No. 21-757

IN THE

Supreme Court of the United States

AMGEN INC., ET AL.,

Petitioners,

v.

SANOFI, ET AL.,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF ARNOLD VENTURES, THE NATIONAL CENTER FOR HEALTH RESEARCH, AND CERTAIN MEDICAL DOCTORS AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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Interest of *Amici Curiae*[1]

This brief is submitted by medical doctors who have dedicated their lives to patient care and public interest organizations concerned about making access to the best medicines fair and affordable for everyone. The amici have seen firsthand the negative impact that bad public policy decisions can have on people that need care. They urge the Court to consider carefully the negative consequences on patient care that are likely to follow if the Court grants broad permission—as Amgen requests—for pharmaceutical companies to obtain improvident monopolies through overbroad genus patent claims covering more than their contribution to the advancement of science and the useful arts.

Dr. Aaron S. Kesselheim, MD, JD, MPH, is a Professor of Medicine at Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital, where he created and co-leads the Program On Regulation, Therapeutics, And Law (PORTAL). An author of over 600 medical and health policy publications, Dr. Kesselheim is one of the top-cited professors on health law in the US and has testified before Congress on pharmaceutical policy, medical device regulation, generic drugs, and modernizing clinical trials. In 2020, he was elected to the National

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[1] No party, counsel for a party, or any person other than amici and their counsel authored or contributed financially to preparing this brief. The amici have no financial interest in any party or the outcome of this case. The parties have each provided blanket consents to the filing of amici curiae briefs as reflected on the docket.

Academy of Medicine, one of the highest honors in US health care.

Dr. Eliot A. Brinton MD, FAHA, FNLA, FACE, is president of the Utah Lipid Center in Salt Lake City. He is past president of the American Board of Clinical Lipidology and of the Pacific Chapter of the National Lipid Association ("NLA") and was a founding member of the Board of Directors of the NLA. He has given nearly 3,000 scientific presentations to medical professional audience, and has coauthored over 100 scientific publications. He has received several honors, including the Robert I. Levy Award of the Lipoprotein Kinetics and Metabolism Society and Paul Dudley White International Scholar of the American Heart Association.

Dr. Michael S Doyle, MD, MPH, is the Medical Director at UnaSource Comprehensive Weight Loss Clinic, and Director at UnaSource Lipid Clinic. Dr. Doyle was awarded The Air Force Commendation Medal for his service as a general medical officer in Okinawa, Japan. Dr. Doyle is a former clinical trialist, having been primary investigator in more than one hundred clinical research trials, including in the areas of obesity, diabetes, hypertension, and lipid disorders. His professional history includes time as Director, Lipid Clinic, at Beaumont Hospital, and as Director, Lipid Clinic, and Medical Director of the Northpointe Health Center. He is a lifetime member of the National Lipid Association.

Dr. Jerry Avorn, M.D., is a Professor of Medicine at Harvard Medical School and Senior Physician in Internal Medicine at the Brigham and Women's Hospital, where he founded the Division of Pharmacoepi-

demiology and Pharmacoeconomics, one of the nation's leading centers for the study of medication use, policy, cost, and outcomes. A graduate of Harvard Medical School, he is the author or co-author of over 600 articles in the medical literature on medication-related policy, prescribing, and drug utilization and one of the most highly cited researchers in his field; he accepts no personal compensation from any pharmaceutical company.

Arnold Ventures is a philanthropic organization founded by Laura and John Arnold, tackling some of the most pressing problems in the United States, including in Advocacy, Criminal Justice, Health, Higher Education, and Public Finance. Arnold Ventures' health care initiatives involve the issues of drug prices, complex care, and Medicare sustainability, among others. Arnold Ventures aims to improve health care delivery, lower costs, and reduce disparities in access for patients in the United States, and they have funded over 500 projects related to these health initiatives since 2010. Arnold Ventures' projects and philanthropic investments are guided by evidence-based policy and based on research, and the organization is comprised of more than 100 subject-matter experts.

The National Center for Health Research (NCHR) is a nonprofit organization that conducts, analyzes, and explains the latest research and works with patients, consumers, and opinion leaders to use that information to improve health and to develop better programs, policies, and services. NCHR provides lawmakers and the public with a research-driven analysis of important health issues, independent of corporate financial interests that may influence the

media and lobbyists. NCHR is an independent organization and does not accept funding from companies that make the treatments or products that it evaluates and studies. It is focused on making health care research and information more understandable and accessible to the public.

Summary of the Argument

The treatment of serious and life-threatening diseases is often not a "one and done" or a "one size fits all" process. Patients benefit from multiple treatment options—drugs having different active ingredients—especially if those drugs share similar mechanisms of action. This has been the case for many decades, across many drug types, and remains true through the relatively recent development of monoclonal antibodies for the treatment of cancer and auto-immune diseases. Amgen's requested change to the enablement standard presents a serious threat to the development and subsequent clinical availability of multiple therapeutic options, and introduces a significant obstacle to the availability of optimal treatment for patients.

The law requires that the claim's full scope be enabled. The *Wands* factors provide the framework for the analysis of this issue and the Federal Circuit correctly applied those factors here to find that Amgen's broad functional genus claims are not enabled.

The standard that Amgen proposes would be a departure from the existing law requiring enablement of the full scope of a claim, in favor of allowing only partial enablement of a functional genus claim—one in which the claimed genus is described by the function it performs and not by any meaningful structural limitations. This radical change would allow overly broad, functional genus claims to proliferate. This, in turn, would allow pharmaceutical companies to file functional genus claims blocking others from developing drugs focused on the same therapeutic target, with ***different active ingredients*** that are directed to the same therapeutic target—or, in some cases, treating a different disease that happens to respond

to drugs with the same mechanism of action. Patients will pay the price in four ways.

First, multiple treatment options will be delayed in development and approval, or not available at all. Drug companies sometimes engage in a "race" to FDA approval of drug products with different active ingredients that have the same mechanisms of action. There was just such a race for the drugs at issue here. This competition motivates drug companies to bring their products to the market quickly, where they can help patients. Even more compelling, sometimes a drug will ultimately fail in development. If a lead agent in a particular field receives an overly broad genus claim, and then its drug fails to make it to market, it can block development of alternatives entirely. Patients may thus lose out on the possibility of any effective drug in the class.

Second, patients will be forced to take medicine that may be either more risky or less efficacious—or both—than an alternative. Frequently, the first drug with a particular mechanism of action to reach the market is not the most effective or safest in its class. Later-developed drugs may have greater efficacy and/or less risk to the patients. In some cases, the later-approved drugs may be found to treat additional diseases. Those superior alternatives will never be developed, however, if other innovators cannot develop competing drugs with different active ingredients and the same mechanism of action because of these overbroad functional claims.

Third, patients may not have the treatment option that works best for their specific circumstances. Drug interactions with the human body are complicated and can vary widely from person to person. Certain

patients respond better to different drugs within the same class, or experience fewer side effects. If a broad, but only partially enabled, functional genus claim blocks other innovators from access to developing additional drugs in a class, the patients with individualized responses or reactions to a particular drug will suffer by virtue of having fewer options (or no options).

Finally, competition between innovators, under the right circumstances, can lower spending on brand-name drugs. High drug prices are a major cause of lack of patient access, or of long-term non-adherence to treatments, which contributes to thousands of excess hospitalizations and deaths annually. Further stifling the possibility of competition between innovators will artificially keep patient costs high, lowering patient access, adherence, and benefit.

