Amgen v. Sanofi: The U.S. Supreme Court Reviews Patent Enablement

Health Policy Portal

Gregory Curfman[1,2] *and Marcia M. Boumil*[3]

1: JAMA, CHICAGO, IL, USA; 2: YALE UNIVERSITY, NEW HAVEN, CT, USA; 3: TUFTS UNIVERSITY, BOSTON, MA, USA.

Keywords: Monoclonal Antibodies, Patent Enablement, Genus Patent Claims, PCSK9 Inhibitors, LDL Receptors

On June 18, 2023, the U.S. Supreme Court in the matter of *Amgen, Inc. et al. v. Sanofi, et al.*[1] unanimously upheld the 2021 decision of the U.S. Court of Appeals for the Federal Circuit,[2] striking down as overbroad Amgen's patent claim to an entire functional genus of monoclonal antibodies. Amgen's patent claims were not limited to antibody structure or *antibody* amino acid sequences. This is significant because Amgen's patent claims did have amino acid sequences, but they were directed to the epitope.

Reversing a previous jury verdict finding infringement, the Court held that describing the full functional genus of antibodies without providing adequate detail to a skilled artisan in the field to make and use them fails to satisfy the legal requirement of patent "enablement."

Antibody Science

Evolocumab (Repatha) is a therapeutic monoclonal antibody produced by Amgen that markedly lowers low density lipoprotein (LDL) cholesterol.[3] The biologic agent claimed protection through multiple patents, whose validity was challenged in a legal action brought against Amgen by Sanofi/Regeneron (*Amgen v. Sanofi*). The U.S. Court of Appeals for the Federal Circuit invalidated Amgen's patents, and this ruling was affirmed by the Supreme Court.

The disputed patents relate to a naturally-occurring protein known as proprotein convertase subtilisin/kexin type 9 ("PCSK9"), which binds to, and degrades, liver cell-surface receptors that remove LDL cholesterol from the bloodstream. LDL receptors have a critical role in maintaining low LDL levels. By binding to a critical 16-amino-acid sequence in PCSK9 (the "sweet spot"), evolocumab prevents PCSK9 from binding to and degrading LDL receptors. The result is an enhanced number of LDL receptors, which remove LDL cholesterol from the circulation and thereby reduce the risk of atherosclerotic coronary artery disease. Amgen applied for, and received, patent protection for what it claimed was an invention.

Sanofi also pursued independent research on monoclonal antibodies that bind to the sweet spot on PCSK9, and identified alirocumab (Praluent), which, like evolocumab, effectively lowers LDL cholesterol by binding to PCSK9 and blocking its ability to degrade LDL receptors. Sanofi does not deny that its patent claims infringe Amgen's core patent but asserted that Amgen's patent was not valid as it failed several of the applicable legal criteria, specifically the "enablement" requirement. In return for being granted a patent, the patent "bargain" requires that the patentee publicly disclose sufficient information about the patented invention. The "enablement" dispute concerns how much detail about the invention is required to be disclosed in the specification of the patent. Enablement requires enough detail that "those skilled in the art" can "make and use" the claimed invention. Enablement also requires that the patent include "sufficient detail" that "those skilled in the art"

Gregory Curfman, M.D., *is affiliated with JAMA and the Solomon Center for Health Law & Policy, Yale Law School;* **Marcia M. Boumil, J.D., LL.M.**, *is affiliated with the Tufts University School of Medicine.*

About This Column

Aaron Kesselheim serves as the editor for Health Policy Portal. Dr. Kesselheim is the *JLME* editor-in-chief and director of the Program On Regulation, Therapeutics, And Law at Brigham and Women's Hospital/Harvard Medical School. This column features timely analyses and perspectives on issues at the intersection of medicine, law, and health policy that are directly relevant to patient care. If you would like to submit to this section of *JLME*, please contact Dr. Kesselheim at akesselheim@bwh.harvard.edu.

The Journal of Law, Medicine & Ethics, 51 (2023): 689-693. © 2023 The Author(s)
DOI: 10.1017/jme.2023.102

https://doi.org/10.1017/jme.2023.102 Published online by Cambridge University Press

can "reach the full scope of claimed embodiments" without undue further research and development.[4] Both of these standards, which are intended to eventually (after expiration or invalidation of the patent protection) make the invention widely available and useful to the pubic, are well-established.

