusing*** to demand that the specification "'enable one skilled in the art to determine, with reasonable certainty before performing the reaction, whether the claimed product will be obtained.'" *Angstadt*, 537 F.2d at 503. Dr. Petsko's testimony that it is "theoretically possible" that ***some*** single amino-acid changes ***might*** have an effect on antibody function, Appx3891(688:21-689:4), does not suggest that ***conservative substitution*** will turn an antibody that binds and blocks into one that does not, much less that it will frequently do so. The hypothesized risk of an occasional dud does not defeat enablement.

Nor did Dr. Rees admit that "'you'd have to test'" every variant produced through Table 1 substitutions. SR.Br.24. Dr. Rees testified that "'unknown'" antibodies require screening. Amgen.Br.57; Appx3914(779:15-16). Table 1 variants are not "unknown." They are variants of antibodies ***already known*** to satisfy the claims. And Dr. Rees explained that, in his experience, antibodies created by conservative substitution do not "lose their binding to their target." Appx3902(733:12-22).

While Sanofi-Regeneron invokes Dr. Mehlin's testimony that he is "always surprised" when "sometimes" a "conservative mutation" affects "protein function," Appx3768-3769(388:24-389:8) (cited SR.Br.23-24), that surprise underscores the rarity of such occurrence. Nor did he testify that conservative substitution affects binding. And contrary to Sanofi-Regeneron's contentions, Dr. Mehlin was not discussing Table 1 substitutions or "reviewing the . . . patent during that testimony." SR.Br.30 (emphasis omitted). Neither the question nor answer was tied to the patents. Appx3768-3769(388:17-389:8).

Having heard the evidence, the jury saw Sanofi-Regeneron's argument that conservative substitutions might not work for what it is: pure speculation. The evidence was overwhelming that conservative substitution is enabled and reliably produces functioning variants. This case does not remotely approach the extraor-

dinarily demanding standard for JMOL for the party that bears a clear-and-convincing burden of proof. *Boehringer*, 320 F.3d at 1353.[9]

D. *Idenix*, *Wyeth*, and *Enzo* Are Inapposite

The district court's JMOL ruling does not "follow[] inescapably"—or at all—from *Idenix*/*Wyeth*/*Enzo*. SR.Br.27.[10] As this Court has explained, the "candidates" approach in those cases applies only where a POSA must "identify[], from among the many concretely identified compounds that meet the [claim's] structural requirements," the "compounds that satisfy the [claim's] functional requirement." *McRO*, 959 F.3d at 1100 n.2. The Court found the patents invalid in those cases because they left POSAs to march through endless permutations of chemical compounds, "searching for a needle in a haystack" to find ***any*** working embodiments. *Idenix*, 941 F.3d at 1161-62. But this case presents the opposite scenario: The patents teach POSAs to obtain all claimed antibodies.

In *Idenix*, the claims recited using small-molecule "nucleoside compounds" for treating hepatitis C. 941 F.3d at 1154. The patent listed possible structures,

[9] Sanofi-Regeneron repeats, but does not defend, the district court's invocation of "random mutations." SR.Br.38-39; *see* Pfizer.Br.12. Neither side argued to the jury about "random mutations," and Sanofi-Regeneron cannot explain what the court meant. *See* Amgen.Br.50. Regardless, the jury was entitled to find immunized mice account for any "random mutations." *See* Amgen.Br.50. Sanofi-Regeneron offers no response.

[10] Sanofi-Regeneron is wrong to suggest (SR.Br.28 n.8) that Amgen cannot distinguish *Idenix*/*Wyeth*/*Enzo* on reply. 16AA Wright & Miller, *Federal Practice and Procedure* § 3974.3 & n.6 (4th ed. 2020).

and "'billions and billions' of compounds literally m[e]t th[os]e structural limitations." *Id.* at 1157. The Court found "the art was unpredictable," and the patent provided no "meaningful guidance" on how to find which of those myriad compounds would treat hepatitis C. *Id.* at 1161-62. POSAs were left to pursue an "'iterative, trial-and-error process'"—blindly picking combinations from a vast array of options, "synthesiz[ing]" compounds with different substituents, and "screen[ing]" them in the hope of finding one that worked. *Id.* at 1161-62. Under those facts, this Court held that the "size disparity" between the "'large number of [candidate compounds]'" and the "'small number [of effective compounds]'" required significant experimentation. *Id.* at 1162 (brackets in original).

