

ANTIBODY CLAIMS AND THE EVOLUTION OF THE WRITTEN DESCRIPTION/ENABLEMENT REQUIREMENT*

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ABSTRACT

Biologic patents are the basis of some of the most valuable technologies in the pharmaceutical industry. Biologic patents include patents to vaccines, antibodies, as well as gene therapy, and isolated blood products. This study focuses on the changing nature of a key biologic product, namely antibody patents.

Antibody technology has dramatically advanced in the past few decades. Initially, antibodies were only used as research and diagnostic tools. Currently, however, antibodies have been transformed into powerful therapeutic agents used to treat a panoply of diseases. Correspondingly, the scope of antibody patents has also changed as the technology has also developed.

In the early stages of development, antibody claims were granted broad scope, being defined only by the

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antigens that they were bound to. Currently, antibody patents have been granted a very narrow scope. The Federal Circuit and the PTO have used the written description and enablement requirements to narrow the scope of antibody patents, which mirrors the dramatic changes in antibody technology. This article outlines the changes in both Federal Circuit caselaw as well as PTO policy when it comes to antibody biologic products.

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INTRODUCTION

Biologics (i.e., biological products) are pharmaceutical products manufactured in, extracted from, or semisynthesized from biological sources, including “vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and,” perhaps the most important way, “recombinant therapeutic proteins.”¹ The enormous success of COVID-19 vaccines has thrust biologics to the forefront of biotechnology law. Antibody technologies represent an important subset of biologic products.

Monoclonal antibodies form the basis for some of the most valuable drugs in the world. In 2021, the forecasted sales for the top 10 drugs included five antibody products with an estimated revenue of \$62.864 billion.² As biologics overtake small molecules as the world’s most valuable drugs, patents on antibodies have taken on an increasingly important role for drug companies, patients, and the medical insurance companies and consumers who foot the bill.

Antibody patents have evolved dramatically from the early 2000s to the present, particularly with respect to claim scope. Previously, antibody patents were granted broad genus type protection defined solely in terms of antigen specificity, encompassing any antibody having specificity for an antigen, e.g., a protein.³ Currently,

¹ *What are “Biologics” Questions and Answers*, FDA (February 6, 2018), <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers> [<https://perma.cc/BVL8-CSEQ>].

² Lisa Urquhart, *Top Product Forecasts for 2021*, 20 NATURE REVS. DRUG DISCOVERY 10, 10 (2021).

³ S. Sean Tu & Christopher M. Holman, *Antibody Patents: Use of the Written Description and Enablement Requirements at the Patent & Trademark Office*, 38 BERKELEY TECH. L.J. 102 (forthcoming 2023).

however, antibody patent claims are generally much narrower, reciting antibodies defined in terms of structure, often by the amino acid sequences of the antibodies complementarity-determining regions (CDRs), which dictate the antibody's binding specificity.

This narrowing of scope has been proven by courts who are now apt to invalidate claims with broad scope through patent law's written description or enablement requirements. For example, in August of 2021, the Federal Circuit invalidated a \$1.1 billion jury verdict on a biotechnology patent based on antibody type technology as being too broad, thereby failing to meet the written description requirement.⁴ Similarly, in February of 2021 the Federal Circuit invalidated a set of patents for lack of enablement.⁵

Many other commentators have written generally about this shift in claim scope.⁶ Still, other commentators have focused on the application of these rules to biotechnology patents.⁷ This article, however, focuses on

⁴ *Juno Therapeutics, Inc. v. Kite Pharm., Inc.*, 10 F.4th 1330, 1334 (Fed. Cir. 2021).

⁵ *Amgen Inc. v. Sanofi, Aventisub L.L.C.*, 987 F.3d 1080, 1088 (Fed. Cir. 2021); *see also Amgen Reports Second Quarter 2021 Financial Results*, AMGEN (Aug. 3, 2021), <https://www.amgen.com/newsroom/press-releases/2021/08/amgen-reports-second-quarter-2021-financial-results> [<https://perma.cc/2BXU-7XV8>] (showing that Repatha helped fuel Amgen's \$6.5 billion second quarter revenues).

⁶ John R. Allison & Lisa L. Ouellette, *How Courts Adjudicate Patent Definiteness and Disclosure*, 65 DUKE L.J. 609, 612 (2016); Dmitry Karstedt, Mark A. Lemley & Sean B. Seymore, *The Death of the Genus Claim*, 35 HARV. J.L. & TECH. 1, 23 (2021, in press).

⁷ Jacob S. Sherkow, *Describing Drugs: A Response to Professors Allison and Ouellette*, 65 DUKE L.J. ONLINE 127, 127 (2016); Dan L. Burk & Mark A. Lemley, *Biotechnology's Uncertainty Principle*, 54 CASE W. RES. L. REV. 691, 705, 739–40 (2004); Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1, 4 (2007) [hereinafter

how the written description and enablement requirements have evolved over time when applied specifically to antibody claims.⁸

This article concentrates on antibody composition of matter claims,⁹ antibody method of use claims,¹⁰ and antibody diagnostic claims.¹¹ Part I describes the evolution of antibody technology. Additionally, Part I describes the

Holman, *Lilly Written Description*]; Christopher M. Holman, *Enablement Invoked as a “Super-Written Description Requirement” to Overturn \$2.5 Billion Jury Verdict*, 37 BIOTECH. L. REP. 63, 65 (2018) [hereinafter Holman, *Enablement Invoked*]; Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 BERKELEY TECH. L.J. 615, 633–34 (1998); Harris A. Pitlick, *The Mutation on the Description Requirement Gene*, 80 J. PAT. & TRADEMARK OFF. SOC’Y 209, 218 (1998); Michael Delmas Plimier, *Genetech, Inc. v. Novo Nordisk & University of California v. Eli Lilly and Co.*, 13 BERKELEY TECH. L.J. 149, 154 (1998); Margaret Sampson, *The Evolution of the Enablement and Written Description Requirements Under 35 U.S.C. § 112 in the Area of Biotechnology*, 15 BERKELEY TECH. L.J. 1233, 1248 (2000).

⁸ Tu & Holman, *supra* note 3; Mark A. Lemley & Jacob S. Sherkow, *The Antibody Patent Paradox*, YALE L.J. (forthcoming 2022); Christopher M. Holman, *For Monoclonal Antibodies, Compliance with the Written Description Requirement Has Become a Moving Target*, 36 BIOTECH. L. REP. 273, 274–75 (2017); James J. Kelley & Gregory A. Cox, *The “Anti”-Written Description Requirement? Antibodies, Examples 16, the Guidelines and Noelle v. Lederman*, 87 J. PAT. & TRADEMARK OFF. SOC’Y 705, 706–07 (2005); Kazunori Hashimoto & Tomomi Aida, *Antibody Patenting Without Antibodies: A Global Trend*, 26 NATURE BIOTECH. 1341, 1342 (2008).

⁹ Composition of matter claims are directed towards the antibody itself. These claims can include the antibody, antibody fragments, pharmaceutical compositions, conjugates and fusion proteins in which antibodies or antibody fragments are combined with other molecules.

¹⁰ Method of use claims usually recite to a method of treating an illness comprising administration of a therapeutically effective amount of antibody to a patient suffering from a specific illness.

¹¹ Diagnostic claims are directed towards the use of antibodies to bind and detect the presence or absence of disease-associated antigens in patients.

legal framework for the written description and enablement requirements. Part II examines the evolution of the written description and enablement requirements for biotechnology patents, focusing on antibody technology. Parts III to VI describe the specific evolution of antibody technology and the corresponding changes to 35 U.S.C. § 112(a) jurisprudence as applied to antibody patents.

I. BACKGROUND

The evolution of antibody patents dramatically shifted from the early 2000s to the present. Previously, antibody patents were granted broad genus type protection.¹² Currently, however, antibody patents usually cover narrow specific antibodies that have well-defined structures, especially when it comes to the structural elements that define the specific binding regions of the antibody.

This narrowing in claim scope began years ago at the PTO, and more recently, the courts have followed suit by invalidating antibody claims with a broad scope. For example, the Federal Circuit recently invalidated patent claims directed towards chimeric antigen receptor T-cell (CAR-T) therapy, a monoclonal antibody-based technology, for failure to satisfy the written description requirement due to overbreadth, wiping out a \$1.1 billion jury verdict.¹³

This section gives a primer on the development of antibody technology. Additionally, this section sets forth

¹² Tu & Holman, *supra* note 3.

¹³ *Juno Therapeutics, Inc. v. Kite Pharm., Inc.*, 10 F.4th 1330, 1334 (Fed. Cir. 2021); *see also* Christopher M. Holman, *In Juno v. Kite the Federal Circuit Strikes Down Patent Directed Towards Pioneering Innovation in CAR T-Cell Therapy*, 40 BIOTECH. L. REP. 372, 372 (2021).

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the basic framework for patent law's written description and enablement requirements.

A. *Antibody Technology*

Antibodies, or immunoglobulins (Igs), are part of the immune system that can identify and neutralize foreign objects, such as pathogens and toxins. Antibodies are Y-shaped, and the tips of each of the Y structures contain six CDRs that gives each individual antibody its remarkable specificity (each antibody specifically recognizes and binds a single epitope on an antigen).

Antibodies serve to identify foreign particles, broadly referred to as antigens, for destruction by other components of the immune system. Antigens can be broadly defined as any substance that can cause an immune system to produce antibodies against it. Antigens can include substances from the environment, for example, chemicals, bacteria, viruses, or pollen, and in some cases, antigens can even form inside the body.

A more in-depth description of antibody technology can be found in Appendix 1.