Patent Law

At issue in this case was the standard for enablement, including whether the full scope of the invention must be enabled or a suitable portion of the full scope is sufficient. In general, courts impose a higher standard for inventions (in this case monoclonal antibodies) when the claims sought would extend broadly to an entire functional genus (and hence all products derived from the genus and its related features), rather than to a limited number of species of antibodies. Functional genus claims are typically broad because they do not describe the product by "what it is," but instead by "what it does." Amgen's patent claims encompassed all monoclonal antibodies that: (a) bind to amino acids in the sweet spot and (b) block binding of the sweet spot to LDL receptors. Thus, there are two functional requirements claimed in Amgen's patents. Such functional requirements would not apply to typical genus-type claims.

Amgen described in its patents 26 monoclonal antibodies for which it has amino-acid sequences (3 of them also have 3-dimensional structures), of which Repatha is one. These antibodies have been structurally characterized, and such structures are patentable. But Amgen's patents were not limited to structures. Specifically, Amgen sought patent protection of all antibodies that bind to PCSK9's sweet spot (referred to as an "epitope") and block its action in degrading LDL receptors. If approved, the Amgen patents would have covered a broad spectrum of sequences including all species with the entire functional genus. This broad range of antibodies is defined by their function, not by their structure, and given the remarkable diversity of antibodies that may be produced and bind to a particular epitope, there may be potentially millions of such antibodies.

Are Genus Claims Different?

Amgen sought patent protection of virtually the entire functional genus of monoclonal antibodies that bind to the sweet spot on PCSK9 and block its binding to LDL receptors, which could amount to millions of antibodies and would include many antibodies that Amgen has not characterized by structure. At best, Amgen characterized approximately 400 antibodies and arguably as few as 26, but in any event many fewer than the millions (or more) that it claimed. Sanofi claimed Amgen's patents are overbroad because it would take significant "time and effort" even for those "skilled in the art" to identify and replicate nearly all embodiments of the invention. The heart of this matter was whether Amgen had adequately specified enough of the species that have structural features representative of the genus so that the patents teach those "skilled in the art" to identify all other members of the genus and make and use of the invention — without undue experimentation that amounted to trial-and-error. As the Court previously held, patents are not a "hunting license … not a reward for trial-and-error."[5]

Sanofi claimed that the Federal Circuit — the appellate court for patent claims — has previously held that patent requirements for functionally-defined genus claims demand a higher standard of enablement disclosures.[6] Amgen challenged that interpretation, observing that the law does not set forth a differing standard depending on the nature of the invention.[7] Amgen urged that requiring all potential embodiments and outcomes would be a nearly-impossible task.[8] Sanofi countered that Amgen had not described for one skilled in the art the minimum set of features or properties within the claimed functional genus, thus failing the enablement requirement.

Enablement requires a written description of the invention including the formula, structure, and physical and other properties of the species that are claimed to fall within the genus.[9] An important issue was whether Amgen's description adequately identifies the genus. Another was whether evaluating the "cumulative effort" required to replicate the invention

For patients the Supreme Court's opinion in Amgen may result in more therapeutic options at a lower cost resulting from the increase in competition. For physicians, having a wider range of therapeutic monoclonal antibodies allows matching a particular antibody to a particular patient, since not all therapies are equally beneficial in all patients. The outcome of this case allows for the discovery of more antibodies directed toward the same antigens, and even the same epitope. The challenge going forward for inventors is to better predict that balance so that the "roadmap" publicized to competitors is not so parsimonious that it fails the "enablement" standard as set forth in this case.

The Journal of Law, Medicine & Ethics, 51 (2023): 689-693. © 2023 The Author(s)

https://doi.org/10.1017/jme.2023.102 Published online by Cambridge University Press

(rather than trial-and-error) is a useful way of thinking about enabling the genus of claimed antibodies. Sanofi alleges that Amgen's patents attempt to protect all "embodiments" of the antibodies that bind to, and block, the particular segment that identifies as the sweet spot of PSCK9. As stated by Sanofi's attorney, Paul Clement, in oral arguments, the more a patent claims, the more it must enable through disclosure.[10]

This dispute was highlighted in two amicus curiae briefs submitted in the case, which serve as bookends for the respective arguments of the two parties. Professor Mark Lemley, writing on behalf of Amgen, claimed that in the past the Federal Circuit has generally permitted genus patents, but in recent years the court has reversed course and is invalidating most of them. In a summary of his brief, he wrote:

> This Court should return the law to its traditional moorings. The enablement doctrine serves important purposes, including policing against overbroad and purely functional claims. But those purposes are served by requiring that patentees give the public enough information that they can make and use the invention without undue experimentation. A further requirement to teach or enable every possible species within the genus is unnecessary and unworkable.[11]

In contrast, Professor Gregory Winter, a 2018 Nobel Laureate in Chemistry, who wrote on behalf of Sanofi, underscored the following point in the summary of his argument:

> Finally, using this case to vitiate the Federal Circuit's long-standing enablement standard would permit an applicant to effectively patent a natural interface on a target of interest. Doing so would stifle innovation and set a dangerous precedent for the scientific and pharmaceutical community at large.[12]

Professor Winter argued that in making patent claims for the entire genus of antibodies that bind to and block the 16 amino-acid sequence in PCSK9, Amgen would have effectively patented the sweet spot itself. Yet, this sequence of amino acids is a natururally occurring structure and was not produced or modifed by Amgen. Thus, in accordance with the Supreme Court's judgment in *Mayo v. Prometheus*[13] and *Myriad Genetics*,[14] the 16 amino acid sequence in PCSK9 that is the epitope for Amgen's and Sanofi's monoclonal antibodies is not patentable. The authors have previously written on the Supreme Court's position that natural phenomena cannot be patented.[15] This aspect of patent ineligibility was recently reiterated in the Patent Eligibility Restoration Act of 2022 (PERA), which has been introduced in the Senate but not yet passed into law. Included among unpatentable materials in the law are: "An unmodified natural material, as that material exists in nature."[16]

Professor Winter made another significant point in his brief. One component of Amgen's roadmap for enabling its patents is the concept of "conservative substitution" of amino acid residues in antibodies. In conservative substitution a single amino acid or a small number of amino acids in the antibody are replaced by different, but similar, amino acids. This changes the amino acid sequence of the antibody, but according to Amgen is unlikely to change its function (binding properties). Thus, Amgen argues that many antibodies can be enabled by simple conservative substitution. Professor Winter notes, however, that even small changes in the amino acid sequence of antibodies may have important effects on their binding properties, and these effects are unpredictable. Even antibodies produced by conservative substitution must, therefore, be tested for their binding properties, which is not a straightforward procedure and is more akin to trial-and-error.

Does the Law Protect Broad Genus Claims?

It is the heterogeneous nature of antibodies that when monoclonal antibodies are produced against an antigen, thousands if not millions are produced in response to that single antigen. The production is wide in scope, and the goal of Amgen's patents was to protect every potential antibody that binds to the segment in which it will be functional. What makes this inquiry particularly challenging is that the immune system is unique in that it operates in a manner that is smart, clever, and diverse. Each antibody has two "heavy" chains and two "light" chains. The chains contain segments that may be highly variable in their amino acid sequences, and thus millions of different antibodies may be produced — hence causing patent protection problems relating to scope. There are few analogous systems and thus no real roadmap or precedent to follow. In short, the law struggles to speak the language of antibodies.

Had Amgen attempted to patent only the 26 antibodies it actually sequenced, Sanofi's infringement argument likely would have been viewed differently. Instead Amgen sought to patent any antibody that will bind to and block the binding of the sweet spot of PSCK9 to the LDL receptors, including those antibodies yet to be discovered, characterized, or sequenced. Indeed, the universe of options is quite large. Amgen does have narrow antibody claims that cover its specific product,[17] but Sanofi's monoclonal antibody would not infringe them because the structure of Sanofi's antibody is too different (even though it binds to the same epitope).

The purpose of patent protection is to reward an inventor with 20 years of exclusivity to encourage innovation and compensate the resources and risks associated with new discoveries. On the other hand, other inventors should not be precluded from investigating in the same space and augmenting, refining, or discovering other important attributes and features. By patenting the entire genus of antibodies, and effectively the

The Journal of Law, Medicine & Ethics, 51 (2023): 689-693. © 2023 The Author(s)
https://doi.org/10.1017/jme.2023.102 Published online by Cambridge University Press

sweet spot itself, Amgen would have made it difficult, if not impossible, for competitors to "design around" Amgen's patents and achieve novel discoveries that could benefit society. This would not be in accordance with the patent bargain, which requires information about the product to be made public in return for a period of patent exclusivity. Here Amgen was attempting to assert patent monopoly rights using overly broad claims, without sufficient detail disclosed to the public.

Sanofi's competing product, introduced subsequent to Amgen's product, went through a Section 351(a) "biologics" and not the Section 351(k) "biosimilar" pathway. Amgen sought to prevent all new products with its functional genus claims even though it characterized only a tiny fraction of the genus. There is no underlying common antibody structure associated with antibodies that bind to this epitope. If there were, Amgen might have been successful on its functional genus claims, as that would not require undue experimentation, a possibility that the Supreme Court left open.