Similarly, in *Wyeth*, the patentee's expert conceded the art's unpredictability, and the patent provided "no guidance" to which of "at least tens of thousands of candidate compounds" in a chemical formula would have the claimed efficacy of treating restenosis. 720 F.3d at 1385-86. That expert also testified that the number of compounds that would exhibit the recited functional effects would be "significantly smaller," thus requiring "synthesizing and screening ***each***" candidate. *Id.* at 1384-85. And in *Enzo*, "at least 'tens of thousands'" of polynucleotides "fit within the [structural] limitations" of the claim, yet the art was highly unpredictable, and the "specification fail[ed] to teach" POSAs how to find those that "exhibit [the] required functionality." 928 F.3d at 1346, 1349.

Amgen's patents could not be more different. Amgen's Dr. Rees explained that the patents' roadmap—using mice/phage display—will "generate the antibodies" covering the full scope of the claims with "certainty." Appx3908(756:8-20, 757:12-14); Appx3909(762:14-20). And there is no disparity between the number of antibodies that meet the claims' structural requirements of binding PCSK9's small sweet spot and those that have the claimed function of blocking the interaction with LDLR—if it binds, it blocks. Appx3876(629:10-18). Neither the mouse/phage systems nor conservative substitution results in a vast number of "candidates" that must be tested to determine which fall within the claims.

Mice/Phage Display. The roadmap predictably produces antibodies that bind the sweet spot and block LDLR using standard techniques that *Wands* found enabled decades ago. While Sanofi-Regeneron claims it is "undisputed" that the patents' roadmap is a "'trial-and-error' process" like that in *Idenix*, SR.Br.25, that was directly controverted by Dr. Rees, Appx3908(756:8-20). The roadmap—using transgenic mice or phage displays—***predictably*** and ***inevitably*** produces the "'relatively speaking small number [of effective]'" antibodies within Amgen's claims, *Idenix*, 941 F.3d at 1162 (brackets in original), by leveraging the immune response to PCSK9, *see* Amgen.Br.21, 40-41; Appx3908(756:8-757:14); Appx3896-3897(709:2-711:11). In the mouse systems, the PCSK9 antigen ***itself*** "selects" the antibodies with the shape and chemical complementarity that "fit" the

sweet spot and block LDLR. Amgen.Br.40-41; Appx3910-3911(766:21-767:5); Appx3874(622:3-21); Appx3876(629:10-18).

Conservative substitutions. Sanofi-Regeneron's effort to shoehorn the patents' teachings on conservative substitution into the *Idenix*/*Wyeth*/*Enzo* framework fares even worse. In *Idenix*/*Wyeth*/*Enzo*, POSAs had to assemble molecule after molecule, randomly varying substituents, hoping to find one that works. *See* pp. 17-18, *supra*. With conservative substitutions, POSAs ***start*** with an antibody ***known*** to work, and substitute an amino acid with another known to have similar properties, as taught by the patents' Table 1, to produce a variant that continues to work. *See* pp. 11-13, *supra*. The patents in *Idenix*/*Wyeth*/*Enzo* gave POSAs "no guidance" on which substituents to choose. *Wyeth*, 720 F.3d at 1386. The patents here provide solutions and structural information—the sequences of 26 antibodies within the claims, Table 1's "[e]xemplary amino acid substitutions," and the crystal structures of PCSK9 and two representative antibodies, 21B12 and 31H4—that guide POSAs to reliably make further variants that bind PCSK9's sweet spot. Amgen.Br.10-12, 16-17; Appx3881(649:10-24); Appx3904(741:10-742:13).

