Antibody Equivalents: Considering Clinical Data

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In June 2023, the Supreme Court published its opinion in Amgen Inc. v. Sanofi. *The Court unanimously affirmed the Federal Circuit's holding that certain functional patent claims directed to a class of monoclonal antibodies were invalid for lack of enablement under 35 U.S.C. §112(a). After* Amgen*, innovators of these astounding medicines are caught between a rock and a hard place: The Court's enablement standard is clear enough, but the current state of the art, saddled with inherent unpredictability, makes it operationally impossible for applicants to satisfy that standard when they attempt to claim more than a handful of discrete antibodies.*

The upshot is an antibody patent singularity—applicants can enable, and thus claim, only the individual antibody structures they actually make, test, and disclose. And yet, a routine practice in the art called conservative replacement permits scientists to exploit known antibody structures to create literally noninfringing competitor antibodies whose properties may be identical to therapies already on the market. One way to counteract this decimation of the literal scope of antibody patents is through the doctrine of equivalents. Therapeutic antibody patent holders will likely assert infringement by equivalents of their narrowed claims against competing antibodies. Courts, however, lack a robust framework to guide the antibody equivalents analysis. Without such a framework, the analysis suffers and leads to undesirable outcomes that hamper innovation.

To prevent antibody innovation from stalling, the clinical properties of antibodies—not their molecular structures—should be the primary determinant of structural therapeutic antibody equivalents. Incorporating clinical data into the infringement inquiry hardly changes the analysis. It merely permits patent holders to assert infringement against other antibody therapeutics that perform the same function in the same way to achieve the same result. This analysis complies with the core tenets of patent law and the doctrine of equivalents.

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Furthermore, a clinical equivalents analysis counterbalances the obliteration of antibody claim scope resulting from Amgen*, insures against the risk of subsidizing follow-on literally noninfringing copiers, and realigns industry incentives to promote innovation in a life-saving field.*

INTRODUCTION

Antibody therapies garner a massive worldwide market.[1] They are also some of the most biotechnologically advanced medicines known to humankind. As a result, patents protecting the exclusive rights to those therapies are highly coveted and are some of the most valuable patents in the world.[2] It is no wonder then that when the Supreme Court decided its first case involving those patents, no less than thirty-three *amici curiae* filed briefs, with both sides receiving support from large pharmaceutical companies.[3]

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1. *See Monoclonal Antibodies Market Sales are Anticipated to Reach US $588.0 Billion by 2032, Increasing at 11.8% CAGR: Market.us Report*, GLOB. NEWS WIRE (May 26, 2023), https://www.globenewswire.com/en/news-release/2023/05/26/2676857/0/en/Monoclonal-Antibodies-Market-Sales-are-Anticipated-to-reach-US-588-0-Billion-by-2032-Increasing-at-11-8-CAGR-Market-us-Report.html [https://perma.cc/72D8-6A7P] [hereinafter GLOBAL NEWS].

2. Mark A. Lemley & Jacob S. Sherkow, *The Antibody Patent Paradox*, 132 YALE L.J. 994, 994 (2023) [hereinafter *Paradox*]; *see also* John R. Allison, Mark A. Lemley & Joshua Walker, *Extreme Values or Trolls on Top? The Characteristics of the Most Litigated Patents*, 158 U. PA. L. REV. 1, 20 (2009) (finding empirical data that the pharmaceutical industry holds a "significant share of the most-litigated patents").

3. *See e.g.*, Brief of Amicus Curiae GSK PLC In Support of Petitioners at 1, Amgen Inc. v. Sanofi, 598 U.S. 594 (2023) (No. 21–757) [hereinafter GSK Brief]; Brief of Genentech, Inc.,

In that case, *Amgen Inc. v. Sanofi*,[4] the Court held petitioner Amgen's asserted patent claims invalid because, as written, the claims failed to satisfy the "enablement" requirement under 35 U.S.C. §112(a).[5] Section 112(a) requires a patent applicant to describe an invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the [invention]."[6] The Court stated that a person having ordinary skill in the art, also known as the PHOSITA, would have to undergo "painstaking experimentation" to "reach the full scope" of the invention's claimed embodiments.[7] The claims were thus invalid as a matter of law.[8]

This Note discusses *Amgen*'s effects on the scope of patents protecting a subset of therapeutics known as monoclonal antibodies and how the doctrine of equivalents may counteract the downward pressures on antibody innovation the decision fosters.

Part I summarizes the Supreme Court's holding in *Amgen* and gives a primer on antibody patents and science. Part II posits that *Amgen*'s holding will naturally lead to narrower claim scope in the antibody arts, likely down to a single embodiment. This phenomenon is referred to as the "antibody patent singularity," which threatens antibody patents of nearly all their value. Part II then discusses why the reduction in scope of valid antibody patents may have proportional effects on the rate of innovation in the biologic pharmaceutical sector. Part II concludes by positing tools to counteract the effects of the singularity. As others have explained before, the doctrine of equivalents will be vital to retain value in the narrowest of antibody patents. Without the doctrine of equivalents to protect against infringement beyond a single claimed antibody, the innovatory and lifesaving monoclonal antibody pipeline may be unduly delayed.

Part III explains the development of the doctrine of equivalents and details the particulars of its two doctrinal "tests" outlined by the Supreme Court: the "function-way-result" and "insubstantial differences" tests. Part III then describes how the doctrine of equivalents may be used to counteract *Amgen*'s hampering effects on antibody patent scope. Part III concludes by illustrating the importance of clinical data and arguing that it deserves a proper role in analyzing equivalence between claimed antibodies and alleged infringing antibodies.

Part IV argues that an antibody's clinical properties should be the primary consideration in analyzing structural equivalence between two therapeutic antibodies. In other words, an antibody patent holder may assert infringement by clinical equivalents by showing that there are insubstantial clinical differences between her therapeutic antibody and an accused one, notwithstanding structural differences.

Astrazeneca Pharmaceuticals LP, Bayer AG, Gilead Sciences, Inc., and Johnson & Johnson as Amici Curiae in Support of Respondents at 1, Amgen Inc. v. Sanofi, 598 U.S. 594 (2023) (No. 21–757).

4. Amgen Inc. v. Sanofi, 598 U.S. 594 (2023).
5. *Id.* at 614.
6. 35 U.S.C. §112(a); *see also Amgen*, 598 U.S. at 594 (alteration in original).
7. *Amgen*, 598 U.S. at 609.
8. *Id.* at 613.

I. LAYING THE FOUNDATION

A. The Importance of Antibody Patents

Antibodies are essential to modern biotechnology and are the darling of the global pharmaceutical industry.[9] Look no further than the top fifty best-selling drugs of 2022, nearly half of which were monoclonal antibodies (mAbs).[10] Since the Food & Drug Administration (FDA) approved the first humanized[11] mAb in 2002,[12] the industry has seen meteoric growth.[13] While only four were approved in the subsequent seven years,[14] by June 2022, there were 162 FDA-approved mAbs on the market[15] treating a wide variety of conditions including asthma,[16] autoimmune disorders,[17] cancer,[18] and multiple sclerosis.[19] The global antibody market (which includes products and uses outside of strictly human therapies) is valued at $198 billion.[20] By one account, the market is projected to reach over half a trillion dollars by 2032.[21] Antibody patents[22] protecting exclusionary rights to antibody therapies are therefore some of the most valuable patents in the world.[23] The Supreme Court's decision explaining the standard to enable patents in the antibody arts, *Amgen Inc. v. Sanofi*, will likely result in rippling effects on the therapeutic antibody market. To fully grasp the implications of the Court's decision and its effects on therapeutic antibody development, an understanding of antibody science is essential.

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9. *See Paradox*, *supra* note 2, at 997.

10. *See* Brian Buntz, *The 50 Best-selling Pharmaceuticals of 2022: COVID-19 Vaccines Poised to Take a Step Back*, DRUG DISCOVERY AND DEVELOPMENT (Apr. 18, 2023), https://www.drugdiscoverytrends.com/50-of-2022s-best-selling-pharmaceuticals/ [https://perma.cc/L8GD-PNEB]. "Monoclonal antibodies" or "mAbs" are antibodies derived from a single B cell clone. This clone results in the ability of scientists to produce a single specific antibody structure in significant quantities. *See* discussion *infra* Section I.B.; *Paradox*, *supra* note 2, at 1007–08 (citing G. Köhler & C. Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 NATURE 495, 495 (1975)).

11. "Humanized" antibodies refer to antibodies whose murine characteristics have been substituted for human amino acid sequences. The body recognizes these antibodies as "self," which reduces the risk of a harmful immune response. *See* Fiona A. Harding, Marcia M. Stickler, Jennifer Razo & Robert B. DuBridge, *The Immunogenicity of Humanized and Fully Human Antibodies*, 2 MABS 256, 256–57 (2010).

12. Aaron L. Nelson, Eugen Dhimolea, & Janice M. Reichert, 9 *Development Trends for Human Monoclonal Antibody Therapeutics*, 9 NATURE REVS. DRUG DISCOVERY: PERSPS. 767, 768 (2010).

13. *See id.*

14. *See id.*

15. Xiaochen Lyu, Qichao Zhao, Julia Hui, Tiffany Wang, Mengyi Lin, Keying Wang, Jialing Zhang, Jiaqian Shentu, Paul A. Dalby, Hongyu Zhang & Bo Liu, *The Global Landscape of Approved Antibody Therapies*, 5 ANTIBODY THERAPEUTICS 233, 234 (2022).

16. *E.g.*, REGENERON PHARMACEUTICALS, INC. & SANOFI-AVENTIS U.S. LLC, DUPIXENT FULL PRESCRIBING INFORMATION §1.2 (2023).

17. *E.g.*, ABBVIE INC., HUMIRA FULL PRESCRIBING INFORMATION §1 (2021).

18. *E.g.*, MERCK & CO., INC., KEYTRUDA FULL PRESCRIBING INFORMATION §1 (2023).

19. *E.g.*, GENENTECH INC., OCREVUS FULL PRESCRIBING INFORMATION §1 (2017).

20. GLOBAL NEWS, *supra* note 1.

21. *Id.*

22. I use "antibody patents" to describe patents that claim any size class of antibody structures, which could range from one to millions, depending on the specific claims. This includes method-of-treatment claims or other claims with a particular antibody structure as an element.

23. *Paradox*, *supra* note 2, at 994.