**B. *35 U.S.C. § 112(a)- Patent Law's Written
Description and Enablement Requirement***

§ 112(a) of the Patent Act serves as the basis for both the written description and enablement requirements. § 112(a) requires that:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set

forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.¹⁴

The written description requirement is a question of fact that is satisfied when the patent specification “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.”¹⁵ Generally, the written description requirement of a genus claim is met by “either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.”¹⁶

Written description issues commonly arise under two circumstances: (1) when the inventor amends his claims and adds elements not described in the original patent application; and (2) when the claims are too broad.¹⁷ When the claims are too broad, the written description analysis greatly overlaps with the enablement analysis.¹⁸

The enablement requirement is one of the most important elements required for an adequate disclosure under § 112. An enabling disclosure is the “quid pro quo of the right to exclude.”¹⁹ Enablement is a question of law that is satisfied when the patent enables one of skill in the

¹⁴ 35 U.S.C. § 112(a). We note that ¶ 1 of 35 U.S.C. § 112 was replaced by § 4(c) of the Leahy-Smith America Invents Act (AIA), Pub.L 112-29, § 4(c), 125 Stat. 284, 296–97 (2011). We refer to both sections 112(a) and 112, first paragraph as “112(a).”

¹⁵ *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

¹⁶ *Id.* at 1350.

¹⁷ ROBERT MERGES & JOHN DUFFY, *PATENT LAW AND POLICY: CASES AND MATERIALS* 462 (8th ed. 2021).

¹⁸ *Id.*

¹⁹ *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int’l, Inc.*, 534 U.S. 124, 142 (2001).

art to make and use the claimed invention without engaging in undue experimentation.²⁰

To meet the enablement requirement, an applicant must “teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.”²¹ Although it is not necessary to disclose every species within a genus, there “must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed.”²²

Both requirements are used by the courts and PTO to police claim scope. The Federal Circuit described the relationship between these two requirements in *Regents of the University of California v. Eli Lilly & Co.*²³ In *Lilly*, the court stated that a disclosure that only describes complementary DNA (cDNA) to rat insulin could not be used to claim human insulin cDNA.²⁴ The court described the relationship between the written description and enablement requirement, stating:

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by a nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion

²⁰ *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984); *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988).

²¹ *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997); *see also In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) (“[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.”).

²² *In re Vaeck*, 947 F.2d at 496.

²³ *See Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

²⁴ *Id.*

of the genus. This is analogous to enablement of a genus under § 112, ¶ 1, by showing the enablement of a representative number of species within the genus.²⁵

The Federal Circuit has held that the written description and enablement requirements are separate and distinct.²⁶ Both doctrines serve a quid pro quo function in which the inventor gives a meaningful disclosure of the invention in exchange for the right of exclusion from practicing the invention for a limited period of time. Both doctrines are applied by the Federal Circuit to strike down patent claims reciting monoclonal antibodies for overbreadth.²⁷

Allison and Ouellette previously reported that the written description requirement is usually applied in a technologically independent manner.²⁸ However, they found one notable exception: non-ANDA pharmaceuticals,²⁹ a category that includes therapeutic antibodies which have fared poorly in written description challenges.³⁰ This article, in part, attempts to expand on

²⁵ *Id.*

²⁶ *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1341–42 (Fed. Cir. 2010) (en banc) (showing that § 112 contains both a written description and enablement requirement that are separate and distinct); *Vas-Cath Inc. v. Mahukar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

²⁷ *See AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1305 (Fed. Cir. 2014) (written description); *Amgen Inc. v. Sanofi, Aventisub L.L.C.*, 987 F.3d 1080, 1088 (Fed. Cir. 2021) (enablement).

²⁸ Allison & Ouellette, *supra* note 6, at 666.

²⁹ Abbreviated New Drug Application (ANDA) patents are usually directed to small molecule drugs. Non-ANDA patents include a variety of biologic compounds such as antibodies. *Id.* at 639–40; *see also Sherkow*, *supra* note 7, at 127.

³⁰ Allison & Ouellette, *supra* note 6, at 668 (showing that most patents across industry groups do not differ significantly in their performance in the face of § 112 assaults, but non-ANDA

the Allison and Ouellette findings by focusing specifically on how the written description and enablement requirements have applied to antibody patents. This article also breaks down the Federal Circuit cases based on time to show the evolution of the written description and enablement requirements as applied to monoclonal antibody claims.

Although the Federal Circuit has specifically stated that the enablement and written description requirements are separate and distinct, in many ways, the requirements function similarly.³¹ Additionally, patent examiners will frequently reject applications based on § 112(a) and will often confuse written description and enablement rationales.³²

II. EVOLUTION OF THE APPLICATION 35 U.S.C. §112(A) TO ANTIBODY PATENTS

The law almost always struggles to keep up with changes in technology. Antibody technology is no different. As antibody technology evolved, so too did the

pharmaceutical patents had weak outcomes on both written description and definiteness.); *see also* Sherkow, *supra* note 7, at 129–30 (describing some of the differences between ANDA and non-ANDA patent litigations).

³¹ *Ariad*, 598 F.3d at 1341 (showing that the written description requirement is distinct from the enablement requirement); *cf.* *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 978, 982 (2002) (Rader, Linn, and Gajarsa, JJ., dissenting). Judges Rader, Linn and Gajarsa argue that “[b]efore 1967 . . . [the court] did not differentiate written description from enablement” and that in 1981 the CCPA noted that “the two rejections were interchangeable.” *Id.* They further argue that the written description requirement has only been separated from the enablement requirement since 1967 and has “operated solely to police priority . . . [and applied only] within the limits of its origin as an ‘equivalent’ or ‘corollary’ of 35 U.S.C. § 132, the new matter section.” *Id.*

³² Tu & Holman, *supra* note 3.

legal framework used to analyze antibody claims. Specifically, as antibody technology advanced, courts increasingly used the written description and enablement requirements to invalidate broad genus type antibody claims. As antibody technology matured from research and diagnostic tools to therapeutic medicines, courts and the PTO sought to narrow the scope of antibody claims to (1) better reflect that which the inventor disclosed and (2) prevent any one firm from hindering the development of antibodies.³³ Thus, narrowing the scope of antibody patents allowed competitors to develop their own antibodies by “designing around” already patented antibodies.³⁴

However, as antibody technology moved from diagnostic tools towards therapeutic uses that depended on specific binding sites, so too have patent claims moved from broad genus claims to narrow species claims.³⁵ The next sections describe the evolution of the written description and enablement requirements that created the current legal standard for antibody patents.³⁶

III. STAGE 1- BROAD ANTIBODY CLAIMS BASED ON ANTIGEN ALONE

In the first stage, antibody patent claims were given broad scope and based only on the antigen structure. The second stage was characterized by a doctrine of antibody exceptionalism. Specifically, antibodies did not require

³³ *Id.*

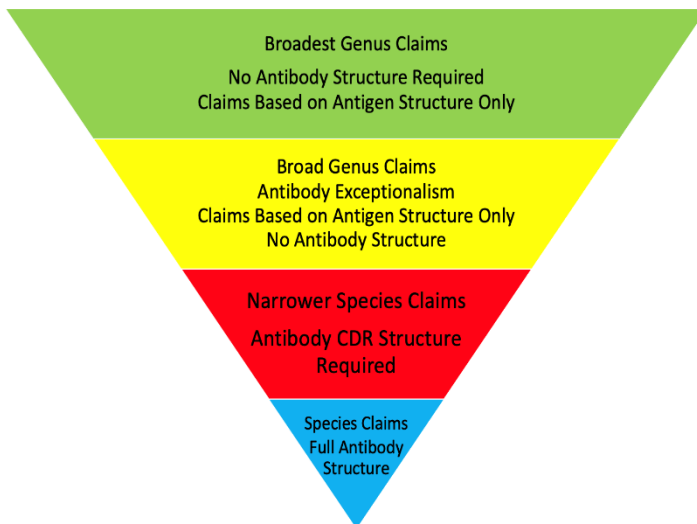
³⁴ *Id.*

³⁵ *See id.*

³⁶ Jeffrey A. Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 BERKELEY TECH. L.J. 1141, 1168, 1170 (2008) (“All patent claims are of infinite scope . . . there is no such thing as a “species” claim, for claims are never restricted to a single physical entity. Insofar as both genus and species are abstractions, the difference between the two is less in kind and more in degree.”).

recitation to structural elements. In contrast to most other areas of biotechnology, the claims required references to specific structural elements to receive a patent. The Federal Circuit then slowly pulled back from this antibody exceptionalism as antibody technology advanced. In the third stage, the courts and the PTO rejected antibody exceptionalism and now require that the antibody be structurally defined before receiving a patent. We believe that, in the future, courts and the PTO will require even more structural elements as antibody technology moves from murine to chimeric, humanized, and single-chain fragment variable (scFv) antibodies.

Figure 1



This early stage corresponds with the time when antibodies were only used for research or diagnostic tools.³⁷ The only functional requirement for an antibody that is used in an immunoassay for diagnostic purposes is for the antibody to bind specifically to the antigen. The epitope to which it binds generally did not matter for these tools. Many successful immunoassay products were developed by purifying an antigen (e.g. protein) and producing a monoclonal antibody to it using hybridoma technology.³⁸

A. *Antibodies Used for Immunoassays and Diagnostic Tools*

During this time period antibodies were mainly used as diagnostic tools. Antibodies were only used to determine if an antigen was present or absent. It did not matter where the antibody bound, i.e., what the specific epitope was, nor the type of antibody; it only mattered if the antibody bound the antigen or did not bind to the antigen.

This binary decision (binding vs. not binding) was consistent with broad patent protection based on antigen structure alone because during this time period, the value of the antibody rested primarily in the antibody's ability to bind and detect the antigen.³⁹ Accordingly, during this early phase in monoclonal antibody development, an applicant could receive a patent by simply characterizing the antigen (without giving any structural elements of the antibody itself).⁴⁰

³⁷ Tu & Holman, *supra* note 3.

³⁸ See Alan H.B. Wu, *A Selected History and Future of Immunoassay Development and Applications in Clinical Chemistry*, 369 CLINICA CHIMICA ACTA 119, 12021 (2006).