On this record, a reasonable jury could conclude the claims are enabled. The court improperly reweighed this evidence and erred in granting JMOL.

E. Sanofi-Regeneron Distorts the "Full Scope" Requirement

The district court erred by measuring undue experimentation in terms of the effort required to "***discover[]***" and make "***every*** antibody within the scope of the claims." Appx15 (emphasis added). While Sanofi-Regeneron insists that was not the court's "actual reasoning," SR.Br.47, it declines to identify the standard the court did apply. Sanofi-Regeneron's arguments rest on the premise that enablement requires POSAs to "find ***every antibody*** that binds to the claimed residues." SR.Br.43 (emphasis added). That defies Supreme Court and this Court's precedents, Amgen.Br.63-69, and the evidence showed that the patents meet even that heightened standard.

II. SANOFI-REGENERON IS NOT ENTITLED TO JMOL ON WRITTEN DESCRIPTION

In the prior appeal, this Court acknowledged the "hotly disputed" issues on written description, itself a question of fact. *Amgen*, 872 F.3d at 1378-79. On remand, Sanofi-Regeneron presented its evidence of post-priority-date antibodies. The jury found Sanofi-Regeneron had not met its clear-and-convincing burden nonetheless. The district court properly denied JMOL. Appx9.

Section 112(a)'s written-description requirement is met where the patent "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date," either by (a) disclosing species "representative" of the genus or (b) showing "structural features common" to the

genus. *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350, 1351 (Fed. Cir. 2010) (en banc).[11] Sanofi-Regeneron can prevail only if every reasonable juror would be compelled to find it had proved, by clear-and-convincing evidence, that ***neither*** test was satisfied. *Boehringer*, 320 F.3d at 1353. Sanofi-Regeneron cannot meet that burden.

A. The Patents Disclose Representative Structures

Sanofi-Regeneron criticizes functional claims because they may claim a result "'without describing species that achieve that result.'" SR.Br.50. But Amgen's patents are not solely functional: The claim term "binds to [residues on PCSK9]," Appx411(427:47-52), conveys to POSAs a genus of antibody ***structures*** that complement, and thereby bind, the sweet spot's three-dimensional structure, Appx3876(629:25-630:13); Appx3877(633:25-634:13); Appx3878(636:11-25, 637:8-17); Appx3880-3881(644:24-647:9). Sanofi-Regeneron's expert agreed that "structure" and "bind[ing]" are inseparably intertwined. Appx3789(470:17-471:2); Appx3787(462:20-22).

Overwhelming evidence showed that Amgen's patents "describe representative antibodies to reflect the structural diversity of the claimed genus." *AbbVie*

[11] For preservation, Amgen disputes that standard. Section 112(a) requires a written description of the invention sufficient to enable others to make and use it—not "possession." Pet. for a Writ of Cert., *Amgen Inc. v. Sanofi*, No. 18-127 (S. Ct. 2019).

Deutschland GmbH & Co. v. Janssen Biotech, *Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014); *see* Appx9. The jury heard that Amgen's anchor antibodies—21B12 and 31H4—"standing alone are sufficiently representative." Appx3881(647:21-648:3). Those antibodies bind side-by-side to different sweet-spot residues and collectively cover the ***entire*** sweet spot. Amgen.Br.11-12; Appx3801(517:2-518:6).

Although 21B12 and 31H4 are sufficient for POSAs to "visualize" the genus, Appx3882(651:1-14), Amgen's patents disclose 24 additional representative antibodies, Appx218(Tbl. 2); Appx236-238(Ex. 3); Appx241-242(Tbl. 8.3); Appx3882-3883(654:23-657:25); Appx3802(523:20-524:9). Where 21B12 and 31H4 bind across different sides of the sweet spot, Amgen's data proved that example antibodies 9C9 and 1A12 bind the sweet spot's middle. Appx182(Fig. 23A); Appx3802-3803(524:12-525:22); Appx3884(660:24-661:1); Appx3907-3908(754:8-755:4). A reasonable jury could credit the patents' "wealth of information," Appx3910(763:1-12), to find that they satisfy the written-description requirement.

