No. 2020-1074

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMGEN INC., AMGEN MANUFACTURING, LTD., AND AMGEN USA, INC.,

Plaintiffs- Appellants,

v.

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

Defendants- Appellees.

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

BRIEF OF *AMICUS CURIAE*
ELI LILLY AND COMPANY.
SUPPORTING DEFENDANTS-APPELLEES

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June 08, 2020

CERTIFICATE OF INTEREST

Counsel for the *amicus curiae* Eli Lilly and Company certifies the following:

1. The name of every party or *amicus* represented by me is:

Eli Lilly and Company.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Eli Lilly and Company.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or *amicus curiae* represented by me are:

None.

4. The names of all law firms and the partners or associates that appeared for the party or *amicus* now represented by me or are expected to appear in this Court are:

DUANE C. MARKS
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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal:

None.

Dated: June 08, 2020

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Eli Lilly and Company ("Lilly") submits this brief as *amicus curiae* in compliance with Rule 29 of Federal Rules of Appellate Procedure and with this Court's Rule 29. Lilly does not have a direct stake in the result of this appeal. The parties to this case have not contributed in any way to the preparation of this brief. The parties have consented to the filing of this brief.

I. STATEMENT OF INTEREST OF *AMICUS CURIAE*

Lilly is a multinational biotechnology and pharmaceutical company headquartered in Indianapolis, Indiana. Like Amgen, Lilly discovers and develops innovative medicines, including therapeutic antibodies, for human diseases and relies on the patent system to protect our groundbreaking medicines. However, Lilly disagrees with the unfounded, and demonstrably false[1] position that, without purely functional antibody claims, "the pace of research and development" will slow and innovation will be hindered.[2]

Respectfully, the difference of opinion between Amgen and Lilly centers on whether elucidating the role of a naturally occurring protein in a disease entitles one, as Amgen asserts, to preempt the development of all therapeutic antibodies to

[1] See, for example, *infra* note 19, 22, 23, 24, 27 describing numerous marketed medicines acting on the same target.
[2] Appx3673(157:1-7); Appx3996(937:23-25; 938:1-15); Brief of Amici Curiae Bristol-Myers Squibb Company and Merck Sharpe & Dohme Corp. in Support of Amgen Inc., page 2.

that protein.[3] Amgen's position is not only legally unsupported, it is detrimental to patients and their doctors and jeopardizes the United States' status as the healthiest medical innovation ecosystem in the world.

II. INTRODUCTION

The Parties return to this Court following a new trial at the district court where Amgen's purely functional antibody genus claims were found to lack enablement across their full scope.[4] While Lilly agrees with the district court's holding regarding lack of enablement, its finding relating to written description is both scientifically and legally unsupported.

When this Court initially addressed written description for Amgen's claims, great strides were made in aligning antibody written description with that of any other material when this Court stated, "the 'newly characterized antigen' test flouts basic legal principles of the written description requirement."[5] However, the record below evidences a need for this Court to further interject and make clearer for the courts below that, for purely functional claims, like Amgen's, the claimed

[3] In the instant case, the naturally occurring protein is proprotein convertase subtilisin/kexin type 9 ("PCSK9").

[4] A "purely functional antibody genus claim" is a claim directed to all antibodies, known now and discovered in the future, capable of performing the specified function(s).

[5] *Amgen, Inc. v. Sanofi, Aventisub LLC*, 872 F.3d 1367, 1378 (Fed Cir. 2017) (stating the newly characterized antigen test "allows patentees to claim antibodies by describing something that is not the invention, *i.e.*, the antigen").

materials must be ***recognizable*** or ***visualizable,*** sufficient to ***distinguish them from unclaimed materials***.

Amgen's claims cover a vast genus of antibodies based only on a description of what they bind to, the "sweet spot" of the naturally occurring protein PCSK9, and the further functional result of "blocking" PCSK9. Although the claims are notionally directed to "antibodies", the contours of the claimed genus are not defined by any common identifiable antibody structural features, nor an identifiable relationship correlating the functional results binding and blocking to antibody structure.[6] The size and scope of the purely functional antibody genus is thus unknowable – making representation of the genus impossible. Simply put, the metes and bounds of Amgen's purely functional antibody genus claims are unknowable because such claims, in effect, cover ***any antibody that works***.[7]

Purely functional claims, like Amgen's, covering anything that works hurt innovation. By claiming any and all antibodies that bind a naturally occurring

[6] A common structural feature would be, for example, antibody structure common to members of the genus such as the amino acid sequences of the complementary determining regions ("CDRs") or variable regions that are known to inure the functions of "binding" and "blocking."