³⁹ Tu & Holman, *supra* note 3, Figure 1.

⁴⁰ *Id.*

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These genus claims did not define the antibody structurally but instead by the antigen that the antibody could bind to specifically.⁴¹ The patentee was only required to disclose the antigen's structure.⁴² The resulting broad scope of antibody claims made sense during this period of antibody development because antibodies were only being used as research or diagnostic tools.⁴³

Example 1

A typical claim from this timeframe can be seen in US Patent No. 7,459,539 where claim 1 reads:

An isolated monoclonal antibody or antibody fragment that specifically binds to a protein having an amino acid sequence of SEQ ID NO: 2570. [Where SEQ ID NO: 2570 is a protein that is 429 amino acids long.]⁴⁴

This claim does not provide any antibody structure and the antibody is defined only by its ability to bind a zinc transporter protein (SEQ ID NO: 2570) which is present in certain types of cancers.⁴⁵ This is a typical broad claim that describes the antibody in a functional manner. Specifically, the antibody is defined only by its ability to bind to a specific antigen.

⁴¹ Tu & Holman, *supra* note 3.

⁴² *Id.*

⁴³ *Id.*

⁴⁴ U.S. Patent No. 7,459,539 col 891-894 (issued Dec. 02, 2008); *see also* Yujin E. Kim, Mark S. Hipp, Andreas Bracher, Manajit Hayer-Hartl, & F. Ulrich Hartl, *Molecular Chaperone Functions in Protein Folding and Proteostasis*, 82 ANN. REV. BIOCHEMISTRY 323, 326 (2013) (stating that the average size of proteins is about 52 kDa in humans.)

⁴⁵ U.S. Patent No. 7,459,539 (issued Dec. 02, 2008).

B. *Earliest Antibody Cases*

In 1986 Judge Rich wrote the opinion in one of the Federal Circuit’s earliest cases involving an antibody patent, *Hybritech Inc. v. Monoclonal Antibodies, Inc.*⁴⁶ In *Hybritech*, the court held that all claims in the US 4,376,110 patent (‘110 patent) were valid.⁴⁷ The broadest claim in the ‘110 patent includes a Jepson claim (claim 19) directed to an immunometric assay:

19. In an immunometric assay to determine the presence or concentration of an antigenic substance in a sample of a fluid comprising forming a ternary complex of a first labelled antibody, said antigenic substance, and a second antibody said second antibody being bound to a solid carrier insoluble in said fluid wherein the presence of the antigenic substance in the samples is determined by measuring either the amount of labelled antibody bound to the solid carrier or the amount of unreacted labelled antibody, the improvement comprising *employing monoclonal antibodies having an affinity for the antigenic substance* of at least about 10^8 liters/mole for each of said labelled antibody and said antibody bound to a sold carrier.⁴⁸

In holding that the claims in the ‘110 patent were enabled, the court stated that there was “not a shred of evidence that undue experimentation was required by those skilled in the art to practice the invention.”⁴⁹ Because the method for producing monoclonal antibodies was well known in the prior art, and screening methods were also

⁴⁶ *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986).

⁴⁷ *Id.*

⁴⁸ U.S. Patent No. 4,376,110 (issued Mar. 8, 1983) (emphasis added).

⁴⁹ *Hybritech*, 802 F.2d at 1384.

routine and well known, the court held that the '110 patent contained an enabling disclosure.⁵⁰

Similarly, in the 1998 decision *In re Wands*, the court reviewed an antibody patent directed towards an immunoassay to detect hepatitis B.⁵¹ The broadest claim recites:

1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of: contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and determining the presence of said substance in said sample; wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1} .⁵²

The *Wands* court held that there was no undue experimentation needed to generate antibodies having the necessary binding affinity constant for HBsAg.⁵³ The court found that the creation of cell fusions used to make hybridoma cells was a routine and conventional practice, and the amount of effort required for the production of these antibodies was not excessive.⁵⁴

Significantly, both the *Hybritech* and *Wands* patents were directed towards method claims and not product claims.⁵⁵ Additionally, the language of the method claims was limited to immunoassays so that the policy would

⁵⁰ *Id.*

⁵¹ *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988) (reviewing US application No 06/188,735 later maturing to US 4,879,219).

⁵² U.S. Patent No. 4,879,219 (issued Nov. 7, 1989).

⁵³ *In re Wands*, 858 F.2d at 740.

⁵⁴ *Id.*

⁵⁵ U.S. Patent No. 4,376,110; U.S. Patent No. 4,879,219.

support a finding of granting broad genus claims for these monoclonal antibodies.⁵⁶

Neither *Hybritech* nor *Wands* directly addresses the question of claim scope. Each case deals with the enablement requirement, and more specifically, the amount of experimentation that would be necessary to generate the antibody. In both cases the court held that undue experimentation would not be required to practice either invention.⁵⁷ Both *Hybritech* and *Wands* illustrate that, during this early time period, antibody claims were broad and usually based only on antigen structure. Additionally, these cases rest on the idea that one of skill in the art, and in possession of the antigen, could, without engaging in undue experimentation, easily generate the recited genus of antibodies.⁵⁸

IV. STAGE 2- ANTIBODY EXCEPTIONALISM: PULL BACK FROM BROAD GENUS CLAIMS FOR DNA, BUT AFFIRMATION OF BROAD GENUS CLAIMS FOR ANTIBODIES

During this time period, even though courts prevented broad genus claims directed towards the more advanced DNA field, they initially seemed to endorse an exception for antibody claims. Courts most likely did so because they did not want to disrupt the previous rules created for antibodies, thereby maintaining the status quo. Additionally, courts most likely did not want to disrupt this new technology, especially in light of the significant negative side effects and failures associated with

⁵⁶ *See id.*

⁵⁷ *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988).

⁵⁸ *See Hybritech*, 802 F.2d at 1384; *In re Wands*, 858 F.2d at 740.

monoclonal antibodies used for therapeutics. Because courts and the PTO still endorsed a standard that would allow broad genus claims for antibodies, claims like Example 1, shown above, were still representative of claims during this time period.

A. *Advances in Antibody Technology*

Monoclonal antibody technology in this time period moved from immunoassays to therapeutics. Antibodies were now being used as pharmaceuticals to target specific areas of antigens with functional outcomes such as neutralization, inhibition of infectivity, interference with pathogen attachment, and inhibition of protein functions.⁵⁹

The binding specificity of these antibodies, which is dictated by the structure of their binding regions, was crucial because some epitopes on the antigen could result in a functional outcome while others did not. For example, antibody X might bind to epitope 1 of antigen A without neutralizing antigen A, while antibody Y might bind to epitope 2 of antigen A and thereby neutralize antigen A. Therefore, knowledge of the structure of antigen A alone might not be sufficient for a researcher to develop a neutralizing antibody, and disclosure of a non-neutralizing antibody capable of recognizing antigen A would not necessarily enable one of skill in the art to make a neutralizing antibody without engaging in undue experimentation.

However, antibodies during this period suffered from a critical flaw. Monoclonal antibodies during this period were derived from mouse (murine) hybridoma cell

⁵⁹ Donald N. Forthal, *Functions of Antibodies*, MICROBIOLOGY SPECTRUM, Aug. 15, 2014, at 1, 1.

lines.⁶⁰ The human body recognized these murine antibodies as foreign and would reject them.⁶¹ This human anti-mouse antibody (HAMA) response compromised the efficiency of antibody treatment when murine antibodies were administered to human patients.⁶² Accordingly, these early therapeutics suffered major setbacks at the FDA and often times did not work well as human medicines.

For example, in 1986, OKT-3 (muromonab-CD3) became the first murine monoclonal antibody to be approved by the FDA.⁶³ OKT-3 was approved for use to prevent kidney transplant rejection.⁶⁴ Unfortunately, there were major, sometimes fatal, side effects associated with the use of the murine antibody including pulmonary edema, hemodynamic instability, shock, respiratory arrest and cardiac arrest.⁶⁵ Subsequently, OKT-3 was pulled from the market due to these side-effects.⁶⁶ The FDA approved the second monoclonal antibody therapeutic in 1994 after eight years of failure with this type of technology, but notably this was chimeric monoclonal antibody, not a murine antibody, the significance of which is discussed below.⁶⁷

⁶⁰ Justin K.H. Liu, *The History of Monoclonal Antibody Development- Progress, Remaining Challenges, and Future Innovations*, 3 ANNALS MED. & SURGERY 113, 114 (2014).

⁶¹ *Id.*

⁶² *Id.*

⁶³ *Id.*

⁶⁴ *Id.*

⁶⁵ C. Sgro, *Side-Effects of a Monoclonal Antibody, Muromonab CD3/ Orthoclone OKT3: Bibliographic Review*, 105 TOXICOLOGY 23, 25–26 (1995).

⁶⁶ Nadim Mahmud, Dusko Klipa & Nasimul Ahsan, *Antibody Immunosuppressive Therapy in Solid-Organ Transplant*, 2 MABS 148, 151 (2010) (showing that OKT3’s “adverse effects proved to be consistently problematic.”).

⁶⁷ See ABCIXIMAB, <https://abciximab.com/> [<https://perma.cc/8M79-2A6E>] (last visited December 28, 2021). FDA approved in 1994, Abciximab is a chimeric human-murine monoclonal antibody that inhibits platelet aggregation by binding to the glycoprotein IIb/IIIa

B. Early 112(a) Cases Preventing Broad Genus Claims to DNA Technology

In the 1997 case, *Regents of Univ. of Cal. v. Eli Lilly & Co.*, the Federal Circuit imposed a new form of the written description requirement that emphasized the disclosure of structural elements.⁶⁸ Although *Lilly* deals with recombinant DNA technology, the holding was not limited to recombinant DNA, and could have been interpreted broadly to also encompass antibody technology.⁶⁹

The *Lilly* court stated:

[The claim] does not define any structural features commonly possessed by members of the genus that distinguish them from others . . . [a] definition by function . . . 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 . . . [a]ccordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.⁷⁰

Lilly's focus on disclosure of structural features would, on its face, seem to dramatically narrow antibody claims by requiring the recitation of antibody structures. However, the PTO and later court decisions seemed to exempt antibody claims from the *Lilly* requirement.

receptor (integrin alpha-IIbeta-3) which is expressed on the surface of human platelets. *Id.*

⁶⁸ *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997) (citation omitted); see also Holman, *Lilly Written Description*, *supra* note 7, at 14.