B. The Immune System, Antibodies, and Antibody Therapies

Humans depend on the immune system to fend off infections by "harmful invaders," called pathogens, which include viruses, bacteria, fungi, and parasites.[24] Without the immune system's protection, pathogens infect the body and disrupt homeostasis. Left untreated, infection ensues and eventually results in death.[25] Luckily, the immune system has evolved two ways to combat infection: the innate and the adaptive immune systems.[26]

The innate immune system is not specific to a particular pathogen. Rather, the innate immune system is a catch-all system that protects the body from all foreign substances.[27] It is the first line of defense against infection.[28] The visible parts of the innate immune system include physical barriers of the body, like skin, mucus, and cilia.[29] Other tools of the innate immune system include symptoms like inflammation and fever, which, although unpleasant, evolved to help survival in the long run.[30] Innate immunity works on the microscopic level too. Even when a pathogen breaches the body's first lines of defense, such as the skin, soldiers of the innate immune system recognize foreign substances, engulf them, and dispose of them through a process called phagocytosis.[31]

The adaptive immune system works differently and is more sophisticated.[32] Unlike the innate immune system that produces a rapid generalized response, the adaptive immune system mounts a slower, but highly specific, response to the pathogen that induces it.[33] At bottom, what the adaptive immune system compromises in speed, it gains in specificity.[34] It takes days for the adaptive immune system to proliferate a targeted response to a specific pathogen.[35] In contrast, cells of the innate immune system respond within hours of bodily infiltration.[36]

Although slower, the adaptive immune system is more destructive than the innate immune system.[37] Indeed, a malfunctioning adaptive immune system is the hallmark of a diverse group of debilitating conditions known as autoimmune

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24. BRUCE ALBERTS, ALEXANDER JOHNSON, JULIAN LEWIS, DAVID MORGAN, MARTIN RAFF, KEITH ROBERTS & PETER WALTER, MOLECULAR BIOLOGY OF THE CELL 1297 (6th ed. 2015).
25. *Id.* at 1315 ("Vertebrates inevitably die of infection if they are unable to make antibodies.").
26. *See id.* at 1297.
27. *Id.*
28. *See id.* at 1298.
29. *Id.* at 1276.
30. *See* BRUCE ALBERTS, ALEXANDER JOHNSON, JULIAN LEWIS, MARTIN RAFF, KEITH ROBERTS & PETER WALTER, MOLECULAR BIOLOGY OF THE CELL 1488, 1533 (5th ed. 2008).
31. ALBERTS, *supra* note 24, at 1281.
32. *Id.* at 1297.
33. *See id.* at 1298.
34. *See id.* at 1305.
35. *Id.* at 1298.
36. Preeti J. Muire, Lauren H. Mangum & Joseph C. Wenke, *Time Course of Immune Response and Immunomodulation During Normal and Delayed Healing of Musculoskeletal Wounds*, 11 FRONTIERS IMMUNOLOGY, June 4, 2020, at 2.
37. *See* ALBERTS, *supra* note 24, at 1297 (contrasting B and T cells' abilities to "directly kill cells infected with [a] pathogen" with the "general defense reactions" of the innate immune system).

diseases, when the body fails to accurately distinguish foreign matter from self.[38] Systemic lupus erythematosus, colloquially known as "lupus," is one such disease.[39] Seasonal allergies are a less deleterious (but still undesirable and potentially debilitating) example of an adaptive immune response overreacting to nonharmful stimuli.[40]

One way the adaptive immune response achieves its extraordinary levels of specificity is through antibodies.[41] Antibodies, or immunoglobulins, are y-shaped proteins formed by chains of individually linked amino acids, also called "residues."[42] Amino acids are small molecule "building blocks" coded by DNA.[43] The sequence of amino acids comprising a protein is its "primary structure."[44] That long structure then "folds" into a three-dimensional structure that ultimately defines the antibody's function.[45] Four chains of linked amino acids, two "heavy chains" and two "light chains," combine to make a whole antibody.[46]

Antibodies are generated and secreted by B cells, a type of white blood cell.[47] Once the immune system identifies the specific antibody needed to eradicate the body of a particular pathogen (through a very complicated process), the body dramatically ramps up that antibody's production.[48] Similar to a lock and key, the antibody's structure dictates its propensity to bind to certain molecular targets.[49] Once the antibody (the key) finds its target (the lock), usually in the form of a cell receptor or other protein, the antibody binds to the antigen[50] and neutralizes the infectious agent through several mechanisms.[51]

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38. *See* David S. Plsetsky, *Pathogenesis of Autoimmune Disease*, 19 NATURE REVS. NEPHROLOGY 509, 510 (2023).

39. Muhammad Atif Ameer, Haroon Chaudhry, Javaria Mushtaq, Osama S. Khan, Maham Babar, Tehmina Hashim, Saima Zeb, Muhammad Ali Tariq, Sridhar R. Patlolla, Junaid Ali, Syeda N. Hashim & Sana Hashim, *An Overview of Systemic Lupus Erythematosus (SLE) Pathogenesis, Classification, and Management*, 14 CUREUS, Oct. 15, 2022, at 1.

40. ALBERTS, *supra* note 24, at 1317 (describing the IgE-mediated process resulting in symptoms of "hay fever," also known as seasonal allergies).

41. *See id.* at 1307.

42. Mark L. Chiu, Dennis R. Goulet, Alexey Teplyakov & Gary L. Gilliland, *Antibody Structure and Function: The Basis for Engineering Therapeutics*, 8 ANTIBODIES 1, 1–2 (2019).

43. Brief for Sir Gregory Paul Winter as Amici Curiae Supporting Respondents at 8, Amgen v. Sanofi, 598 U.S. 594 (2023) (No. 21–757) [hereinafter *Winter Brief*]. Sir Gregory Winter won a share of the Nobel Prize in Chemistry in 2018 for his work on "the phage display of peptides and antibodies." *The Nobel Prize in Chemistry 2018*, THE NOBEL PRIZE https://www.nobelprize.org/prizes/chemistry/2018/summary/ [https://perma.cc/42QC-3USJ] (last visited Oct. 18, 2024).

44. *Winter Brief*, *supra* note 43, at 10.

45. *See id.* at 10–11.

46. *Id.* at 9; Chiu, *supra* note 42, at 1.

47. *See* ALBERTS, *supra* note 24, at 1297.

48. *See id.* at 1310.

49. *Id.* at 1318.

50. Literally **anti**body **gen**erator. *Id.* at 1307.

51. Antibodies neutralize pathogens directly, interfere with pathogen attachment, recruit complement, and initiate cellular cytotoxicity. *See* Donald N. Forthal, *Functions of Antibodies*, 2 MICROBIOLOGY SPECTRUM 1, 1–6 (2014).

The ability of antibodies to eradicate infections stems from their unfathomable diversity of possible structures.[52] There are twenty different amino acids.[53] Each antibody consists of four amino acid chains, with each chain comprising over 100 amino acids each.[54] In theory, the number of unique antibodies the body could produce is 10^{12} (ten trillion) on the low end and possibly up to 10^{18} (ten quintillion) on the high end.[55] In (arguably) more cognizable terms, if every potential antibody represented one second into the past, the estimated number of possible antibodies would go back between 316,880 years (about the age of the oldest human fossils) and 300 billion years—roughly twenty-three times the age of the universe.[56]

This structural diversity derives partly from an antibody's "hypervariable regions."[57] At the tips of the y-shaped structure, each antibody contains an "antigen-binding site" consisting of six hypervariable regions, also known as complementarity-determining regions, or "CDRs" for short.[58] CDRs are subject to randomized change.[59] And changing just a single amino acid may affect an antibody's overall structure and function.[60] It is no exaggeration to say that the body could create an antibody capable of binding to any other biological molecule.[61] This is possible not only because of antibodies' diversity of structure but also because antigens may display multiple "epitopes."[62] An epitope is a specific area of an antigen to which an antibody binds.[63] Notably, an antibody binds to a single antigen, and usually a single epitope, but an antigen may bind to many—sometimes millions—of antibodies.[64]

Mentioned before, "monoclonal antibodies," or mAbs, are antibodies of a single amino acid sequence capable of being produced on a commercial scale.[65] The original Nobel Prize-winning[66] process to create them involves a few steps. First, a

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52. *See* ALBERTS, *supra* note 24, at 1307.

53. S. Saha, S. Barman (Mandal) & M. Roy, *Spectral Analysis of Amino Acid Sequence*, 2ND INT'L CONF. ON NANOTECHNOLOGY & BIOSENSORS, at 11, 12, 12 tbl.1 (2011).

54. ALBERTS, *supra* note 24, at 1318.

55. Bryan Briney, Anne Inderbitzen, Collin Joyce & Dennis R. Burton, *Commonality Despite Exceptional Diversity in the Baseline Human Antibody Repertoire*, 566 NATURE 393, 393 (2019).

56. 10^{12} seconds/~31,557,600 seconds per year = 316,880 years. 10^{18} seconds/~31,557,600 seconds per year = 316 billion years. *See* Brian Handwerk, *An Evolutionary Timeline of Homo Sapiens*, SMITHSONIAN MAGAZINE: SCIENCE (Feb. 2, 2021), https://www.smithsonianmag.com/science-nature/essential-timeline-understanding-evolution-homo-sapiens-180976807/ [https://perma.cc/52KX-3R6L]; Michael S. Turner, *Origin of the Universe*, 301 SCI. AM. 36, 36 (2009).

57. ALBERTS, *supra* note 24, at 1318.

58. *See* Chiu, *supra* note 42, at 4.

59. *See* ALBERTS, *supra* note 24, at 1324.

60. *Winter Brief*, *supra* note 43, at 14.

61. ALBERTS, *supra* note 24, at 1307.

62. *See Winter Brief*, *supra* note 43, at 19.

63. *Id.* at 10.

64. *See* Amgen Inc. v. Sanofi, 598 U.S. 594, 599 (2023).

65. *See Monoclonal antibody*, MERRIAM-WEBSTER, https://merriam-webster.com/dictionary/monoclonal%20antibody [https://perma.cc/GYT5-2BEE] (last visited Oct. 18, 2024).

66. *The Nobel Prize in Physiology or Medicine 1984*, THE NOBEL PRIZE, https://www.nobelprize.org/prizes/medicine/1984/summary/ [https://perma.cc/FN6L-VNJA] (last visited Oct. 18, 2024).

desired antibody of interest must be isolated, usually by inoculating an animal (a mouse, for example) and screening the antibodies resulting from the animal's natural immune response.[67] Once an antibody is selected for mass production, it must be "immortalized."[68] This process involves fusing a cancer cell with the antibody-producing cell.[69] The result is a "hybridoma," a group of cells which perpetually multiply while simultaneously producing the single desired antibody.[70] Today, antibodies are harvested and further refined into pharmaceutical compositions fit for human administration.[71] Subsequent advances in recombinant DNA technology have created alternative processes without the need for hybridoma technology.[72]

As a result of mAb production technologies, today's therapeutic antibodies exert their pharmacological effects on the body and deliver drugs in exciting ways. Some mAbs bind to receptors on the surfaces of tumor cells and prevent the cells' normal functioning and proliferation.[73] This is the mechanism of trastuzumab, which binds to the HER2 receptor on the surface of breast cancer cells, thereby recruiting other immune cells to kill the antibody-tagged cell.[74] Other mAbs bind to proteins that circulate naturally in the blood, such as bevacizumab.[75] Bevacizumab binds to VEGF,[76] a protein that promotes new blood vessel formation.[77] Interruption of VEGF's natural interaction with its receptor starves tumor cells of vital nutrients and leads to cell death.[78] Moreover, some antibodies deliver a "biological missile" of an antibody/small molecule combination.[79] A drug called sacitizumab govitecan-hziy uses an antibody to "seek out" cancer cells.[80] Like a Trojan horse, it enters the cell before releasing a highly toxic drug.[81] In oncology, patients are now routinely screened prior to treatment to determine which specific

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67. G. Köhler & C. Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 NATURE 495, 495 (1975).

68. Renate Kunert & David Reinhart, *Advances in Recombinant Antibody Manufacturing*, 100 APPLIED MICROBIOLOGY & BIOTECHNOLOGY 3451, 3451 (2016).

69. *Id.*

70. *See* John P. Manis, *Overview of Therapeutic Monoclonal Antibodies*, UPTODATE (Apr. 10, 2024), https://www.uptodate.com/contents/overview-of-therapeutic-monoclonal-antibodies#H250024379 [https://perma.cc/9Q6C-N2E4].

71. *Id.* (discussing post-purification modifications).

72. D.L. Siegel, *Recombinant Monoclonal Antibody Technology*, 9 TRANSFUSION CLINIQUE ET BIOLOGIQUE 15, 16 (2002).

73. This mechanism is called antibody-dependent cellular cytotoxicity. GENENTECH INC., HERCEPTIN FULL PRESCRIBING INFORMATION § 12.1 (2010).

74. *Id.*

75. *See* GENENTECH INC., AVASTIN FULL PRESCRIBING INFORMATION § 12.1 (2022).

76. Vascular endothelial growth factor. The acronym is usually pronounced "veg-ef."

77. GENENTECH INC., AVASTIN FULL PRESCRIBING INFORMATION §12.1 (2022).

78. *Id.*

79. Zhiwen Fu, Shijun Li, Sifei Han, Chen Shi & Yu Zhang, *Antibody Drug Conjugate: The "Biological Missile" for Targeted Cancer Therapy*, 7 SIGNAL TRANSDUCTION & TARGETED THERAPY, Mar. 22, 2022, at 1, 10.