Argument

I. The Current Enablement Law Is Equipped To Address Functional Genus Claims in an Unpredictable Art

A. The *Wands* Factors Aptly Apply Section 112 Enablement to Any Genus Claim

In applying the statutory enablement requirement, the Federal Circuit has set forth several relevant factors to consider in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). They are: (1) the amount of direction or guidance presented in the disclosure, (2) the existence of working examples, (3) the nature of the invention, (4) the predictability or unpredict-ability of the art, (5) the artisan's level of skill, (6) the state of the prior art (preexisting knowledge and technology already available to the public), (7) the breadth of the claims, and (8) the amount of experimentation necessary to practice the claimed invention. *Id.* These factors are flexible and well-suited to determine whether the patentee has attempted to claim more than the law allows.

The Federal Circuit's precedent reflects a flexible approach in weighing these factors, and their order of importance, for each particular case. This makes sense because the facts of any given case will determine the evaluation and application of the factors. In the case of a functional genus claim, claim breadth (or scope)—factor (7)—is an appropriate starting point. The question of claim breadth necessarily includes an analysis of the specificity of the function claimed. This specificity is particularly relevant where, as here, there is no meaningful limitation on the claimed structures and the claimed function provides the only meaningful boundaries to the scope of the claim.

In this situation, the predictability or unpredictability of the art may also have a heightened importance. The link between structure and function is weaker in unpredictable fields, like human biology and biochemistry. A given structure may not perform the expected function, and likewise the claimed function may be performed by an unexpected structure. In the case of human drugs, drugs designed to engage a certain target or treat a certain disease may look flawless in the laboratory, but when administered to animals or later to humans may not perform as expected or have important off-target side effects. The unpredictability of the antibody science at issue in this case cannot seriously be disputed.[2]

The *Wands* factors—applied by the Federal Circuit below—aptly account for these two heightened considerations in the case of a purely functional genus claim. Neither Amgen nor its supporting amici challenge the *Wands* factors on their face. In fact, nearly everyone expressly agrees that the *Wands* factors are useful and workable. Instead, because Amgen does not like the result of applying the *Wands* factors in this case, it attempts to recast the decision below as a change to the law of enablement that will effectively "kill" the genus claim. In truth, genus claims that comport with the bargain a patentee must make with the public to secure patent protection—i.e., meeting the statutory requirements including enablement—will remain an option, as they have always been under *Wands*.

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[2] *See*, *e.g.*, Sanofi's Responsive Brief and the Brief of Sir Gregory Paul Winter and Interested Scientists as *Amici Curiae* in Support of Respondents ("Antibody Scientists Brief").

B. Not All Genus Claims Are the Same

The genus claim in general is not under attack in this case. Genus claims have long been permitted as long as they meet the statutory requirements, including enablement. *See, e.g.*, *Bayer Healthcare LLC v. Baxalta Inc.*, 989 F.3d 964, 970-71, 980-81 (Fed. Cir. 2021) (finding a genus claim to recombinant forms of human factor VIII enabled because the specification provided instructions and examples that enabled the "full scope"); *Erfindergemeinschaft UroPep GbR v. Eli Lilly and Co.*, 276 F. Supp. 3d 629, 659-663 (E.D. Tex. 2017) (finding a genus claim to PDE5 inhibitors to treat benign prostatic hyperplasia enabled), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018); *Pfizer Inc. v. Teva Pharms. USA, Inc.*, No. 2012-1576, 2014 WL 463757, *4 (Fed. Cir. 2014) (non-precedential); *Monsanto Co. v. Scruggs*, 459 F.3d 1328, 1338 (Fed. Cir. 2006), cert. denied, 127 S.Ct. 2062 (U.S. 2007). The genus claim is a staple of patent law, particularly in the chemical arts.

But contrary to the suggestion of Amgen and many supporting amici, not all genus claims are the same. In particular, Amgen implies that all, or nearly all, genus claims are functional genus claims. *See, e.g.*, Brief of Petitioners at 18, 24 (Dec. 27, 2022) (citing D. Karshtedt *et al.*, *The Death of the Genus Claim*, 35 Harv. J.L. & Tech. 1 (2021) ("Karshtedt")). Purely functional genus claims are merely one type of genus claim. A genus claim is more broadly, and accurately,

defined as a claim "covering a class of entities characterized by a common property."[3]

This case is not about genus claims in a predictable art, in which the claimed category of structures have known and expected properties. *See, e.g.*, *In re Smythe*, 480 F.2d 1376, 1383 (Fed. Cir. 2004) (finding disclosure sufficient, in part because "[t]his is not a case where there is any unpredictability").

Nor is this case about claims to a genus of chemical compounds, where the molecular structures are known even if their properties are unpredictable. These structurally-defined genus claims may also be directed to a particular function, but crucially include limitations on the chemical structure at issue. For example, patents on statin drugs are directed to the function of lowering cholesterol by inhibiting the HMG CoA reductase enzyme, but are limited to groups of structurally related compounds.[4]

Instead, this case is about an entirely functional genus claim in an ***unpredictable art*** that covers millions of undisclosed species, with no limitation on the specific structure of those species other than that they be "monoclonal antibodies." *See* Amgen Patents

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[3] Jeffrey A. Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 Berkeley Tech. L.J. 1141, 1168 (2008).

[4] Irena Royzman, *Why Broad Functional Patent Claims Suppress Medical Innovation*, BL, (Jan 9, 2023, 4:00 AM), *available at* http://news.bloomberglaw.com/us-law.week/why-broad-functional-patent-claims-suppress-medical-innovation. *See also Pfizer*, 2014 WL 463757, at *4 (claims directed to all compositions of 3-isobutylGABA, without limitation as to isomeric form, enabled even though they covered hundreds of permutations of non-racemic mixtures).

8,829,165 (claims 1, 29, 29) and 8,859,741 (claims 1, 2, 7). This total lack of structure, accompanied by the breadth of claim scope, renders the genus claims at issue here particularly susceptible to a finding of non-enablement.

C. The Current Law Correctly Treats Genus Claims Without Meaningful Structural Limitations as the Most Difficult To Enable

As early as 1853, the Supreme Court held that broad, functional genus claims without disclosure in the specification of sufficient structure to enable the full breadth of the claim are invalid. *O'Reilly v. Morse*, 56 U.S. 62 (1853). Although § 112 as it exists today was not enacted at the time, the Supreme Court in *O'Reilly* held that the inventor of the telegraph could not maintain his broad claim covering "the use of the motive power of the electric or galvanic current … however developed for marking or printing intelligible characters … at any distances." *Id.* at 112. The Supreme Court found it invalid:

> For aught that we now know some future inventor, in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in the plaintiff's specification.

Id. at 113. In other words, the full, broad scope of the functional claim was not enabled by corresponding structure in the specification.