⁶⁹ See *Lilly*, 119 F.3d at 1568–69.

⁷⁰ *Id.* at 1568.

C. *Antibody Exceptionalism at the PTO*

The PTO responded to *Lilly* by narrowly interpreting *Lilly* to exclude antibodies.⁷¹ Although the PTO interpreted *Lilly* broadly to significantly limit the scope genus claims to polynucleotides and proteins in general, it made a specific exception for antibodies in its Synopsis of Application of Written Description Guidelines.⁷² These guidelines included an example involving an isolated antibody (Example 16).⁷³ The PTO removed these guidelines from its website and replaced them with a revised version, but the March 2008 USPTO Written Description Training Materials Revision 1 retained the antibody example, renumbered as Example 13.⁷⁴

In Example 13 of the 2008 Written Description Training Materials the PTO considered a claim directed to “An isolated antibody capable of binding to antigen X.” In this example, the PTO assumes that the specification *does not describe*: (1) an actual reduction to practice of an antibody that binds to antigen X, (2) a partial structure of the claimed antibody, or (3) any physical or chemical properties of the claimed antibody.⁷⁵ The specification does, however, disclose that a protein designated antigen X has been isolated and discloses its amino acid sequence.⁷⁶

⁷¹ See U.S.P.T.O., WRITTEN DESCRIPTION TRAINING MATERIALS 1 (2008), <https://www.uspto.gov/sites/default/files/web/menu/written.pdf> [<https://perma.cc/M7ZU-EC8X>]; see also Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, “Written Description” Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001) [hereinafter *Guidelines*].

⁷² Holman, *Lilly Written Description*, *supra* note 7, at 44–45.

⁷³ *Id.* at 65.

⁷⁴ See Kaitlyn Taylor, *The Patentability of Antibodies for Use in Medications After Amgen v. Sanofi*, 6 U. CIN. INTELL. PROP. & COMPUT. L.J. 1, 11 (2020); see also U.S.P.T.O., *supra* note 71.

⁷⁵ See U.S.P.T.O., *supra* note 71, at 45.

⁷⁶ *Id.*

The PTO concluded that the claim was in compliance with the written description requirement based on “the fact that antibody technology was well developed and mature” and “the routine art-recognized method of making antigen-specific antibodies.”⁷⁷ This interpretation of *Lilly* purports to allow broad genus level protection to antibodies based solely on the disclosure of a newly characterized antigen. Significantly, the Guidelines say nothing about the claim’s compliance with the enablement requirement.⁷⁸

Why did the PTO in its Guidelines decide to exempt antibodies from the *Lilly* written description requirement? Unfortunately, the PTO’s official explanation in the Guidelines does not really hold up to scrutiny, but we think there is a quite plausible explanation based on Federal Circuit precedent, innovation policy, and the nature of how monoclonal antibodies were made and used in the early years of monoclonal antibody patenting.

As described in Section III(B) above, in *Wands* the Federal Circuit reversed the PTO’s rejection of a patent claim specifically because the Board found that the applicant had failed to enable a genus of monoclonal antibodies defined in terms of function, i.e., a high affinity for hepatitis B-surface antigen.⁷⁹ In *Hybritech*, the Federal Circuit held that a claim reciting “monoclonal antibodies having an affinity for [an] antigenic substance of at least about 10⁸ liters/mole” was enabled “as a matter of law.”⁸⁰

Hybritech and *Wands* both involved process claims, but the PTO could have applied the same rule to product claims. At the time *Lilly* was decided the PTO was routinely allowing product claims reciting monoclonal antibodies defined in broad, functional terms, as discussed

⁷⁷ *Id.* at 45–46.

⁷⁸ *See id.*

⁷⁹ *See supra* notes 51–54 and accompanying text.

⁸⁰ *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384–85 (Fed. Cir. 1986).

in Section II(A).⁸¹ A literal application of *Lilly*, and its requirement of structural disclosure, to monoclonal antibody claims would have basically withdrawn from inventors the claim scope for monoclonal antibodies that *Wands* appeared to support. In the Guidelines the PTO appears to be digging in its heels and refusing to invalidate claims under *Lilly*'s new interpretation of the written description requirement that the PTO had already found to be valid under the long-established doctrine for policing claim scope, the enablement requirement.

1. Innovation Policy as a Rationale for Antibody Exceptionalism

The rationale for the PTO's antibody exceptionalism can be supported on scientific grounds. Broad claim scope was justified in the early days of monoclonal antibody patenting because the predominant use of monoclonal antibodies was for the detection of antigens and for research/diagnostic purposes. As described above, the value of an antibody in these early stages of antibody technology was linked only to the antibody's ability to recognize a particular antigen with a sufficient degree of specificity. It did not matter where the binding occurs on the antigen, i.e., the particular epitope that is bound, and the chemical nature of the antibody was also irrelevant.

During this early period of antibody technology, antibody patents would be nearly worthless if they were limited to narrow claims covering only the disclosed antibodies and close structural analogs. This is because the value of the antibody patent during this time period was based only on its ability to bind the antigen. By granting broad patents, and thereby preventing competitors from making minor alterations to avoid the patent, the PTO and courts protected the value of this nascent technology.

⁸¹ Tu & Holman, *supra* note 3.

2. Antibody Manufacturing Techniques as a Rationale for Antibody Exceptionalism

Another rationale for antibody exceptionalism is found in the method in which monoclonal antibodies were made in the early days of monoclonal antibody patenting. Modern biotechnology was really kicked off by two groundbreaking innovations: (1) recombinant DNA technology for the production of recombinant nucleic acids and proteins, and (2) hybridoma technology for producing monoclonal antibodies.

With the exception of monoclonal antibodies, most commercially significant nucleic acids and proteins discovered and patented in the early days of biotechnology were the product of recombinant DNA technology, and it was generally very easy to determine the chemical structure of the nucleic acid or protein owing to the ease with which DNA could be sequenced.⁸² In fact, determining the amino acid or nucleic acid sequence of a recombinant protein or DNA is generally inherent in the process of “isolating” the molecule, and so an inventor seeking patent protection for recombinant proteins or nucleic acids would generally have the sequence data available when applying for a patent. As a result, disclosure of the chemical sequence of most new proteins or nucleic acids which patent protection is sought is generally easy, and applicants do so using the prescribed “SEQ ID NO:” format. Note that in the PTO’s Guidelines all of the protein or nucleic acid examples, except for the antibody examples, involve a scenario in which the applicant has defined the biomolecule’s structure by means

⁸² Recombinant proteins are produced by the expression of this corresponding recombinant DNA sequence, i.e., the “gene,” and the amino acid sequence of a recombinant protein is determined by sequencing the DNA and translating that into the amino acid sequence, rather than sequencing the protein directly, which would be difficult if not impossible as a practical matter.

of a SEQ ID NO.⁸³ Accordingly, the patentees of most protein/DNA inventions were able to describe the invention by using structural elements, by disclosing a SEQ ID NO.

Unlike most biotechnology inventions of the time, monoclonal antibody technology was produced using hybridoma cells and not recombinant DNA. Specifically, scientists did not know the sequence of the hybridoma DNA molecules encoding the antibody. In fact, during this time period, it was extremely difficult, if not impossible, to determine the amino acid sequence of the antibody directly. In order to make more antibodies, scientists needed to have access to the hybridoma cell line that corresponded to the antibody. Patent applicants enabled others to make and use the antibody by making the cell line publicly accessible by depositing the cell line to an international depository authority.⁸⁴ Accordingly, during this time period, the patentee of antibody technology could not describe the antibody using structural elements.

D. Antibody Exceptionalism at the Federal Circuit

In 2002 the Federal Circuit endorsed the PTO's Guidelines in *Enzo Biochem*, particularly noting that the PTO "would find compliance with 112, 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody."⁸⁵ The court's discussion of the antibody example should be considered pure dicta, however, given

⁸³ See U.S.P.T.O., *supra* note 71, at 13–28, 31–54.

⁸⁴ Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure, Apr. 28, 1977, 32 UST 1241, TIAS 9768; *see also* U.S.P.T.O., *Budapest Treaty*, <https://www.uspto.gov/ip-policy/patent-policy/budapest-treaty> [<https://perma.cc/7SUM-UAJK>] (last visited February 28, 2022).

⁸⁵ *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002).

that there was no antibody, or even a protein at issue in the case; instead, the claims were directed towards nucleic acids.⁸⁶

In *Noelle v. Lederman*, decided in 2004, the Federal Circuit cited the above-quoted language from *Enzo Biochem* for the proposition that

based on our past precedent, as long as an applicant has disclosed a ‘fully characterized antigen,’ either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.⁸⁷

As was the case in *Enzo Biochem*, this statement regarding the application of the written description requirement to a genus of monoclonal antibodies was pure dicta, given that in *Noelle* all of the monoclonal antibody claims at issue were found to be invalid for failure to satisfy the written district requirement.⁸⁸

E. The Federal Circuit Slowly Pulls Back from Antibody Exceptionalism

In *Chiron v. Genetech*, the Federal Circuit hinted that there might be a shift in its antibody jurisprudence.⁸⁹ In *Chiron*, the Federal Circuit invalidated a functional antibody claim that was defined only by its antigen.⁹⁰ The alleged infringing product was a *chimeric* antibody which

⁸⁶ *See id.* at 960–61.