The district court correctly held that "substantial evidence supports the jury verdict under the representative species test." Appx9. Using three-dimensional models reproduced from crystal-structure data, Amgen's experts showed that the example antibodies and Competitor Antibodies share shapes and biochemical properties that make them "complementary" to the sweet spot so they can bind there. Appx3877-3878(633:12-637:17); Appx3880-3881(646:22-647:5); Appx3885(666:1-

17); Appx3879(640:1-6); Appx3874(621:5-622:2); Appx4197; Appx4205-4213. For example, crystal structures showed that Amgen's 1A12 antibody and the Competitor Antibodies have the same "pocket or . . . cup region" near the "D238" sweet-spot residue that was "essential" for binding there. Appx3913(775:1-10).

The jury was entitled to accept Amgen's example antibodies as structurally representative. For the same reasons, the jury could have concluded that Amgen's claims satisfy the common-structural-features test. *See Ariad*, 598 F.3d at 1350.

B. A Reasonable Jury Could Reject Sanofi-Regeneron's Arguments

Sanofi-Regeneron argues that the "disclosed antibodies are not representative" because they do not bind the same numbers, and combinations, of sweet-spot residues as the "Competitor Antibodies" and "'don't look anything like'" them "'***in terms of their sequences***.'" SR.Br.51-52 (emphasis added). But representativeness—including deciding which features are relevant—is a "question of fact" that jurors could resolve against Sanofi-Regeneron on this record, *Ariad*, 598 F.3d at 1351.

Sequence does not disprove representativeness. The jury heard ample evidence that antibodies' "three-dimensional structure," not sequence, "was the appropriate metric for comparison." Appx9. "[S]equence," the experts testified, is "not the best tool for comparing antibodies." Appx3894(699:8-13); Appx3890-3891(686:23-687:1); Appx3911(768:6-20). POSAs instead "approach the issue of

representativeness" with "structural comparison" based on antibodies' "tertiary" or "three-dimensional" structure. Appx3910(765:4-766:12); Appx3878(635:12-637:17); Appx3900-3901(725:21-727:4); Appx4197; Appx4205-4213.[12]

But even comparing amino-acid sequences, the jury was entitled to reject Sanofi-Regeneron's argument—as the district court observed. Appx9-10. Applying an 80% threshold for comparing antibody sequences, SR.Br.51, Sanofi-Regeneron's expert agreed "there's an 80-percent similarity" between the amino-acid sequences of Amgen's 9H6 antibody and Sanofi-Regeneron's Praluent in the CDR3 regions, Appx3765(374:4-24)—the area "most important for determining what the antibody is going to bind to," Appx3692(233:17-20); Appx3765(374:4-24) ("'amino acids in that match is 80 percent'"); Appx10. Sanofi-Regeneron re-argues the "sequence comparison," SR.Br.53-54, but a reasonable jury could have found 9H6 representative of Praluent. Nor was the jury required to find purported "differences" in sequence between Amgen's examples and other Competitor Antibodies dispositive. SR.Br.53. Patents need not describe "every species." *Re-*