Of the 26 antibodies that Amgen claims to have sequenced, none bind to all 16 amino acids in the sweet spot of PCSK9, but instead usually bind to only 1 or 2 and no more than 9 of the 16 amino acids. In contrast, Sanofi's monoclonal antibody, alirocumab, binds to nearly all 16 of the amino acids in the sequence. Still, Amgen sought to patent all antibodies that bind to any number of amino acids in that segment. Whether the numerous others matter as clinical therapies is unknown; statistically it is likely that some do, but further characterization and sequencing are not available to inform this process. A significant question is whether Amgen could patent monoclonal antibodies that bind to more than 9 of the 16 amino acid residues in the sweet spot. Amgen contended that it may patent all antibodies that bind to the sweet spot and block its effect on LDL receptors. Yet, it is possible that monoclonal antibodies that bind to more than 9 residues may have different binding properties than those that bind to 9 or fewer, and such antibodies have not been characterized by Amgen despite its patent claims on antibodies that it has not identified.

Discussion

Patent claims themselves are abstractions, imprecise and typically describing a minimum set of features or properties that a product or process must possess to be considered infringed. The goal of a patent applicant is to attempt to claim the broadest possible scope for the invention. The question then becomes to what degree the patent applicant has fully enabled the invention, sufficient for one ordinarily skilled in the art, without the need for undue experimentation or excessive trial-and-error, to produce it. It is also interesting to consider that, for functional genus claims, such as Amgen's patent claims in this case, it is necessary to define a common element in the genus that results in the functional outcome. In contrast, for (non-functional) genus claims, just providing enough examples that cover most of the genus would be sufficient. This is an important distinction because in this opinion the Supreme Court did not give any guidance on how much trial-and-error is enough and how much is not enough.

Sanofi argued that "enablement" requires identifying a particular antibody structure (typically defined as the amino acid sequences of the 6 complementarity-determining regions of heavy and light chains, which serve as the binding sites of antibodies to their antigens). That would allow competitors to design around the structure and create new antibodies directed to the same epitope, limiting Amgen's patent protection to its specific antibodies. Amgen, however, urged a functional genus claim, defining antibodies by their epitopes and laying claim to all potential antibodies that bind to and block the same epitope. Approval of Amgen's patents could have inhibited or delayed incremental improvements to antibody innovation in general and alternative anti-PCSK9 monoclonal antibodies in particular.[18] As noted previously, Amgen, by patenting the entire functional genus of antibodies, is effectively patenting the epitope, and since it is a part of nature, it must not be patented.

Doctrinally, actual reduction to practice is not required by the enablement provision of patent law; "constructive" reduction to practice suffices. "Actual" means a real working thing that was built in the real world; constructive means the patent specification has sufficient detail to enable one having ordinary skill in the art to make and use a real working thing, even if that has not been done before. Here the question seems to have been what constitutes a sufficient "constructive" reduction to practice. While Amgen argued that it has provided sufficient information for a person skilled in the art, Sanofi disputed this claim based on Amgen's patents covering the entire functional genus of antibodies and disclosing structural information for only 26 of the antibodies.

The U.S. Supreme Court

Enablement is one of the few areas of patent law that the U.S. Supreme Court had not previously explored in sufficient detail in over a century, but the outcome of *Amgen* is consistent with prior opinions evolving in this field.[19] While the balance is always to weigh the reward of innovation with patent protection against the risk of limiting competition, the trend in recent years has been to err on the side of not eliminating or restricting competition. Narrow patents to antibody composition of matter claims promote competition, allowing design-arounds and innovation for improvement. Novel design-arounds may then receive their own patents. The appellate courts have been supportive of competition by requiring patent claims that are focused and provide a clear path for new innovation that builds upon the patent-protected discoveries. While Amgen did provide what was described as a "roadmap" of sorts, allowing subsequent innovators to discover new antibodies, the path was not sufficiently "enabled" or specified for a skilled artisan to replicate those discoveries without undue further research and development. The Court affirmed that it would not

The Journal of Law, Medicine & Ethics, 51 (2023): 689-693. © 2023 The Author(s)

https://doi.org/10.1017/jme.2023.102 Published online by Cambridge University Press

set a higher bar for patenting genus claims, but commented that Amgen's "roadmap" fell short of the "full scope" required to satisfy the legal standard for enablement.

Final Comments

The unanimous opinion in *Amgen* reaffirms the Supeme Court's preservation of the status quo that has endured for a century: commitment to rewarding innovation by means of narrowly tailored claims while also promoting further innovation by means of competition. For antibody science the Patent and Trademark Office has done the same for nearly a decade, narrowing the scope and forcing patent practioners to adjust.[20] The Court emphasized its obligation under Section 112 of the U.S. Patent Act to strike a balance that encourages reward for the disclosure of "enabled" innovation while also ensuring that further breakthroughs are also incentivized. Overbroad functional claims suppress rather than encourage innovation of better products.