The cases on which the Federal Circuit relied below and in prior enablement decisions similarly illustrate that the lack of corresponding structure was a key factor in its analysis here. In the *Wands* case itself, the claims also related to antibody technology, but they required at least one meaningful structural limitation—they be of the IgM isotype. *Amgen, Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1085-86 (Fed. Cir. 2021) (explaining *Wands*). The *Wands* court explained that there are several different immunoglobulin classes of antibodies, called "isotypes." Although "most immunoassay methods use IgG, the claimed invention uses only IgM antibodies." *Wands,* 858 F.2d at 733. This structural limitation contributed to the ultimate decision that the claims were enabled. *Id.*

Conversely, the lack of meaningful structural limitations tied to the claimed functionality contributed to the Federal Circuit's decision that the claims were not enabled in *Wyeth and Enzo*.[5] In *Wyeth*, functional genus claims were invalid for lack of enablement due to "the large number of possible candidates within the scope of the claims and the specification's corresponding lack of structural guidance." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013). The genus at issue was "rapamycin," which was defined by the structural limitation of having a "macrocyclic triene ring structure," as well as by the function "having immunosuppressive and anti-

[5] Certain amici assert that these cases were decided incorrectly, illustrates the magnitude of the change in law sought by Amgen in this case. *See*, *e.g.*, Amicus Brief of Chemistry and the Law Division of the American Chemical Society. Amgen itself does not dispute that these cases and *Idenix* were rightly decided. Brief for Petitioners at 39, 44 (Dec. 27, 2022).

restenotic effects." *Id.* at 1383. That claim was not enabled because the specification disclosed only one formulation (species) of rapamycin, and provided no guidance regarding which of the other tens of thousands of compounds having the claimed structure would exhibit the claimed function. *Id.* at 1384.

Similarly, in *Enzo*, the claimed structure was any polynucleotide with labels attached to a phosphate, and the related function was that it be hybridizable and detectable upon hybridization. *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1344 (Fed. Cir. 2019). The court noted that "[t]he claim places almost no limitations on the structure of the claimed polynucleotide." *Id.* at 1346. In *Idenix*, the claimed structure was slightly more defined: a nucleoside containing a sugar ring having five carbon atoms (1'-5'), with a methyl group at a specific position on the 2' carbon atom. *Idenix Pharms. LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1154 (Fed. Cir. 2019). The related function was its efficacy in treating infection with hepatitis C virus ("HCV"). *Id.* Based in part on the fact that the structural requirements still left many thousands (or far more) of potentially covered compounds, and the specification did not explain how to identify which of those compounds could perform the claimed function, the Federal Circuit upheld the finding of non-enablement. *Id.* at 1162.

The Federal Circuit's decision in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), is also instructive. In holding that the patent was invalid for lack of written description, the Federal Circuit stated:

> A definition by function, as we have previously indicated, does not suffice to

> define the genus because it is only an indication of what the gene does, rather than what it is. It is only a definition of a useful result rather than a definition of what achieves that result.... The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention.

Id. at 1568.

Finally, although the present case is not being considered through the lens of 35 U.S.C. § 112(f), the policy considerations underlying that provision are instructive. As other amici have noted, these purely functional genus claims bear a resemblance to claims structured under § 112(f),[6] which allows inventors in certain circumstances to express a claim element as a specified function, as Amgen has done here, "without the recital of structure, material, or acts in support thereof." Section 112(f), however, crucially dictates that such claims must be construed to cover ***only*** the corresponding structures described in the specification and their equivalents. 35 U.S.C. §112(f). The

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[6] In their January 3, 2023 Brief as *Amici Curiae*, the High Tech Inventors Alliance and the Computer & Communications Industry Association assert that such "naked functional claims" are rare in the life sciences industry, though they proliferate in the software industry. The case law reviewed in this section demonstrates that "naked functional claims" are, in fact, prevalent in the life sciences industry, but are rarely viewed through the lens of 112(f); instead, they are typically analyzed under the written description and enablement requirements.

goal of this requirement is to ensure that the claims do not cover more than what was invented.

In this case, the Federal Circuit achieved that laudable Congressional goal through a correct, routine application of the unchallenged *Wands* factors.

II. The Federal Circuit Correctly Held That Amgen's Functional Genus Claims Were Not Commensurate in Scope with Its Disclosure

Amgen has broadly claimed material that is not commensurate with its actual invention, or its disclosure. Amgen did not discover the important scientific insight that PCSK9 lowers LDLR protein levels on the surface of the liver cell, nor that it thus raises LDL-C levels in the circulation. Amgen also did not invent antibody "binding" or "blocking."

As seen in Figure 1, researchers at the University of Texas Southwestern discovered a connection between high cholesterol and the LDL receptor in 1974. Goldstein & Brown, *Familial Hypercholesterolemia: A Genetic regulatory Defect in Cholesterol Metabolism*, 58 Am. J. Med. 2 (Feb. 1975).[7] By 2005—three years before the filing of the provisional application to which the patents-in-suit claim priority—academic scientists disclosed in work funded by the National Institutes of Health their conclusion that inhibiting PCSK9 would increase LDL receptors and, consequently, lower LDL cholesterol. Shirya Rashid, et al., *Decreased plasma cholesterol and hypersensitivity to*

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[7] In 1985, Brown and Goldstein received the Nobel Prize in Physiology or Medicine for this work. *See* The Nobel Prize in Physiology or Medicine 1985, The Nobel Prize, *available at* https://www.nobelprize.org/prizes/medicine/1985/summary.

statins in mice lacking Pcsk9, 102 Proc. Nat'l Acad. Sci. U. S. 5374-5379, (2005). Between 2005 and 2009, a number of scientists did further work supporting the conclusions that administering antibodies that inhibit PCSK9 would lower LDL cholesterol in patients. A selection of these are depicted in the timeline above.

For example, as early as July 2006 (depicted as ① on the timeline) researcher Helen Hobbs at University of Texas Southwestern Medical Center identified the first human who genetically lacked the PCSK9 protein and had a very low LDL cholesterol level, which further suggested that inhibitors of PCSK9 activity are attractive candidates to lower LDL cholesterol in humans.[8] In November 2006, scientists at Merck filed a patent on the use of anti-PCSK9 antibodies to enhance LDL cholesterol uptake in vitro (② on timeline).[9] In April 2007, scientists at Novartis filed an Australian patent on generating anti-PCSK9 antibodies (③ on timeline);[10] scientists at Pfizer published the first 3-D structure of PCSK9 protein, confirmed PCSK9 binds to LDLR, and indicated that it was working on anti-PCSK9 antibodies that will lower

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[8] Zhenze Zhao et al., *Molecular characterization of Loss-of-Function Mutations in PCSK9 and Identification of a Compound Heterozygote*, 79 Am. J. Hum. Genetics 514 (Sept. 2006).

[9] U.S. Patent Application No. 60/857,293, "Antagonists of PCSK9," filed November 7, 2006.

[10] WO 2008/125623, "Molecules and methods for modulating proprotein convertase subtilisin/kexin type 9 (PCSK9)," published 23 October 2008, (claiming priority to April 13, 2007).