80. GILEAD SCIENCES, INC., TRODELVY FULL PRESCRIBING INFORMATION § 12.1 (2023).

81. *Id.*

"biomarkers" their tumors exhibit and then matched with mAb therapies specifically targeted to tumors that present those attributes.[82] Antibodies' fantastic molecular specificity and diversity have revolutionized precision medicine and given patients access to more tailored therapies than ever before, particularly in the field of oncology.[83]

Antibody science, however, is still evolving. Even today, scientists cannot predict an antibody's structure nor function solely from its primary structure.[84] Furthermore, scientists cannot predict how changing a single residue will affect the resultant antibody's structure and function, despite it representing only a minute change to the amino acid sequence.[85] "It's going to get a Nobel Prize for somebody at some point, but translating that [amino acid] sequence into a known three-dimensional structure is still not possible."[86] Relatedly, an antibody's sequence cannot be reverse engineered simply by knowing which antigen, or even which epitope it binds to; an antigen can bind to potentially "millions" of different antibodies, and an epitope can be bound at multiple sites in multiple configurations.[87] Whether the complexities and associated limitations of antibody science, however, also limited the patentability of functional antibody claims remained unsettled until the Supreme Court decided *Amgen Inc. v. Sanofi*.[88]

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82. Peter Hulick, *Next-generation DNA Sequencing (NGS): Principles and Clinical Applications*, UPTODATE, (Feb. 7, 2024), https://www.uptodate.com/contents/next-generation-dna-sequencing-ngs-principles-and-clinical-applications [https://perma.cc/6JWH-PVTH] (discussing cancer screening and management with targeted gene panels).

83. Chuanhui Han & Qimin Zhan, *Precision Medicine Revolutionizes Cancer Diagnosis and Treatment*, 2 MED. REV. 541, 542 (2022).

84. *See Winter Brief*, *supra* note 43, at 14 ("It is not well understood in antibody science even today precisely *how* a particular change in the amino acid sequence . . . will affect the antibody's structure and function."); *see also* Monica L. Fernández-Quintero, Janik Kokot, Franz Waibl, Anna-Lena M. Fischer, Patrick K. Quoika, Charlotte M. Deane & Klaus R. Liedl, *Challenges in Antibody Structure Prediction*, 15 MABS, Jan. 27, 2023, at 1 (describing prediction of antibody structure "based solely on the amino-acid sequence" as "one of the grand challenges in the field of protein structure prediction" and "critical to understand[ing protein] function") (footnote omitted).

85. *Winter Brief*, *supra* note 43, at 14.

86. *Id.* at 15. *But see* John Jumper, Richard Evans, Alexander Pritzel, Tim Green, Michael Figurnov, Olaf Ronneberger, Kathryn Tunyasuvunakool, Russ Bates, Augustin Žídek, Anna Potapenko, Alex Bridgland, Clemens Meyer, Simon A. A. Kohl, Andrew J. Ballard, Andrew Cowie, Bernardino Romera-Paredes, Stanislav Nikolov, Rishub Jain, Jonas Adler, Trevor Back, Stig Petersen, David Reiman, Ellen Clancy, Michael Zielinski, Martin Steinegger, Michalina Pacholska, Tamas Berghammer, Sebastian Bodenstein, David Silver, Oriol Vinyals, Andrew W. Senior, Koray Kavukcuoglu, Pushmeet Kohli & Demis Hassabis, *Highly Accurate Protein Structure Prediction with AlphaFold*, 596 NATURE 583 (2021); Kathryn Tunyasuvunakool, Jonas Adler, Zachary Wu, Tim Green, Michal Zielinski, Augustin Žídek, Alex Bridgland, Andrew Cowie, Clemens Meyer, Agata Laydon, Sameer Velankar, Gerard J. Kleywegt, Alex Bateman, Richard Evans, Alexander Pritzel, Michael Figurnov, Olaf Ronneberger, Russ Bates, Simon A. A. Kohl, Anna Potapenko, Andrew J. Ballard, Bernardino Romera-Paredes, Stanislav Nikolov, Rishub Jain, Ellen Clancy, David Reiman, Stig Petersen, Andrew W. Senior, Koray Kavukcuoglu, Ewan Birney, Pushmeet Kohli, John Jumper & Demis Hassabis, *Highly Accurate Protein Structure Prediction for the Human Proteome*, 596 NATURE 590 (2021) (using artificial intelligence to more accurately predict protein structure from amino acid sequences).

87. *Winter Brief*, *supra* note 43, at 18.

88. 598 U.S. 594 (2023).

C. Amgen Inc. v. Sanofi

At the heart of the debate in *Amgen* is an age-old question of patent law: How should our laws "promote the Progress of Science and useful Arts?"[89] In patent law, one way this question manifests is by defining the legal scope of patents, both individually and collectively. A grant too large risks stifling the rate of innovation.[90] A grant too little may chill innovation entirely as the marginal incentive to innovate decreases.[91] The enablement doctrine is one tool Congress has promulgated to attempt to carve the right balance.[92] And in *Amgen*, where the dispute centered on lifesaving medicines indicated for millions of patients, the answer to this question became literally a matter of life and death.[93] In *Amgen*, the Supreme Court unanimously affirmed the Federal Circuit's holding that Amgen's claims were not enabled under 35 U.S.C. §112(a). In other words, Amgen's patent disclosure did not "enable" a PHOSITA to "make and use"[94] the invention without "undue experimentation."[95]

To put the Supreme Court's opinion in context, it helps to briefly explain the history of the litigation that led to the 2023 decision. In 2014, Amgen, a California-based, multinational, and multi-billion-dollar biotechnology company, obtained U.S. Patent Nos. 8,829,165 and 8,859,741.[96] The patents covered Amgen's therapy evolocumab,[97] a monoclonal antibody indicated to reduce the risk of heart attack and stroke in patients with high cholesterol.[98] Amgen immediately sued Sanofi, a

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89. U.S. CONST. art. 1, § 8, cl. 8.

90. *See, e.g.*, Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1597 (2003) ("For obvious reasons, the value of a patent in encouraging R&D will vary depending both on how easy it is to get that patent and on how much protection that patent gives to products that are sold for revenue in the real world."); Mark A. Lemley, *Romantic Authorship and the Rhetoric of Property*, 75 TEX. L. REV. 873, 890 (1996-1997) ("[M]any of the fundamental issues in intellectual property law are shaped . . . by the desire to protect intellectual property adequately without overprotecting it.") (mentioning the enablement requirement).

91. *See* Burk & Lemley, *supra* note 90, at 1597.

92. *Id.* at 1593 ("Patent scope is necessarily interrelated with obviousness and enablement.").

93. *See generally* Brief of Arnold Ventures, The National Center for Health Research, and Certain Medical Doctors as Amici Curiae In Support of Respondents at 27–43, Amgen v. Sanofi, 598 U.S. 594 (2023) (No. 21–757) (arguing that "partially enabled genus claims" will "in the end, chill innovation and harm patients").

94. 35 U.S.C. §112(a).

95. *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); *see also* Amgen Inc. v. Sanofi, 598 U.S. 594, 612 (2023) (discussing the "reasonable" experimentation standard).

96. Amgen Inc. v. Sanofi, 227 F. Supp. 3d 333, 337 (D. Del. 2017), *rev'd in part*, 872 F.3d 1367 (Fed. Cir. 2017).

97. That each antibody's name ends in "mab" is no accident. But in 2021, the International Nonproprietary Names Programme of the World Health Organization issued new guidance for antibody nomenclature. If adopted in the United States, antibodies developed under the new guidance would employ four suffixes, namely, "-tug," "-bart," "-ment," and "-mig," which would replace the overcrowded "-mab" suffix. For more on monoclonal antibody naming conventions, *see generally* Sofia S. Guimaraes Koch, Robin Thorpe, Nana Kawasaki, Marie-Paule Lefranc, Sarel Malan, Andrew C.R. Martin, Gilles Mignot, Andreas Plückthun, Menico Rizzi, Stephanie Shubat, Karin Weisser & Raffaella Balocco, *International Nonproprietary Names for Monoclonal Antibodies: An Evolving Nomenclature System* 14 MABS, May 4, 2022.

98. 227 F. Supp. 3d at 338.

different Paris-based, multinational, and multi-billion-dollar biotechnology company, in the District Court for the District of Delaware for infringement of its newly obtained patents.[99] Amgen asserted that Sanofi's similar mAb product, alirocumab, infringed its patents.[100]

The mAbs in question target and bind to proprotein convertase subtilisin/kexin type 9 (PCSK9), an endogenous protein primarily produced in the liver.[101] PCSK9 naturally binds to low-density lipoprotein (LDL) receptors.[102] LDL receptors, unsurprisingly, bind to LDL, also known as "bad" cholesterol because excess LDL leads to heart attacks, strokes, and other atherosclerotic complications.[103] In its normal course of action, PCSK9 binds to an LDL receptor and marks it for cellular degradation.[104] The receptor is then removed from the cell surface.[105] En masse, the fewer LDL receptors available to bind LDL, the more remains in the bloodstream.[106] Over time, excess cholesterol leads to arterial plaques.[107] When a plaque ruptures, it can cause an acute life-threatening blockage of blood flow.[108] A blockage of a coronary artery is a heart attack, while a blockage of a cerebral artery is a stroke.[109] When evolocumab or alirocumab arrive and bind to PCSK9, they inhibit PCSK9 from binding to the LDL receptor.[110] The upshot is that more LDL receptors are available to bind to LDL and remove it from the bloodstream.[111] Both evolocumab and alirocumab (the only two mAb PCSK9 inhibitors on the market) have been shown to significantly reduce LDL levels in patients taking standard "statin" therapies.[112] In turn, PCSK9 inhibitors lower a patient's risk of stroke and heart attack.[113]

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99. *See id.* at 336–37.

100. *Id.* at 336.

101. Amgen Inc. v. Sanofi, 872 F.3d 1367, 1371 (Fed. Cir. 2017).

102. Murray W. Huff, Alan Daugherty & Hong Lu, *Atherosclerosis*, *in* BIOCHEMISTRY OF LIPIDS, LIPOPROTEINS AND MEMBRANES 519, 543 (Neale D. Ridgway & Roger S. McLeod eds., 2016).

103. *See id.* at 520.

104. Thomas A. Lagace, *PCSK9 and LDLR Degradation: Regulatory Mechanisms in Circulation and in Cells*, 25 CURRENT OP. LIPIDOLOGY 387, 388 (2014).

105. *Id.*

106. *See id.* at 388–89.

107. Huff et al., *supra* note 102, at 520.

108. *Id.*

109. *See id.*

110. REGENERON PHARMACEUTICALS, INC., PRALUENT FULL PRESCRIBING INFORMATION §12.1 (2021).

111. *Id.* Drugs that inhibit PCSK9's interaction with the LDL receptor are, unceremoniously, called PCSK9 inhibitors.

112. *See* Marc S. Sabatine, Robert P. Giugliano, Anthony C. Keech, Narimon Honarpour, Stephen D. Wiviott, Sabina A. Murphy, Julia F. Kuder, Huei Wang, Thomas Liu, Scott M. Wasserman, Peter S. Sever & Terje R. Pedersen, *Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease*, 376 NEW. ENG. J. MED. 1713, 1713 (2017); Gregory G. Schwartz, P. Gabriel Steg, Michael Szarek, Deepak L. Bhatt, Vera A. Bittner, Rafael Diaz, Jay M. Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert A. Harrington, J. Wouter Jukema, Guillaume Lecorps, Kenneth W. Mahaffey, Angèle Moryusef, Robert Pordy, Kirby Quintero, Matthew T. Roe, William J. Sasiela, Jean-François Tamby, Pierluigi Tricoci, Harvey D. White & Andreas M. Zeiher, *Alirocumab and Cardiovascular Outcomes After Acute Coronary Syndrome*, 379 NEW. ENG. J. MED. 2097, 2097 (2018).

113. *See* Sabatine et al., *supra* note 112, at 1713; Schwartz et al., *supra* note 112, at 2097.