[7] See, for example, *The Incandescent Lamp Patent*, 159 U.S. 465, 472 (1895), explaining the patentee is not "entitled to a monopoly of all fibrous and textile materials for incandescent conductors" unless the patentee has "discovered…a quality common to them all…as distinguishing then from other materials…and such quality or characteristic adapted them peculiarly to incandescent conductors."

biological target, or particular region thereof, Amgen seeks to coopt an entire class of medicines, therapeutic antibodies, and block the target's use in antibody drug discovery and development.[8] This is a concerning outcome given that different antibodies that bind the same biological target can elicit widely different, medically relevant, responses.[9] And, this outcome is particularly concerning for biological targets associated with diseases for which there are no effective treatments. Nevertheless, Amgen, and amici in support of Amgen, assert these claims are appropriate compensation for "invest[ing] enormous sums in discovering the underlying target."[10] However, financial investment dictates neither claim breadth nor patentability and this Court has already rejected the newly characterized antigen (*i.e.*, target) test as having any basis in law.[11]

Further, purely functional claims like those at issue preempt future inventions and are thus inconsistent with one of the most fundamental policies underlying patent law; disclosure of an invention in exchange for exclusive rights

[8] This Court, in *Ariad*, held that the discovery of the biological target NF-kB did not entitle the applicant to claim all compounds that bind to and inhibit the target. Similarly, Amgen's discovery of the sweet spot should not entitle them to claim all antibodies thereto.
[9] *Infra* note 23, 24, 25.
[10] *Supra* note 2.
[11] *Amgen*, *Inc*., 872 F.3d at 1378 (Fed. Cir. 2017).

commensurate only with the disclosed invention.[12] Properly applied, 35 U.S.C. §112 is an essential safeguard against such preemption because it allows for the use of functional language ***only*** when the art establishes, or the patentee discloses, a relationship between the function and materials having that function, or the disclosure represents the full diversity of those materials. Such disclosure makes claimed and unclaimed materials predictable, thereby aligning claim breadth with the disclosure as required by this Court's precedent.[13]

The instant case presents this Court with an opportunity to make clearer for the courts below that the disclosure requirements for a genus of claimed antibodies are the same as for all other materials. Lilly asks this Court to do more than just find the claims at issue lack sufficient written description. Lilly also asks this Court to take this opportunity to clarify that, in the absence of yet-to-be-discovered Nobel prize worthy technology,[14] purely functional antibody genus claims like those here are *per se* invalid as being incapable of description under 35 U.S.C. §112(a).

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[12] *Fiers v. Revel*, 984 F.2d 1164, 1169 (Fed. Cir. 1993), stating "the policy behind the [written description] statute … is to promote disclosure of inventions, not of research plans."

[13] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1345-1347 (Fed. Cir. 2010).

[14] Appx3910(765:10-19), Amgen witness, Dr. Rees, admitting that predicting antibody function and three-dimensional structure from an antibody's amino acid sequence (and *vice versa*) is "not possible" and that discovering how to make such predictions will "get a Nobel Prize."

III. ARGUMENT

A. Purely Functional Patent Claims Like Those at Issue Violate the Spirit and Intent of the U.S. Patent System and are Invalid as a Matter of Law

The claims in this case fail the foundational quid pro quo of patent law; in exchange for the exclusionary rights bestowed by a patent, one must "describe their invention."[15] This fundamental tenet protects the public from monopolies that exceed the scope of actual inventions, extracts a public benefit derived from disclosure of inventions and protects inventions properly described. In the absence of sufficient identifying disclosure, purely functional antibody claims turn the patent system into a "gotcha game" played amongst innovators where one blocks all others from using the same basic tools of science.[16] However, as this Court aptly noted in *Ariad*:

> "'[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.' … Requiring a written description of the invention limits patent protection to those who actually perform the difficult work of 'invention'…and disclose the fruits of that effort to the public…."[17]

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[15] *Ariad Pharms., Inc.*, 598 F.3d at 1353 (Fed. Cir. 2010) (quoting *Brenner v. Manson*, 383 U.S. 519, 536 (1966)).

[16] Amici in support of Amgen played this "gotcha game", see, Bristol Myers Squibb Press Release, Jan. 20, 217, available at https://news.bms.com/press-release/partnering-news/bristol-myers-squibb-and-ono-pharmaceutical-company-enter-settlement-a.

[17] *Ariad Pharms., Inc.*, 598 F.3d at 1353 (Fed. Cir. 2010), quoting *Brenner,* 383 U.S. at 536 (1966).

