THE FUTURE OF PATENTING ANTIBODIES AFTER *AMGEN V. SANOFI*

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I. ABSTRACT

Antibodies have become the popular treatment of various diseases and illnesses, with pharmaceuticals such as Humira to treat arthritis and Avastin to treat certain forms of cancer. Lately, pharmaceutical companies have moved from describing the structure of their antibodies to describing the function of their antibodies, which grants a broader patent protection. Specifically, in Amgen v. Sanofi, Amgen claimed its antibody genus by disclosing the structure of specific epitope residue to which its antibodies bind. The United States District Court for the District of Delaware and later the Federal Circuit ruled on written description and enablement concerning Amgen's claim scope. By comparing the scientific and legal paradigms surrounding antibodies, this note analyzes the trend toward these broader claims and its potential impact on pharmaceuticals.

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II. INTRODUCTION

Should antibody patents claim an antibody structurally by its amino acid sequence or functionally by the sequence of its target epitope residue? Recently in *Amgen v. Sanofi* a jury declared Amgen's patent valid, which functionally claimed the active antibody of Repatha by the amino acid sequence of epitope residues on the target antigen, proprotein convertase subtilisin kexin type 9 (hereinafter PCKS9) and not other structural components of the anti-PCKS9 antibody. Amgen claimed a broad genus of antibodies that attach to specified epitope residues on PCSK9 without disclosing a specific amino acid sequence of the anti-PCKS9 antibody itself. Amgen's claims were valid even though Sanofi argued that Amgen's patent claim scope was broader than the patent application's disclosure. Is this

the direction of modern antibody patenting? Why did the United States Patent and Trademark Office (hereinafter PTO) and the court allow such a broad antibody claim? Is this type of claiming necessary to get over the vast prior art antibody references or is there some other reason? This article explores the future of functionally claiming antibodies by the structure of the antibody's target epitope residues after this recent decision in *Amgen v. Sanofi*.

I. SCIENTIFIC PARADIGM VERSUS LEGAL PARADIGM

These questions concerning the direction of patenting antibodies may come down to the differences between how the scientific community views an antibody and how the legal community views an antibody. This is the distinction between how a scientist understands his or her invention, the scientific paradigm, compared to what the patent actually claims, the legal paradigm. The word "paradigm" means "[a] set of assumptions, concepts, values, and practices that constitutes a way of viewing reality for the community that shares them."[2] Here, a scientific paradigm refers to how the scientific community views the invention of an antibody, while a legal paradigm is how patent practitioners write claims to cover the same invention. For example, in U.S. Patent 8,420,081 (hereinafter '081) AbbVie Inc. directs the parent patent in which an embodiment of this patent covers what is informally known as "Humira", formally known as "Adalimumab."[3] In the scientific paradigm, Humira is used as a treatment for Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing

[2] The American Heritage College dictionary 1008 (4th ed. 2002).
[3] U.S. Patent No. 8,420,081 (issued April 16, 2013).

Spondylitis, Crohn's Diseases, and Plaque Psoriasis.[4] The scientific community describes Humira as a "recombinant human IgG1 monoclonal antibody" that binds to human tumor necrosis factor-alpha and blocks interaction with certain cell surface TNF receptors in order to reduce symptoms of the above specified conditions.[5] Therefore, within the scientific paradigm Humira is viewed by its structure, "recombinant human IgG1 monoclonal antibody" and its function of binding to TNF receptors to reduce symptoms of specified conditions.[6] Within the legal paradigm, Humira is an embodiment of '081 claims 1, 22, and 25. Claim 25 reads "[t]he formulation of claim 22, wherein that anti-TNF.alpha antibody, or antigen-binding fragment thereof, is adalimumab."[7] A combination of claims 1 and 22 refers to:

> An aqueous formulation comprising an antibody, or antigen-binding fragment thereof, at a concentration of at least about 20 mg/mL and water, wherein the formulation has a conductivity of less than about 2.5 mS/cm and the antibody, or antigen-binding fragment thereof, has a molecular weight (M.sub.w) greater than about 47 kDa . . . wherein the antibody, or antigen-binding fragment thereof, is an anti-tumor necrosis factor alpha (TNF.alpha.) or an anti-interleukin-12 (IL-12) antibody, or antigen-binding fragment thereof.[8]

While the scientific community views Humira by its chemical structure and function, the legal perspective of

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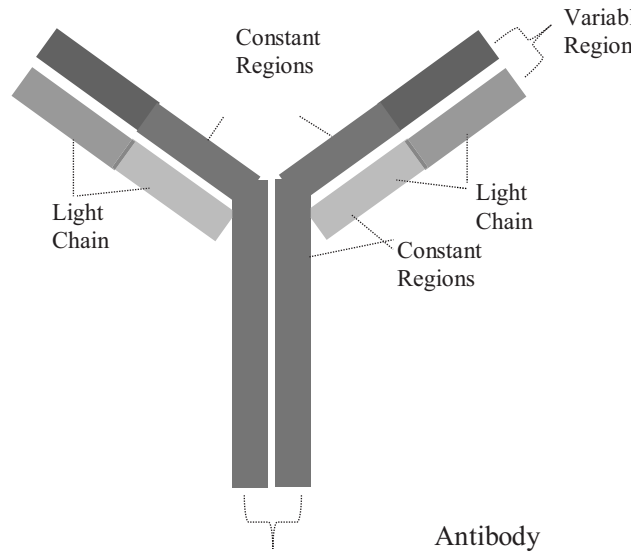
[4] Prescribing Information of Humira, Abbvie (May 2017), http://www.rxabbvie.com/pdf/humira.pdf [https://perma.cc/24HD-6REV].
[5] *Id.*
[6] *Id.*
[7] '081 Patent, claim 25.
[8] '081 Patent claims 1 and 22 (issued April 16, 2013).

Humira refers to a genus of antibodies, in which Humira is but one embodiment. This difference between scientific perspective and legal perspective is what may lead to the discrepancies between what a company thinks it claimed, what the patent actually claims, and what competitors think the patent covers. The patent applicant represents the scientist's view of the invention while the court represents the legal view. The PTO is the intermediary trying to resolve the discrepancies between the scientific paradigm and the legal paradigm.

II. SCIENTIFIC PARADIGM

A. What is an Antibody?

The human body produces antibodies in response to the presence of a foreign substance called an antigen. An antibody is a protein produced by B-cells that is part of the body's adaptive immune system, made up of two immunoglobulin proteins that bind together in a Y-shaped structure formed of two heavy chains and two light chains.[9]



Antibody Structure

[9] Liz Cohen & Vanessa Rieu, *Patent Protection for Antibodies: The Evolving Challenges*, 14 BIO-SCIENCE L. REV. 9, 9 (2014); Lauren Sompayrac, HOW THE IMMUNE SYSTEM WORKS 4 (3rd ed. 2008).