⁸⁷ *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004).

⁸⁸ *See id.* at 1350.

⁸⁹ *See Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247 (Fed. Cir. 2004).

⁹⁰ *Id.* at 1262 (“Claim 1 recites: A monoclonal antibody that binds to a human breast cancer antigen that is also bound by monoclonal antibody 454C11.”).

would literally infringe the broad genus patent.⁹¹ However, the genus claim was filed in 1984, a time when chimeric antibodies were not yet discovered. In holding the genus claim invalid, the *Chiron* court seemed uncomfortable in allowing a broad genus claim that would cover a technology that had not been enabled at the time the patent was filed.

In *Centocor*, decided in 2011, the Federal Circuit began to explicitly step back from the PTO Guidelines and *Noelle*, by distinguishing between newly characterized antigens and known antigens.⁹² *Centocor* was the first time the Federal Circuit was presented with a case involving an allegation that a therapeutic monoclonal antibody infringed an antibody claim. The court took a significant step back from its previous endorsement of the PTO Guideline’s antibody example.⁹³ *Centocor* argued, quite reasonably, that *Noelle* and the PTO Guidelines “support[ed] the view that fully disclosing the human TNF-alpha protein provides adequate written description for any antibody that binds to human TNF-alpha.”⁹⁴ But the *Centocor* panel backed away from *Noelle* and the PTO Guidelines, finding that *Centocor*’s reading of *Noelle* was “based on an unduly broad characterization of the Guidelines and our precedent.”⁹⁵

The *Centocor* panel “clarified” the standard endorsed in *Noelle* only applied to novel, newly characterized antigens. The panel pointed out that the PTO’s antibody example, on which the *Noelle* standard was based, “presumes that the applicant is disclosing a novel protein and then claiming both the protein and antibody

⁹¹ *Id.* at 1254.

⁹² *Centocor Ortho Biotech, Inc. v. Abbott Lab’s*, 636 F.3d 1341, 1352 (Fed. Cir. 2011).

⁹³ *See id.* at 1351–52.

⁹⁴ *Id.* at 1351.

⁹⁵ *Id.*

that binds to it.”⁹⁶ The court stated, “[A]n applicant can claim an antibody to novel protein X without describing the antibody when (1) the applicant fully discloses a *novel* protein and (2) generating the claimed antibody is so routine that possessing the protein places the applicant in possession of an antibody.”⁹⁷

Since the antigen defining the claimed antibodies, TNF-alpha, was well-characterized in the prior art, it was not a novel protein, and thus fell outside of what came to be known as *Centocor*’s “newly characterized antigen test.”⁹⁸ But it bears noting that neither the PTO Guidelines nor *Noelle* suggest that the novelty of the antigen has any bearing on compliance with the written description requirement, which the Federal Circuit has repeatedly stated the focus is on what the applicant was in “possession” of at the time of filing. The PTO Guidelines merely note that the antigen is “well-characterized,” and *Noelle* refers to “fully characterized antigens.”⁹⁹

It makes no sense to suggest that the novelty of an antigen has any bearing on the extent to which a putative inventor is in “possession” of antibodies specific for that antigen. The rational explanation for *Centocor*’s parsing of the PTO Guidelines is that the Federal Circuit saw this as a way to invalidate the patent claims at issue without expressly disavowing *Noelle*’s dicta. The court’s full disavowal of *Noelle* came later, as discussed in Section II(D) below, when the Federal Circuit was confronted with another antibody therapeutic case in which the claimed

⁹⁶ *Id.*

⁹⁷ *Centocor Ortho Biotech, Inc. v. Abbott Lab’s*, 636 F.3d 1341, 1351 (Fed. Cir. 2011) (emphasis added).

⁹⁸ *Id.* at 1352–53.

⁹⁹ U.S.P.T.O., *supra* note 71, at 45–46; *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004).

antibodies were defined in terms of a newly characterized antigen.¹⁰⁰

V. STAGE 3- ANTIBODY BINDING REGION STRUCTURE REQUIRED

Antibody technology advanced as scientists recognized that specific epitope recognition, even on the same antigen, could have dramatically different functional effects when these antibodies were used as therapeutics. Additionally, as the use of new chimeric monoclonal therapeutic antibodies became more ubiquitous and prominent, courts pushed back against the broad genus claims the PTO had been issuing.¹⁰¹ The PTO also began tightening its standard. Courts and the PTO used the written description and enablement requirements to narrow antibody claims by requiring disclosure of the antibody structure, usually focused on the regions of the antibody that dictate antigen binding. Thus, claims during this period typically recite the structure of the antibody's CDRs.

Narrowing the claims also makes public policy sense when considering the quid pro quo rationale for patents. If an applicant is granted broad scope for any antibody that recognizes the antigen, then the claim would likely encompass many alternate monoclonal antibodies that have significantly different and/or improved functional characteristics from those antibodies disclosed by the patentee. This is a public policy concern because we would likely stifle innovation by granting broad patents that would

¹⁰⁰ See *Amgen*, 987 F.3d at 1088; see also Holman, *supra* note 11, at 280–82.

¹⁰¹ Tu & Holman, *supra* note 3.

prevent competitors from creating a host of functionally different and improved products.¹⁰²

Example 2

Patents issued during this period typically include claims that define the key structural regions of the antibody, such as their Complementarity Determining Regions (CDRs).¹⁰³ These CDRs define the binding site of the antibody to antigen and are crucial for antibody specificity.

A typical claim from this timeframe can be seen in US Patent No. 9,353,181 where claim 1 reads:

An isolated IL-23p19 antibody, comprising a light chain variable region and a heavy chain variable region, said light chain variable region comprising: a complementarity determining region light chain 1 (CDRL1) amino acid sequence of SEQ ID NO:50; a CDRL2 amino acid sequence of SEQ ID NO:56; and a CDRL3 amino acid sequence of SEQ ID NO:73, said heavy chain variable region comprising: a complementarity determining region heavy chain 1 (CDRH1) amino acid sequence of SEQ ID NO:5; a CDRH2 amino acid sequence of SEQ ID NO:28; and a CDRH3 amino acid sequence of SEQ ID NO:44.¹⁰⁴

As can be seen by the amino acid lengths, the CDRs are defined by relatively short amino acid sequences, which

¹⁰² There may be an argument, however, to expanding the use of the reverse doctrine of equivalents to exclude these types of antibodies from the literal scope of the claims.

¹⁰³ The CDRs are sometimes referred to as “hypervariable regions” and help define the antigen specificity generated by lymphocytes.

¹⁰⁴ U.S. Patent No. 9,353,181 (issued May 31, 2016). SEQ ID NOs 50, 56, 73, 5, 28 and 44 are 14, 7, 11, 5, 17, and 8 amino acids in length, respectively.

leads to broader claims since the framework regions of the antibody are still not structurally defined.

A. *Advances in Antibody Technology*

Antibody technology evolved yet again by overcoming the limitations associated with fully murine antibodies, such as HAMA. Scientists created “chimeric” antibodies, which are fusion antibodies where the variable domain of the antibody was from one host species (e.g. mouse, rabbit, llama, etc.) and the constant domain of the antibody from a different species (e.g. human).¹⁰⁵ Chimeric antibodies such as abciximab (ReoPro), basiliximab (Simulect), cetuximab (Erbitux), infliximab (Remicade) and rituximab (Rituxan) quickly became blockbuster drugs, garnering billions of dollars for the pharmaceutical industry.¹⁰⁶

B. *Public Policy Behind Narrowing Scope of Antibody Claims*

Courts were forced to catch up to the technology and interpret the requirements of patentability in a way that promotes innovation in antibody-based technology by limiting antibody patent scope. In part, this was accomplished by disavowing the exceptional treatment of antibody claims set forth in the PTO Guidelines and seemingly endorsed by the Federal Circuit and beginning to apply the enhanced *Lilly* written description standard to

¹⁰⁵ See Koteswara R. Chintalacharuvu & Sherie L. Morrison, *Chimeric Antibodies: Production and Applications*, 8 METHODS 73, 73–74 (1995).

¹⁰⁶ See Benedette Cuffari, *What are Chimeric Antibodies?*, AZO LIFE SCIENCES (Apr. 9, 2021), <https://www.azolifesciences.com/article/What-are-Chimeric-Antibodies.aspx> [https://perma.cc/F6G5-SFDE].

antibodies in a manner consistent with the way the PTO and courts apply the standard to other biomolecules.¹⁰⁷

The policy rationale for effectively narrowing the permitted scope of antibody patents made sense because antibodies were now being used primarily as therapeutics. Different antibodies to the same antigen that bind to different areas of the antigen, i.e., different epitopes, might have dramatically different pharmaceutical effects in terms of safety and efficacy. Courts and the PTO are forced to walk a policy tightrope, on one hand balancing the possibility of harming competition by granting patents that are too broad, and on the other hand the possibility of failing to adequately incentivize innovation by granting patents that are too narrow.

On one side of the coin, a patentee who first discloses a therapeutic monoclonal antibody is a pioneer, and should be accorded some scope of coverage to prevent a competitor from making minor structural alterations to escape liability. The downside, however, is that if we grant the pioneer inventor broad patent rights to a suboptimal solution, then we inhibit future superior products that are later developed but that target the same antigen.

On the other side of the coin, granting only a narrow scope for antibody patents allows others to develop other antibodies that target the same antigen but a substantially different structure, which will often correspond to different functionality, granting exclusive rights to the earlier inventors that is arguably commensurate with the scope of what they disclosed to the public. Thus, narrow patent rights allow for future growth of superior products. By narrowing the scope of antibody claims, the public could benefit from more innovation and a panoply of new antibodies with different therapeutic functions. The downside, however, is if we narrowed

¹⁰⁷ See *supra* Section IV.D.

claims to only those specific examples given or to specific hybridoma cell lines, then the scope of the claims might be too narrow. If claim scope is too easy to design around, then inventors might not make the costly initial investment to innovate in this area.