Amgen unquestionably invented several antibodies, including Repatha®, which are claimed in patents not at issue. Those claims recite structural elements (*e.g.*, full or partial amino acid sequences) of the antibodies and nobody is challenging their propriety. However, the claims at issue here are much broader because they define the antibodies solely by functions even though the ability to predict antibodies having those functions is nonexistent.[18] Thus, patents like those at issue here reward only the search without providing a written description of its successful completion.

1. Amgen's Purely Functional Claims do not Promote Science but Instead Block all Antibody Innovation and Market Competition to a Naturally Occurring Biological Target

The Parties and amici likely agree that, without patent protection preventing biosimilar or generic manufacturers from copying their medicines, pharmaceutical companies would lack an essential incentive for undertaking the expensive and highly unpredictable work of drug discovery. Copyists could manufacture the same medicine, knowing it is already safe and effective and enjoy an expedited, lower cost, approval process. Patent protection is, thus, essential to innovative

[18] It is noted that antibodies sharing common, functionally relevant, structure (*e.g.*, the same CDRs) with the disclosed antibodies would predictably possess the recited functions. However, prediction is nonexistent for antibodies, such as Praluent®, that do not share functionally relevant structure with Amgen's disclosed antibodies.

drug development and patients all over the world have benefited from a patent and medical innovation ecosystem that has operated under that principle for decades.

Praluent®, however, is not a copy of any Amgen product and experts from both parties acknowledged Praluent®'s structure (*i.e.*, amino acid sequence) is not recognizable or visualizable from Amgen's patent. Nevertheless, armed with purely functional claims that necessarily cover Praluent®, Amgen seeks to remove this innovative antibody medicine from the hands of doctors and patients. A particularly sobering outcome given that Praluent® is not a biosimilar of Amgen's Repatha® and thus no less innovative than other U.S. Food and Drug Administration ("FDA") approved, subsequent antibody therapies to the same biological target.[19] Amgen effectively asserts ownership over the biological target PCSK9's use in antibody innovation and attempts to block *all* antibody competitors in that field.

In any event, purely functional antibody claims, like Amgen's, are not needed to prevent copyists from making biosimilars. For one, the FDA expects that biosimilars will have "the same primary amino acid sequence as its reference

[19] Examples include Amgen's Vectibix® in view of Lilly's Erbitux® (both EGFR antibodies for cancer) and BMS' Opdivo® in view of Merck's Keytruda® (both PD1 antibodies for cancer).

product."[20] Therefore, patent claims reciting even a portion of a reference antibody's amino acid sequence would necessarily be infringed by a biosimilar copyist. For example, an antibody genus claim that recites both binding and the CDR amino acid sequences[21] fully describes the genus, blocks copyists and does not preempt future antibody innovation.[22] Amgen's claims, by their design, are not intended to protect antibodies they actually invented and described from copyists, but are instead intended to block other innovators, such as Sanofi.

Purely functional antibody genus claims cordon off entire areas of antibody development and thereby chill medical innovation to the detriment of patients and the healthcare providers who treat them. Rather than allowing the use of a naturally occurring protein to be preempted by patents like Amgen's, patients need multiple innovators and multiple shots on goal. For example, less than 10% of compounds that show promise as a therapeutic actually achieve approval.[23] Also,

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[20] Food and Drug Administration, Draft Guidance for Industry, Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations, Docket Number FDA-2019-D-2102, May 2019, at p.11.

[21] Complementarity Determining Regions ("CDRs"): structural portions of an antibody considered primarily responsible for binding an antigen.

[22] In view of FDA's "same primary amino acid sequence" expectation for biosimilars, such claims further address the irrational concern that claims reciting an antibody's full sequence are too easy to design around.

[23] Thomas, David W., et al., June 2016, "*Clinical Development Success Rates 2006-2015*" published by Biomedtracker, Sagient Research Systems, Informa, San Diego, California, USA.

the first approved therapeutic to a biological target rarely provides best-in-class treatment, a fact highlighted recently in the fields of HIV and oncology.[24] In fact, even when two different therapeutic antibodies bind similar regions of a biological target, multiple studies have shown they can elicit widely different, and medically relevant, responses.[25] And, imagine the public detriment from a patent directed to all antibodies to the SARS CoV-2 virus.[26] Such a patent would, in violation of laws intended to *promote* science, preempt the more than a dozen pharmaceutical companies developing therapeutic antibodies to combat this viral pandemic .[27] It is

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[24] Caskey, et al., 2019 "*Broadly neutralizing anti-HIV-1 monoclonal antibodies in the clinic*", Nature Medicine, V.25, pp 547–53, explaining that only second-generation antibodies successfully treated AIDS; US National Library of Medicine ClinicalTrials.gov, available at https://clinicaltrials.gov/ct2/home, listing 31 different therapeutic antibodies targeting PD1, for the treatment of cancer, presently in clinical trials.