The constant region of the antibody, the "tail" of the Y shape, forms the receptor binding region that binds to the surface of host cells.[10] The constant region of the antibody determines the antibody's immunoglobulin class: IgA, IgD, IgE, IgM, and IgG.[11] Since there are five classes of antibody constant regions, patent applicants tend not to describe the structural sequence of an antibody by its constant region because an antibody constant region is not a distinguishing feature. Instead, an antibody's identifying features come from its variable region. The variable region of the antibody, the top of the "hands" of the Y shape, forms the antigen binding region that binds to an antigen.[12] The variable region is made up of complementarity-determining regions, three on the light chain and three on the heavy chain.[13] The complementarity-determining regions are described by their amino acid sequence, which vary based on the antibody's target antigen.[14] Patent applicants generally have to disclose the amino acid sequences of all six complementarity-determining regions in an antibody patent application, otherwise the examiner will likely reject the application for failure of written description and enablement (failure to describe and enable one of ordinary skill in the art to make the claimed antibody). Specifically, the variable region of an antibody binds to the epitope residue of the antibody's target antigen.[15] An epitope is formed from residue amino acid sequences on an antigen; therefore, epitopes are just as

[10] Lauren Sompayrac, HOW THE IMMUNE SYSTEM WORKS 4 (3rd ed. 2008).
[11] *Id.*
[12] *Id.*
[13] Payam Moradian, *Antibody and Epitope Patent Prosecution Tips: Part 1*, Law 360. (Oct. 26, 2016), https://www.law360.com/articles/854929/antibody-and-epitope-patent-prosecution-tips-part-1[https://perma.cc/2QLV-9QDK].
[14] *Id.*
[15] *Id.*

specific as the antibody variable regions because of the multiple amino acid sequences that can make up an epitope residue.[16] An antibody binds to the epitope residues of its target antigen. Polyclonal antibodies can bind to a variety of epitopes because polyclonal antibodies are produced by multiple B lymphocyte with different specifies and affinities.[17] Alternatively, monoclonal antibodies bind to a specific epitope because monoclonal antibodies come from a single B lymphocyte cell.[18] While a monoclonal antibody variable region can only bind to a specified, unilateral epitope, that epitope can bind to multiple antibody variable regions. Instead of describing an antibody by the antibody's amino acid sequence, the antibody may be described by the amino acid sequence of the antibody's target epitope residue.[19] Here, the patent applicant is not claiming the epitope, just the antibody though a description of its target epitope residue.[20] This is functional claiming because an antibody, as released by a company, is not already attached to its target epitope; instead, the antibody is composed of two immunoglobulin proteins. There are multiple ways to describe the epitope residue to which the antibody binds, including the specific amino acid sequence of the target epitope residue, the alpha-helix, the beta-helix, or by reference to another known antibody.[21] Additionally, applicants may not claim an epitope itself because unlike an antibody, the epitope is naturally produced, therefore

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[16] *Id.*
[17] Liz Cohen & Vanessa Rieu, *Patent Protection for Antibodies: The Evolving Challenges*, 14 BIO-SCIENCE L. REV. 9, 9-10 (2014).
[18] *Id.*
[19] *Supra* note 16.
[20] *Id.*
[21] Colin G. Sandercock & Ulrich Storz, *Antibody specification beyond the target: claiming a later-generation therapeutic antibody by its target epitope*, 30 NATURE 615, 617 (2012).

epitopes fall under one of the judicial exceptions, natural phenomena, to 35 U.S.C. §101 patentable subject matter.[22]

B. History of Patenting Antibodies

The first method of producing monoclonal antibodies was developed in 1975 by Céasar Milstein, dubbed the father of modern immunology, and Georges Köhler when they successfully created antibodies against sheep red blood cells by mixing mouse cells with sheep red blood cells on an agar plate.[23] This discovery led to modern hybridoma technology and monoclonal antibodies, antibodies produced from a single cloned immune cell, a single hybrid.[24] Even though Kohler and Milstein were awarded a Nobel Peace Prize for their research, they were not able to patent their discovery because they published their *Nature* article prior to patenting; at that time British patent law did not allow an applicant to disclose his work, such as through publication, prior to filing.[25] The first official patents on a method for making monoclonal antibodies were in October 1979 and April 1980, granted to

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[22] 35 U.S.C. § 101 (2012); Payam Moradian, *Antibody and Epitope Patent Prosecution Tips: Part 2*, LAW 360 (Oct. 27, 2016), https://www.law360.com/articles/854935?scroll=1 [https://perma.cc/P4XU-9NNE].

[23] G. Köhler & C. Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 NATURE 495, 496 (Aug. 7, 1975).

[24] Andre T. Serafini et al., *Monoclonal Antibody Patents: Evolving Law & Strategies*, FENWICK & WEST LLP (Oct. 1, 2012), https://www.fenwick.com/publications/pages/monoclonal-antibody-patents-evolving-law-and-strategies.aspx [https://perma.cc/6X5Z-RML5].

[25] *See* Welcome Witnesses to Twentieth Century Medicine, vol. 1 (E.M. Tansey et al. eds., 1997); *A Missed Opportunity? The Patent Saga*, WHAT IS BIOTECHNOLOGY? (2017), http://www.whatisbiotechnology.org/index.php/exhibitions/milstein/patents [https://perma.cc/HS5J-TX5W].

Hilary Koprowski, Carlo Croce, and Walter Gerhard for monoclonal antibodies against tumor and influenza antigens.[26] While these patents instigated a major controversy in the British and international scientific community because the patents merely used Milstein and Kohler's unpatented technique to make their own monoclonal antibodies, this first antibody patent initiated subsequent antibody patents on improving monoclonal antibody production.[27] Since the technique for producing monoclonal antibodies has long been established, antibody patenting has moved from method claims of producing the antibody to composition of matter claims with applicants claiming the antibody itself. These composition of matter claims allow for a broader claim scope. Biotechnology companies have invested countless dollars into the research and development costs of producing monoclonal antibodies; one study found that the cost of developing a new biologic is around 1.2 billion dollars.[28] Likewise, litigation over monoclonal antibodies remains the most expensive form of litigation in the biotechnology industry.[29] Without a broad claim scope for a

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[26] *A Missed Opportunity? The Patent Saga*, WHAT IS BIOTECHNOLOGY? (2017), http://www.whatisbiotechnology.org/index.php/exhibitions/milstein/patents [https://perma.cc/HS5J-TX5W].

[27] *A Missed Opportunity? The Patent Saga*, WHAT IS BIOTECHNOLOGY? (2017), http://www.whatisbiotechnology.org/index.php/exhibitions/milstein/patents [https://perma.cc/HS5J-TX5W]; Andre T. Serafini et al., *Monoclonal Antibody Patents: Evolving Law & Strategies*, FENWICK & WEST LLP. (Oct. 1, 2012), https://www.fenwick.com/publications/pages/monoclonal-antibody-patents-evolving-law-and-strategies.aspx [https://perma.cc/6X5Z-RML5].

[28] Ulrich Storz, *Rituximab: How Approval History is Reflected by a Corresponding Patent Filing Strategy*, 6 LANDES BIOSCIENCE 820, 820 (2014).

[29] Serafini, supra note 24.

biotechnology company's antibody, these companies are not likely to invest the money into monoclonal antibody production. Since monoclonal antibody patenting changed from methods to composition of matter claims, applicants have a choice in how they wish to claim their monoclonal antibody: by the amino acid sequence of the antibody itself (structurally) or the amino acid sequence of the epitope residue on the antibody's target antigen (functionally). Which type of claim provides better protection? Biotechnology companies do not merely want a claim on a single antibody, they often want a broader claim scope to an entire genus of antibodies with this same function of attaching to a specified target antigen. How can these companies guarantee a broad patent scope on its antibody, while at the same time protect against future research that potentially develops similar antibodies that perform the same function? More broadly, how can these claims to a genus of antibodies satisfy the patent bargain if an application is directed towards a broad claim scope over an entire genus of antibodies while, at the same time only disclosing a specified number of species within that genus?