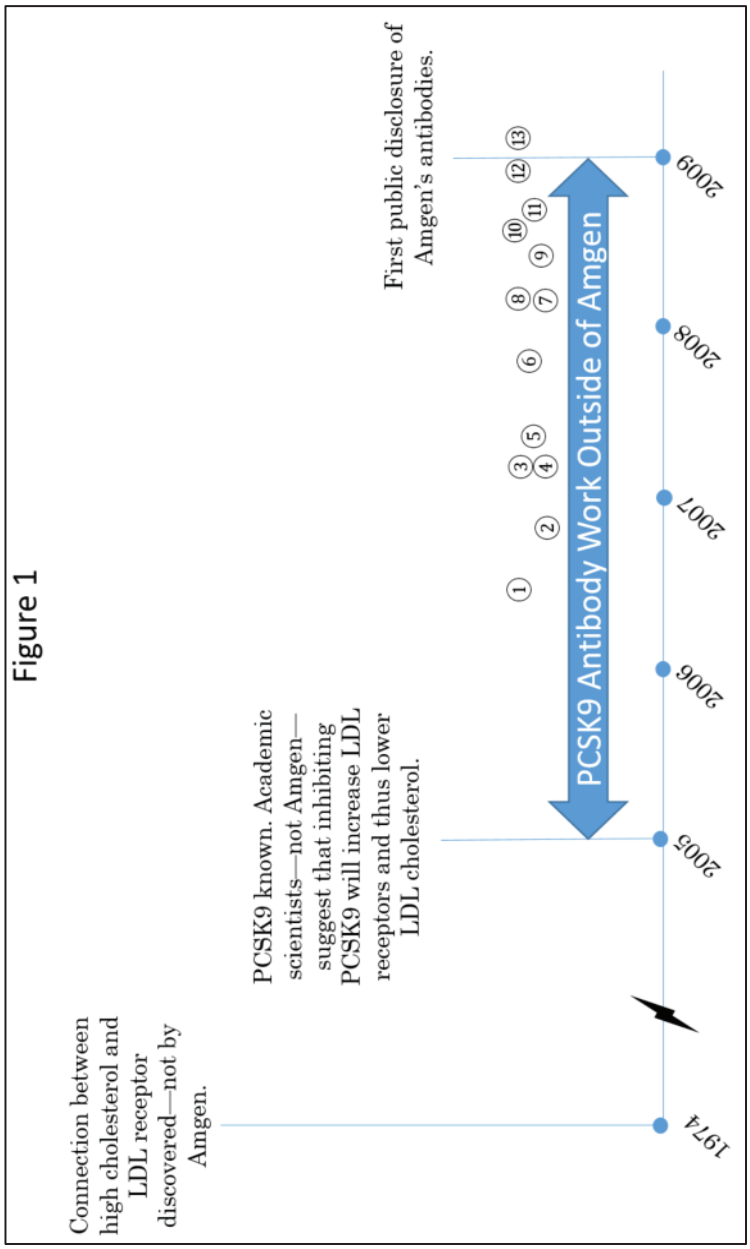
Figure 1
Connection between high cholesterol and LDL receptor discovered—not by Amgen.
PCSK9 known. Academic scientists—not Amgen—suggest that inhibiting PCSK9 will increase LDL receptors and thus lower LDL cholesterol.
First public disclosure of Amgen's antibodies.
PCSK9 Antibody Work Outside of Amgen
1974
2005
2006
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LDL cholesterol in blood (④ on timeline);[11] and Helen Hobbs (with others) determined that PCSK9 binds to a specific region of LDLR (⑤ on timeline).[12] This finding clarified the key detail of the site at which antibody binding to PCSK9 might be therapeutically effective.

Thereafter, in 2007 and 2008, various researchers in academia and industry, including Regeneron, explored PCSK9 as an antibody target.[13] In February

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[11] David Cunningham et al., *Structural and biophysical studies of PCSK9 and its mutants linked to familial hypercholesterolemia,* 14 Nat Struct Mol Biol 413-419 (2007).

[12] Da-Wei Zhang et al., *Binding of proprotein convertase subtilisin/kexin type 9 to epidermal growth factor-like repeat A of low density lipoprotein receptor decreases receptor recycling and increases degradation*, 22 J. Biol Chem.18602-18612 (2007).

[13] The approximate dates along with the specific events associated with points 6-12 of the timeline are:

⑥ –October 2007: ***Schering-Plough*** files provisional application disclosing anti-PCSK9 antibodies that interfere with PCSK9 binding with LDLR, lowering LDL cholesterol. WO 2009/055783, "Anti-PCSK9 and Methods for Treating Lipid and Cholesterol Disorders." Publication Apr. 30, 2009 (claims priority to 26 Oct. 2007). ⑦ –February 2008: Researchers ***Hyock Kwon and Jay Horton*** (UT Southwestern Medical Center) publish PCSK9 3-D structure data revealing the interacting area between PCSK9 and LDLR and highlighting key residues that make up the contact interface. Hyock Joo Kwonn et al., *Molecular basis for LDL receptor recognition by PCSK9*, 106 PNAS 6, 1820-1825 (Feb. 12, 2008). ⑧ –February 2008: ***Merck*** files provisional application disclosing its second set of anti-PCSK9 antibodies which block binding of PCSK9 to LDLR. U.S. Patent No. 8,188,234, "1D05

2009, Regeneron began its first pharmacokinetic and pharmacodynamic study in monkeys with Praluent®, demonstrating lower LDL cholesterol in primate blood. U.S. Patent App. 61/210,566 at Example 9 (filed March 18, 2009, ⑬ on timeline).

Building on this prior knowledge, Amgen disclosed in a patent application published in early 2009 certain specific antibodies that bind to PCSK9 and block it from binding to LDLRs.[14] Many others concurrently did the same thing—including Sanofi-Regeneron—without any knowledge of what Amgen, or each other, were doing.

Amgen patented several of its disclosed antibodies, including claims narrowly drawn to its specific drug product, Repatha®. *See* U.S. Patent No. 8,030,457. Subsequently, but only after Amgen had

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PCSK9 Antagonists" (May 29, 2012) (claiming priority to Provisional Applications filed in Feb. 2008) ⑨ –June 2008: ***Regeneron*** isolates and characterizes antibodies to PCSK9 from immunized mice. Decl. of Huang, ¶ 3, Opp. Against EP2215124 B1 (3 July 2019). ⑩ –August 2008: ***Regeneron*** lead anti-PSCK9 antibody functionally characterized and amino acid sequence determined. *Id.* ⑪ –September 2008: ***Pfizer*** files international patent application (WO 2010-029513) disclosing PCSK9 antibodies, which have been tested through Phase 3 clinical trials. WO 2010/029513 to Liang, et al., "PCSK9 Antagonists," filed 11 Sept. 2009. ⑫ –December 2008: ***Regeneron*** Files provisional application directed to anti-PCSK9 antibodies capable of reducing LDL cholesterol. U.S. Patent Application No. 61/122,482, "High Affinity Human Antibodies to PCSK9" (filed Dec. 15, 2008).

[14] International Publication No. WO 2009/026558 A1, "Antigen Binding Proteins to Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9).

seen the competitors' antibodies, Amgen drafted the broad claims covering the standard antibody functions of binding and blocking, and applying it to PCSK9 generally. But with such a broad functional genus claim, and no enabling structure in the specification, it is no surprise that Amgen failed to enable the full scope of this claim. There is no dispute that the functional genus claims at issue cover more than the embodiments that Amgen disclosed—and, indeed, no dispute that the number of embodiments might number in the millions.

The Federal Circuit correctly applied the *Wands* factors here. It considered the quantity of experimentation necessary to make and use the full scope of the claim. *Amgen*, 1086-88. "The only ways for a person of ordinary skill to discover undisclosed claimed embodiments would be through either 'trial and error, by making changes to the disclosed antibodies and then screening those antibodies for the desired binding and blocking properties,' or else 'by discovering the antibodies de novo' according to a randomization-and-screening 'roadmap'." *Id.* at 1088.