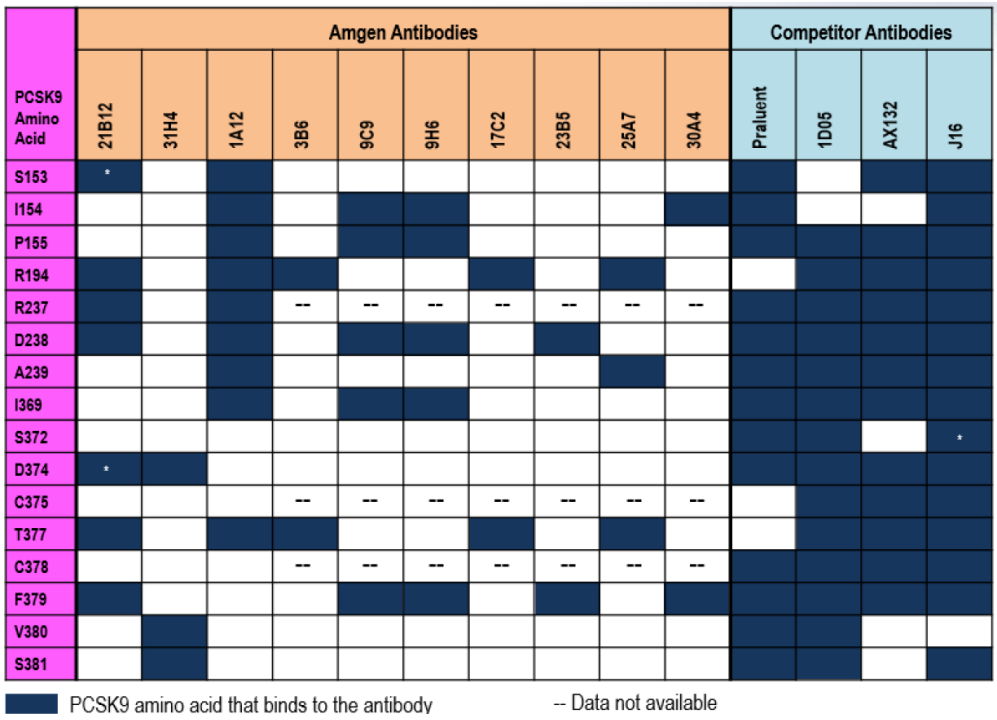
[12] *AbbVie* (cited SR.Br.51, 53) is not to the contrary. This Court upheld the ***jury's verdict*** of invalidity because the jury ***could*** have found, on the record there, that a lack of similarity in amino-acid sequence evidenced inadequate written description. 759 F.3d at 1290, 1300. It did not hold, as Sanofi-Regeneron appears to suggest, that every reasonable juror ***must*** find amino-acid sequence dispositive. To the contrary, no "'particular form of disclosure'" is required "[t]o satisfy the written description requirement." *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008).

gents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997). There is no "requirement to provide [an amino-acid-by-amino-acid] recitation of the entire genus." *Ariad*, 598 F.3d at 1352. The law requires "representative"—not identical—species. *Id.* at 1350.

Sanofi-Regeneron argues that "'describing a limited number of species'" is insufficient because "even a slight difference in amino acid sequence can have substantial effects on antibody function." SR.Br.56 (quoting *In re Alonso*, 545 F.3d 1015, 1020 (Fed. Cir. 2008)). But there was ***no*** proof of ***any*** antibody within the genus that yielded a different "result[]" vis-à-vis the claimed functionality. *Alonso*, 545 F.3d at 1020. The experts agreed that ***all*** antibodies that bind PCSK9's sweet spot will block PCSK9's interaction with LDLR. Appx3876(629:8-18); Appx3787(462:20-22). A reasonable jury could have found that Sanofi-Regeneron failed to prove, by clear-and-convincing evidence, that the disclosed antibodies are not sufficiently representative.

The number of residues bound is not a relevant distinction. Sanofi-Regeneron's argument that the patents' examples "are not representative" based on the numbers and combinations of sweet-spot residues bound, SR.Br.51-52, is also contradicted by substantial evidence, Appx3881(647:21-648:25); Appx3882(652:15-654:22); Appx3885(663:24-664:6); *see* Appx9-10. Sanofi-Regeneron's own chart,

depicting just 10 of Amgen's 26 example antibodies, shows they bind a wide variety of residues:



SR.Br.52; Appx4283. And all ten block PCSK9's interaction with LDLR. Appx3882(652:15-24); Appx3883(655:17-22); Appx3787(461:19-25).