III. LEGAL PARADIGM

A. Written Description Requirement and Antibodies

A patent application must satisfy all requirements laid out in 35 U.S.C. § 112, including the written description requirement. The written description requirement of 35 U.S.C. § 112 requires the patent applicant to sufficiently and particularly disclose his or her invention.[30] In the PTO Written Description Materials, the PTO decided that a patent which claims an antibody by its target antigen satisfies the 35 U.S.C. § 112 written description requirements because

[30] 35 U.S.C. §112(a) (2012).

one skilled in the art would know how to produce antibody specific antigen.[31] Specifically, the PTO's example 13, "Antibodies to a Single Protein" in its written description guidelines states that functionally claiming an antibody is permissible when the isolated antibody described is "capable of binding to antigen X" and the specification sufficiently describes the protein X (an antigen is a protein).[32] The PTO stated that the specification did not need to describe an actual reduction to practice of an antibody binding to antigen X, describe the antibody in structural terms, provide a relation between the antibody binding to antigen X and the structure of that antibody, or provide a method for the antibody to bind to antigen X because with of a sufficient description of antigen X, usually structural, the antibody will be apparent to one of ordinary skill in the art based on the routineness of producing antigen-specific antibodies.[33] Overall, in these written description requirements the PTO reasoned that all that is needed for an antibody claim to a single protein is the structure of the specific antigen; one of ordinary skill in the art did not consider the amino acid sequence of the variable regions of the specific antibody to be necessary in reproducing the specific anti-X antibody.[34]

Similarly, the PTO declared that a patent may claim a genus of antibodies without disclosing multiple, specific amino acid sequences of example antibodies so long as the specification enables one skilled in the art to reproduce the antibody.[35] Specifically, in written description guidelines example 14 "Antibodies to a Genus of Proteins," the PTO

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[31] U.S.P.T.O, WRITTEN DESCRIPTION TRAINING MATERIALS, Revision 1, 45-6 (2008), https://www.uspto.gov/sites/default/files/web/menu/written.pdf [https://perma.cc/3XJG-DEQP].
[32] *Id.*
[33] *Id.*
[34] *Id.*
[35] *Id.* at 47-9 (*see* Example 14).

used the same principle it applied in example 13, "Antibodies to a Single Protein," that an applicant may claim a genus of antibodies without fully disclosing the structure of each antibody when the applicant fully discloses the protein to which those antibodies attach, the antigen, and those skilled in the art would know how to produce these antigen-specific antibodies.[36] The PTO created this antibody exception even though it is in conflict with the PTO's default written description and enablement requirements of 35 U.S.C. § 112, wherein the patent application must disclose that the inventor was in actual possession of the invention at the time of filing and enable someone skilled in the art to produce the invention.[37]

The difference with antibody patents, as compared to electrical and even other chemical patents, is that it may not be possible for the inventor to know all the possible antibody sequences against a certain target epitope residue at the time of filing a patent application.[38] If an inventor were only allowed an antibody patent on what he disclosed or proved was in his possession, such restrictions would lead to very narrow patents. While the inventor would be able to prevent others from copying his exact antibody (i.e., what was disclosed in the patent application), he would not be able to exclude others from making and patenting similar antibodies, even with the same functionalities of targeting the same antigen.[39] While in the short term this would develop healthy competition and perhaps lower prices for consumers, I propose that in the long term this would lead to

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[36] *Id.*
[37] 35 U.S.C. §112 (2015).
[38] Oskar Liivak, *Guest Post: Centocur, the Antibody Exception, and Claiming Only What Was Invented*, Patentlyo (Feb. 27, 2011), http://patentlyo.com/patent/2011/02/guest-post-centocor-the-antibody-exception-and-claiming-only-what-was-invented.html [https://perma.cc/P48Q-P5TR].
[39] *Id.*

less antibody development. Pharmaceutical companies would stop investing in antibody research and production because the research and development costs of producing an antibody are very high while the costs of copying, slightly changing the antibody to find a different variant, are much lower. This led to the PTO declaring an antibody exception to 35 U.S.C. § 112 including a lesser written description requirement, wherein an inventor could claim an antibody without disclosing the antibody's specific structure (the amino acid sequence of the antibody's variable regions) so long as the applicant provides enough details in the specification such that one of ordinary skill in the art would know how to produce the claimed antibody(ies) and the outer boundaries of the patent.[40]

B. Functionally Claiming Antibodies

While PTO examiners may prefer when an applicant describes his invention using structural language, the PTO has declared that an applicant may alternatively explain his invention by what it does rather than what it is, known as functional language.[41] A functional claim does not always limit the claim to a 35 U.S.C. § 112(f) means-plus-function limitation, especially when the claim uses functional language in connection with structural language.[42] Usually, this requires one of ordinary skill in the art to know how to make and use the invention, meeting the 35 U.S.C. § 112 written description and enablement requirements, based on the presented functional limitation.[43] Often, patent claims to

[40] U.S.P.T.O, WRITTEN DESCRIPTION TRAINING MATERIALS, Revision 1, 45 (2008), https://www.uspto.gov/sites/default/files/web/menu/written.pdf [https://perma.cc/3XJG-DEQP].
[41] MPEP (9th ed. Nov. 2015) (*see* § 2173.05(g)).
[42] *Id.*
[43] *Id.*

novel therapeutic antibodies (e.g., monoclonal antibody therapy) functionally claim the inventive antibody because the applicant typically has not physically produced the claimed antibody.[44] These claims are allowed under constructive possession, so long as the claimed antibody is described sufficiently for a person skilled in the art to produce such antibody.[45] An antibody claimed by the structure of a target epitope residue on its specified antigen is a functional claim even though the claim provides structure, because this is the structure of a part of the antigen and not the antibody itself. This claims the antibody in use, when the antibody is administered, rather than sitting on the shelf of a warehouse. As the PTO explained in example 13 of its written description guidelines, this type of functional claiming of antibodies is acceptable so long as the applicant fully described the specified antigen and one of ordinary skill in the art would know how to make these antibodies by routine and conventional methods.[46]

C. Claiming an Antibody Genus

The default written description requirement of 35 U.S.C. § 112 states that the applicant must disclose enough so that one skilled in the art would know with reasonably clarity that the inventor was in possession of the claimed invention as of the filing date.[47] The PTO has stated that an applicant can show possession of the claimed invention by an actual reduction to practice, with the inventor actually having the invention in hand, or by constructive reduction to practice, by proving that the invention was ready for patenting though drawings, chemical formulas, or identifying distinguishing characteristics of the claimed

[44] Sandercock & Storz, supra note 21.
[45] *Id.*
[46] Sandercock & Storz, supra note 21.
[47] U.S.P.T.O, supra note 41.

invention.[48] While an invention as claimed in the specification will put the public on notice of what the inventor possess at the time of invention, what about other similar inventions that are practically the same as that of the inventor, but the inventor did not actually possess as of the filing date? This is particularly problematic in the field of biologics where a lot of research and development costs go into developing a drug or an antibody, and a competitor can copy the inventor's disclosed drug and make enough modifications such that the drug will not fall within the inventor's claim scope, but the drug still behaves similarly to the inventor's drug. For example, many antibodies can target the same epitope residue on an antigen. If an inventor claims an antibody that attaches to epitope 1, a competitor can slightly change the variable region of that inventor's disclosed antibody without changing its affinity to also attach to epitope 1. This presents a problem in drug development because pharmaceutical companies will not invest in research and development if the company will only be allowed to obtain a small patent scope as for its specified drug, and will only get the disclosed antibody structure. Consequently, this could either lead to pharmaceutical companies not investing at all in drug development and innovation, or alternatively these same companies not disclosing, but instead keeping its drugs a trade secret until enough research has been done to identify all possibly known variants. Though, it is more likely that pharmaceutical companies will not invest in research and development because drug development is a race with many companies performing the same research. Without the guarantee of a strong and broad patent claim scope, these companies will most likely not take the chance that they will be the first to discover all the drug variants and take the time to obtain a patent for each one.