[25] See, for example, Shim, et al., *One target, different effects: a comparison of distinct therapeutic antibodies against the same targets*. Experimental & Molecular Medicine.;43:539–49 (2011), discussing differences in therapeutic effects of multiple HER2-targeting therapeutic antibodies; see also, Oflazoglu, E. & Audoly, L. P. Evolution of anti-CD20 monoclonal antibody therapeutics in oncology. *mAbs* **2**, 1–6 (2010), reviewing data from four different therapeutic antibodies all binding to the same region of the CD20 protein and having dramatically different profiles and signaling mechanisms; see also, Strohl, W. R. Optimization of Fc-mediated effector functions of monoclonal antibodies. *Curr. Opin. Biotechnol.* **20**, 685–691 (2009), disclosing the third generation CD20-specific antibody obinutuzumab is less immunogenic than rituximab, has a different mechanism of action and triggers increased cytotoxicity.

[26] See, for example, CN110951756A and CN110974950A to Guangzhou Boon Bio Pharmaceutical Technology Co., LTD.

[27] Vanquishing the Virus: 160+ COVID-19 Drug and Vaccine Candidates in Development, Genetic Engineering & Biotechnology News, Alex Philippidis

therefore imperative that purely functional antibody genus claims be rejected and recognized for what they do: chill multiple, diverse therapeutic antibody research and development efforts against the same biological target.

2. Amgen's Purely Functional Antibody Claims Serve as Subterfuge for Preempting the Use of a Naturally Occurring Biological Target

The Supreme Court has long recognized that allowing a patent to monopolize basic tools of scientific work "would be at odds with the very point of patents" and risks impeding innovation as opposed to promoting it.[28] While Amgen's claims are notionally directed to an "antibody" genus, upon examination a facade is removed revealing nothing more than a claim that preempts use of PCSK9 – a naturally occurring protein – in antibody drug development.

In particular, Amgen's claims recite only: (i) one or two residues of PCSK9; and (ii) the generic term "isolated monoclonal antibody." It is uncontested that PCSK9 is a naturally occurring protein; Amgen neither created nor altered any portion of PCSK9. Furthermore, "monoclonal antibody" is a nonce term, providing no meaningful description of ***what*** interacts with PCSK9 beyond a generic linkage to a technological field. Thus, unlike claims directed to antibodies

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(13April2020), available at https://www.genengnews.com/a-lists/vanquishing-the-virus-160-covid-19-drug-and-vaccine-candidates-in-development/.

[28] *Diamond*, 447 U.S. at 309 (1980); see also, *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

which allow the skilled person to recognize and visualize the claimed antibodies (*e.g.*, via recitation of the CDR sequences),[29] Amgen's claims only allow the skilled person to recognize or visualize a region of a naturally occurring protein. And, as a result, the claims preempt, as opposed to promote, the use of PCSK9 in antibody research and development.

The Supreme Court warned against claims like those at issue, which preempt all uses of a building block of nature[30]; rejecting such claims under §112(a) for overbreadth.[31] Here, Amgen's claims overreach, serving as subterfuge for preempting the use of PCSK9 in the field of therapeutic antibody research and development. The written description requirement of §112(a), however, serves as a check on such overreach and preemption by mandating the claimed antibodies be described in a meaningful manner (*i.e.*, sufficient to distinguish them from other

[29] See, for example, U.S. Patent No. 8,030,457 to Amgen, which claims a genus of antibodies, including RePatha®, by reciting CDRs (*i.e.*, structural elements common to antibodies within the claimed genus that impart the recited function).
[30] *Mayo Collaborative Services v. Prometheus Labs, Inc.*, 566 U.S. 66, 69 (2012).
[31] See, for example, *O'Reilly v. Morse*, 56 U.S. 62 (1854); *Holland Furniture Co. v. Perkins Glue Co.*, 277 U.S. 245, 258 (1928) (stating, "As a description of the invention it is insufficient and if allowed would extend the monopoly beyond the invention."); *GE Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 371 (1938) (finding, "Claim 25 vividly illustrates the vice of a description in term of function. As a description of the invention it is insufficient and if allowed would extend the monopoly beyond the invention.") (internal citations omitted).

materials). Absent that meaningful disclosure, as is the case here, the claims are invalid as lacking proper written description.

3. Purely Functional Claims that do not Correlate the Claimed Function to Structure, and that are not Construable Under 35 U.S.C. §112(f), are Invalid as a Matter of Law.