For patients the Supreme Court's opinion in *Amgen* may result in more therapeutic options at a lower cost resulting from the increase in competition. For physicians, having a wider range of therapeutic monoclonal antibodies allows matching a particular antibody to a particular patient, since not all therapies are equally beneficial in all patients. The outcome of this case allows for the discovery of more antibodies directed toward the same antigens, and even the same epitope. The challenge going forward for inventors is to better predict that balance so that the "roadmap" publicized to competitors is not so parsimonious that it fails the "enablement" standard as set forth in this case.

Note

The authors have no conflicts of interest to disclose.

References

1. 598 U.S. __ (2023).
2. 987 F.3d 1080 (2021).
3. See L. Fala, "Repatha (Evolocumab): Second PCSK9 Inhibitor Approved by the FDA for Patients with Familial Hypercholesterolemia," *American Health & Drug Benefits* 9 (Spec Feature) (2016): 136-139, PMID: 27668060; PMCID: PMC5013843.
4. *Brenner v. Mason*, 383 U.S. 519 (1966).
5. *Id.*
6. D. Holman et al., Case Studies and Trends at the PTAB Involving 35 U.S.C. § 112, *available at* <https://www.sternekessler.com/sites/default/files/2022-02/ptab_year_in_review_2021_35_usc_section_112_article_final.pdf> (last visited Sept. 12, 2023).
7. 35 USC section 112(a).
8. See *Mowry v. Whitney*, 81 US 620 (1871).
9. 35 USC Section 112(a).
10. [Oral Argument], *Amgen, Inc. et. al. v. Sanofi, et al.*, No. 21-757, Heritage Rep. Corp., p. 56, U.S. Sup. Ct. March 27, 2023, *available at* <https://www.supremecourt.gov/oral_arguments/argument_transcripts/2022/21-757_5h26.pdf> (last visited Sept. 12, 2023)
11. [Brief of Intellectual Property Professors as *Amici Curae* In Support of Petitioners], *Amgen, Inc. et. al. v. Sanofi, et al.*, No. 21-757], p.2, *available at* <https://www.supremecourt.gov/DocketPDF/21/21-757/251201/20230103084920246_Amicus%20Brief.pdf> (last visited Sept. 12, 2023).
12. [Brief of Sir Gregory Paul Winter and Interested Scientists as Amici Curae In Support of Respondents], *Amgen, Inc. et. al. v. Sanofi, et al.*, No. 21-757], p.7, *available at* <https://www.supremecourt.gov/DocketPDF/21/21-757/254497/20230210100916044_WinterSanofi%20Amici%20Main%20E%20FILE%20Feb%2010%2023.pdf> (last visited Sept. 12, 2023).
13. 566 U.S. 66 (2012).
14. 569 U.S. 576 (2013).
15. M.M. Boumil and G. Curfman, "Patenting Laws of Nature: Effect on Cardiovascular Innovation," *JAMA Cardiology* 3, no. 11 (2018): 1031-1032, doi: 10.1001/jamacardio.2018.3365. PMID: 30347007.
16. S.4734 — Patent Eligibility Restoration Act of 2022.
17. US 8,030,457 (Continuation of 8829165); US 8,030,457 (continuation of 8859741) and US 9,045,547 (a method of use patent)(Continuation of 8859741).
18. Brief of Arnold Ventures, The National Center for Health Research and Certain Medical Doctors as Amicus Curiae in Support of Respondents, p. 25, *Amgen, Inc. et. al v. Sanofi, et. al,* 598 U.S. __ (2023).
19. See [CRS Report, Patent-Eligble Subject Matter Reform: Background and Issues for Congress, No. R-45918, Dec. 1, 2022, *available at* <https://sgp.fas.org/crs/misc/R45918.pdf> (last visited Sept. 12, 2023).
20. S. Tu and C.M. Holman, "Antibody Patents: Use of the Written Description and Enablement Requirements at the Patent & Trademark Office," *Berkeley Technology Law Journal* (2022), Forthcoming, WVU College of Law Research Paper No. 2022-005, *available at* <https://ssrn.com/abstract=4025167> or <http://dx.doi.org/10.2139/ssrn.4025167> (figure 2) (last visited Sept. 12, 2023).

The Journal of Law, Medicine & Ethics, 51 (2023): 689-693. © 2023 The Author(s)

https://doi.org/10.1017/jme.2023.102 Published online by Cambridge University Press