[48] *Id.*

In addition to the antibody exception to the default written description requirement, the PTO allows an applicant to claim a genus without disclosing every species within that genus.[49] The PTO has stated that an applicant can obtain protection over species not claimed in the application when one of ordinary skill in the art could "envisage" a specified species based on the disclosures in the specification, by either drawing a structural formula or writing the compound names of species that fall under the disclosed generic formula.[50] The Federal Circuit interpreted the PTO's guidelines on claiming a genus in *Regents of Univ. of Cal. v. Eli Lilly & Co.* (hereinafter *Regents of Univ. of Cal.*) by holding that an applicant may secure patent protection over a genus by disclosing a representative number of species within the genus or disclosing a structural feature that is common to all species within this genus.[51] Here the court held that The Regents of University of California's '525 and '740 patents directed towards cDNA and which disclose techniques for incorporating human proinsulin cDNA into a recombinant plasmid using a specific semi-synthetic DNA incorporated into a suitable transfer vector were invalid for lack of written description.[52] The Regents of University of California's '740 patent claimed "[a] DNA transfer vector comprising an inserted cDNA consisting essentially of a deoxynucleotide sequence coding for human proinsulin…"[53] The Regent of University of California attempted to claim the entire genus of human proinsulin cDNA made by any method of DNA incorporation into a transfer vector. Eli Lilly also produced human proinsulin cDNA using a cleavable fusion protein by a bacterial protein, transfer

[49] U.S.P.T.O, supra note 41.
[50] *Id.*
[51] Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997).
[52] *Id.* at 1563-64.
[53] *Id.* at 1563.

vector, fusing with human proinsulin.[54] The Regents of University of California only disclosed its method of producing cDNA using rat insulin and tried to claim a patent scope over all vertebrate or mammalian insulin cDNA.[55] Since Eli Lilly used a bacterial protein instead of rat insulin, the Federal Circuit disregarded the Regents of University of California's argument that Eli Lilly's human proinsulin cDNA was the same as its claimed human proinsulin cDNA either literally or under the doctrine of equivalents.[56] Instead, the Federal Circuit agreed with Eli Lilly's argument that its cDNA did not fall under the cDNA disclosed by the Regents of University of California in patents '525 and '740 and that its claim, as previously granted, was invalid under the written description requirement because it attempted to gage a larger claim scope than what was disclosed.[57] Similarly, in *Centocor Ortho Biotech, Inc. v. Abbott Labs.* (hereinafter *Centocor*) the Federal Circuit held that Centocor's claim 2 in patent '755 towards an isolated recombinant anti-TNF-alpha antibody was invalid for lack of written description because Centocor only disclosed chimeric antibodies, but attempted to cover all antibodies that had a human constant region and variable region from any source.[58] Like *Regents of Univ. of Cal.*, Centocor only disclosed anti-TNF-alpha antibodies with chimeric antibodies, combining human genetic material with genetic material from a non-human source, whereas Abbott constructed a fully-human antibody, leading to the Food and Drug Administration approving its drug Humira (which occurred prior to issuing of Centocor's chimeric antibody

[54] *Id.*
[55] *Id.* at 1568.
[56] *Id.* at 1562, 1568.
[57] *Id.* at 1569.
[58] Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1346-47, 1353 (Fed. Cir. 2011).

patent).[59] In *Centocor*, the Federal Circuit interpreted antibody example 13 of the PTO's Written Description guidelines of an antibody to a single protein to indicate that an applicant may claim an antibody without fully describing the structure (amino acid sequence of the antibody) when the applicant fully discloses the "novel protein," antigen in the specification and the method of producing the antibody is routine and well understood at the time of filing.[60] Since Centocor did not completely describe a fully-human antibody at the time of filing (Centocor only disclosed chimeric antibodies) the Federal Circuit held that Centocor's claim towards anti-TNF-alpha antibodies did not encompass Abbott's fully-human antibody; therefore, Centocor's claim towards anti-TNF-alpha antibodies was invalid under 35 U.S.C. § 112 for lack of written description.[61] The Federal Circuit in *Centocor* articulated the proposition that while an applicant does not need to provide examples or a reduction to practice of the claimed antibody, the applicant must specifically disclose an antibody that binds to human TNF-alpha even if human TNF-alpha protein and antibodies to that protein are already known in the field.[62] This is a case where the claim would meet the enablement requirement of 35 U.S.C. § 112 since one of ordinary skill in the art would know how to make and use these anti-human TNF-alpha antibodies, but the claim would fail for lack of written description requirement under 35 U.S.C. § 112 for not proving that the inventor "possessed" an anti-human TNF-alpha antibody at the time of filing. This seems to be the start of the Federal Circuit narrowing the PTO's antibody exception to the written description requirement by requiring

[59] *Id.* at 1346.
[60] Moradian, supra note 13; Centocor Ortho Biotech, Inc., 636 F.3d at 1351-52.
[61] Centocor Ortho Biotech, Inc., 636 F.3d at 1353.
[62] *Id.* at 1352.

"possession," though the Federal Circuit does not explicitly state this presumption.

D. Interpreting the PTO's Antibody Exception

In 2014, the Federal Circuit interpreted the PTO's antibody exception to the written description requirement in *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.* (hereinafter *Abbvie*). AbbVie owns patents 6,914,128 and 7,504, 485 (hereinafter '128 and '485, respectively) directed towards an anti-human interleukin-12 (hereinafter IL-12) antibody that discloses the amino acid sequence of the complementarity-determining regions of 300 antibodies that bind to IL-12, where all the disclosed amino acid sequences share 90% similarity in the variable region.[63] At issue in this case was claim 29 of AbbVie's '128 patent which reads "[a] neutralizing isolated human antibody, or antigen-binding portion thereof that binds to human IL-12 and disassociates from human IL-12 with a k_{off} rate constant of $1x10^{-2}$ s^{-1} or less, as determined by surface plasmon resonance."[64] Centocor filed its patent application 10/912,994 (hereinafter '994), also on an anti-IL-12 antibody with a 50% amino acid sequence to AbbVie's anti-IL12 antibodies, and initiated an interference with AbbVie's '128 patent because, like AbbVie's '128 claim 29, Centocor's antibody also bound to human IL-12 and had a dissociation rate of $1x10^{-2}$ s^{-1} or less.[65] While AbbVie and Centocor's respective antibodies function similarly, Centocor's claimed antibody is not structurally similar to AbbVie's disclosed antibody sequences. One of the concerns in *Abbvie* that is important here was whether AbbVie's '128 patent met the sufficient