Amgen's patent claims covered antibodies binding to specific residues on PCSK9, known as the "sweet spot," thereby preventing PCSK9 from binding to LDL receptors.[114] The exact number of antibodies exhibiting the functional characteristics specified in Amgen's claims remains unknown. In the relevant patents, Amgen disclosed twenty-six embodiments of the class.[115] But the class likely contained "millions" of individual structures.[116] The antibody structure-function relationship, to this day, limits scientists' ability to describe every antibody within Amgen's claimed class.[117]

In 2016, a jury found the asserted claims valid after the parties had stipulated to infringement.[118] In 2017, the district judge granted Amgen's motion for a permanent injunction against Sanofi.[119] The Federal Circuit, however, vacated the permanent injunction and remanded the case for a new trial because the jury failed to hear relevant post-priority-date evidence regarding written description and enablement.[120] In a second trial, the jury again found two asserted claims valid but found another invalid for lack of written description.[121] In 2019, after the verdict was entered, the district judge (this time a different one) granted Sanofi's motion for judgment as a matter of law for lack of enablement under section 112(a) as to the claims found valid by the jury.[122] In 2021, on appeal to the Federal Circuit for the second time, the court affirmed the district court's holding that Amgen's relevant claims lacked enablement.[123] In November 2022, the Supreme Court granted certiorari.[124] Oral argument was held in March 2023.[125] The Court announced its decision, detailed below, in June 2023.[126]

In the Court's unanimous opinion, Justice Gorsuch emphasized history and precedent as the primary justifications for finding a lack of enablement.[127] The Court characterized its holding as simply applying settled law to a different scientific context.[128] In holding such, the Court recounted three of its previous decisions:

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114. Amgen Inc. v. Sanofi, 598 U.S. 594, 613 (2023); *see also* U.S. Patent Nos. 8,829,165; 8,859,741.

115. *Amgen*, 598 U.S. at 602.

116. *Id.* at 613.

117. *See Winter Brief*, *supra* note 43, at 17 ("[S]imply knowing what an antibody does (*e.g.*, its function) does not inform an antibody scientist as to what the sequence or structure of such an antibody would be.").

118. Amgen Inc. v. Sanofi, 872 F.3d 1367, 1372 (Fed. Cir. 2017).

119. Amgen Inc. v. Sanofi, No. 14-1317-SLR, 2017 WL 61725 at *1 (D. Del. Jan. 5, 2017) *vacated and remanded*, 872 F.3d 1367 (Fed. Cir. 2017).

120. Amgen Inc. v. Sanofi, 872 F.3d 1367, 1379 (Fed. Cir. 2017).

121. Amgen Inc. v. Sanofi, No. 14-1317-RGA, 2019 WL 494620 at *1 (D. Del. Feb. 8, 2019).

122. Amgen Inc. v. Sanofi, No. 14-1317-RGA, 2019 WL 4058927 at *13 (D. Del. Aug. 28, 2019) *aff'd*, 987 F.3d 1080 (Fed. Cir. 2021) *aff'd*, 598 U.S. 594 (2023).

123. Amgen Inc. v. Sanofi, 987 F.3d 1080 (Fed. Cir. 2021) *aff'd*, 598 U.S. 594 (2023).

124. Order List, 598 U.S. ___ (Nov. 4, 2022) (granting certiorari).

125. *See* Transcript of Oral Argument at 58, Amgen Inc. v. Sanofi, 598 U.S. 594 (2023) (No. 21–757) (Mar. 27, 2023).

126. Amgen Inc. v. Sanofi, 598 U.S. 594 (2023).

127. *See id.* at 616.

128. *See id.*

Morse, *Incandescent Lamp*, and *Holland Furniture*, the earliest of which was from 1853. "While the technologies in these older cases may seem a world away from the antibody treatments of today, the decisions are no less instructive for it."[129] The Court "reinforce[d]" section 112(a)'s "simple statutory command": When a patent "claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class."[130] In other words, "[t]he more one claims, the more one must enable."[131]

To illustrate the concept, the Court began with *Morse*.[132] Samuel Morse received a patent for the telegraph in 1840, which reissued in 1848.[133] Eventually Morse sued Henry O'Reilly, asserting that O'Reilly's telegraphic system between Louisville and Nashville infringed Morse's patent. The Supreme Court held that Morse's most expansive claim describing "the use of the motive power of the electric or galvanic current . . . however developed for marking or printing intelligible characters, signs, or letters, at any distances" was invalid.[134] It was "too broad, and not warranted by law"[135] because it claimed all means of telegraphic communication at all distances, which Morse did not invent. In other words, Morse invented the telegraph, but he did not invent the fax machine.[136]

The Court attempted to further reify the concept in *Incandescent Lamp*.[137] William Sawyer and Albon Man obtained a patent for an "electric lamp" with an "incandescing conductor" made of "carbonized fibrous or textile material."[138] The problem for them, however, was that they claimed the use of "all fibrous and textile materials for incandescent conductors."[139] So, when they sued Thomas Edison for infringement, the issue was whether they enabled that entire class.[140] The Court said no.[141] Edison, unlike the patentees, had gone through the "painstaking experimentation" to discover that bamboo had superior qualities as a filament to Sawyer and Man's carbonized paper version.[142] And "the fact that paper happens to belong to the fibrous kingdom did not invest Sawyer and Man with sovereignty over this entire kingdom" because they did not describe some "'general quality . . . running through' the class that gives it 'a peculiar fitness for the particular purpose.'"[143]

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129. *Id.* at 606.
130. *Id.* at 610.
131. *Id.*
132. O'Reilly v. Morse, 56 U.S. (15 How.) 62 (1853).
133. *See id.* at 81–83.
134. *Id.* at 112.
135. *Id.* at 113.
136. *See* Transcript of Oral Argument at 58, Amgen Inc. v. Sanofi, 598 U.S. 594 (2023) (No. 21–757).
137. Consol. Elec. Light Co. v. McKeesport Light Co., 159 U.S. 465 (1895) [hereinafter *Incandescent Lamp*].
138. *Id.* at 468.
139. *Id.* at 472.
140. *Id.*
141. *Id.*
142. *Id.* at 475; Amgen Inc. v. Sanofi, 598 U.S. 594, 609 (2023).
143. *Amgen*, 598 U.S. at 611 (quoting *Incandescent Lamp*, 159 U.S. at 475).

As its third and final example, the Court reiterated its holding in *Holland Furniture*.[144] In that case, the Perkins Glue Company patented a starch glue similar to animal glue.[145] Perkins claimed all "starch glue which, combined with about three parts or less by weight of water, will have substantially the same properties as animal glue."[146] But the "starch ingredient" that was essential to the glue was described "in terms of its 'use or function' rather than its 'physical characteristics or chemical properties.'"[147] The company's claims were therefore invalid for lack of enablement because a glue practitioner attempting to use Perkins' discovery "could do so only after elaborate experimentation."[148]

After recapitulating its enablement jurisprudence of old, the Court applied the same principles to the facts in *Amgen*. Amgen had claimed a class of antibodies containing potentially "millions" of additional antibodies not disclosed nor described in its specifications.[149] Amgen only disclosed twenty-six specific antibodies of that class.[150] Those embodiments were undoubtedly enabled, but Amgen's claims still could not be upheld. Disclosing only twenty-six examples of a potential class of "millions" of antibodies that bind to PCSK9's sweet spot and block the LDL receptor, the Court explained, amounted to "little more than two research assignments."[151] In other words, Amgen asked the PHOSITA to engage in an "[un]reasonable degree of experimentation" to meet "the full scope of the invention as defined by its claims."[152] The Court clarified that enabling the "full scope" of the invention does not require every single embodiment in the claimed class to be described "with particularity."[153] Even so, Amgen failed to enable all that it claimed.

Amgen's arguments to the contrary were unavailing. First, Amgen argued that it had created a "roadmap" by which the PHOSITA could, after following the requisite steps, allow her to eventually "produce all antibodies within the claims."[154] Second, Amgen argued the practice of "conservative substitution"—replacing select amino acids in an antibody's primary sequence with other amino acids with similar chemical properties—further enabled the PHOSITA to reach the full scope of the claims.[155] "We cannot agree," the Court concluded, that the combination of these practices amounts to enablement.[156] The roadmap "merely describes step-by-step Amgen's own trial-and-error method for finding functional antibodies—calling on scientists to create a wide range of candidate antibodies and then screen each to see

144. Holland Furniture Co. v. Perkins Glue Co., 277 U.S. 245 (1928).
145. *See id.* at 247.
146. *Id.* at 251.
147. *Amgen*, 598 U.S. at 610 (quoting *Holland Furniture*, 277 U.S. at 256).
148. *Holland Furniture*, 277 U.S. at 257.
149. *Amgen*, 598 U.S. at 613.
150. *See id.* at 604.
151. *Id.* at 614.
152. *Id.* at 613, 610.
153. *Id.* at 610.
154. Brief for Petitioners at 3, Amgen Inc. v. Sanofi, 598 U.S. 594 (No. 21–757) (emphasis omitted).
155. *Id.* at 49–50.
156. *Amgen*, 598 U.S. at 614.

which happen to bind to PCSK9 in the right place and block it from binding to LDL receptors."[157] Furthermore, conservative substitution "isn't much different" because it requires scientists to "make substitutions to the amino acid sequences of antibodies known to work and then test the resulting antibodies to see if they do too."[158] The unpredictability of the art made each test a speculative foray rather than a targeted attempt at confirming a likely hypothesis.[159] "That is not enablement," the Court held.[160] "More nearly, it is a 'hunting license'" to engage in "painstaking experimentation."[161] The Court therefore affirmed the Federal Circuit's judgment of invalidity.[162]

II. THE ANTIBODY PATENT SINGULARITY

A. Defining the Singularity

The fallout from *Amgen* so far is unclear. For some, *Amgen* likely brings an issue described as the "death of the genus claim" to its head.[163] Those authors emphasize a quiet yet monumental shift in patent jurisprudence regarding courts', and specifically the Federal Circuit's, treatment of functional genus claims in the biological arts.[164] This "death" has particular salience in the context of antibody patents, where the Federal Circuit and now Supreme Court's articulated tests for enablement do not mesh with the realities of the technology. But whether recent jurisprudence on the issue is more aptly characterized as the "death" of functional biotechnological genus claims or simply the application of settled law to modern problems in the unpredictable arts, as the Court characterized it, is beyond the scope of this Note.

What is apparent, however, is that post-*Amgen*, antibody patent applicants face significant headwinds in securing claims directed to classes of antibodies. The result is a detriment to the research and development (R&D) of groundbreaking antibody therapies. Relatedly, *Amgen* represents a significant dent in the pure pecuniary value of any single valid antibody patent. This is because claims that pass muster under *Amgen*'s enablement standard are now severely limited in scope, in terms of the permissible absolute number of discrete antibody structures within a valid, enabled claim. In essence, antibody patents are now doubly constrained, with the science on one side and the law on the other. To be sure, *Amgen* did not completely foreclose

157. *Id.*
158. *Id.*
159. *See id.*
160. *Id.*
161. *Id.*
162. *Id.* at 616.
163. Dmitry Karshtedt, Mark A. Lemley & Sean B. Seymore, *The Death of the Genus Claim*, 35 HARV. J.L. & TECH. 1 (2021).
164. *See id.* at 27 (discussing "the new law" of genus claims); *see also Paradox*, *supra* note 2, at 1013 (beginning discussion on "the death of antibody patent claims").

valid functional genus claims directed to classes of antibodies.[165] The *Amgen* Court merely reinforced commensurability as a critical inquiry under section 112(a). In simple terms, the doctrine of commensurability decrees "[t]he more one claims, the more one must enable."[166] And in more doctrinal terms, "[t]he enablement requirement ensures that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims."[167]

A commensurate disclosure to a class of functionally claimed antibodies, however, is nonsensical given the science. The Court recognized that the class of antibodies Amgen claimed contained "at least millions of candidates."[168] In accordance with *Amgen*, to describe the "full scope" of an antibody genus would require the applicant to describe nearly every antibody in the class according to its DNA or amino acid sequence—an onerous and unworkable standard. The sheer multiplicity of antibodies makes that endeavor a Sisyphean task. To describe in "full, clear, concise, . . . exact,"[169] and *non-functional* terms, some "quality common to every functional embodiment" of a class of antibodies would turn a patent to an encyclopedia and a scientist to an infinite rock pusher.[170]

In the past, applicants attempted to circumvent this issue by claiming antibodies according to the "tightness" of the antibody-antigen interaction (affinity) or the stability of the antibody-antigen complex (avidity).[171] Applicants also tried to confine the claimed genus to classes of only a few hundred antibodies, usually by claiming only the class that binds to a specific epitope in a specific way. But those attempts still claimed the class by its function.[172] Today, predicting an antibody's 3D structure from its amino acid sequence remains "inadequate" and "disappointing."[173] What is more, as previously discussed, "[c]hanging even one amino acid in the entire sequence can alter an antibody's 3D structure and function."[174] In other words, even when scientists can name and order every building block of an antibody, they cannot predict what it looks like.[175] Nor can they predict what it does.[176] Moreover, the slightest change can compromise the entire makeup.[177]

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165. *See Amgen*, 598 U.S. at 614 (suggesting functional genus claims enabled when the inventor "identifies a quality common to every functional embodiment").