Concerns about functional claims "preempting the future before it has arrived" have been a focus of both the Supreme Court and this Court for decades.[32] Courts have stressed the importance of balancing the rights of private parties to claim all that they have invented, with the public's right to innovate freely in the space beyond the described invention. And, even in the context of truly pioneering and ground-breaking discoveries, courts have historically held that using a functional claim limitation invalidates the claim.[33]

The Supreme Court's decision in *Haliburton* represented a turning point in functional claiming jurisprudence. Clearly troubled by the prospect of "broad functional claims" preempting future developments, the Supreme Court made it

[32] *O'Reilly v. Morse*, 56 U.S. 62 (1853); see also, for example, *Halliburton Oil Well Cementing Co., v. Walker*, 329 U.S. 1 (1946) and *Gottschalk v. Benson*, 409 U.S. 63 (1972).

[33] See, for example, *O'Reilly*, 56 U.S. 62 (1853), where functional claims encompassing the groundbreaking discovery of the electric telegraph were held invalid. And, in any event, Amgen is no pioneer here: Amgen did not discover PCSK9, the structure of PCSK9 or the fact that it plays a role in cholesterol regulation and there is no evidence in this case that Amgen led Sanofi anywhere.

clear that claims are invalid as a matter of law if they use purely functional language at the exact point of novelty.[34]

In response to *Haliburton*, Congress enacted 35 U.S.C. §112(6),[35] thereby creating a limited exception to the Supreme Court's prohibition of functional claiming. The statute's limited, claim-saving, exception applies when functional language is used to define at least one element amongst a combination of elements that make up a claimed invention[36] and the functional claim element fails to recite sufficiently definite structure.[37] However, if a structure-function correlation is established by the art or disclosure, an inventor's use of that function to define a claim element would not invoke §112(f).[38] In the absence of a structure function relationship, a functional claim is "saved" and limited by §112(f)'s statutorily mandated construction (*i.e.*, structures in the specification and equivalents thereof) or, per *Halliburton*, the claim is invalid.

[34] *Halliburton Oil Well Cementing Co., v. Walker*, 329 U.S. at 8, 12 (1946).
[35] Now codified, and referred to throughout, as 35 U.S.C. §112(f).
[36] *Halliburton Oil Well Cementing Co., v. Walker*, 329 U.S. at 12-13 (1946).
[37] *Williams v. Citrix Online, LLC*, 792 F.3d 1339, 1348 (Fed. Cir. 2015), holding §112(f) also applies if the structure recited is in the form of a "nonce" that fails to connote "sufficiently definite structure."
[38] *Id*.

However, because §112(f)'s saving provisions apply only to "combination" claims, the statute cannot be used to save Amgen's claims.[39] Thus, under *Halliburton* and its progeny, Amgen's claims are valid only if they use functional language "sufficiently definite in meaning as the name for structure."[40] Because the factual record in this case in no way establishes that binding and neutralizing activity correlates to identifiable antibody structure, Amgen's claims are invalid.

In fact, claims like those at issue have been referred to by this Court as "single-means" claims that are invalid as a matter of law for failure to comply with §112.[41] This Court, for example, in *In re Hyatt*, explained, "The long-recognized problem with a single-means claim is that it covers every conceivable means for achieving the stated result, while the specification discloses at most only those means known to the inventor."[42] Although this Court, in *Hyatt*, reasoned §112(f) may save a combination claim by providing a construction narrow enough to avoid "undue breadth" (as forbidden by §112(a)), no provision under §112 or otherwise

[39] Amgen's claims, which generically recite a "monoclonal antibody", do not recite any elements of the antibody; functional results achieved by an antibody is not a combination of elements of the antibodies.
[40] *Supra* note 38.
[41] See, for example, *In re Hyatt*, 708 F.2d 712 (Fed. Cir. 1983), *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993).
[42] *In re Hyatt*, 78 F.2d at 714 (Fed. Cir. 1983).

saves a single-means claim.[43] Thus, it is not possible to satisfy §112 – the description set forth in the specification will never be commensurate with the scope of the claim.

B. The Skilled Person is Unable to Recognize or Visualize Members Across Amgen's Purely Functional Genus - Amgen did not Possess the Claimed Invention

While often expressed in terms of distinct "tests," this Court has been clear that, in the context of a genus claim, there is only one standard by which possession of the invention through its written description is assessed. The members of the genus must be visualizable or recognizable from the disclosure in a manner "sufficient to distinguish the genus from other materials."[44] Such disclosure makes materials within the claim and, just as importantly, the claim's boundary predictable.

Amgen, using *only a functional description*, claims a vast genus of antibodies. However, no correlation exits between antibody function and structure that allows the skilled person to recognize or predict antibodies possessing the claimed function. Thus, the size and scope of the claimed genus is not discernable

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[43] *Id*. at 715; see also, *Fiers,* 984 F.2d at 1168 (Fed. Cir. 1993), where this Court held a claim to all DNA that encodes the protein interferon-beta, where that protein's amino acid sequence was unknown and not disclosed, is "analogous to a single-means claim which has been held not to comply with the first paragraph of section 112."