[63] Abbvie Deutschland GmbH & Co. v Janssen Biotech, Inc., 759 F.3d 1285, 1291 (2014).
[64] U.S. Patent No. 6,914,128, at col. 386 l. 55 (filed Mar. 24, 2000).
[65] Abbvie Deutschland GmbH & Co., 759 F.3d at 1292.

written description requirements, specifically the PTO's antibody exception to the written description requirements to claim a broad genus of antibodies that associate with IL-12, as articulated by claim 29.[66] AbbVie argued that it met the written description requirement for this genus of antibodies because it disclosed all known amino acid sequences for its anti-IL-12 antibody and as per the PTO's antibody exception it was not required to provide all sequences within this genus.[67] In the specification, AbbVie's disclosure of known amino acid sequences for its anti-IL-12 antibody is narrower than the language of its claim 29 towards all human antibodies that bind to human IL-12. The Federal Circuit agreed with Centocor's argument that AbbVie was trying to obtain a broader scope than its disclosure contained, which is in violation of the written description requirement of 35 U.S.C. § 112.[68] The Court further reasoned that AbbVie would have been able to claim a genus of anti-IL-12 antibodies without disclosing the structure of each species if all the species shared a common structural feature or the patent discloses a sufficient representative number of species.[69] Since the anti-IL-12 antibodies in AbbVie patents do not share a common structural feature common, AbbVie had to prove that it disclosed a sufficient number of representative antibodies to stake a claim in this genus.[70] The PTO does not define a sufficient number of representatives species, therefore it is up to the courts (i.e. the legal paradigm) to determine whether a patent applicant meets this requirement. The Federal Circuit concluded that AbbVie's claims did not meet the sufficient number of representative species to claim a

[66] *Id.* at 1297.
[67] *Id.* at 1298.
[68] *Id.*
[69] Abbvie Deutschland GmbH & Co, 759 F.3d 1285 at 1299; 6 PATENT OFFICE RULES AND PRACTICE, Example 14 (2008).
[70] Abbvie Deutschland GmbH & Co, 759 F.3d 1285 at 1299.

genus over all anti-IL-12 antibodies.[71] The Federal Circuit reasoned that the antibodies disclosed in AbbVie's patents shared 90% of the same complementarity-determining regions and all contain VH3 (variable) heavy chains and Lambda type light chains.[72] Unlike AbbVie's disclosed antibodies, Centocor's antibody has a VH5 heavy and Kappa type light chains.[73] Structurally, Centocor's VH5 and Kappa anti-IL-12 antibody is about 50% different from AbbVie's disclosed VH3 and Lambda anti-IL-12 antibodies. Ultimately, the Federal Circuit ruled that AbbVie only disclosed anti-IL-12 antibodies with VH3 heavy chain and Lambda light chains, but claimed that these heavy and light chains can be modified to yield other anti-IL-12 antibodies; therefore, AbbVie could not claim this entire genus of anti-IL-12 antibodies with only a disclosure of a particular species (Sanofi's antibody was not a VH3 Lambda, therefore it did not fall within AbbVie's disclosure).[74] The Federal Circuit's holding in *Abbvie* narrows the PTO's antibody exception to the written description requirement, almost going back to the default written description requirement minus proof of a reduction to practice, in ruling that to claim a wide genus of antibodies, the specification must structurally disclose a representative of each species within the genus. Though, the Federal Circuit's ruling may also be narrower due to the fact that AbbVie's patent claimed its anti-IL-12 antibodies in claim 29 functionally rather than structurally by the amino acid sequence of an antibody itself.[75] The Federal Circuit ruled that in order to claim a

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[71] *Id.* at 1300.
[72] *Id.*
[73] *Id.*
[74] Abbvie Deutschland GmbH & Co, 759 F.3d 1285 at 1300; Payam Moradian, *Antibody and Epitope Patent Prosecution Tips: Part 2*, Law 360. (Oct. 27, 2016), https://www.law360.com/articles/854929/antibody-and-epitope-patent-prosecution-tips-part-2 [https://perma.cc/P4XU-9NNE].
[75] *Id.* at 1299.

genus using functional language, the specification must sufficiently identify what the applicant wishes to claim as a generic invention and that the applicant must disclose a sufficient number of species, all of which achieve this generic result.[76] As previously discussed, the Federal Circuit explicitly stated that AbbVie did not disclose a species that encumbered Centocor's VH5 and Kappa anti-Il-12 antibody, therefore AbbVie did not provide a sufficient disclosure to merit its protection for the genus claimed in patent '128 claim 29.[77] The Federal Circuit further implied that while it narrowed the PTO's antibody exception for the written disclosure requirement by not granting AbbVie protection for the genus of anti-IL-12 antibodies even though Centocor's Stelara was not known at the time AbbVie filed its patent application, AbbVie's patent '128 claim 29 may have been considered valid and the Federal Circuit may have granted the broader scope if AbbVie provided disclosure of an antibody structurally similar to Stelara (VH5 and Kappa variable complementarity-determining regions).[78] Here, the Federal Circuit is not fully closing the door on the PTO's antibody exception to the written description requirement, but merely narrowing the requirements to suggest that if an applicant wants to claim a broad genus of antibodies, the applicant must disclose a structurally representative antibody of each species within that genus.

Though, how does this narrower requirement hold true in the evolving nature of antibody research, where like AbbVie, the applicant can only disclose the antibodies known at the time of filing? Simple or complicated but well known techniques can create a structurally different enough antibody that would not be included under the *Abbvie* court's narrower interpretation of the PTO's antibody exception.

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[76] *Id.*
[77] *Id.* at 1301.
[78] *Id.*

IV. AMGEN V. SANOFI

A. Amgen and Written Description

After *Regents of Univ. of Cal.* and *Abbvie*, where the Federal Circuit vastly narrowed the PTO's antibody exception to the written description requirement by stating that for an applicant to claim a genus of antibodies, that applicant must disclose all possible structures of the antibody its patent is to cover,[79] many companies most likely switched from disclosing an antibody's complementarity-determining regions, as AbbVie did, to disclosing the amino acid sequences (epitope residues) of an antibody's target antigen. It may be easier to figure out known epitope residues, to which these antibodies bind, than possible antibody structures; therefore, these companies' patents are more likely to remain valid with the evolution of research by just describing the epitope residues.

The United States District Court for the District of Delaware upheld the jury verdict in *Amgen Inc. v. Sanofi* (hereinafter *Amgen*), that Amgen's patent claims directed towards a genus of antibodies that bind to specified epitopes on PCSK9 was valid under the written description and enablement requirements. This case is directed towards a genus of antibodies that lower the level of low-density lipoprotein (hereinafter LDL), also known as bad cholesterol, in the blood.[80] Amgen is a Delaware corporation that developed a drug with its active ingredient being an antibody that binds to PCKS9. Amgen filed a U.S. patent family which includes patents 8,829,165 (hereinafter '165) and 8,859,741 (hereinafter '741) that issued September 9, 2014 and October 14, 2014, respectively.[81]

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[79] *Supra* note 53, 59.
[80] Amgen Inc. v. Sanofi, No. 14-1317-SLR, 2017 U.S. Dist. LEXIS 192, at *7 (D. Del. Jan. 3, 2017).
[81] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *4.