The court also considered the guidance in the specification, concluding "no reasonable factfinder could conclude that there was adequate guidance beyond the narrow scope of the working examples that the patent's 'roadmap' produced." *Id.* at 1088. It considered the presence of working examples in the specification, including that the working examples represented only a small subset of possible embodiments. *See id.* at n.1.

The court considered the state of the prior art and the nature of the invention, explaining LDL and its effects, as well as PCSK9 and its role in raising LDL

levels, and the use of antibodies to block this interaction. It also discussed the nature of the invention in the context of prior case law, comparing it to *Wands*, *Wyeth*, *Enzo*, and *Idenix* at length.

The Federal Circuit also considered the fact that the invention was in an unpredictable field of science, including that there was a "conspicuous absence of nonconclusory evidence that the full scope of the broad claims can predictably be generated by the described methods." *Id.* at 1087-88. And finally, perhaps most significantly, it considered the breadth of the claims, including that they were functional claims, covering potentially millions of embodiments, and that the claims are "far broader in functional diversity than the disclosed examples." *Id.* at 1087.

The law that the Federal Circuit applied in this decision was neither new, nor a departure from the text of the patent laws of the United States.[15] If you claim more, you must enable more. That should not be a controversial proposition.

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[15] It is worth noting that Amgen's broad, functional genus claims have been invalidated in Europe. Sanofi Press Release: "*European Patent Office rules in favor of Sanofi and Regeneron concerning Praluent (alirocumab)*," (Oct. 29, 2020), *available at* https://www.sanofi.com/en/media-room/press-releases/2020/2020-10-29-13-50-00-2117063. Further, on January 26, 2023, the Japanese Intellectual Property High Court ruled that Amgen's claims are not patentable. Decisions of Intellectual Property High Court of Japan in Case Nos. 10093, 10094.

III. The Court Should Reject Amgen's Request To Ensconce Overbroad Genus Claims in the Law Through Partial Enablement

Amgen asks the Court to permit what amounts to a "partial enablement" standard. Specifically, it admits that a patent must "reasonably enable the entire scope of the claim—there cannot be large tracts of claimed subject matter that are not enabled." Brief for Petitioners at 28 (Dec. 27, 2022). But by implication, this means that in Amgen's view there ***can be some tracts of claimed subject matter that are not enabled***.[16]

In other words, Amgen asks the Court to find that in the case of a purely functional genus claim, the patentee should ***not*** be required to enable the full scope of the claim, but instead may enable only some portion of it. Amgen seeks to lower the standard to "partially enabled" because, as the Federal Circuit noted, truly enabling a broad functional genus claim is a "high hurdle." *Amgen*, 987 F.3d at 1087. And so it should be. If an inventor wants to claim a broad genus, defined by a function rather than a structure, and potentially covering millions of embodiments, the corresponding disclosure must be sufficiently robust to enable that full claim scope. Otherwise, the *quid pro quo* underlying United States patent law is violated. The patentee is given ownership of the millions of embodiments, without clearly teaching the public how to make them without undue experimentation.

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[16] Amgen's partial enablement standard is endorsed by several amici as well. *See*, *e.g.*, Amicus Brief of IP Law Professors.

Amgen admits that "some tracts of claimed subject matter" can be not enabled, but it offers no workable standard as to where to draw the line. It also violates the statute's requirement for the specification to enable "the invention."[17] In Amgen's case, this partial enablement standard comes into play because Amgen claimed monoclonal antibodies with a particular function, but did not teach a skilled artisan how to make antibodies with that function. Instead, it taught how to make a subset of millions of antibodies that ***might*** have that function, and would have to be individually screened to confirm. Thus in the context of Amgen's broad functional genus claims—claims authored by Amgen itself—Amgen taught how to hunt for an invention, not how to make and use it. The Federal Circuit properly found that this effort required undue experimentation, and that Amgen had not upheld its end of the bargain.

Although Amgen's partial enablement standard disrupts the Patent Act's *quid pro quo* for granting a patentee a monopoly for all types of technology, this approach would be particularly damaging in the context of the pharmaceutical industry, in which it will upend incentives and harm patients.

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[17] The Government makes this point well in its cert-stage brief. Brief of the United States As Amicus Curiae, p. 16-17. The statutory reference to "the invention" unquestionably means the whole thing, not part of it.

A. The Existing Enablement Standard Adequately Protects Transformative Innovation

United States patent laws are a *quid pro quo* between the inventors and the public. This bargain requires a balancing of the interest of the inventor on the one hand, and the interests of the public on the other. The scope of the claims must be carefully set: it must protect the inventor, so that commercial development is encouraged; but the claims must be commensurate with the inventor's ***contribution***. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970).

This case does not involve truly transformative or "disruptive" scientific ideas, which are often supported by public funding and arise from academic institutions or government laboratories (like Boyer and Cohen's invention of genetic engineering, for which they received three patents that have been licensed over 350 times[18]) before being taken up by manufacturers.[19] But even when a marketplace actor comes up with a truly transformative or "disruptive" innovation, the Patent Act does not, and should not, exempt such an innovation from the patent bargain. This remains true even in the unlikely hypothetical scenario where a transformative invention can be described

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[18] "Herbert Boyer and Stanley Cohen," Lemelson-MIT, https://lemelson.mit.edu/award-winners/herbert-boyer-and-stanley-cohen.

[19] *See*, *e.g.*, Aaron S. Kesselheim, Yongtian Tina Tan & Jerry Avorn, *The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs*, 34 Health Affairs 286-294 (2015).

only using a functional genus claim with no meaningful limits on structure. The inventor cannot claim what the inventor has not enabled.

Indeed, the *Wands* factors account for the degree of transformation attributable to the invention, as can be seen in the required evaluation of the "nature of the invention" (*Wands* factor 3) in combination with the "state of the prior art" (*Wands* factor 6), which together ably capture this consideration. For example, in *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*, the Federal Circuit considered the fact that "there [was] no dispute in the record that the co-inventors of the '819 patent were the first to create and claim the chemical compound 3-isobytylGABA" (one enantiomer of which is the active ingredient in pregabalin (Lyrica), a drug for treating seizures and certain types of pain) in holding that those inventors had enabled all enantiomers of the compound. 2014 WL 463757, at *4. That is not the case here.

In reality, although Amgen and many of its supporting amici argue that the Federal Circuit's decision in this case will stifle "transformative innovation," such policy considerations are entirely hypothetical, not applicable in this case, and fundamentally incorrect in any event. Amgen's invention here is not transformative. Amgen did not invent the use of monoclonal antibodies to treat diseases by binding to specific antigens; nor did it invent the methods for creating or testing those monoclonal antibodies. Amgen did not identify PCSK9 or make the connection between PCSK9 and high cholesterol. Rather, Amgen was merely the first to broadly claim the entire genus of antibodies, even though others were concurrently

and independently investigating different antibody species within that genus. *See* Fig. 1, *supra*.

In any event, because existing law, including the *Wands* factors, already adequately protects transformative innovations, there is no need to use this case as a stepping stone to make policy changes that allegedly protect "transformative" innovations.