166. *Id.* at 610.

167. Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc., 166 F.3d 1190, 1195–96 (Fed. Cir. 1999); *see also* R. CARL MOY, MOY'S WALKER ON PATENTS §7:23 (2020).

168. *Amgen*, 598 U.S. at 613.

169. 35 U.S.C. §112(a).

170. *See Paradox*, *supra* note 2, at 1013 (analogizing describing biological molecules atom-by-atom to describing an F-16 fighter jet by every nut and bolt).

171. *Id.* at 994.

172. *Id.* at 1014. For more discussion of how antibody classes have been historically claimed at the U.S. Patent and Trademark Office (PTO), see *id.* at 1013–37.

173. Chiu, *supra* note 42, at 11.

174. *Winter Brief*, *supra* note 43, at 14.

175. *Id.* at 14–15.

176. *See id.* at 14.

177. *See id.*

At bottom, *Amgen* foreclosed all opportunity for applicants to "enable" any sizeable class of antibodies—to describe some "quality common" amongst all antibodies which, for example, bind to a single antigen. The "death of antibody patent claims"[178] is just one example then of a case where patent laws have refused to differentiate technological industries to the detriment of innovation.[179] The only insurance antibody patent applicants now have against invalidation for lack of enablement is to claim individual antibodies by their primary structures.[180] In other words, the minimal guarantee antibody applicants may glean from *Amgen* is that disclosure of an antibody's primary amino acid sequence satisfies section 112(a), but *only as to that specific antibody*.[181] What will result is an extreme exacerbation of the phenomenon of what empirical data has already shown[182]: Antibody patents have reached a singularity. Claims to any undescribed and undisclosed antibody risk invalidation.

Post-*Amgen*, at a minimum, pharmaceutical companies will still pursue protection for the individual antibodies they reduce to practice. Given the immense value of patents protecting these life-saving therapies, firms will gladly undertake the marginal cost of extra patent prosecution for guaranteed exclusive rights. If applicants decide to move toward this narrow approach to patenting antibodies out of an aversion to invalidated claims under section 112(a), it will certainly fix their enablement problems. By divulging an amino acid sequence, a PHOSITA would be able to "make and use" the resultant antibody.[183] Therefore, post-*Amgen*, what antibody patents lose in scope, they gain in procedural certainty. Additionally, though dubious, it remains *theoretically* possible to enable and literally claim undisclosed antibodies under the *Amgen* standard. But when each mAb therapy has the potential to become a top fifty best-selling drug, applicants will safeguard their investments.[184] They will likely opt for procedural certainty under section 112(a) over broader claim scope, given that the next patent is but a filing fee away.[185] Firms may not risk invalidating their exclusive rights on the whims of a single jury (or, in

178. *Paradox*, *supra* note 2, at 1013.

179. *See* DAN L. BURK & MARK A. LEMLEY, THE PATENT CRISIS AND HOW COURTS CAN SOLVE IT 155 (2009) [hereinafter PATENT CRISIS] (discussing how "policy levers" can be developed through common law to differentiate and tailor innovation in different technological fields).

180. *See* Amgen Inc. v. Sanofi, 598 U.S. 594, 612 (2023) ("[W]e do not doubt that Amgen's specification enables the 26 exemplary antibodies it identifies by their amino acid sequences.").

181. *See Amgen*, 598 U.S. at 612.

182. Sean Tu & Christopher Holman, *Antibody Patents: Use of the Written Description and Enablement Requirements at the Patent & Trademark Office*, 38 BERKELEY TECH. L.J. 1, 24, 30 (2023).

183. *Amgen*, 598 U.S. at 612.

184. Under 42 U.S.C. §262(k)(7)(A), new monoclonal antibody therapeutics are entitled to a twelve-year FDA exclusivity period, during which time the FDA cannot "ma[k]e effective" any application for a "biosimilar" of that product. But patents can prevent biosimilars coming onto the market for years after the FDA-exclusivity period expires.

185. In addition, firms may file congeries of applications of varied claim breadth to test the limits of *Amgen*, but lower courts do not seem agog to distinguish *Amgen*. *E.g.*, *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1363 (Fed. Cir. 2023) (invalidating classes of antibodies that "bind[] Factor IX" for lack of enablement and rejecting "an attempt to distinguish *Amgen*").

Amgen's case, two). Nor will the prospects of bench trials likely assuage concerns over invalidation.[186]

In fact, applicants were already narrowing antibody claims prior to *Amgen*. Professors Tu and Holman studied empirical data of antibody patents at the PTO.[187] They concluded that antibody claims have been narrowing for some time to account for the Federal Circuit's shift in section 112(a) jurisprudence, which includes the law of enablement and also the "written description" requirement.[188] The study further suggests that to account for the drop-off in scope, applicants are applying for a larger number of narrow patents, potentially to "try and achieve the same broad patent scope that they were previously able to attain with one genus patent" in piecemeal fashion.[189] *Amgen* exacerbates this practice and minimizes the valid scope of antibody patents to a singularity. The impact of this singularity on innovation throughout the drug pipeline, however, remains to be seen.

B. Patent Scope and Innovation

The singularity presents applicants with a new challenge—or perhaps an old one in a different form. As the scope of a patent claim decreases, the ease by which competitors may "invent around" the claim increases.[190] Thus, claiming antibodies only by their primary structure would seem to vitiate antibody patents of all value. After all, shameless "duplication is a dull and very rare type of infringement."[191] Without adequate protection against those who would prefer to bypass innovation, narrow antibody patents risk being converted to "hollow and useless thing[s]."[192] The narrowing of claim scope in the antibody arts therefore risks hampering innovation in antibody therapeutics.[193]

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186. Indeed, massive reversals of jury verdicts have been as judgments as matters of law. *See* Amgen Inc. v. Sanofi, No. 14-1317-RGA, 2019 WL 4058927 at *13 (D. Del. Aug. 28, 2019); Idenix Pharms. LLC v. Gilead Scis., Inc., 941 F.3d 1149, 1153 (Fed. Cir. 2019); Baxalta Inc. v. Genentech, Inc., 81 F.4th 1362, 1363 (Fed. Cir. 2023); Teva Pharms. Int'l GMBH v. Eli Lilly and Co., No. 18-cv-12029-ADB 2023 WL 6282898 (D. Mass. Sep. 26, 2023), *appeal docketed*, No. 24-1094 (Fed. Cir. Oct. 30, 2023).

187. Tu & Holman, *supra* note 182, at 24, 30.

188. *Id.*

189. *Id.* at 31–32 ("It is possible that innovators have responded to the narrowing scope of antibody patents by obtaining a larger number of patents with relatively narrow claims.").

190. *See* Dan L. Burk & Mark A. Lemley, *Biotechnology's Uncertainty Principle*, 54 CASE W. RSRV. L. REV. 691, 727 (2004).

191. Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co., 339 U.S. 605, 607 (1950).

192. *Id.* at 607–08.

193. *See* Burk & Lemley, *supra* note 90, at 1576. ("Patent law is our primary policy tool to promote innovation, encourage the development of new technologies, and increase the fund of human knowledge.") Later, Burk and Lemley note that because Kitch's "prospect theory" of economic incentives in patent law maps particularly well onto the pharmaceutical sector, "it is likely that innovation would drop substantially in the pharmaceutical industry in the absence of effective patent protection." *Id.* at 1616–17 (footnote omitted). And later, Burk and Lemley explain that "anticommons theory" also maps well onto the biotechnology industry. Both theories apply to antibody patents. But post-*Amgen*, anticommons theory is particularly salient because "the existence of numerous functional equivalents to a particular [antibody] means that patent protection must be broad enough to effectively exclude simple design-arounds." *Id.* at 1625. At first glance, it may appear that clinical equivalents, *infra*

Some post-*Amgen* prosecutors may remain stubborn and attempt to slide functional genus claims past examiners and appeal validity all the way to the Federal Circuit. But unless patent applicants disclose "the full scope of the invention as defined by its claims" (i.e., nearly every claimed embodiment), this will likely be to no avail.[194] Other prosecutors, seeing these fruitless attempts, may choose a different path. Consistent with Tu and Holman's observations described above, they may obtain large swaths ("thickets")[195] of patents directed to single antibody structures.

Even if antibody patent applicants attempt a piecemeal approach to patenting antibody genera, to encourage innovation, patent holders require assurances that their rights extend beyond the structures listed in their patents.[196] Without such guarantees, *Amgen*'s acceleration towards an antibody patent singularity may have profound effects on innovation in the therapeutic antibody field. As it currently stands, the state of antibody science and the unpredictability in the field likely prevents functional claiming of a genus of antibodies from ever satisfying *Amgen*'s "meet the full scope" test. If *Amgen* has cut off antibody patents at their knees, drugmakers may divert research and development funds to other projects, for example, the development of small molecule therapies. Clinical trials aren't cheap. On average, it costs about $1 billion[197] and takes the better part of two decades to bring a new drug to market.[198] The cost of clinical trials constitutes the bulk of that investment.[199] Moreover, the development of mAb therapies costs more than that of small molecules.[200] And there is evidence that pharmaceutical stakeholders

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Part IV, exacerbates anticommons risk. But Burk and Lemley were mainly concerned with research tool patents preempting downstream utilitarian products in a scenario where fragmented property rights require integration, usually between competitors, prior to innovation. In the scenario I envision for clinical equivalents, it is unlikely patented research tools will preempt follow-on antibody innovation. At a minimum, horizontal anticommons risk is null under a clinical equivalents analysis. Anticommons risk arises from a scheme of "complementarity of products." Burk & Lemley, *supra* note 90, at 1612. Antibodies are not beleaguered by complementarity. They are fundamentally at or near the smallest unit of patentable matter. What is more, horizontal anticommons theory assumes narrowness of patents, but *not* a singularity. In the "n of 1" post-*Amgen* scenario, horizontal anticommons risk is impossible because each amino acid sequence is discrete.

194. Amgen Inc. v. Sanofi, 598 U.S. 594, 610 (2023).

195. As originally termed, a patent thicket refers to "a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology." Carl Shapiro, *Navigating the Patent Thicket: Cross Licensing, Patent Pools, and Standard Setting*, 1 INNOVATION POL'Y & ECON. 119, 120 (2001).

196. *See* Ashish Arora, Marco Ceccagnoli & Wesley M. Cohen, *R&D and the Patent Premium*, 26 INT'L J. INDUST. ORG. 1153, 1156 (2002) (showing that the biotechnology industry maintains one of the highest expected "patent premiums," defined as a patent's incremental effect on the pecuniary value of an innovation and discussing changes in R&D investment as a response to high patent premiums).