Amgen's drug, Repatha, with the active ingredient, evolocumab, is a monoclonal antibody that binds to PCSK9 to prevent PCSK9 from binding to low density lipoprotein receptor (hereinafter LDLR), thus lowering LDL cholesterol in the blood.[82] Sanofi is a French company (though also incorporated under the laws of Delaware) which also developed a drug against bad cholesterol, Praluent, with the active ingredient alirocumab, a monoclonal antibody that also reduces LDL cholesterol levels in the blood.[83] While Amgen filed this patent family on August 23, 2007, with patent '165 on April 10, 2013 and '741 on April 24, 2014, Sanofi obtained Federal Drug Administration (hereinafter FDA) approval for Praluent in July 2015 while Amgen did not obtain FDA approval for Repatha until August 2015.[84] On October 17, 2014, right after Amgen's patent '741 issued, Amgen sued Sanofi alleging that Sanofi's Praluent infringed its '698, '165, and '741 patents (all that is left in this case are the two patents '165 and '741), specifically claim 1 of both patents.[85] Sanofi counterclaimed arguing that claim 1 of both patents '165 and '741 were invalid for lack of written description and enablement, and were also obvious in light of the prior art[86] (this note is only discussing Sanofi's assertion that the claims were invalid for lack of written description). Claim 1 in Amgen's '165 and '741 patents claims an isolated monoclonal antibody that binds to given residues on PCSK9,[87] epitope residues on PCSK9. Specifically, Sanofi argues that Amgen broadly claimed all anti-PCSK9 antibodies that bound to specified epitope

[82] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *7.
[83] *Id.*
[84] U.S. Patent No. 8,859,741 (issued Oct. 14, 2014); U.S. Patent No. 8,829,165 (issued Sept. 9, 2014); Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *7.
[85] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *2.
[86] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *6-7.
[87] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *7.

residues without disclosing a representative number of antibodies and there was no common structural feature among anti-PCSK9 antibodies for Amgen to obtain such a broad patent scope.[88] Amgen's specification, which is the same in both '165 and '741, articulates that more than 3,000 monoclonal antibodies were screened for binding affinity to PCSK9, of which 100 strongly blocked the interaction between PCSK9 and LDLR, and Amgen provided the amino acid sequence of over twenty-four of these identified antibodies.[89] Both Amgen and Sanofi presented expert testimony interpreting Amgen's disclosures in the specification, whether Amgen's specification provided enough detail that would enable one of skill in the art to know the full scope of Amgen's patent claim, and whether this covered the entire genus of antibodies or just the species disclosed. The main issue with *Amgen*, which differentiated it from *Abbvie* and *Centocor* was that Amgen was claiming a genus of antibodies, not by the amino acid sequence of the antibody itself but by the amino acid sequences of the antibody's target epitopes residues. This is structure-by-function claiming, whereby Amgen claimed evolocumab by its function in the human body of binding to specified epitope residues and not evolocumab sitting on the shelf of a pharmacy. Here, the district court uses the PTO's antibody exception to the written description requirements, as interpreted by *Abbvie*, but this time with specified epitope residues instead of specified amino acid sequences of the antibodies themselves. The jury ultimately concluded that these claims were not invalid for lack of written description or enablement, thus concluding that as presented here Amgen provided enough disclosed antibodies (only twenty four) to claim a wide genus of antibodies that bind to specified epitope resides of PCSK9.[90] Since this ruling, the

[88] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *16-21.
[89] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *5.
[90] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *34.

district court has affirmed the jury's ruling by granting Amgen's motion for a permanent injunction, prohibiting Sanofi from marketing Praulent, and denying Sanofi's motion to stay entry of the permanent injunction, though recently the Federal Circuit reversed the injunction and remanded back to the district court with new jury instructions.[91]

B. Comparing Repatha and Praulent

Since the district court held that Sanofi's Praulent fell within Amgen's patents '165 and '741, how similar are Repatha and Praulent? Clearly, the court did not think that Amgen fell into the same trap as *Abbvie*, where the Federal Circuit held that AbbVie only disclosed VH3 and Lambda anti-IL-12 antibody, so AbbVie's claim scope did not include Centocor's VH5 and Kappa anti-IL-12 antibody, a supposedly structurally distinct antibody.[92] Amgen's Evolocumab is a monoclonal antibody with a molecular weight of 141.8kDa and consists of immunoglobulin G2 (IgG_2) comprised of gamma 2 heavy chains bound to a lambda light chain by disulfide bonds.[93] Sanofi's Alirocumab is a monoclonal antibody with a molecular weight of about 146kDa and consist of immunoglobulin G1 (IgG_1) comprised of gamma 1 heavy chains bound to a kappa

[91] Amgen Inc. v. Sanofi, No. 14-1317-SLR, 2017 U.S. Dist. LEXIS 1315, at *9 (D. Del., Jan. 5, 2017); Amgen Inc. v. Sanofi, No. 14-1317-SLR, 2017 U.S. Dist. LEXIS 2883, at *3 (D. Del. Jan. 9, 2017). The Federal Circuit recently reversed the district court's permanent injunction in *Amgen Inc. v. Sanofi*, 2017 U.S. LEXIS 19416* (Fed. Cir. 2017).

[92] *Supra* note 54-57.

[93] Arrigo FG Cicero, Alessandro Colletti, & Claudio Borghi, *Profile of evolocumab and its potential in the treatment of hyperlipidemia*, 9 DRUG DESIGN, DEV. AND THERAPY 3073, 3074 (2015).

light chain by disulfide bonds.[94] While Evolocumab and Alirocumab have slightly different molecular weights, they are both within the same immunoglobulin class, IgG. Unlike *Abbvie*, where the court held that AbbVie's anti-IL-12 antibody with a lambda light chain was structurally different enough from Centocor's anti-IL-12 antibody with a kappa light chain, the district court in *Amgen* reasoned that Amgen's IgG_2 with a lambda light chain was structurally similar enough to Sanofi's IgG_1 with a kappa light chain.

Why do these two cases have different results? Is this due to AbbVie disclosing only antibodies with VH3 and Centocor's antibody having a VH5? This difference is more likely due to how both parties claimed their respective antibody species rather than each party's disclosure. In addition to disclosing experimental results, both AbbVie and Amgen disclosed species of anti-IL-12/anti-PCSK9 antibodies by sequences of particular heavy and light chains.[95] Amgen only provided the sequence of twenty-four of these antibody sequences, while AbbVie disclosed many more. In addition, Amgen also disclosed the amino acid sequences of epitope residues on PCSK9.[96] AbbVie was not silent on which epitopes anti-IL-12 antibody bound, but AbbVie was not as specific as Amgen with identifying such epitopes; for example, in the specification AbbVie states that a group of identified heavy and light chain regions recognize the p40 epitope.[97] AbbVie mentions more of these groups throughout the rest of the specification. Amgen provides the amino acid sequence of particular epitope residues as well as where on the antigen (the PCSK9 protein) an antibody will