[44] *Ariad Pharms., Inc.*, 598 F.3d at 1350 (Fed. Cir. 2010) (citing *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

from the disclosure. And, Amgen has deliberately chosen, based on their purely functional claim format, to avoid limiting their claims to any structural features correlated with the recited function. By any "test" then, the skilled person is unable to recognize or visualize (*i.e.*, predict) antibodies within the claimed genus sufficient to distinguish them from other antibodies – Amgen did not possess the claimed genus.

1. The Functions Binding and Blocking do not allow the Skilled Person to Recognize or Predict Structure of Antibodies within the Claimed Genus

As this Court noted in *Abbvie Deutschland GmbH v. Janssen Biotech, Inc.*, "Genus claims that are defined solely by function in the chemical arts are inherently vulnerable to a finding of lack of written description where it is difficult to predict what would be covered by the claims."[45] And the experts in this case previously agreed that one of skill in the art cannot visualize or recognize the identity of the members of the claimed genus from their disclosed functions.[46]

Stuck with this factual record, Amgen overtly posited to the jury that amino acid sequence information is unnecessary to visualize or recognize an antibody. Beyond simply being false, Amgen's assertion led to multiple admissions that

[45] *Abbvie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014).
[46] Appx3921(808:24-809:12).

doom their claims, again, for lacking written description. For example, during direct examination, Amgen's expert, Dr. Rees, stated:

> Q. Why wouldn't the skilled antibody scientist look to [amino acid] sequence?
>
> A. Well, I think you have heard that … amino acid sequence, this long chain of amino acids that forms up to form those compact three-dimensional structure. The way in which you get from sequence to that three-dimensional structure isn't fully understood today. It's going to get a Nobel Prize for somebody at some point, but translating that sequence into a known three-dimensional structure is still not possible.[47]

Dr. Rees conceded what everyone already knew: an antibody's amino acid sequence determines both its three-dimensional structure and its function in an unpredictable way. Given the amino acid sequence determines antibody function, visualizing or recognizing a purely functional antibody genus across its full scope, in a manner sufficient to distinguish claimed from unclaimed antibodies, is simply not possible. In the face of that impossibility, and following this Court's rejection of the newly characterized antigen test, Amgen is essentially asking this Court to create a new written description exception for antibodies. More specifically, Amgen asks this Court to effectively take judicial notice that demonstrating possession of antibodies does not require describing the composition of the

[47] Appx3910(765:10-19).

antibodies.[48] In doing so, Amgen asks this Court to violate *Halliburton* and ignore its established precedent which holds recognition and visualization as its cornerstone.

2. Members of the Purely Functional Genus are not Visualizable or Recognizable Based on the Disclosed Members – Prediction based on Representation is not Possible

Although the written description "representative number of species" guidepost for genus claims set forth in *Ariad* is facially consistent with *Halliburton,* as applied at the district court, it was not. Lilly asks this Court to make clearer for the courts below that "representation" of a purely functional genus is not established unless the alleged representation makes undisclosed members of the genus recognizable or visualizable (*i.e.*, predictable) sufficient to distinguish them from unclaimed members. That is, this Court needs to clarify that representation must be across the scope of the ***claimed materials*** (*i.e.*, their

[48] Amgen's assertion that amino acid sequences comprising the antibody do not matter for recognizing or visualizing the claimed genus is demonstrably false. For example, Amgen describes Repatha® (in U.S. Patent No. 8,030,457) by amino sequence; the FDA describes antibodies by amino acid sequence and expects biosimilars to have the same amino acid sequence as the reference antibody; and the United States Adopted Names Council describes antibodies by amino acid sequence.

structural diversity) ***not***, as Amgen proffered at the district court, a representation of the recited functions.[49]

Turning to the claims at issue, in view of the admissions regarding a lack of a connection between the claimed function and antibodies having that function, no reasonable jury could have found, consistent with *Ariad* and *Halliburton*, that Amgen's purely functional claims were represented by the disclosed species. Additionally, the "outer boundary" of Amgen's purely functional claimed genus is unknowable (both in terms of number of antibodies and the structural diversity of its members). And, Amgen's expert, Dr. Petsko, on direct examination admitted that predictions based on the disclosed antibodies is extremely limited.