197. Olivier J. Wouters, Martin Mckee & Jeroen Luyten, *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018*, 323 JAMA 844, 848 (2022).

198. Qing Lin, *A Proposed Test for Applying the Doctrine of Equivalents to Biotechnology Inventions: The Nonobviousness Test*, 74 WASH. L. REV. 885, 890 (1999).

199. *See* Wouters, *supra* note 197, at 848 ("After accounting for costs of failed trials," the median outlay to bring a new drug to market went from $319M to $1,141M).

200. *See id.* at 848, 850 (Costs of developing cancer drugs were the highest and "median costs for biologic drugs . . . were higher than those for pharmacologic drugs").

disproportionately modulate R&D investments in response to changes in patent policy, even when compared to other industries notorious for valuing patents.[201] In *Amgen*, several pharmaceutical innovators remarked, as *amici*, that they would be "reluctant to invest the substantial time and money necessary to make significant discoveries"[202] if the Court held as it did. In other words, post-*Amgen*, biotechnological innovators may determine that the scope of the claims they can predictably enable is too scant to invest a billion dollars into. The combined forces of the unpredictability in the art and *Amgen*'s holding requires the innovator to "redirect resources into impractical [and] wasteful experiments just to shore up her patent disclosure to teach how to cumulatively produce all the variants of her invention."[203]

Amgen therefore merely incentivizes more *patents*—not more *innovation*. The decision decimates the marginal value of an enabled antibody patent without providing any counterbalance. Simultaneously, while the scope of valid, enabled antibody patent rights is at its nadir, without the prospect of how to prevent, exclude, or disincentivize competitors from tweaking patented antibody structures, a follow-on competitor could discover a groundbreaking antibody, save massively on the upfront cost of development, and avoid infringement. As a result, firms may decide that tangential copying is a more profitable business model than innovative discovery.

In short, in a post-*Amgen* world, uncertainty abounds. One thing, however, is clear: Antibody patent applicants and patent owners now know that the bar for enablement in this technology is high, if not impossible to meet, in the case of functional claiming. How they choose to meet this challenge will impact the rate at which groundbreaking biologics are coming onto the market and the overall rate of scientific progress at all stages of the drug pipeline.

C. Counteracting the Singularity

To counteract the move towards an antibody patent singularity, Professors Lemley and Sherkow suggest two approaches to expand the legal scope of antibody patents beyond only patent-disclosed structures: means-plus-function claiming and the doctrine of equivalents.[204]

Congress codified means-plus-function claims as an appropriate way to describe inventions in functional terms.[205] In 1946, the Supreme Court invalidated a patent claiming a resonator "which performs the functions of a sound filter."[206] In response, in 1952, Congress explicitly codified then-section 112 ¶6, allowing an applicant to claim an element "as a means or step for performing a specified function without the recital of structure."[207] This pragmatic approach mandates that

201. Arora, *supra* note 196, at 1156.
202. GSK Brief, *supra* note 3, at 6–7.
203. *Id.*
204. *See Paradox*, *supra* note 2, at 1055.
205. *See id.* at 1056.
206. Halliburton Oil Well Cementing Co. v. Walker, 329 U.S. 1, 8 (1946).
207. 35 U.S.C. §112(f).

a claim "shall be construed to cover the corresponding structure . . . and equivalents thereof."[208] Now codified in section 112(f), "equivalents" are limited to equivalents of embodiments "described in the specification."[209] Means-plus-function claiming to a class of antibodies therefore may not implicate millions of antibody structures, but significantly fewer embodiments. This "intriguing intermediate possibility between pure functional claims and narrow species claims" may play a significant role in relieving apprehensions toward continued heavy investments into speculative antibody therapy R&D pipelines in a post-*Amgen* world.[210]

This Note, however, focuses on the second prescription. Another way for applicants to counteract the effects of the singularity, suggested by Lemley and Sherkow, is to employ the doctrine of equivalents.[211] Under the doctrine of equivalents (DoE), "a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention."[212]

Amgen implicitly urges patentees with the narrowest of antibody species claims to assert infringement under the DoE.[213] One clear rule from *Amgen* is that the disclosure of an antibody's amino acid sequence unequivocally enables the PHOSITA to "make and use" the invention.[214] Large global pharmaceutical conglomerates will not simply roll over. Firms will naturally attempt to extend and expand their market exclusivity for as long as possible and stave off "patent cliffs," referring to the "immediate decline in revenue" directly after the expiration of patent protection in the pharmaceutical industry.[215] Given the stakes, firms will employ every legal means available to bring competitors within the confines of their claims.

If firms cannot bring undisclosed and undescribed antibody structures within the jurisdiction of their claims via the doctrine of equivalents, innovation in the field of therapeutic mAbs may be chilled.[216] A patent directed to an antibody that satisfies enablement under the articulated *Amgen* standard is easily dodged by competitors. Conservative replacement describes the practice in protein engineering of substituting or "replacing" an amino acid with another amino acid with similar physicochemical properties.[217] The accordant assumption is that the substitution will not (or very minorly) influence the stability and function of the subsequent

208. *Id.*

209. *Id.*

210. *Paradox*, *supra* note 2, at 1057; *see* GSK Brief, *supra* note 3, at 6–7.

211. *Paradox*, *supra* note 2, at 1054.

212. Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 21 (1997) (citing Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co., 339 U.S. 605, 609 (1950)).

213. *See supra* Section II.B.

214. 35 U.S.C. §112(a); *see supra* Section II.A.

215. Chie Hoon Song & Jeung-Whan Han, *Patent Cliff and Strategic Switch: Exploring Strategic Design Possibilities in the Pharmaceutical Industry*, 5 SPRINGERPLUS, no. 1, 2016, at 1.

216. *See supra* Section II.B.

217. *See* Per Harold Jonson & Steffen B. Petersen, *A Critical View on Conservative Mutations*, 14 PROTEIN ENG'G, DESIGN, & SELECTION 397, 397 (2001).

protein.[218] In some cases, this assumption holds true. In others, it can be audaciously wrong.[219] And there is the rub for antibody patents. Antibody patents operate in an unpredictable art. What a scientist expects to be a "conservative" replacement may turn out to be "not conservative at all . . . in terms of protein function."[220] But in the cases where a residue replacement results in substantially the same structure, function, and biological effects as the patented antibody, this would not amount to literal infringement of a claim directed to a singular antibody structure.

Amgen therefore pressures applicants to accept the narrowest claim scope imaginable in a field where a practice that is well known in the art (conservative replacement) brings resultant structures outside the literal scope of those claims while (sometimes) resulting in an antibody with largely the same effects and therapeutic properties.[221] Antibody patent applicants will bristle at the thought of having no protection against a follow-on competitor that differs by only a handful of amino acids to one that is patented. Given the principles of conservative substitution, a competitor antibody may differ by only one methyl group—four atoms—in a molecule of roughly tens of thousands of others,[222] and fail to literally infringe the relevant claim. A single antibody structure may give rise to thousands of structural iterations through the principles of conservative replacement.[223] The DoE will therefore be vital to give firms the assurance that their enormous investments will be protected and cannot be "invented around" by trivial changes. To protect innovation incentives in this critical field, the DoE will likely be more frequently asserted to extend exclusionary rights to undisclosed, after-arising, antibody structures.

In Part IV below, this Note discusses substantive considerations of how the DoE may be applied to therapeutic antibodies by accounting for the drug's clinical attributes. In other words, this Note offers an attempt to partially answer "the ultimate question . . . equal parts science, philosophy, and claim construction"—what makes an antibody "equivalent" to another and what should be the guiding principles courts use to grapple with this question?[224] First, Part III discusses the law of the doctrine of equivalents.

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218. *Id.*

219. *See Winter Brief*, *supra* note 43, at 14 ("Structure determines function, but not vice versa.").

220. *Id.* at 16.

221. An antibody structure created through conservative replacement may still infringe by equivalents, but discussed *infra*, there is no guarantee it performs the same function in the same way to achieve the same result.

222. The Kyoto Encyclopedia of Genes and Genomes shows a formula of $C_{6242}H_{9648}N_{1668}O_{1996}S_{56}$ for evolocumab. KEGG DRUG DATABASE, https://www.kegg.jp/entry/D10557 [https://perma.cc/EHS4-KH3J] (last visited Oct. 18, 2024).

223. *Cf. id.* (showing the chemical formula of evolocumab).

224. *Paradox*, *supra* note 2, at 1058.

III. THE DOCTRINE OF EQUIVALENTS

In the words of Judge Learned Hand, "after all aids to interpretation have been exhausted, and the scope of the claims has been enlarged as far as the words can be stretched, on proper occasions courts make them cover more than their meaning will bear."[225] Put another way, sometimes, because "the nature of language makes it impossible to capture the essence of a thing in a patent application,"[226] courts may and should find patent infringement beyond the literal confines of the claims. "If patents were always interpreted by their literal terms, their value would be greatly diminished."[227] Therefore, under the DoE, "[t]he scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims described."[228]

Although the DoE has no basis in statute, the Supreme Court has embraced it on several occasions as far back as 1853.[229] The judge-made[230] doctrine attempts to balance two policies: the need to protect patentees from those who make insignificant changes to an invention to avoid literal infringement, and the need to give notice to the public of the boundaries of patent rights.[231] Both policies further the Constitution's aim to "promote the Progress of Science and useful Arts."[232] The "unscrupulous copyist," making minor changes to "practice fraud on a patent," would undermine innovative efforts by depriving an inventor of the fruits of her labor and "convert the protection of the patent grant into a hollow and useless thing."[233] On the other hand, blurred claim boundaries may suppress inventors from improving existing technologies out of fear of infringement liability.[234] Indeed, as Justice Black noted, the DoE may deprive a responsible competitor from relying on the language of the patent claims.[235] Instead, "[h]e must be able, at the peril of heavy infringement damages, to forecast how far a court relatively unversed in a particular technological field will expand the claim's language . . . ."[236]

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225. Royal Typewriter Co. v. Remington Rand, Inc., 168 F.2d 691, 692 (2d Cir. 1948) (Learned Hand, J.).

226. Festo Corp. v. Shoketsu Kinzoku Kobyo Kabushiki Co., Ltd., 535 U.S. 722, 731 (2002).

227. *Id.*

228. *Id.* at 732 (citing Winans v. Denmead, 56 U.S. (15 How.) 330, 347 (1853)).

229. *E.g.*, Winans v. Denmead, 56 U.S. (15 How.) 330 (1853).

230. *See, e.g.*, Hilton Davis Chem. Co. v. Warner-Jenkinson Co., Inc., 62 F.3d 1512, 1540 (Fed. Cir. 1995) (Plager, J., dissenting) ("The doctrine of equivalents is a judge-made exception to these statutory mandates."); Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd., 344 F.3d 1359, 1377 (Fed. Cir. 2003) (Newman, J., concurring in part, dissenting in part) ("The doctrine of equivalents is part of that balance. The importance of the issue led the Federal Circuit and the Supreme Court to reconsider this body of long-established judge-made law.").

231. Lin, *supra* note 198, at 891.

232. U.S. CONST. art. I, § 8, cl. 8.

233. Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co., 339 U.S. 605, 607–08 (1950).

234. *Id.* at 607.

235. *Id.* at 617 (Black, J., dissenting).