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[94] Marina Manniello & Michele Pisano, *Alirocumab (Praluent): First in the New Class of PCSK9 Inhibitors*, 1 PHARMACY AND THERAPEUTICS 28, 28-29 (Jan. 2016).
[95] U.S. Patent No. 6,914,128, at Drawings (issued Jul. 5, 2005).
[96] U.S. Patent No. 8,829,165, at 125-427 (issued Sep. 9, 2014).
[97] U.S. Patent No. 6,914,128, at 13:56-67 (issued Jul. 5, 2005).

bind.[98] The real difference between Amgen and AbbVie is in the claims, leading the Federal Circuit to declare that AbbVie's claimed antibody genus was invalid under the written description requirement for lack of a disclosure of a sufficient number of representative species and the U.S. District Court of Delaware declaring that Amgen's claimed antibody genus was valid under the written description requirement.[99]

C. Claim Construction

Prior to the jury trial, the court held a Markman hearing to interpret claim 1 of both Amgen's patents '165 and '741. Claim 1 of Amgen patent '165 reads:

> An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, Il54, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V389, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.[100]

At the Markman hearing on October 20, 2015 the district court judge interpreted "an isolated monoclonal antibody," to refer to proteins with two full-length or fragmented heavy chains and two full-length or fragmented light chains, and any variants thereon.[101] The district court judge based this finding on the specification's use of the term "antibody" to refer to any intact or fragmented immunoglobulin of any

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[98] U.S. Patent No. 8,829,165, at 61-63 (issued Sep. 9, 2014).
[99] U.S. Patent No. 8,829,165, at Claims (issued Sep. 9, 2014); U.S. Patent No. 6,914,128, at Claims (issued Jul. 5, 2005); Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *34; Abbvie Deutschland GmbH & Co, 759 F.3d 1285 at 1300, 1302.
[100] U.S. Patent No. 8,829,165 (issued Sep. 9. 2014).
[101] Amgen Inc. v. Sanofi, No. 14-1317-SLR, 2015 U.S. Dist. LEXIS 142256, at *3 (D. Del. Oct. 20, 2015).

isotype that specifically binds to the target antigen.[102] The district court judge interpreted "binds to . . . residues" to refer to the specification's "antigen binding region," specifically the antigen's epitope residues, where the specification defines "epitope" as "a region of an antigen that is bound by an antigen binding protein that targets the antigen, and when the antigen is a protein, includes specific amino acids that directly contact the antigen binding protein."[103] The district court judge also articulated, as stated in the specification, that epitopes can be functionally or structurally defined.[104] The specification mostly disclosed structural epitopes by their unique residues in the antigen, and the amino acid sequence of those residues.[105] Amgen's patent '741 is similar to '165, except claim 1 of '741 includes different epitope residues. Patent '741 claim 1 reads:

> An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.[106]

The district court judge construed "at least one of residues 237 or 238" to refer to a region on PCSK9 with one or both residues that is also recognized by an antibody.[107] Lastly, the district court judge interpreted "PCSK9" as the polypeptide sequence specified in the specification in its

[102] Amgen Inc., 2015 U.S. Dist. LEXIS 142256, at *2.
[103] Amgen Inc., 2015 U.S. Dist. LEXIS 142256, at *5, *6; *See also* U.S. Patent No. 8,829,165, at 36:50-54 (issued Sep. 9, 2014).
[104] Amgen Inc., 2015 U.S. Dist. LEXIS 142256, at *6; *See also* U.S. Patent No. 8,829,165, at 114:66-115:4, 114:4-5 (issued Sep. 9, 2014).
[105] U.S. Patent No. 8,829,165, at Drawings (issued Sep. 9, 2014).
[106] U.S. Patent No. 8.859,741, at Claims (issued Oct. 14, 2014).
[107] Amgen Inc., 2015 U.S. Dist. LEXIS 142256, at *8.

entirety or fragmented portions.[108] The district court judge, later in the proceeding, asserted that Amgen intended claim 1 of both '165 and '741 to be directed against a genus of antibodies.[109] As seen on its face, both claim 1 in '165 and '741 would encompass any anti-PCSK9 antibody that binds to PCSK9 at S153, Il54, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V389, S381, 237, or 238 of SEQ ID NO:3. These identified sequences represent the epitope residues where Amgen's antibodies bind.

In the specification, Amgen states that based on these sequences, one skilled in the art would be able to identify other antigen binding molecules, antibodies, that bind at or near one of these specified residues.[110] Comparatively, AbbVie patent '128 claim 1 reads;

> An isolated human antibody or antigen-binding protein thereof that binds to human IL-12 and dissociates from human IL-12 with a K_4 of $1x10^{-10}$ M or less and a k_{0ff} rate constant of $1x10^{-3}$ s^{-1} or less, as determined by surface plasmon resonance.[111]

Comparing AbbVie patent '128 claim 1 to Amgen patent '741 claim 1 both start by claiming "an isolated human antibody" that binds to human IL12/ PCSK9.[112] The differences between these two patents is apparent in how each claims the antibody itself. AbbieVie uses functional claiming to claim an "isolated human antibody, or antigen-binding protein" separate from the antigen, human IL-12, while Amgen is a bit more structural (though still functional because Amgen is claiming epitope residues, which are not

[108] Amgen Inc., 2015 U.S. Dist. LEXIS 142256, at *9; *See also* U.S. Patent No. 8,829,165, at Specification SEQ ID No 1 (issued Sep. 9, 2014).
[109] Amgen Inc. v. Sanofi, No. 14-1317-SLR, 2016 U.S. Dist. LEXIS 19525, at *1 (D. Del. Feb. 18, 2016).
[110] U.S. Patent No. 8,829,165, at 104:36-38 (issued Sep. 9, 2014).
[111] U.S. Patent No. 6,914,128, at 385:11-15 (issued Jul. 5, 2005).
[112] U.S. Patent No. 8,859,741 at 427:36 (issued Oct. 14, 2014); U.S. Patent No. 6,914,128, at 385:11-15 (issued Jul. 5, 2005).

a part of the structure of the anti-PCSK9 antibody) by claiming particular epitope residues where anti-PCSK9 monoclonal antibody will attach to PCSK9.[113] The Federal Circuit in *Abbvie*, agreed with the District Court of Massachusetts in *Abbott GmBh & Co., KG v. Centocor Ortho Biotech* (lower court opinion for *Abbvie*) that claims of the '128 patent failed for lack of written description because the application did not disclose a sufficient representative number of species within the anti-IL-12 antibody genus to claim this entire genus.[114] The district court in *Amgen* seemed to think that by claiming particular epitope residues along with a disclosure of the sequences of these epitope residues, and the twenty-four anti-PCSK9 monoclonal antibodies was enough of a sufficient representation number of species enough that one of ordinary skill in the art would recognize the full genus scope of Amgen's patent.[115]

D. Amgen's Global Filing Strategy

Both Amgen and AbbVie had vast global filing strategies when each company first started patenting its respective antibody, thus each company was confident in the strength of its claims. AbbVie filed 103 patent applications towards its claimed genus of anti-IL-12 antibodies in about thirty-four different intellectual property offices.[116] Amgen, like AbbVie, filed eighty-one patent applications towards anti-PCSK9 antibodies in thirty-one different intellectual

[113] *Supra* note 95.
[114] Abbott GmBh & Co., KG v. Centocor Ortho Biotech, Inc., 971 F. Supp. 2d 171, 175-76 (D. Mass. 2013).
[115] Amgen Inc., 2017 U.S. Dist. LEXIS 192, at *32-34.
[116] US 6914128, USPTO Global Dossier, https://globaldossier.uspto.gov/#/result/patent/US/6914128/104096 [https://perma.cc/5URJ-TEA8].