B. Overbroad, Partially Enabled Genus Claims Will Discourage Development of New Products with the Same Target or Mechanism of Action

Amgen's requested relief here will, in the end, chill innovation and harm patients. The availability of multiple treatment options for a given medical condition can be crucial to optimal patient care. "[W]e can't underestimate the benefit of new drug competition from when a second-to-market novel therapy enters a new drug category. In addition to offering patients important therapeutic variety that can improve health outcomes, we often see significant cost savings from facilitating this sort of much needed market competition."[20]

Allowing one innovator to obtain a broad genus claim on a therapeutic target without providing a commensurate disclosure, as in this case, precludes other manufacturers from developing chemically distinct products that treat the same condition using a

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[20] Scott Gottlieb, *Advancing Patient Care Through Competition*, (Apr. 18, 2018), *available at* https://www.fda.gov/news-events/speeches-fda-officials/advancing-patient-care-through-competition-04192018.

similar mechanism of action. In such a case, the patients are the ones who will suffer.

It is common in drug development for more than one FDA-approved product to bind to the same antigen, or otherwise to have the same mechanism of action. Some examples—by no means an exhaustive list—are included below:

Table 1[21]

Drug Name	**Manufacturer**	**FDA Approval Date**
Multiple Myeloma (cancer of the plasma cells), treated with monoclonal antibodies targeting antigen CD38		
daratumumab (Darzalex)	Janssen Biotech	2015
isatuximab-irfc (Sarclisa)	Sanofi-Aventis	2020
Multiple Sclerosis treated with monoclonal antibodies targeting antigen CD20		
ofatumumab (Kesimpta)	Novartis	2009
ocrelizumab (Ocrevus)	Genentech	2017
Chronic Lymphocytic Leukemia, treated using monoclonal antibodies targeting antigen CD20		
rituximab (Rituxan)	Genentech	1997
ofatumumab (Arzerra)	Novartis	2009
obinutuzumab (Gazyva)	Genentech	2013
Philadelphia chromosome positive chronic myeloid leukemia, treated with BCR-ABL tyrosine kinase inhibitors		
imatinib mesylate (Gleevec)	Novartis	2001
dasatinib (Sprycel)	Bristol-Myers	2006

[21] Unless otherwise stated, the information in this table was obtained by searching for the either the brand name or the generic name of each drug at FDA Approval History located at drugs.com/history (last visited January 31, 2023.).

Drug Name	Manufacturer	FDA Approval Date
nilotinib (Tasigna)	Novartis	2007
ponatinib (Iclusig)	Ariad	2012
bosutinib (Bosulif)	Pfizer	2012
Melanoma and/or Carcinoma (skin cancers), treated with monoclonal antibodies that bind to PD-1 receptor		
nivolumab (Opdivo)	Bristol-Myers	2014
pembrolizumab (Keytruda)	Merck &Co.	2014
cemiplimab-rwlc (Libtayo)	Regeneron	2018
Melanoma and/or Carcinoma (skin cancers) treated with monoclonal antibodies that bind to PD-L1 receptor		
atezolizumab (Tecentriq)	Genentech	2016
avelumab (Bavencio)	EMD Serono	2017
durvalumab (Imfinzi)	AstraZeneca	2017
Breast cancer, treated with inhibitors of cyclin-dependent kinases (CDK) 4 and 6		
palbociclib (Ibrance)	Pfizer	2015
ribociclib (Kisqali)	Novartis	2017
abemaciclib (Verzenio)	Eli Lilly & Co.	2017
High Cholesterol, treated with statins		
lovastatin[22]	Merck	1987
pravastatin (Pravachol)[23]	Bristol-Myers	1991

[22] Rachel Hajar, *Statins: Past and Present,* 12 Heart Views, 121-127, (2011), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3345145/.

[23] Pravachol Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019898s062lbl.pdf

Drug Name	Manufacturer	FDA Approval Date
simvastatin (Zocor)[24]	Merck	1991
fluvastatin (Lescol)[25]	Novartis	1994
atorvastatin (Lipitor)[26]	Warner-Lambert	1996
rosuvastatin (Crestor)[27]	AstraZeneca	2003
pitavastatin (Livalo)	Kowa Company	2009
HIV, treated with integrase inhibitors		
raltegravir (Isentress)	Merck & Co	2007
bictegravir	Gilead	2008
elvitegravir (Vitekta)	Gilead	2014
dolutegravir (Tivicay)	ViiV Healthcare	2013
cabotegravir	ViiV Healthcare	2021
Immune System Diseases (e.g., Rheumatoid Arthritis), treated with monoclonal antibody TNF blockers		
infliximab (Remicade)	Janssen Biotech	1998
etanercept (Enbrel)	Amgen	1998
adalimumab (Humira)	AbbVie	2002
certolizumab pegol (Cimzia)	UCB, Inc.	2008
golimumab (Simponi)	Centocor, Inc.	2009

[24] Zocor Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019766s081lbl.pdf

[25] Lescol Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021192s019lbl.pdf

[26] Profile: Lipitor (atorvastatin calcium), WCG CenterWatch, *available at* https://cms.centerwatch.com/directories/1067-fda-approved-drugs/listing/3768-lipitor-atorvastatin-calcium.

[27] Crestor Drug Approval Package, Application NO. 021366, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-366_crestor.cfm

Drug Name	Manufacturer	FDA Approval Date
Rheumatoid Arthritis, treated with JAK inhibitors		
tofacitinib (Xeljanz)	Pfizer	2012
baricitinib (Olumiant)	Eli Lilly	2018
upadacitinib (Rinvoq)	AbbVie	2019

The importance of a system that promotes, rather than discourages, the availability of multiple drugs in a class is hard to overstate. As one doctor put it, "[t]he potential of having two new drugs, whenever they are available, is a wonderful development for my patients…. Any new options that are going to be available are going to help people with these diseases…."[28] Allowing Amgen's proposed partial enablement standard for broad functional genus claims will do serious harm to this system in four respects: first, it will slow the progress of new drugs to market; second, it will lead to fewer patients being treated with the optimal medicine for that patient; third, it will limit opportunities to improve upon current drugs in a class; and fourth, it will keep brand name drug prices high.

[28] R. Volansky, *Arthritis drug market rattles as upadacitinib wins race to FDA approval*, Healio News, (August 16, 2019): *available at* https://www.healio.com/news/rheumatology/20190816/arthritis-drug-market-rattles-as-upadacitinib-filgotinib-race-toward-fda-approval.

1. Overbroad Claims Will Lead to a Slower Progress to Market, Delaying Patient Access to Effective New Therapies

Numerous manufacturers commonly have their own versions of products with the same or similar mechanisms of action in development concurrently. Broad functional claims covering the entire genus, without fully enabling it, will chill this innovation to the detriment of patients. It will prevent other treatment options from coming to market until the patent expires; in some cases, it may leave patients with no treatment options in a class during that time; and it will slow the FDA approval process by stifling the competition that motivates innovators to bring their drugs to market expeditiously.

The FDA has acknowledged the advantages to bringing additional drugs in a class to the market quickly, and has even taken steps to change its clinical trial designs to decrease delay.

> We've found that it's taking much longer after a new drug is approved to get a second or third drug to the market that's in the same class as the original medicine. That means that new drugs are enjoying monopolies for longer periods of time, and consumers aren't benefiting from price competition. Also, patients aren't getting the benefits from a choice between different drugs in a new class of medicines, where each drug is similar but might have slightly different profiles,

> and where one drug may work better for an individual patient.[29]

If a patent claim blocks access to an entire genus, without fully enabling that genus, it will prevent patients from accessing different treatment options in that class until the patent expires. This concern is not theoretical. For evolocumab, Amgen obtained and enforced an injunction in Germany that was subsequently overturned after the European Patent Office invalidated Amgen's European patent. German patients were without multiple drug options for over a year. Similarly, in Japan, Amgen also obtained and enforced an injunction that is still in effect. The Intellectual Property High Court in Japan recently issued a ruling that Amgen's patents do not meet the requirements for patentability in Japan, but patients in Japan are still without multiple antibody drug options, and have been for years. Amgen obtained an injunction in the United States that was stayed by the Federal Circuit before it was enforced, but if Amgen had its way, patients here would also have been limited to a single treatment option.