Sanofi-Regeneron argues that the examples are not representative because Competitor Antibodies bind to additional residues, or at different sweet-spot locations. SR.Br.51-53. But the issue is representativeness, not whether every permutation is shown in a working example. Indeed, every Competitor Antibody overlaps in binding sites with the example antibodies; not one binds solely to residues not already covered by them. The jury could find it irrelevant that the Competitor Antibodies bind residues ***in addition to*** those common binding sites. Appx4283.

Dr. Petsko testified that POSAs would not view antibodies that merely bind to additional residues, or to different combinations of residues, as "some different category or some different class." Appx3877(632:3-6). The experts agreed, moreover, that "how ***many residues*** [an antibody] bind[s] to or ***where those residues are*** on the sweet spot doesn't have any bearing on" whether that antibody will block PCSK9's interaction with LDLR. Appx3877(631:5-12) (emphasis added); *see* Appx3882(651:1-14); Appx3871(607:19-24); Appx3787(461:19-462:23). Sanofi-Regeneron's expert conceded "there's no correlation between the number of amino acids that are bound and the blocking." Appx3787(462:11-13). Binding one sweet-spot residue is enough to block.

Sanofi-Regeneron's refrain that Amgen's patents "'preempt[] the future before it has arrived,'" SR.Br.53, thus rings hollow. The jury was entitled to conclude that whether an antibody binds additional or different sweet-spot residues makes not a whit of difference.

Amgen had middle binders. Sanofi-Regeneron's claim that the patents do not disclose antibodies that "'s[i]t right on top of PCSK9,'" SR.Br.52-53, also fails. The jury saw data showing that Amgen's 9C9 and 1A12 antibodies bind atop PCSK9, in the middle of the sweet spot. Appx182(Fig. 23A); Appx3802-3803(524:12-525:22); Appx3907-3908(754:8-755:4); Appx3884-3885(660:24-661:1).

Sanofi-Regeneron complains about the admission of that data because it was compiled after the priority date. SR.Br.62-63. But Sanofi-Regeneron relied on the very evidence it complains of, Appx3693(237:16-238:6); Appx3747(302:21-303:4); Appx3776(418:13-22); Appx4283, and thus cannot challenge its admission now, *Sulzer Textil A.G. v. Picanol N.V.*, 358 F.3d 1356, 1367 (Fed. Cir. 2004). Besides, it is well-established that data showing "inherent propert[ies]" of disclosed embodiments may be considered in determining a disclosure's adequacy. *Kennecott Corp. v. Kyocera Int'l, Inc.*, 835 F.2d 1419, 1423 (Fed. Cir. 1987); *see Yeda Rsch. & Dev. Co. v. Abbott GMBH & Co.*, 837 F.3d 1341, 1345 (Fed. Cir. 2016). Here, the antibodies "are disclosed by sequence," and a POSA could "make the antibodies" and examine inherent properties (like binding sites) using "routine techniques." Appx33-34. There was no abuse of discretion in admitting the data.

III. THE DISTRICT COURT DID NOT ABUSE ITS DISCRETION EXCLUDING CERTAIN POST-PRIORITY-DATE DOCUMENTS

Sanofi-Regeneron's challenge to the district court's evidentiary rulings does not show the "abuse of discretion" necessary to justify a new trial. *Glass v. Phila. Elec. Co.*, 34 F.3d 188, 191 (3d Cir. 1994). Because the court's decision was made "under Rule 403," it receives "particular deference, and . . . may not be reversed unless the determination is 'arbitrary and irrational.'" *In re Paoli R.R. Yard PCB Litig.*, 113 F.3d 444, 453 (3d Cir. 1997). Having "read [this Court's] opinion in

this case more than once," Appx9854(49:13-16), the district court complied with this Court's directives.