property offices.[117] AbbVie included fifteen applications in its U.S. patent family, while Amgen filed thirty U.S. patent applications towards anti-PCSK9 antibodies.[118] Both Amgen and AbbVie seemed pretty confident in its respective patents, in that each spent time and money filing many applications across the world to protect its exclusive right to make these antibodies. While AbbVie lost its anti-IL-12 antibody genus claim in *Abbvie Deutschland GmbH & Co.*, Amgen took a chance on filing its vast patent family prior to the *Amgen v. Sanofi* decision. The Federal Circuit in *Abbvie Deutschland GmbH & Co.* reversed the well-established practice of claiming a group antibodies by only disclosing a limited number antibodies within the group and distinguishing disclosed antibodies by function when it held that Abbvie did not provide enough structural features in the antibodies disclosed that were true to all antibodies within that genus.[119] After *Abbvie*, scholars seemed to think that antibody claiming was moving away from the PTO's antibody exception and back towards claiming antibodies by structure, not broad antibody genus claims.[120] These scholars predicated that the court would rule similarly with *Amgen v. Sanofi* and claim that Amgen's patent claims disclosing specified epitope residues were invalid for lack of

[117] US 8859741, USPTO Global Dossier, https://globaldossier.uspto.gov/#/result/patent/US/8859741/121875 [https://perma.cc/KMT7-MGTR].
[118] U.S. Patent No. 8,829,165, at continuity data (issued Sep. 9, 2014); U.S. Patent No. 8,859,741 at continuity data (issued Oct. 14, 2014); U.S. Patent No. 6,914,128, at continuity data (issued Jul. 5, 2005).
[119] Abbvie Deutschland GmbH & Co, 759 F.3d 1285 at 1300, 1302; John T. Aquino, *Antibody Claims Must Move Toward Structure, Panelists Say*, BLOOMBERG BNA, (Nov. 20, 2015), https://www.bna.com/antibody-claims-move-n57982063795/ [https://perma.cc/N7HK-FLG8].
[120] John T. Aquino, *Antibody Claims Must Move Toward Structure, Panelists Say*, BLOOMBERG BNA, (Nov. 20, 2015), https://www.bna.com/antibody-claims-move-n57982063795/ [https://perma.cc/N7HK-FLG8].

written description (not providing a sufficient number of representative species).[121] How did Amgen know that claiming an antibody by its target epitope residue would be sufficient to satisfy the written description requirement? How did Amgen predict that the district court would adhere more towards the older PTO antibody exception to the written description requirement rather than the Federal Circuit's decision in *AbbVie* narrowing this exception? Amgen probably interpreted the Federal Circuit's holding in *AbbVie* to mean not a move from functional to structural claiming, but a declaration to claim a genus of antibodies, one must disclose an example of every possible "structure" within that genus, such that one of ordinary skill in the art would understand the scope of the claimed invention. Since it is impossible to know all possible antibody variations at the outset, Amgen took a chance that claiming the epitope regions would be sufficient to count as "structural features common to the genus" component. While there are many possible antibodies against an antigen, an antigen only has so many antigen binding sites (epitope residues).

V. CONCLUSION

How will *Amgen* affect future pharmaceutical development? Almost immediately after the U.S. District Court of Delaware ruled that Amgen's claims in its '741 and '165 patents were valid under the written description requirement, the Court granted Amgen's motion for a permanent injunction against Sanofi from selling Praulent;

[121] Brian Feroldi, *This Amgen News Could Be a Game-Changer in its Fight Against Sanofi and Regeneron Pharmaceuticals*, The Motley Fool (Apr. 5, 2016), http://www.fool.com/investing/general/2016/04/05/this-amgen-news-could-be-a-game-changer-in-its-fig.aspx .

this was later overturned by the Federal Circuit.[122] Both Sanofi and Amgen invested millions in research and development for Praulent and Repatha, respectively, though with this permanent injunction, by February 4, 2017 (thirty days after grant of permanent injunction)[123] Sanofi would have had to have pulled Praulent off the market. While Sanofi appealed this permanent injunction and was denied the appeal, this permanent injunction was pushed back for another forty-five days, and then later reversed by the Federal Circuit.[124] While this may seem like Amgen trying to gain control of all anti-PCSK9 antibodies (the cholesterol market), one can also view this decision as incentivizing innovation. The cost of research and development for antibodies, the active ingredient in pharmaceutical drugs, against a specific antigen is very high, while the cost of copying and modifying these antibodies are quite low. The method of producing antibodies is conventional and routine in the biotechnology field, hence why these patent applications are towards composition of matter claims and not method claims. While in the immediate future this may increase prices for drug monopolies and stifle drug competition because a single pharmaceutical company may have exclusive rights towards a specific drug, in the long run this will promote further innovation and earlier patent application filings. If instead the district court in *Amgen v. Sanofi* invalidated Amgen's patent claims, a patent applicant would be left without any way to claim a genus of antibodies without disclosing every possible antibody structure within the

[122] Amgen Inc. v. Sanofi, No. 14-1317-SLR, 2017 U.S. Dist. LEXIS 1351, at *9 (D. Del. Jan. 5, 2017).
[123] *Id.* The Federal Circuit recently reversed the district court's permanent injunction in *Amgen Inc. v. Sanofi*, 2017 U.S. LEXIS 19416* (Fed. Cir. 2017).
[124] Amgen Inc. v. Sanofi, No. 14-1317-SLR, 2017 U.S. Dist. LEXIS 2883, at *3 (D. Del. Jan. 9, 2017).

group. This would have led towards pharmaceutical companies waiting longer to file patent application until they knew they had researched every possible variant, or possibly lead to pharmaceutical companies not investing in research at all.

Are courts inept to analyze these patent claims? The Federal Circuit in *Abbvie* narrowed the PTO's stated antibody exception, while the district court in *Amgen* reverted towards the PTO's guidelines on antibody claiming (the antibody exception). How are these courts (and laymen of juries), without scientific backgrounds, able to understand a patent disclosure, such as antibody sequences and functions, to decide whether this patent disclosure is enough to validate the applicant's genus claim? The future of antibody claiming is reverting to the PTO's guidelines (created by a board of scientific experts) on antibody species and genus claiming with granting a genus antibody claim so long as one of ordinary skill in the field would understand the scope of the invention. It is debatable that one of ordinary skill in the art may or may not have understood the scope of AbbVie's anti-IL-12 antibody genus claim, with all these well-known methods of antibody modification and production; it is common knowledge and skill to produce variants upon another's sequence. Though, Amgen took AbbVie a step further, and created an even broader genus scope, all antibodies that attach to specified PCSK9 epitope residues. This broader claim is even more indefinite than AbbVie's claims, yet Amgen's claims are valid? It is hard to reconcile the different court holdings in *Abbvie* and *Amgen*, though ultimately this comes down to this following PTO guidelines and protecting innovation. Without the patent bargain of exclusivity in exchange for disclosure there may be no research at all. So far, the future of antibody claiming is moving towards a broad genus of functional antibody claims that functionally identify antibodies by

epitope residues, antigen-binding sites, rather than by the structure of the antibody itself.