With respect to antibody patents, courts and the PTO abandoned their earlier interpretation of Section 112(a) that would allow for broad genus claims and are now using the written description and enablement requirements to force applicants to narrow their claims or to invalidate issued claims.¹⁰⁸ In order to obtain patent protection, putative inventors are now required to claim more narrowly, limited to the specific structure of the CDRs, or including functional limitations with respect to the exact epitope bound, binding specificity, disassociation constants, therapeutic effect(s), etc.¹⁰⁹

C. Use of 112(a) to Narrow Scope of Antibody Claims

Courts and the PTO have responded to changes in antibody technology by continuing to narrow the scope of antibody claims using the enablement and written description requirements.¹¹⁰ The Federal Circuit backed away from its broad endorsement of the PTO's written description guidelines. Although not completely shutting the door for broader genus claims, the Federal Circuit and PTO seem to now rigidly apply the written description and enablement standards to prevent broad antibody claims.

¹⁰⁸ Tu & Holman, *supra* note 3; Lemley & Sherkow, *supra* note 8.

¹⁰⁹ Tu & Holman, *supra* note 3, at 29–30.

¹¹⁰ Tu & Holman, *supra* note 3; Lemley & Sherkow, *supra* note 8.

1. The Federal Circuit Rejects Example 13 and Narrows Antibody Claims

In *Amgen Inc. v. Sanofi*, the Federal Circuit explicitly disavowed the Guideline’s Example 13, *Noelle*, and *Centocor*’s nonsensical “newly characterized antigen” standard.¹¹¹ *Amgen* and *Juno* are two recent Federal Circuit cases that reveal how courts will likely deal with antibody patents for years to come.¹¹²

In *Amgen* the patentee attempted to claim “An isolated monoclonal antibody [that] binds to [one of the residues of PCSK9] and . . . blocks binding of PCSK9 to LDRL.”¹¹³ In invalidating the claims, the Federal Circuit held that “the functional limitations here are broad, the disclosed examples and guidance are narrow, and no reasonable jury could conclude . . . that anything but ‘substantial time and effort’ would be required to reach the full scope of claimed embodiments.”¹¹⁴

The *Amgen* court focused on the fact that the only way for a person of ordinary skill to discover new embodiments would be through either trial and error or discovering the antibodies *de novo* through a randomization-and-screening roadmap.¹¹⁵ The court found that these types of haphazard techniques would require undue experimentation, thus did not meet the enablement requirement.¹¹⁶ Accordingly, functional claims that encompass a large genus likely will require some sort of

¹¹¹ *Amgen Inc. v. Sanofi*, *Aventisub L.L.C.*, 987 F.3d 1080, 1088 (Fed. Cir. 2021); *see also* Holman, *supra* note 8, at 281.

¹¹² *See Juno Therapeutics, Inc. v. Kite Pharm., Inc.*, 10 F.4th 1330, 1340–42 (Fed. Cir. 2021).

¹¹³ U.S. Patent No. 8,829,165 claim 1; *see* U.S. Patent No. 8,859,741 claim 1.

¹¹⁴ *Amgen*, 987 F.3d at 1088 (affirming the district court’s holding that the claims were invalid for lack of enablement).

¹¹⁵ *Id.*

¹¹⁶ *Id.*

common structural guidance to meet the enablement requirement.

Similarly, in *Juno Therapeutics*, the Federal Circuit reversed a \$1.2 billion infringement finding by invalidating the claims for lack of adequate written description.¹¹⁷ The claims in the U.S. 7,446,190 patent were directed towards a DNA molecule that encodes for a “binding element that specifically interacts with a selected target.”¹¹⁸ The patent only disclosed two specific “binding elements, single-chain antibody variable fragments (scFv) specific for two different proteins.”¹¹⁹ Interestingly, it was the double-inclusion of ζ chain and the costimulatory region that made the invention novel, and the scFv fragments were simply used as a targeting mechanism.¹²⁰

The ‘190 patent was invalidated for a lack of written description.¹²¹ The court found that there were “no details” provided about the specific embodiments that would cover the full scope of the invention.¹²² Additionally, there were no examples, structures or general characteristics that would show that the inventor was in full possession of the genus.¹²³

In *Juno*, the written description analysis is used to determine if the inventor had “possession” of the claimed invention. For these genus claims, the court is looking if the inventor is in possession of the “full scope” of the invention. Similar to the *Amgen* case, even though in *Amgen* it is in the rubric of enablement, the court looks for structural features common to the members of the genus or

¹¹⁷ *Juno Therapeutics*, 10 F.4th at 1342; see also Holman, *supra* note 13, at 378.

¹¹⁸ U.S. Patent No. 7,446,190 claim 1.

¹¹⁹ See *id.*

¹²⁰ See *id.*; see also Lemley & Sherkow, *supra* note 8.

¹²¹ *Juno Therapeutics, Inc. v. Kite Pharm., Inc.*, 10 F.4th 1330, 1342 (Fed. Cir. 2021).

¹²² *Id.* at 1336.

¹²³ *Id.* at 1337.

a representative number of species that fall within the scope of the genus. This test is difficult to meet for functionally defined genus claims.

2. The PTO Reverses Example 13 in 2018 Clarification of Written Description Guidelines

On February 22, 2018, the PTO put out a “Clarification of Written Description Guidance for Claims Drawn to Antibodies and Status of 2008 Training Materials.”¹²⁴ The updated guidance cited to *Amgen* and stated that the “so-called ‘newly characterized antigen’ test, which had been based on [Example 13 of the 2008 Written Description Training Materials] . . . should not be used in determining whether there is adequate written description under 35 U.S.C. § 112(a) for a claim drawn to an antibody.”¹²⁵

Additionally, the PTO updated its written description guidelines in MPEP § 2163(II)(3). In repealing its previous guidance, the current MPEP guidelines states, that disclosure of “an antigen fully characterized by its structure, formula, chemical name, physical properties, or a deposit in a public depository does not, without more, provide an adequate written description of an antibody claimed by its binding affinity to that antigen, even when preparation of such an antibody is routine and conventional.”¹²⁶

Thus, the PTO has now formally adopted the general *Lilly* standard for antibody claims, stating that “describing a composition by function alone typically will not suffice to sufficiently describe the composition . . . [an]

¹²⁴ ROBERT W. BAHR, CLARIFICATION OF WRITTEN DESCRIPTION GUIDANCE FOR CLAIMS DRAWN TO ANTIBODIES AND STATUS OF 2008 TRAINING MATERIALS (2018).

¹²⁵ *Id.*

¹²⁶ MPEP § 2163(II)(A)(3) (9th ed. Rev. 10, June 2020).

adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed.”¹²⁷

VI. STAGE 4- THE FUTURE OF ANTIBODY CLAIMS- HEAVY AND LIGHT CHAIN ANTIBODY STRUCTURE REQUIRED

Monoclonal antibody technology has now evolved beyond the murine antibodies directly produced by hybridoma cells, to recombinant monoclonal antibodies, e.g., chimeric antibodies, humanized antibodies, antibody fragments, etc. For these molecules, determination of chemical structure is relatively easy and inherent in the process of molecular design. Because antibody structure is now easily defined, patent law now requires the disclosure of sequence structure for antibody patent.

As explained in Section (IV)(C)(2), the rationale for broad claims based on structure may have been based on the fact that it was difficult if not impossible to give structural elements during that time frame. However, antibody technology has advanced to the point where scientists can now easily define antibodies based on structure. Accordingly, the current PTO guidelines have evolved to match up with this scientific reality. Most antibodies are now claimed solely by using structural elements of the antibody.¹²⁸

Example 3

A typical claim from this timeframe can be seen in US Patent No. 10,822,397 where claim 1 reads:

¹²⁷ *Id.*

¹²⁸ Tu & Holman, *supra* note 3, at 10.

An isolated antibody or epitope-binding fragment thereof that specifically binds to at least one conformational (non-linear) epitope of enterovirus 71 (EV71), wherein the antibody comprises at least one variable light chain and at least one variable heavy chain, wherein the variable light chain comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 3, and wherein the variable heavy chain comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 4 or SEQ ID NO: 5, wherein the antibody or epitope-binding fragment thereof is neutralizing.¹²⁹

In contrast to *Example 2*, in *Example 3* both the variable region as well as the framework regions of the antibody are structurally defined. These are narrower claims that are more susceptible to design arounds due to detailed structural requirements embodied in the specific amino acid sequence in addition to the functional requirements embodied in both binding to a specific epitope and a neutralizing requirement.

A. *Advances in Antibody Technology*

Antibody technology developed yet again by creating “humanized” antibodies. By using recombinant DNA, scientists can now create an antibody that is mostly human except for the binding region which has been altered to bind a specific epitope. Antibody technology has now advanced such that we are using more chimeric, humanized and scFv antibodies for therapeutic purposes.

Humanized antibodies have three main advantages over the original mouse monoclonal antibodies: (1) they

¹²⁹ U.S. Patent No. 10,822,397 (issued Nov. 3, 2020). SEQ ID NOs 3, 4 and 5 are 112, 122, and 119 amino acids in length, respectively.

have reduced immunogenicity (reduced HAMA problems), (2) the human C region allows for human effector functions to take place, and (3) the serum half-life of the antibody is significantly increased.¹³⁰ Unlike previous iterations, the DNA structures are known for these antibodies. Accordingly, the primary structure of these antibodies can be well defined.