A. The District Court Properly Excluded the Documents Under Rules 402 and 403

This Court previously remanded for a new trial because the district court had erred by "categorically" excluding evidence of antibodies "simply because [they] post-dated the claims' priority date." *Amgen*, 872 F.3d at 1375. On remand, Sanofi-Regeneron was permitted to introduce every concrete post-priority-date antibody that, in its view, supported invalidity. *See* pp. 3, 27, *supra*. Sanofi-Regeneron nevertheless claims that "key post-priority-date evidence" was "again improperly excluded." SR.Br.59. But nothing in the Court's prior ruling required all post-priority evidence be admitted without regard to the Federal Rules of Evidence. The district court carefully assessed each proffered document. It admitted certain post-priority evidence, but excluded some documents under Rules 402 and 403.

1. Pre-trial, the district court ruled that evidence of Amgen's later-state-of-the-art catabolic research program was not admissible for enablement, but it allowed evidence of post-priority antibodies for written description's representative-species analysis. Appx5429-5431. Despite introducing every post-priority Competitor Antibody it wished, Sanofi-Regeneron sought admission of documents from Amgen's catabolic program. The court told Sanofi-Regeneron "to offer these

exhibits as you go," Amgen "can make objections," and the court "will rule on them." Appx3658(97:2-5).

When Sanofi-Regeneron did so, the court either found the proffered documents irrelevant under Rule 402, or found any relevance outweighed by unfair prejudice and likelihood of jury confusion. *See* Appx3636-3638(10:21-18:23); Appx3656-3657(92:10-96:3); Appx3684-3685(204:12-205:12); Appx3686-3687(210:23-215:16); Appx9870-9951; Appx3736-3737(257:2-262:21); Appx3807-3808(542:11-545:10); Appx3809-3814(550:1-570:12); Appx3869-3870(602:6-603:22, 605:22-606:25); Appx3872(612:13-17). Sanofi-Regeneron does not address the court's document-specific rulings. That omission is fatal. *Innogenetics v. Abbott Labs.*, 512 F.3d 1363, 1375 (Fed. Cir. 2008).

2. Sanofi-Regeneron stresses relevancy's "'low threshold'" under Rule 402, SR.Br.60, but ignores the district court's "broad discretion to determine the admissibility of relevant evidence" under Rule 403, *Egan v. Del. River Port Auth.*, 851 F.3d 263, 275 (3d Cir. 2017). The court found that, "to the extent there is any marginal relevance" to the proffered documents—which it "highly doubt[ed]"—"confusion would substantially outweigh the probative value." Appx3814(569:18-21). That ruling was within its discretion.

Sanofi-Regeneron argues that the excluded documents demonstrate that Amgen continued looking for certain claimed antibodies—what it calls "middle-

bind[ers]" and "EGFa mimic[s]"—after the priority date. SR.Br.59-60; *see* SR.Br.11-15 (describing evidence).[13] But the documents concerned Amgen's "subsequent state of the art" program to develop "catabolic" antibodies. Appx27; Appx3870(603:25-605:12); Appx9851(39:21-40:10). "[E]vidence illuminating the state of the art subsequent to the priority date is not relevant." *Amgen*, 872 F.3d at 1373-74.

Sanofi-Regeneron urges that "creating a antibody property antibody required" Amgen "***first*** to have a antibody property antibody' within the scope of the claims," so Amgen could "***then*** engineer antibody property into it" to make it catabolic. SR.Br.60-61. It insists the documents showed EGFa mimics "'could not be produced quickly and easily using the patents' roadmap.'" SR.Br.42-43. As the district court recognized, the documents "did not actually show that." Appx27-28. Further, Sanofi-Regeneron's made-for-trial contention that the term "EGFa mimic" refers exclusively to an antibody that covers the sweet spot's "'middle area,'" ***and*** binds almost all sweet-spot residues, is wrong. SR.Br.12; Appx3753(325:8-16). The trial testimony and the excluded documents show that Amgen used "EGFa mimic" in other ways, including a non-antibody therapeutic based on LDLR's

[13] Sanofi-Regeneron forfeited several documents—Appx9690; Appx9694-9697; Appx9705-9706; Appx9712; Appx9717-9718; Appx9722-9723; Appx9725-9727—by failing to offer them "at trial." *Walden v. Georgia-Pacific Corp.*, 126 F.3d 506, 519 (3d Cir. 1997).