Amgen is not shy about the effect of its claim. In December, 2022, Amgen's Chief Patent Counsel stated that these claims leave PCSK9 open for future

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[29] FDA in Brief: *FDA modernizes clinical trial designs and approaches for drug development, proposing new guidance on the use of adaptive designs and master protocols*, (Sept. 28, 2018), *available at* https://www.fda.gov/news-events/fda-brief/fda-brief-fda-modernizes-clinical-trial-designs-and-approaches-drug-development-proposing-new.

innovation in fields like siRNA and small molecules, but competitors must "stop[] working on antibodies."[30]

Patent claims like those at issue here may even prevent patients from having access to ***any*** treatments in a class. The product in development by the patent holder may ultimately be ineffective,[31] or have safety or manufacturing problems that prevent it from being approved by the FDA. If other competitors are blocked, then no products will be approved. Sometimes, an FDA approved drug is withdrawn from the market for post-approval safety issues. [32] In fact, recent work suggests that this concern may exist in even this case. A reanalysis of data from a late-stage trial (FOURIER) of Repatha suggests that it may lead to

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[30] *See* IPO.org, *Enablement and Written Description in the Spotlight* (Dec. 1, 2022).

[31] For example, Pfizer filed a provisional patent application for a PCSK9 antibody by structure, but ultimately abandoned its attempts to develop that antibody after disappointing clinical results. Pfizer Press Release: *Pfizer Discontinues Global Development of Bococizumab, Its Investigational PCSK9 Inhibitor*, (Nov. 1, 2016), *available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer_discontinues_global_development_of_bococizumab_its_investigational_pcsk9_inhibitor.

[32] For example, cerivastatin (Baycol), made by Bayer Pharmaceuticals, was recalled in August 2001 after four years on the market, when it was linked to 31 U.S. deaths and at least 9 more fatalities abroad. Charles Marwick, *Bayer Is Forced to Release Documents Over Withdrawal of Cerivastatin*, 326 BMJ 7388 (Mar. 2003). Twelve other drugs were taken off the market between 1997 and 2006 for dangerous side effects. Lauren Neergaard, *Deaths Spur Cholesterol Drug Recall*, CBS News (July 10, 2006), https://www.cbsnews.com/news/deaths-spur-cholesterol-drug-recall-10-07-2006/.

cardiac harm.[33] If Repatha is later taken off the market, and Amgen is successful in keeping Praluent out of the market as well, patients would be left with no options in this class of drugs.

Finally, competition between innovators can lead to a "race" to drug approval because being the first to market brings economic benefits. For example, as demonstrated in Table 1 above, the three different skin cancer treatments using monoclonal antibodies that bind to the PD-L1 receptor were all approved in under two years. Similarly, the three breast cancer treatments using inhibitors of cyclin-dependent kinases (CDK) 4 and 6 were approved in a two year span. Janssen Biotech and Amgen raced for FDA approval of their TNF blockers, with Janssen's Remicade receiving its FDA approval on August 24, 1998, and Amgen's Enbrel receiving approval on November 2, 1998.

This race also occurred here. Multiple manufacturers were all working to develop a treatment for high cholesterol using monoclonal antibodies targeting PCSK9. *See* Fig. 1, *supra*. They did that under a legal regime without the risk of a competitor obtaining broad functional genus claims that it did not deserve.

If broad, partially enabled, purely functional genus claims are allowed, competition between innovators will falter. There will be less pressure on manufacturers to complete their necessary clinical trials as

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[33] Tristan Manalac, *Reanalysis of Key Trial Flags Fresh Safety Concerns for Amgen's Repatha (Updated)*, Biospace (Jan 4, 2023), https://www.biospace.com/article/reanalysis-of-key-trial-flags-fresh-safety-concerns-with-amgen-s-repatha/.

speedily as possible. Where the drugs are useful alternatives to one another, the patients will suffer for having delayed, or no, access to the useful alternative.

2. Overbroad Claims Will Limit Opportunities To Improve Upon Current Drugs in a Class

Overbroad, purely functional genus claims will limit the ability of other manufacturers to improve on an initial or early drug by developing other compounds using the same mechanism of action. The statins provide a good example. Lovastatin was the first statin to reach the market, but later entrants Zocor, Lipitor, and Crestor were more powerful, and offered better options for patients post-myocardial infarction.[34] Glitazones (a class of drugs treating type 2 diabetes) are another example: troglitazone was the first in its class, but was withdrawn because it caused liver failure; use of rosiglitazone, the next on the market, dropped to near zero because it caused heart attacks; pioglitazone, the third one in this class, is the only one still on the market.

Second and subsequent-in-class drugs may also distinguish themselves from the original drug by testing in other diseases, thus expanding the range of possible effective uses of a drug (often expanding the range of the entire class). The first TNF blocker, Remicade, was originally approved to treat Crohn's

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[34] *See* Neil J. Stone, et al., *2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults*, 129 AHA Journals 25, Suppl. 2, Table 5 (June 2014).

disease.[35] The second, Enbrel, was originally approved to treat rheumatoid arthritis.[36] Shortly thereafter, Remicade was approved to treat rheumatoid arthritis, and Enbrel was then approved to treat polyarticular juvenile idiopathic arthritis, and thereafter, in January 2002, for ankylosing spondylitis. Remicade was approved to treat ankylosing spondylitis in 2004. This pattern continued, and broadened with the additions of Humira, Cimzia, and Simponi to the list of TNF blockers in later years.

JAK inhibitors were initially indicated for use to treat rheumatoid arthritis, beginning with Xeljanz in 2012,[37] and followed by Olumiant in 2018[38] and Rinvoq in 2019.[39] Olumiant was then given emergency approval to treat Covid-19 in November 2020. In January 2022, Rinvoq was approved to treat atopic dermatitis (eczema). And in June, 2022 Olumiant was approved as the first and only systemic medicine for severe alopecia areata. This broadening to other diseases by the second and third-in-class drugs would not have been possible if Pfizer, the maker of Xeljanz, was in possession of a patent like the one Amgen attempts

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[35] Remicade FDA Approval History, https://drugs.com/history/remicade.html

[36] Enbrel FDA Approval History, https://www.drugs.com/history/enbrel.html

[37] Xeljanz FDA Approval History, https://www.drugs.com/history/xeljanz.html

[38] Olumiant FDA Approval History, https://www.drugs.com/history/olumiant.html

[39] Rinvoq FDA Approval History, https://www.drugs.com/history/rinvoq.html

to defend here, which it could use to block these other compounds from being developed.

3. Overbroad Claims Will Lead to Fewer Patients Treated with Medicines That Work for Them

Patients may respond differently to drugs with similar mechanisms of actions. For example, according to the scientific literature, there is broad genetic variability in the responsiveness of patients to statin treatment.[40] In addition to this genetic consideration, doctors must also consider the potency of different statins, their differing risks of causing myopathy, their risk of new-onset diabestes, and their drug-drug interactions (i.e., how a given statin interacts with other medications the patient is taking), all of which vary among statins in deciding which statin to prescribe to their patients.