236. *Id.*

A. The Tests for Equivalence

"Equivalence . . . is not the prisoner of a formula and is not an absolute to be considered in vacuum."[237] Courts should consider a plurality of factors when analyzing equivalence.[238] There are, however, usually two doctrinal "tests" to determine whether an element in an accused device or process is "equivalent" to the analogous element in a patent claim: the tripartite test, also known as the function-way-result test, and the insubstantial differences test.[239]

1. The Function-Way-Result Test

The Supreme Court has attempted to clarify what makes an accused element an "equivalent" on several occasions. In its 1950 decision in *Graver Tank & Manufacturing Co. v. Linde Air Products Co.* (*Graver Tank*),[240] the Court validated the existence of the DoE first recognized in the 19th century[241] and attempted to clarify its proper application. The Supreme Court stated in *Graver Tank* that an alleged infringer may be found liable by equivalence if the accused article "performs substantially the same function in substantially the same way to obtain the same result."[242]

Linde Air owned a patent containing four claims directed to welding fluxes.[243] Linde claimed fluxes made partly of a combination of alkaline earth metal silicates, mainly calcium and magnesium.[244] The accused flux substituted calcium and magnesium for a combination of calcium and manganese silicates.[245] Manganese, unlike magnesium and calcium, is not an alkaline earth metal.[246] The fluxes, however, were "identical in operation and produce[d] the same kind and quality of weld."[247]

The Court upheld the lower court's judgment of infringement.[248] The differences between the accused flux and the patented flux were "colorable only."[249] Because infringement is a factual issue, the Court scrutinized the district court's finding for clear error.[250] Finding none, Justice Jackson, writing for the majority, upheld the district court's conclusion that "'for all *practical purposes*, manganese silicate can be efficiently and effectively substituted for calcium and magnesium silicates."[251] In other words, the manganese flux was equivalent to the magnesium flux because it

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237. *Id.* at 609 (majority opinion).
238. *Id.*
239. *See* Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 40 (1997).
240. 339 U.S. 605 (1950).
241. *See* Winans v. Denmead, 56 U.S. (15 How.) 330 (1853).
242. *Graver Tank*, 339 U.S. at 608 (quoting Sanitary Refrigerator Co. v. Winters, 280 U.S. 30, 42 (1929)).
243. *Id.* at 606.
244. *Id.* at 610.
245. *Id.*
246. *Id.*
247. *Id.*
248. *Id.* at 612.
249. *Id.*
250. *Id.* at 610.
251. *Id.* at 611–12 (emphasis added).

performed the same function, in the same way, to achieve the same result.

2. The Insubstantial Differences Test

Almost fifty years after *Graver Tank*, the Court reaffirmed "the modern contours of what is known in patent law as the 'doctrine of equivalents.'"[252] The *Warner-Jenkinson* Court found that the "lengthy history of the doctrine of equivalents strongly supports adherence to our refusal in *Graver Tank* to find that the Patent Act conflicts with that doctrine. Congress can legislate the doctrine of equivalents out of existence any time it chooses."[253] There, among other things, the Court articulated the so-called "all elements rule," requiring courts to apply the DoE to each element of a patent claim, rather than "the invention as a whole."[254]

Petitioner Warner-Jenkinson and respondent Hilton Davis Chemical Co. both manufactured dyes.[255] A patented process of ultrafiltration removed impurities in the dyes.[256] Hilton Davis owned a patent directed to using the ultrafiltration process "at a pH from approximately 6.0 to 9.0."[257] This pH limitation phrasing, particularly the lower bound of 6.0, was added during prosecution.[258] After learning about Warner-Jenkinson's use of the ultrafiltration technology at a pH of 5.0, Hilton Davis sued, claiming infringement by equivalence.[259] A jury found that Warner-Jenkinson infringed under the DoE and an en banc Federal Circuit affirmed.[260]

The Supreme Court reversed and remanded for further proceedings.[261] The Federal Circuit "did not consider all of the requirements" of the doctrine elucidated in the Court's opinion.[262] In particular, the Court clarified the "all elements rule," which requires the DoE to be "applied to individual elements of the claim."[263] Additionally, the Court created a rebuttable presumption to the application of prosecution history estoppel: Unless a patent holder can articulate some reason unrelated to patentability as to why a claim limitation was introduced during prosecution, the reason will be presumed to be related to patentability, and prosecution history estoppel applies.[264] The estoppel bars "the application of the doctrine of equivalents to that element."[265]

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252. Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 21 (1997).
253. *Id.* at 28.
254. *Id.* at 29; *see also* Pennwalt Corp. v. Durand-Wayland, Inc., 833 F.2d 931, 935 (Fed. Cir. 1987) (en banc).
255. *Warner-Jenkinson*, 520 U.S. at 21.
256. *Id.*
257. *Id.* at 22 (emphasis omitted).
258. *Id.*
259. *Id.* at 23.
260. *Id.*
261. *Id.* at 41.
262. *Id.*
263. *Id.* at 29.
264. *Id.* at 33.
265. *Id.*

Of relevance here, the *Warner-Jenkinson* Court was notably unconcerned with defining a single test to determine equivalence between elements of an accused device and the asserted claim.[266] In doing so, the Court acknowledged that the equivalence analysis ought to depend, at least in part, on the technology at issue.[267] The Court therefore declined to adopt a mandatory "linguistic framework" to analyze equivalence.[268] The tripartite test may be "suitable for analyzing mechanical devices, [but] it often provides a poor framework for analyzing other products or processes," such as in the unpredictable arts.[269] Ultimately, the "particular linguistic framework used is less important than whether the test is probative of the essential inquiry: Does the accused product or process contain elements identical or equivalent to each claimed element of the patented invention?"[270] To answer this question, courts should consider the "context" of the patent, the prior art, the idiosyncrasies of the facts, an element's "purpose" within the invention, the "qualities" an element has "when combined" with other elements, and the "function" an element "is intended to perform."[271]

In addition, an "important factor" to analyze equivalence is "whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was."[272] In particular, whether a PHOSITA would know that two elements are interchangeable "is not relevant for its own sake, but rather for what it tells the factfinder about the similarities or differences between those elements."[273] Furthermore, what the PHOSITA "knows" to be "interchangeable" might evolve over time. This is because "knowledge of interchangeability between elements" is determined "at the time of infringement, not at the time the patent was issued."[274] Consequently, the DoE allows a patentee to assert infringement by equivalents of after-arising technologies, including those "unforeseeable at the time of the [patent] application."[275]

B. The Doctrine Counterbalances the Singularity

The doctrine of equivalents will be crucial to stave off post-*Amgen* R&D divestments of therapeutic antibody development.[276] And the DoE is likely to be employed more frequently by antibody patentees. Infringement by equivalents is tailor-made to the realm of antibodies. The DoE is established in the law, vetted in

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266. *See id.* at 40.
267. *See id.* at 39–40.
268. *Id.* at 40.
269. *Id.* at 39–40.
270. *Id.* at 40.
271. *Id.* at 25 (quoting Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co., 339 U.S. 605, 609 (1950)).
272. *Id.*
273. *Id.* at 37.
274. *Id.*
275. Festo Corp. v. Shoketsu Kinzoku Kobyo Kabushiki Co., Ltd., 535 U.S. 722, 740 (2002).
276. *See supra* Section II.A.

its application to antibody patents, and the finer points of the doctrine address issues clearly presented to antibody patent applicants.

The DoE is an appropriate, established tool for antibody patent holders to justify continued investment in antibody therapies. For one, the DoE is an established doctrine in patent law, blessed by the Supreme Court as far back as the 1800s.[277] Applying the DoE to antibodies would not require the development of new common law doctrines, nor an act from Congress.[278] Because the Supreme Court has remarked several times on the doctrine, there is at least some ultimate guidance on how the doctrine ought to apply not just in the antibody context, but in every context.[279] And courts should not be reluctant to apply established tenets of patent law to a new technology. Such is par for the course at the intersection of technology and the law. The Court recognized so in *Amgen*.[280]

In addition, scholars and litigants who are active in the debate and intimate with the core issues argue that the DoE is an adequate tool to protect antibody patent scope consistent with established precedent. Aside from Professors Lemley and Sherkow,[281] other *amici*, including the United States, also believe the DoE is an appropriate tool for antibody patentees to protect their inventions. For example, in its merits brief and at oral argument in the Supreme Court, the United States argued that the DoE can be used to militate against structurally similar antibodies escaping infringement of valid patents.[282]

Finally, the DoE is tailor made to this situation. For example, the DoE already allows a patentee to assert infringement of after-arising technologies. Indeed, "the proper time for evaluating equivalency . . . is at the time of infringement, not at the time the patent was issued."[283] Because antibody classes are vast, it is impracticable to require an applicant to know of every single embodiment within any class at the time of application. The DoE allows patentees to account for and consider this fact to avoid being "at the mercy of verbalism."[284] Characterizing antibodies atom by atom has been aptly described as "akin to describing a fighter jet by listing every nut and bolt."[285] The DoE is specifically adapted to prevent the law from

277. Winans v. Denmead, 56 U.S. (15 How.) 330, 343 (1853).

278. *See supra* note 230 (discussing the DoE as a judge-made doctrine); *see also* Burk & Lemley, *supra* note 90, at 1640 ("The patent statute equips courts with precisely such discretion [to dictate technology-specific patent policy] via a series of doctrinal policy levers."); PATENT CRISIS, *supra* note 179, at 155.

279. *E.g.*, Winans v. Denmead, 56 U.S. (15 How.) 330 (1853).

280. *See* Amgen Inc. v. Sanofi, 598 U.S. 594, 606 (2023) ("While the technologies in these older cases may seem a world away from the antibody treatments of today, the decisions are no less instructive for it.").

281. *See Paradox*, *supra* note 2, at 1061.

282. Brief for the United States as Amicus Curiae Supporting Respondents at 32, Amgen v. Sanofi, 598 U.S. 594 (2023) (No. 21–757); Transcript of Oral Argument at 90-91, Amgen Inc. v. Sanofi, 598 U.S. 594 (2023) (No. 21–757). To the extent Amgen argued its claims would be too narrow under the Federal Circuit's holding, the United States rebutted that Amgen may deploy the DoE at its disposal.

283. Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 37 (1997).

284. Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co., 339 U.S. 605, 607 (1950).

285. *Paradox*, *supra* note 2, at 998.

"subordinating substance to form."[286] Instead of requiring all the up-front research and experimentation to find, describe, and patent every amino acid sequence of every antibody, which, for example, binds to PCSK9 and blocks the LDL receptor, the DoE assuages concerns over the sunk costs of needless experimentation.

At the same time, the DoE, as applied to antibodies, would not unreasonably expand the scope of antibody claims. In fact, the DoE does not expand the scope of patent claims whatsoever.[287] The doctrine merely attempts to "look past the exact wording of the patent claim to the technological substance of what it *appears* the patentee was trying to claim."[288] Therefore, in the antibody context, the heart of the analysis is the same. Equivalence is only found in those antibodies that are insubstantially different from a patented antibody.[289] Courts, however, should be mindful to account for the innate linguistic limitations of describing antibody structures.

C. The Importance of Clinical Data

A question naturally arising in response to the discussion above is *exactly* how to define an antibody's properties for the purposes of an equivalents analysis. In Part IV below, this Note argues that a therapeutic antibody's clinical effects and data should be the primary inquiry in structural antibody equivalence.[290] Before explaining why clinical data should dictate the antibody equivalence analysis, it will be helpful to first illustrate the issues of omitting that data.

In short, omission of clinical data incentivizes therapeutic pluralism in lieu of innovation. To begin, it is worth conceding that antibody equivalence is a mightily difficult question. In some ways, it is unanswerable. Professors Lemley and Sherkow define antibody equivalence as the "ultimate question" involving "equal parts science, philosophy, and claim construction."[291] Any attempt to construct a framework to analyze antibody equivalence is a formidable task. Lack of such a framework, however, risks disorienting the analysis from its underlying policy. Without considering clinical data in the equivalents analysis, an antibody that is structurally dissimilar from a claimed antibody, but which performs substantially the

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286. *Graver Tank*, 339 U.S. at 607.

287. *See* Festo Corp. v. Shoketsu Kinzoku Kobyo Kabushiki Co., Ltd., 535 U.S. 722, 732 (2002) ("[T]he clearest rule of patent interpretation, literalism, may conserve judicial resources but is not necessarily the most efficient rule. The scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims described."); *cf. Graver Tank*, 339 U.S. at 607 ("Outright and forthright duplication is a dull and very rare type of infringement.").

288. R. CARL MOY, MOY'S WALKER ON PATENTS § 13:69 (2020).

289. *Supra* Section III.A.