"EGFa domain," and catabolic antibodies having a longer duration in the body. Appx3870(604:12-605:7); Appx9708. The court recognized that the mismatch in terminology would create juror confusion.

Dr. Jackson testified that Amgen never specifically tried—much less failed—to make a so-called "EGFa mimic" like Pfizer's J16. Appx3870(605:8-12); Appx3813-3814(568:7-570:11). And Amgen already had EGFa mimics insofar as that term could also describe antibodies that bind the "middle" or "co-bin[]." Appx3871(607:3-10); Appx9968-9969; Appx9972-9973. Amgen made those types of antibodies (9C9 and 1A12) following the roadmap. *See* p. 28, *supra*.[14]

The court thus recognized that introducing documents about Amgen's catabolic program would open a "great big can of worms," requiring a mini-trial to explain Amgen's later-state-of-the-art program, Appx3810(554:14-15), and parse out marginally relevant theories from clearly irrelevant evidence about "the state of the art subsequent to the priority date," *Amgen*, 872 F.3d at 1373-74. Avoiding that confusing side-show was not "'arbitrary and irrational.'" *Paoli*, 113 F.3d at 453. Sanofi-Regeneron's one-line assertion "that relevance [is not] 'substantially out-

[14] The evidence also showed the roadmap made the Competitor Antibodies, Appx3908-3909(757:12-760:21); Appx3918-3919(798:25-799:5), which Sanofi-Regeneron described as EGFa mimics, Appx3685-3686(208:4-16, 209:22-210:5).

weighed' by the possibility of juror confusion," SR.Br.61, hardly proves an abuse of discretion.

B. Sanofi-Regeneron Suffered No Prejudice

Sanofi-Regeneron does not show prejudice. *Egan*, 851 F.3d at 276. For written description, Sanofi-Regeneron's expert drew a near-replica of the so-called "missing epitope" document the court excluded. *Compare* Appx4300, *with* Appx9529. Using his drawing, Dr. Boyd testified (1) what he considered an EGFa mimic to be, Appx3685(206:18-207:11); Appx3753(325:10-16); (2) that Amgen's patents cover such antibodies, Appx3685(207:12-22); and (3) that Amgen's patents (in his view) do not disclose "even a single EGFa mimic antibody" (using the Competitor Antibodies as examples of EGFa mimics), Appx3686(209:19-210:5). He thus urged that the patents did not meet the written-description requirement, Appx3686(209:19-210:22), as did Sanofi-Regeneron's counsel, Appx3987-3988(904:2-906:4).

On enablement, Sanofi-Regeneron likewise fully presented its position that the roadmap could not generate the Competitor Antibodies it characterized as EGFa mimics. *See, e.g.*, Appx3753(325:24-326:6, 327:2-328:2). Sanofi-Regeneron was able to introduce each Competitor Antibody as a putative example, and its expert testified that Amgen was not able "to make even a single EGFa

mimic antibody" "[u]sing th[e] road map." Appx3753(326:25-328:2). The jury just rejected those arguments. Sanofi-Regeneron is not entitled to yet another trial.

CONCLUSION

The district court's judgment of non-enablement should be reversed.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I certify that today, July 23, 2020, I electronically filed the foregoing document with the Clerk of the Court for the U.S. Court of Appeals for the Federal Circuit using the appellate CM/ECF system.

I certify that today, July 23, 2020, I caused the confidential version of the foregoing document to be served on counsel for Defendants-Appellees by email at matthew.wolf@arnoldporter.com.

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July 2020

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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