The binding affinities of humanized antibodies are often decreased compared to their original mouse monoclonal antibodies.¹³¹ However, these affinities can be increased by making framework substitutions and varying the CDR sequences.¹³² Specifically, when different framework regions are combined with the same CDRs, humanized antibodies specific for the same antigen can elicit different effector functions, thereby extending their therapeutic benefits.¹³³

B. Antibody Claims Requiring both Heavy and Light Chain Structures or Complete Structure

As shown in Example 3, antibody claims now not only require the CDR regions but the full heavy chain and light chain structural sequences. This is because the heavy and light chain regions of humanized and chimeric antibodies contain the key structural elements necessary to diminish the negative effects of the human anti-mouse antibody (HAMA) response.¹³⁴

Accordingly, the future of antibody composition of matter claims may lie in even narrower claims. Antibodies

¹³⁰ TAK W. MAK & MARY E. SAUNDERS, THE IMMUNE RESPONSE: BASIC AND CLINICAL PRINCIPLES 153 (2006).

¹³¹ *Id.*

¹³² *Id.*

¹³³ *Id.*

¹³⁴ *See infra* Appendix 1 (discussing the HAMA response).

that are defined by their full structure meet the written description and enablement requirements, however, they may be so narrow that they are not worth much to the patentee. Specifically, if it only takes a few changes to the constant region of the antibody to avoid infringement, then design arrounds will remove the value of these patents.

VII. CONCLUSIONS

Antibody caselaw has evolved dramatically. In the early days of antibody technology, antibody patents were afforded broad scope and could be defined solely by the antigen that they bound (Stage 1). Later we see a time where antibodies claims were treated as the exception to the general *Lilly* rule, which required more structural elements (Stage 2). Still later in time we saw that antibody patents were no longer treated as an exception to the rule, and now required disclosure of key structural elements, such as their CDRs (Stage 3). Finally, we see even more structural elements required to obtain an antibody patent, which requires disclosure of the full antibody structure including the full sequence for both the heavy and light chain regions of the antibody (Stage 4).

The evolution of antibody caselaw mirrored the changes in antibody technology development. It made sense to give broad antibody claims based on antigen structure alone in a time when antibodies were only used for research tools and diagnostic tools. The value of antibody patents during this early timeframe (Stage 1) was based on the antibody's ability to bind to an antigen, regardless of the specific epitope.

As other biotechnological inventions required more structural definition, antibodies escaped this general requirement (Stage 2). We believe this might have been because both the PTO and the courts did not want to squelch innovation in this nascent field by dramatically

narrowing the scope of antibody patents. Accordingly, the PTO, along with the Federal Circuit, developed an antibody exception.

We saw a slight shift in the way antibodies were treated when antibodies moved from diagnostic tools to therapeutic tools (Stage 3). During this stage it became clear that the value of the antibody resided in the specific epitope that the antibody bound to. Different epitopes could have dramatically different functional characteristics. Again, new shifts in antibody technology necessitated shifts in the way we treated antibody patents. Thus, antibody claims were now narrowed by requiring key structural elements, usually defined by the antibody's CDRs, which define the specific epitope binding site.

Current antibody therapies are based on yet another shift in antibody technology. Now antibodies are based on chimeric, humanized antibodies or antibody fragments. These new antibodies not only function as therapies, but also do not illicit the negative side effects present in older antibody therapies. These results are achieved by having heavy and light chains that mimic human antibodies. Accordingly, now antibody claims are even narrower requiring the full structure of the heavy and light chains as well as the CDR binding regions.

Has the pendulum shifted too far towards narrow claims? Can we balance the need for broad claims to incentivize investment in the risky business of drug development, while also balancing the need to narrow claims enough to prevent overclaiming and stifling innovation?

One author (Tu) has proposed use of the reverse doctrine of equivalents to allow for broader claims to recapture some of the breath allotted to prior antibody claims, while preventing minor alterations in structure to

avoid liability.¹³⁵ Lemley and Sherkow have made similar proposals invoking the doctrine of equivalents and using “structure-plus” or means-plus-function claiming.¹³⁶ Only time will tell if our current antibody jurisprudence will help or harm innovation, or if Congress or the courts will intervene to change the current narrowing of antibody claims.

¹³⁵ Tu & Holman, *supra* note 3.

¹³⁶ Lemley & Sherkow, *supra* note 8.

APPENDIX- ANTIBODY FUNDAMENTALS

A. *General Definitions*

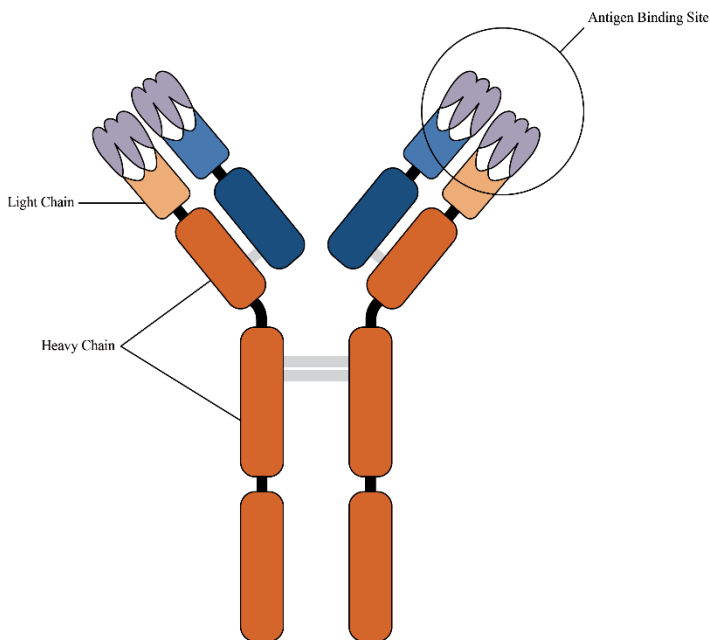
1. Antigen: the target molecule that the antibody binds to.
2. Epitope: the specific region of an antigen that the antibody binds to.
3. Paratope: the region of an antibody that is responsible for binding to the epitope.
4. Complementarity Determining Regions (CDRs): six regions on the antibody that collectively come into contact with the antigen. There are three CDR loops per variable domain in antibodies (three on the light chain and three on the heavy chain). CDRs on the light chain are labeled CDR L1, CRD L2 and CDR L3. CDRs on the heavy chain are labeled CDR H1, CRD H2 and CDR H3.
5. Light Chain / Heavy Chain: antibodies are comprised of two light chains and two heavy chains in a Y-structure shown in Figure 2. Each Y contains two identical copies of a heavy chain and two identical copies of a light chain which are different in their sequence and length. The top of the Y shape is defined by the CDR sequences which form the paratope, which binds tightly and specifically to an epitope on the antigen.

6. Variable region: the region defined by the CDRs and surrounding framework regions.
7. Constant region: the part of an antibody that is common to its particular class. The constant region is involved in triggering the immune response and determines the mechanism by which the antigen is destroyed.
8. Polyclonal Antibody: a diverse population of antibodies targeted to the same antigen.
9. Monoclonal Antibody: a single antibody directed to a target epitope.
10. Bispecific Antibody: an antibody that can bind two targets.
11. Chimeric Antibody: an antibody that has been engineered from more than one different species. Commonly, the variable region is defined by a non-human antibody which is then linked to the constant region of a human antibody. This is done to limit the human immune response to a mouse antibody.
12. Humanized antibody: a subclass of chimeric antibody where most of the sequences are human in origin.

B. *Antibody Structure, Function and Method of Production*

Antibodies, also known as immunoglobulins, are natural products of the body that are secreted by B-cells as part of an immunological response to neutralize antigens such as bacteria and viruses. The structure of an antibody is shown in Figure 2. The antibody structure is a classic Y-shaped molecule composed of two heavy chains (connected by a linker) and two light chains (connected to the heavy chains). Each tip of the “Y” contains a paratope which can bind only one epitope on an antigen. This allows the antibody to bind its antigen with precision. There are two main types of antibodies: polyclonal and monoclonal. Polyclonal and monoclonal antibodies can be distinguished by the means in which they are created in lymphocytes.

Figure 2



Polyclonal antibodies (pAbs) are a mixture of heterogenous antibodies which are usually produced by different B cell lines in the body. Thus, pAbs recognize and bind to many different epitopes of a single antigen. pAbs are usually generated by injecting an animal with an antigen. After injection, the animal elicits a primary immune response, and then given a secondary injection (and sometimes a third injection) to boost the immune response. The serum¹³⁷ can then be collected and pAbs to the antigen can then be isolated using an immobilized antigen.

There are several benefits associated with pAbs. First, is the relative ease and cost of production of pAbs. pAbs are highly stable and can tolerate pH or buffer changes. pAbs bind more than one epitope and can help amplify the signal from a target protein even with low expression levels. Accordingly, pAbs are ideal for immunoprecipitation and chromatin immunoprecipitation. Finally, pAbs are less sensitive to antigen changes such as denaturation, polymorphisms and different glycosylation patterns. One major downside to pAbs, however, is the fact that there is batch to batch variability because each animal will mount a different immune response to the antigen injection. pAbs have been used as components of antivenom, antitoxin, and transplant antirejection drugs. Importantly pAbs are also used to *detect* disease in blood or tissue samples. For examples, pAbs have been used to detect for viruses, cancers, encephalitis, HIV and Lyme disease.