> Q. You heard Dr. Boyd testify that even a small change in amino acid sequence can make a significant difference in the antibodies function. Do you agree with that?
>
> A. Yes, that's absolutely right.[50]

And, since one cannot predict the structure or number of antibodies falling within the scope of the genus, assessment of "representation" is not possible.[51]

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[49] *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1352 (Fed. Cir. 2011), explaining the variation that must be represented by the disclosure is not just the "previously known" molecules within the claimed genus.

[50] Appx3878(638:2-11).

[51] To put it in mathematical terms, when one doesn't have any information about the denominator for a given fraction, the numerator is meaningless.

Unless this Court provides needed clarification, juries will continue to be asked, where the size and scope of the genus is unknowable, the improper question of whether the disclosed species represents the scope of the "presently known" molecules within the genus.[52] And, faced with nothing but a functional description of a genus, asking a jury, as happened here, to compare an accused product to an embodiment in the patent and determine, "is it close enough" is a poor and improper surrogate for assessing written description through representation. Instead, consistent with this Court's precedent, representation must provide predictability, not just of the accused product, but across the claim's scope. In view of Amgen's admissions, it is clear the size and structural diversity of the genus remains unknown and, as such, no reasonable jury could find Amgen's claims were properly described.

3. Amgen Improperly Seeks to Substitute *Functional Results* for a Common *Structural Feature*.

With no disclosed or known structure shared by the functionally claimed genus, Amgen seeks to substitute a functional result. This Court should make clear, however, that a functional result shared by members of the genus, that does

[52] *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1352 (Fed. Cir. 2011), explaining the variation that must be represented by the disclosure is not just the "previously known" molecules within the claimed genus.

not allow the skilled person to recognize or visualize the members, does not demonstrate possession of the genus.

When the limits of a claim are defined solely by functional results, those results must correlate to recognizable structure providing the recited functions. In this way, claims to "DNA that encodes a protein having the amino acid sequence of SEQ ID NO. 1" places the skilled person in possession of the claimed DNA because the function of encoding a defined amino acid sequence correlates to the DNA structure (*e.g.* nucleotide sequence) that provides the encoding function.[53] Amgen's claims, however, cover a vast genus of antibodies defined only by the functional results of "binding and blocking." Unlike the claims to DNA, experts from both parties agree it is not possible to correlate (*e.g.*, recognize or predict) antibody amino acid sequences that bind and block. As such, Amgen's purely functional claims preempt all antibodies that bind and block PCSK9 without describing them.

Furthermore, Amgen's contentions that the genus of claimed antibodies shares a common structural feature, referred to by Amgen as "shape and chemical complementarity", is both scientifically and legally unsupported.[54] A common

[53] The correlation between the function of "encoding", and the nucleotide sequence that performs that function, is provided by the genetic code.
[54] Appx3876(629:25-630:4), Amgen expert, Dr. Petsko, stating the claim term "binding" is "structural."

structural feature that demonstrates possession of a claimed genus links the genus in a way that allows the skilled person to recognize and visualize members of the genus. For example, a claim to a genus of antibodies that bind the same target ***and*** share the same CDRs are linked such that the skilled person can recognize antibodies within the genus. Here, however, Amgen provides no identifiable disclosure of a shared "shape and chemical complementarity." Additionally, the so called "shape and chemical complementarity" does not allow the skilled person to determine if an antibody will bind and block a given antigen.[55] In this way, Amgen's "shape and chemical complementarity" is nothing more than a repackaging of the recited functional limitations. In fact, Amgen's expert described these concepts as, "you start with function…and work back from there."[56] Amgen's position, thus, amounts to nothing more than self-proving, circular, reasoning, and does not aid the skilled person in recognizing or visualizing antibodies within the claimed genus.

Amgen attempts to substitute the functions "binding and blocking" for a description of the genus of antibodies they claim. However, these functional results do not correlate to any identifiable antibody structure that achieve these

[55] Appx3785(454:15-18) (455:21-456-4), Dr. Boyd stating the proffered, "shape and chemical complementarity", does not tell the skilled person if an antibody will meet claim functions.
[56] Appx3879(639:13-18).

results and do not put the public on notice of what has been patented. As such, this Court should reject Amgen's attempt to preempt all antibodies that bind and block PCSK9 without describing them.

C. Amgen's Limited Disclosure Fails to Enable the Full Scope of the Purely Functional Claims

When, as here, genus claims covering a vast, unpredictable scope are supported by a disclosure that brings the skilled artisan no closer to undisclosed, but claimed, species than trial-and error research, undue experimentation is required for practicing the full scope of the claims. As such, the district court correctly held the claims at issue lack enablement as a matter of law.