Treatment of HIV infection represents another dramatic example of this issue. Effective treatment requires multiple medications from multiple classes, including integrase inhibitors, to control HIV replication and prevent transmission. The choice of which integrase inhibitor (or combination thereof) should be used for a specific patient requires balancing therapeutic potency, dangerous drug-drug interactions, and widely varying side effects. Integrase inhibitors also vary in safety, reliability, and tolerance during pregnancy, when viral suppression is essential to prevent transmission of HIV to the child. Lastly, HIV continues to mutate and can develop mutations that

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[40] Alberico Catapano, et al, *2016 ESC/EAS Guidelines for the Management of Dyslipidaemias*, 37 Eur. Heart J. 2999-3058 (2016).

cause partial or total resistance to one or more integrase inhibitors. A partially enabled, purely functional genus claim that blocked other manufacturers from making integrase inhibitors to treat HIV would be a bad outcome for patients in these circumstances.

The concern over differing efficacy for different patients is not hypothetical in this case, either. Dr. Michael Doyle, one of the undersigned amici, is a medical doctor who treats patients with both Praluent and Repatha, and has had a patient who ***did not respond to Repatha***, but did respond to Praluent.[41] Further, Praluent has two dosing options, which provides flexibility over Repatha in ensuring the best dosage size depending on a particular patient's profile.

Patients may also need a different drug, with a similar mechanism of action, if they become refractory (i.e., late-onset non-responsiveness) to treatment with the original drug. This condition occurs with relative frequency in cancer treatments, as an example. Overbroad, functional, and partially enabled patent claims

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[41] Michael Doyle, *Differential Responses to the PCSK9 Inhibitors, Evolocumab and Alirocumab, in a Patient with Heterozygous Familial Hypercholesterolemia: A Case Report*, Journal of Clinical Lipidology Vol 12 No 2. P5880-559 (April 2018). Dr. Doyle presented this case report at the April 2018 National Lipid Association Meeting. Another study found that Praluent is more effective for patients with high CV risk who were not at LDL-C target goals, but Repatha is more effective for patients with heterogeneous familiar hypercholesterolemia and patients with varied CV risk who were not at LDL-C target goals. Marian McDonagh et al., *A Systematic Review of PCSK9 Inhibitors Alirocumab and Evolocumab*, J. Manag. Care Spec. Pharm., V. 22, I:6, 641-653, at Abstract (Jun 2016).

like Amgen's could prevent those patients from having access to any alternatives in that situation.

4. Overbroad Claims Will Limit Competition Between Innovators on Already Approved Drugs, Keeping Net Prices Artificially High

Competition can lead to more patient friendly prices, assuming other complementary factors in the market.[42] Even where competition between innovators does not encourage the makers of those drugs to lower their list prices, it is rare that each drug in a class would be offered for the exact same net price.

Contracting between manufacturers, payers, and pharmacy benefit management (PBM) companies, and also "bundling" of multiple agents by manufacturers, often result in wide variability from patient to patient in access to a given drug. When there are multiple drugs in a class, there may be an acceptable option offered at a lower net price. But when there is only one drug in a class, it results in many patients having poor access because their payer and PBM do not align well with the sole manufacturer of the drug they need. The speed with which later drugs in the same class can reach the market may also affect the net price to patients.

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[42] Ameet Sarpatwari et al., *Diabetes Drugs: List Price Increases Were Not Always Reflected In Net Price; Impact Of Brand Competition Unclear*. 40 Health Aff. 772 (2021) ("Decreasing net prices might have been spurred by increasing brand-brand competition. During the study period, thirteen DPP4 inhibitors and nine SGLT2 inhibitors entered the market.").

The reality is that the cost of drugs is a significant factor in their effectiveness for patients. United States brand name drug prices are the highest in the world. Drug spending accounts for 9% of health care spending in the United States.[43] High drug prices lead to increased health care spending, which causes payors, like Medicaid, to cut back on services.[44] Furthermore, high drug prices unsurprisingly may lead to non-adherence and, consequently, worse patient outcomes.[45] If a patient cannot afford treatment, then that patient will get sub-optimal treatment, or no treatment at all. "By some estimates, each year, drug

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[43] CMS National Health Expenditures 2021 Highlights, https://www.cms.gov/files/document/highlights.pdf.

[44] Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 8, 864 (Aug. 2016).

[45] *See, e.g.*, Liz Hamel et al., *Public Opinion on Prescription Drugs and their Prices*, Kaiser Family Foundation, (March 15-22, 2022), https://www.kff.org/health-costs/poll-finding/public-opinion-on-prescription-drugs-and-their-prices/, (three in ten adults say they haven't taken their medicine as prescribed in the past year due to costs); Linda Beer et al., *Nonadherence to Any Prescribed Medication Due to Costs Among Adults with HIV Infection — United States, 2016–2017,* 68 Morb Mortal Wkly. Rep. 1129-1133 (2019), http://dx.doi.org/10.15585/mmwr.mm6849a1 (noting that "[a]ddressing financial barriers to antiretroviral therapy (ART) adherence might improve levels of viral suppression, which is central to ending the HIV epidemic in this country); Jennifer Huizen, *Taking Drugs As Advertized: What Are The Barriers?*, Medical News Today, (April 12, 2021), https://www.medicalnewstoday.com/articles/taking-drugs-as-advised-what-are-the-barriers ("The cost of medications is a key reason for nonadherence.") ("Huizen").

nonadherence causes approximately 125,000 preventable deaths in the United States and $100 billion to $290 billion in avoidable costs." Huizen.

The United States is unique in the world for not negotiating brand-name drug prices after launch.[46] It is not the purpose of this brief to criticize this practice, nor to propose a policy shift aimed at forcing drug prices down. As a result of this system, however, competition among drugs with similar targets or mechanisms of action is, in many cases, the only hope consumers have for achieving lower prices for brand-name drugs until generics become available. Even if direct competition between innovators does not lower drug list prices, it can at least provide leverage for insurers during price negotiations. According to former Medicare Director Gail Wilensky, "[t]he way you get leverage is by threatening to exclude unless the seller gives you the price discount that you think is appropriate. But if you're not willing to exclude, you lose most of your clout."[47] When there is only one available drug in a class, the threat of exclusion has no teeth. Individual insurers negotiate rebates to get to net

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[46] The Inflation Reduction Act, signed into law on August 16, 2022, contains a provision requiring the Federal Government to negotiate prices with drug companies for a small subset of drugs causing the highest total Medicare spending, beginning in 2026. Drugs are excluded from this negotiation process until they are 9 years (for small-molecule drugs) or 13 years (for biological products) from their FDA-approval or licensure date. Medicare Part B Rebate By Manufacturers, H.R.5376, § 11101 (2022).

[47] Tony Pugh, *Push to Negotiate Medicare Drug Prices Prompts Look at VA Model*, BL, (May 11, 2021 5:30 AM), http://news.bloomberglaw.com/health-law-and-business//push-to-negotiate-medicare-drug-prices-prompts-look-at-va-model.

prices as best they can, and their ability to do that is aided substantially if there are other competitors in class that the insurers can use to play the manufacturers off each other, securing lower net prices on more treatment options for patients.

Conclusion

For the reasons above, amici respectfully request the Court to affirm the judgment of the court of appeals.

Respectfully submitted,

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