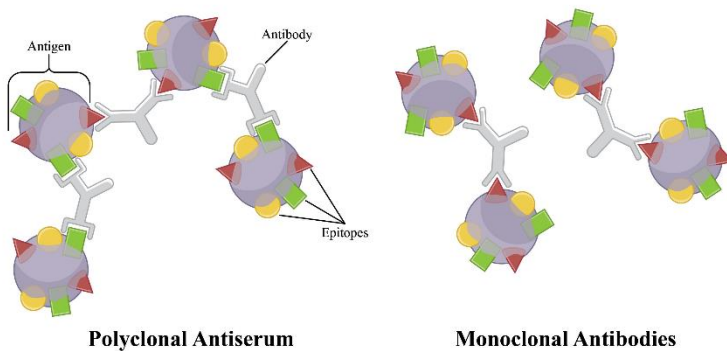
Monoclonal antibodies (mAbs) revolutionized antibody technology. In contrast to pAbs, mAbs are usually not produced in live animals. In 1975, Nobel

¹³⁷ Serum consists of blood where the clotting proteins and red blood cells are removed.

laureates Kohler and Milstein produced the first mAbs.¹³⁸ mAbs are generated using hybridoma technology, which is a product of splenocyte and myeloma cell fusions creating an immortalized B-cell-myeloma hybridoma. The hybridomas are able to grown continuously in culture while producing antibodies. These antibodies are then screened for the desired mAbs. Importantly, mAbs exhibit *precise and reproducible binding properties*. mAbs bind one specific epitope on an antigen.

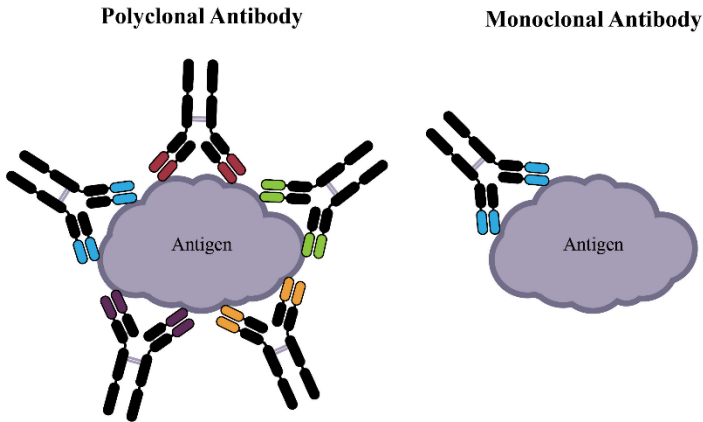
Figure 3A describes the different binding specificities of mAbs compared to pAbs. pAbs have the ability to bind different epitopes (triangles and rectangles) on the same antigen. In contrast, mAbs can bind only one specific epitope (triangles) on an antigen. Figure 3B shows that pAbs bind to multiple epitopes on the same antigen, while mAbs can bind to only one epitope.

Figure 3A



¹³⁸ See George Köhler & Cesar Milstein, *Continuous cultures of fused cells secreting antibody of predefined specificity*, 256 NATURE 495 (1975) (sharing the 1984 Nobel prize in medicine for this breakthrough).

Figure 3B



The benefits of using mAbs cannot be understated. First, mAbs are highly specific and recognize only one epitope of an antigen. Second, once an immortal hybridoma cell line is created, the firm has the ability to produce unlimited quantities of the mAb. Because mAbs recognize only one epitope, the results of mAbs are highly consistent with minimal background noise and cross-reactivity. However, the cost and time needed to generate mAbs is considerably greater than pAbs. Additionally, it takes a much longer amount of time and requires highly technical knowledge to create these hybridomas. Further, mAbs are vulnerable to changes in the epitope and even small changes in antigen conformation may lead to dramatically reduced binding capacity. Due to these consistent results, mAbs are much better suited to be used for therapeutic treatments. Accordingly, mAbs have been

used to treat diseases such as rheumatoid arthritis¹³⁹, asthma¹⁴⁰, psoriasis¹⁴¹ and many forms of cancer.¹⁴²

mAbs produced using mouse hybridomas are not ideal for use as human therapeutics. This is because humans injected with mouse mAbs will mount an immune response because the human body will recognize the mouse mAb as foreign and attempt to remove it from the body. This response is known as the Human Anti-Mouse Antibody (HAMA) response and occurs when the human immune system recognizes the mouse antibody as foreign and attack it. A HAMA response can cause toxic shock or even death in a patient. Additionally, most mouse mAbs suffer from a short serum half-life in humans.

¹³⁹ Adalimumab (Humira) from Abbvie is a fully human antibody against TNF used to treat rheumatoid arthritis. *Humira*, DRUGS.COM (Mar. 25, 2022), <https://www.drugs.com/humira.html> [<https://perma.cc/2KLS-D8P2>].

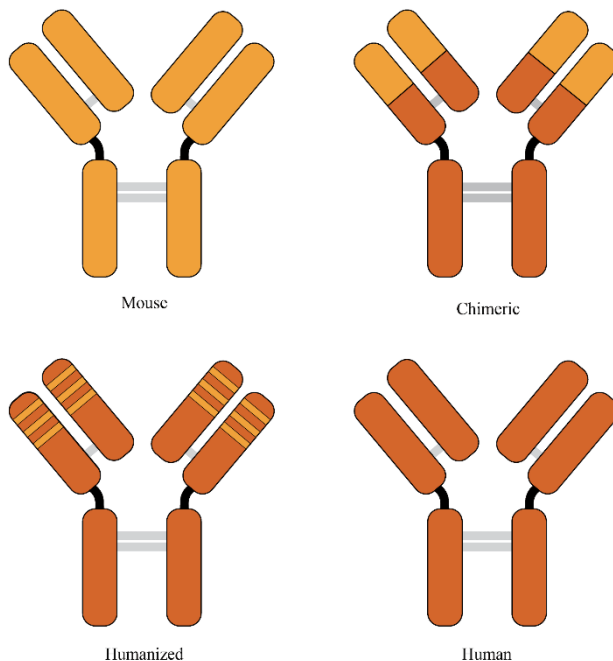
¹⁴⁰ Dupilumab (Dupixent) from Regeneron Pharmaceuticals is a fully human antibody against IL4RA used to treat atopic dermatitis and asthma. *Dupixent*, DRUGS.COM (Oct. 18, 2022), <https://www.drugs.com/dupixent.html> [<https://perma.cc/AD7E-N6FF>].

¹⁴¹ Infliximab (Remicade) from Centocor is a chimeric antibody against TNF that is used to treat Chron’s disease and plaque psoriasis. *Remicade*, DRUGS.COM (Aug. 22, 2022), <https://www.drugs.com/remicade.html> [<https://perma.cc/HR4T-M3QD>].

¹⁴² Atezolizumab (Tecentriq) from Genentech is a humanized antibody against PD-L1 that is used to treat Urothelial carcinoma and metastatic non-small cell lung cancer. *Tecentriq*, DRUGS.COM (May 12, 2022), <https://www.drugs.com/tecentriq.html> [<https://perma.cc/P3G4-4TML>]. Bevacizumab (Avastin) from Genentech is a humanized antibody against vEGF used to treat metastatic colorectal cancer. *Avastin*, DRUGS.COM (Apr. 6, 2022), <https://www.drugs.com/avastin.html> [<https://perma.cc/6PBB-X88V>]. Pembrolizumab (Keytruda) from Merck is a humanized antibody against PD-1 that is used to treat metastatic melanoma. *Keytruda*, DRUGS.COM (Feb. 23, 2022), <https://www.drugs.com/keytruda.html> [<https://perma.cc/846M-Y5VU>]. Rituximab (Rituxan) from Genentech is a chimeric antibody against CD20 that is used to treat B-cell non-Hodgkin’s lymphoma. *Rituxan*, DRUGS.COM (Feb. 3, 2021), <https://www.drugs.com/rituxan.html> [<https://perma.cc/SF4C-ELQN>].

Accordingly, additional steps are required for mAbs that will be used for treatment of disease in humans. mAbs must be “humanized” for human clinical use. Figure 4 shows the humanized and chimeric versions compared to mouse antibodies. Chimeric and humanized antibodies reduce the likelihood of a HAMA response by minimizing the non-human portions of administered antibodies. Thus, because most regions of the chimeric and humanized antibodies are human, these antibodies do not elicit as much of an immune response from the patient. Furthermore, chimeric and humanized antibodies have the additional benefit of activating secondary human immune responses such as antibody dependent cellular cytotoxicity. Furthermore, these chimeric/humanized antibodies have a much longer serum half-life.

Figure 4



Chimeric antibodies are created by substituting the mouse constant region with a human constant region. Thus, the chimeric antibody consists mainly of a human constant region with only the variable regions of the antibody of mouse origin.

Humanized mAbs are created through genetically engineering the mouse B-cell so that the variable regions of the mouse light and heavy chain genes are ligated to human constant regions. This creates an antibody that most of the mouse sequence has been replaced with human Ig sequence. This process results in the production of a mAb that is mostly “human” with only the antigen binding site being of mouse origin. Because the mAb is mostly human in origin, the patient does not recognize the humanized mAb as foreign and does not generate large quantities of anti-mAb antibodies that would hinder the therapeutic mAb’s effectiveness.

One of the newest antibody technologies involves use of a phage display library to artificially construct soluble Fab fragments. Fab fragments are antibody fragments that consist of only one arm of the “Y” structure (they contain only a single antigen binding site and does not contain the Fc fragment, including the hinge region).¹⁴³ These Fab fragments have the ability to penetrate tissues efficiently and do not need to be processed through the endoplasmic reticulum. However, one major drawback to this approach is that a new phage library must be constructed for every antigen, which is a time-consuming process. Additionally, Fabs are not full-length antibodies and lack the C region which is responsible for effector functions. Further, Fabs are produced in bacteria and

¹⁴³ *Monovalent Fab Fragments of Affinity-Purified Secondary Antibodies*, JACKSON IMMUNORESEARCH, <https://www.jacksonimmuno.com/technical/products/groups/fab> [<https://perma.cc/88JF-UQ96>] (last visited Oct. 24, 2022).

therefore are not glycosylated, which leads to a much shorter half-life.

Finally, mAbs are being produced in plants for use in humans. These “plantibodies” are full length antibodies that are glycosylated and thus have a longer half-life in the patient’s body. Plantibodies are generated by creating a transgenic plant that express human mAbs without harming their own metabolism. Accordingly, large quantities of human mAb can be created cheaply and the seeds produced by these plants can be easily stored.