Purely functional claims like Amgen's, broadly drawn to all therapeutic antibodies that bind and block PCSK9, are particularly susceptible to enablement challenges.[57] The susceptibility of Amgen's claims to enablement deficits is compounded by the unpredictable nature of the therapeutic antibody art.[58] When the skilled artisan "cannot readily anticipate change" within the claimed subject matter, or extrapolate from the disclosed embodiments and results to the full scope

[57] See, for example, *Amgen v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213-1214 (Fed. Cir. 1991), *In re Wright,* 999 F.2d 1557, 1562 (Fed. Cir. 1993).
[58] See, for example, *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1346 (Fed. Cir. 2019) and *Idenix Pharms. LLC v. Gilead Scis., Inc.*, 941 F.3d 1149 (Fed. Cir. 2019).

of the claimed invention, the art is unpredictable.[59] Such is the case here, where an inventor of the patents at issue testified that the skilled person cannot anticipate whether new or modified antibodies will possess the claimed binding and blocking properties.[60] And, the district court rightly rejected Amgen's attempt to downplay this unpredictability by pointing to a non-existing structure-function relationship.[61] The present lack of a structure-function relationship is a hallmark of this unpredictable field.

Having provided only a relatively limited disclosure in view of the breadth of the claims, Amgen is unable to cure the enablement defects of the purely functional genus claims.[62] The limited working examples in Amgen's specification bring the skilled artisan no closer to predicting whether other antibodies will bind to, and block, PCSK9 as required by the claims at issue. And,

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[59] See, *Amgen*, 927 F.2d at 1213 (Fed. Cir. 1991), *In re Marzocchi,* 439 F.2d 220, 223-24 (CCPA 1971); see also MPEP 2164.03, Relationship of Predictability of the Art and the Enablement Requirement.

[60] Appx3768-3769(388:21-389:2), Amgen inventor Mehlin, stating, "conservative mutations are better tolerated, but I'm always surprised. You can't tell a priori that your mutation will be tolerated."

[61] Appx19, holding, "[t]here is no testimony from any expert that the structure-function relationship [of the antigen to embodiments of antibodies]" would create the requisite predictability by "eliminat[ing] the need for testing newly-created antibodies to determine whether they had the functions of blocking and binding."

[62] See, *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366 (Fed. Cir. 1997), stating, "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."

while Amgen attempts to package the conventional antibody development and screening process as a "roadmap", it too places the skilled artisan no closer to undisclosed, but claimed species,[63] and at best highlights the undue quantity of experimentation needed for enabling the vastness of the antibody genus claimed. Thus, the district court appropriately held undue experimentation is required to enable the full scope of Amgen's indeterminately broad genus claims.

IV. CONCLUSION

Antibodies, like small molecule medicines, are a vitally important tool in treating a wide array of human disease. Yet, unlike other medicines, antibodies face a unique risk from patent claims, like Amgen's, that use purely functional language to cover ***anything that works***. Such claims have the effect of preempting the use of biological targets in the field of antibody research and development, threatening to chill or enjoin medical innovation – an outcome detrimental to patients and the healthcare professionals who treat them.

Purely functional antibody claims, like Amgen's, are not only bad for healthcare, they violate the very tenets at the foundation of the U.S. patent system. Here, Amgen seeks this Court's endorsement of such violation through an exception, solely applicable to antibodies, that would exempt purely functional

[63] It is notable that the claims do not recite this "roadmap", nor are they limited to antibodies identified from the "roadmap."

antibody genus claims from the requirement that members of the claimed genus be ***recognizable*** or ***visualizable*** "sufficient to distinguish them from unclaimed materials."

This case provides this Court an opportunity to make clear that the disclosure requirements of §112, and this Court's precedent related thereto, apply in a technology-neutral manner. Lilly requests this Court affirm the invalidity of Amgen's claims as lacking enablement ***and*** make clear that, until such time as this wholly unpredictable field becomes predictable, purely functional antibody claims are *per se* invalid as lacking sufficient written description. Without clarity from this Court, antibody innovators will continue to face uncertainty and risk from purely functional antibody claims, like Amgen's, that preempt the use of biological targets in antibody research and development and thereby limit treatment options available to patients and the doctors who treat them.

CERTIFICATE OF COMPLIANCE WITH RULE 32

1. I certify that this brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B). According to the word-processing system used to prepare it, this brief contains 6,248 words, excluding the parts exempted by Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b).

2. I certify that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) by using Microsoft Office Word in Times New Roman 14 point font.

Date: June 8, 2020

Respectfully submitted,

/s/ Duane C. Marks
Duane C. Marks

CERTIFICATE OF SERVICE

I hereby certify that on June 8, 2020, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the CM/ECF system. I certify that all participants in this case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

Date: June 8, 2020

/s/ Duane C. Marks
Duane C. Marks