290. I do not see, however, why this analysis should not also be applied to all biologics, at least when comparing therapeutic macromolecules. This analysis would apply only when a biologic structure is being compared to another either as an independent claim or as an element of a claim. The analysis also does not apply within the context of litigation pursuant to the Biologics Price Competition and Innovation Act (BPCIA), as litigation under that statute inherently concedes product equivalence. *See* 42 U.S.C §§262(i)–(l).

291. *Paradox*, *supra* note 2, at 1058.

same function, in the same way, to achieve the same result, will be held *not* liable.[292]

When drugmakers exploit such a rule to its logical conclusion, the result is exacerbation of the "me-too" drug phenomenon, where companies attempt to gain market share within an established therapeutic area by developing new medications with "purely incidental" therapeutic benefits.[293] To be sure, there are laudable reasons to develop "me-too" drugs.[294] But the rationale is limited to the more predictable small-molecule field. Biologics are different. Structural changes to antibodies may not exhibit the same level of observable clinical and pharmacological differences when administered to humans, in comparison to small molecule drugs. To disregard clinical data in the antibody equivalents analysis would exacerbate the "me-too" phenomenon to the extreme. Indeed, without regard for clinical data, a structurally inequivalent antibody may be held, as a matter of law, literally noninfringing *and* noninfringing by equivalents, yet simultaneously be insubstantially *clinically* different from an antibody in an asserted claim. To prevent this incongruent result, courts must establish whether, and to what extent, clinical data relating to therapeutic antibodies is relevant to the inquiry of therapeutic antibody equivalence.

To promote "Progress" in the field, the answer must be that the inherent clinical properties of a therapeutic antibody structure are paramount to determine its equivalents. Neglecting clinical data distorts innovatory incentives in the pharmaceutical industry. Illustrated below, in part, the difficulty of antibody equivalence originates from the science's fundamental incompatibility with the established legal tests for equivalence, our inadequate definitions of antibodies as physical objects, and their simultaneous status as extraordinary medical therapeutics. A disparity exists between the empirical legal analysis of antibody equivalents and the perception of antibody equivalence by clinically trained artisans.[295] Mainly this

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292. And it is likely, under such a rule, that courts would grant motions to dismiss for failure to state a claim if the inquiry is a rote side-by-side comparison of amino acid sequences. *See* FED. R. CIV. P. 12(b)(6).

293. Jeffrey K. Aronson & A. Richard Green, *Me-too Pharmaceutical Products: History, Definitions, Examples, and Relevance to Drug Shortages and Essential Medicines Lists*, 86 BRIT. J. CLINICAL PHARMACOLOGY 2114, 2115 (2020) (quoting DESMOND LAURENCE & JOHN CARPENTER, A DICTIONARY OF PHARMACOLOGY AND CLINICAL DRUG EVALUATION (1994)). Aronson and Green define a "me-too drug" as "[a] pharmacologically active compound that is structurally related to a first-in-class compound, regarded as belonging to the same therapeutic class as the original compound, and used for the same therapeutic purposes, but which may differ in some respects, such as specificity of pharmacological action, adverse reactions profile, or drug-drug interactions." *Id.* at 2116 tbl.1. To be sure, under this definition, because even "me-too" drugs "differ in some respects," *id.*, they would not be clinically equivalent, and therefore noninfringing. *See* Part IV *infra*.

294. *E.g.*, Aronson & Green*, supra* note 293, at 2117 tbl.2 ("[t]o reduce the risks of . . . adverse reactions and drug-drug interactions," "[t]o increase the chance of benefit . . . in a subset of patients," "[t]o improve drug delivery and pharmacokinetics," "[t]o use as replacements when there are drug shortages," "[t]o offer cheaper alternatives," and "[i]ncremental innovation").

295. *See* Jessica Ailani, Rebecca C. Burch & Matthew S. Robbins, *The American Headache Society Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice*, 61 HEADACHE 1021, 1029 tbl.7 (2021) (describing migraine-treating anti-CGRP antibodies as a class and not distinguishing between the members of that class in its clinical recommendations).

mismatch derives from, for one reason or another, a legal reverence for structural primacy over empirical clinical data.[296] The importation of misplaced structural primacy in therapeutic antibody equivalence leads to undesirable outcomes given the policies of patent law and the DoE itself.

An example of how one company argued for the use of clinical data to establish antibody equivalence, which was rejected by a district court, illustrates the relevance of clinical data and the difficulty of incorporating it into the analysis while adhering to DoE precedent.[297] Teva, a drug manufacturer, owned patents directed to classes of therapeutic antibodies with certain CDR sequences used to treat migraines and other headache disorders.[298] One in particular, fremanezumab, is currently marketed in the United States as Ajovy.[299] Another, made by Eli Lilly, is call galcanezumab and is marketed under the name Emgality.[300] Both antibodies work by binding to calcitonin gene-related peptide (CGRP), a protein involved in migraine pathophysiology.[301]

Teva asserted that Lilly's antibody infringed Teva's patent.[302] Although Teva agreed that its patent claiming "a specific subset of anti-CGRP antibodies that antagonize CGRP function" was not literally infringed, Teva still asserted infringement under the doctrine of equivalents.[303] Teva specifically claimed a handful of antibodies with particular amino acid sequences in certain CDRs.[304] Lilly's accused antibody had CDR sequences that were 29.9% similar, in terms of strict amino acid sequence, to one disclosed (and claimed) antibody structure in

296. Structural primacy results mainly from the observational level of inquiry. Although structural primacy remains faithful to the often molecular language of pharmaceutical claims, its use can become overzealously hypercritical in an equivalents analysis. *See e.g.*, Mylan Institutional LLC v. Aurobindo Pharma Ltd., 857 F.3d 858, 866–71 (Fed. Cir. 2017) (Lourie, J.). Of course, claim construction will always heavily influence the analysis. And this may explain why the *Teva* court, discussed below, contemplated pure homological similarity as the dispositive factor of equivalence. The paradigmatic cases, however, of when to apply a clinical equivalents analysis involves two instances. The first is when comparing pure composition of matter claims to individual antibody structures, as defined by their amino acid sequences. The second is when comparing an antibody structure as a claim element in a method of treatment claim to a competing antibody indicated for the same disease state.

297. Teva Pharms. Int'l GmbH v. Eli Lilly and Co., No. 18-cv-12029-ADV 2022 WL 4824318 (D. Mass. Oct. 3, 2022).

298. *Id.* at *1.

299. TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION (2022).

300. ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION (2021).

301. *Teva*, 2022 WL 4824318 at *1; *see also* Anne-Sophie Wattiez, Levi P. Sowers & Andrew F. Russo, *Calcitonin Gene-Related Peptide (CGRP): Role in Migraine Pathophysiology and Therapeutic Targeting*, 24 EXPERT OP. ON THERAPEUTIC TARGETS 91, 93 (2020).

302. *Teva*, 2022 WL 4824318 at *1.

303. *Id.* at *2.

304. Teva claimed "[a] method for reducing incidence of or treating headache in a human, comprising administering to the human an effective amount of an anti-CGRP antagonist antibody, wherein said anti-CGRP antagonist antibody is a human monoclonal antibody or a humanized monoclonal antibody . . . wherein the anti-CGRP antagonist antibody is: an antibody having a CDR H1 as set forth in SEQ ID NO: 3 . . . [listing amino acid sequences]." *Id.* at *3; U.S. Patent No. 8,586,045 col. 100 ll. 3–16.

Teva's specifications.[305] Additionally, the heavy and light chain variable domains of the antibodies (the parts primarily responsible for binding to antigens) had "50.8% and 64.5% sequence identities, respectively."[306]

Teva argued, however, that the court should *not* look to the exact amino acid sequences to determine equivalency.[307] Perhaps Teva was concerned that even the highest number at 64.5% sequence homology was, on its face, not enough to obtain summary judgment on equivalence.[308] Instead, Teva argued Lilly's antibody was "equivalent because the differences in amino acid sequence do not translate into *meaningful real-world biological differences* when the antibodies are deployed to treat headache patients."[309] Specifically, Teva argued under the tripartite framework that the antibodies described in its patent and Lilly's accused antibody

> (i) perform substantially the same biochemical function by binding to CGRP such that CGRP is blocked from engaging with its receptor; (ii) do this in substantially the same way by binding to the particular regions of CGRP required for receptor engagement with high affinity, selectivity, and duration; and (iii) achieve substantially the same result—the treatment of headache symptoms in patients due to a reduction in CGRP signaling.[310]

In other words, Teva argued antibody equivalence should focus on real world clinical data—the drug's ultimate effects on people, their bodies, and their disease state—rather than mechanical claim interpretation and molecular minutiae.

Judge Burroughs rejected this argument.[311] In doing so, the district court first concluded that it had to make a mutually exclusive choice of whether to analyze the antibodies under the tripartite test or insubstantial differences test.[312] The court chose the latter, concluding that the tripartite test was "poorly suited" for the equivalence analysis.[313]

The court then rejected Teva's argument that the inquiry into whether Lilly's antibody infringed by equivalents should account for clinical data.[314] In fact, it did

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305. *Teva*, 2022 WL 4824318 at *16 (citations omitted).

306. *Id.* These relatively low levels of homology imply that Lilly did not discover the antibody sequence via deliberate conservative replacement. Conservative replacement aside, I argue that structural differences have absolutely no bearing on the clinical equivalents analysis. *Infra* Part IV. To the extent antibodies with similar sequences exhibit similar clinical qualities, that should be incidental to courts.

307. *See Teva*, 2022 WL 4824318 at *18 ("In Teva's view, the key inquiry is not whether the amino acid sequences are different, but whether the differences matter in the claimed method—i.e., treating headache.") (citation omitted).

308. In fact, it was not enough. *Id.* at *19 ("Galcanezumab has CDRs and variable regions with amino acid sequences that are substantially different from Antibody G1 or any of its variants.").

309. *Id.* at *18 (emphasis added).

310. *Id.*

311. *Id.*

312. *Id.*

313. *Id.*

314. *See id.*

not reach the question as to whether the two antibodies were clinically different—whether their "real world meaningful biological differences" were insubstantial.[315] The clinical argument was "a bridge too far."[316] A "biological" analysis "would read the amino acid sequence limitation out of [the claims] and effectively expand the scope of that limitation to encompass any amino acid sequence in a full-length antibody that has the effect of sufficiently antagonizing CGRP."[317] Teva had only claimed the sequences of CDRs and variable domains of its patented structure.[318] Perhaps fatally, it did not *claim* the entire antibody sequence (although the entire structure of both the heavy and light chains were disclosed in the specification).[319] Thus, the court was wary to entertain the "biological" analysis when Teva had not even claimed an entire antibody structure.[320] It is unclear whether the court would have been convinced otherwise if Teva claimed the entire antibody sequence in lieu of just the CDR sequences.

Despite its declination, the court did look past the literal amino acid sequences on one occasion and noted, in *dicta*, that the antibodies have "functional differences."[321] These functional differences focused on the antibodies' molecular properties (e.g., where the antibody bound to CGRP). One bound in the "mid-region" and another bound to a different epitope, the C-terminal end.[322] Another difference was that Lilly's antibody bound to CGRP "five-times more rapidly" than Teva's.[323] The court defined these molecular distinctions as "functional differences," but remarked no further on them.[324] It did not mention "functional differences" in its infringement analysis.[325]

Teva also argued that there was a genuine dispute as to the "proper scientific framework used to perform the [tripartite] test, [and] the meaning and significance of clinical and pre-clinical data."[326] But the court declined to address those questions too, concluding that even if those issues were disputed, they were immaterial to the equivalence analysis.[327] Thus, the court granted summary judgment on the issue of noninfringement, and seemingly reduced the inquiry to a strict comparison of homological percentages.[328]

It is clear that defining antibody equivalence and applying the DoE to antibody structures engenders confusion and discontent. On one hand, a strict

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315. *Id.*
316. *Id.*
317. *Id.* at *19.
318. *See id.* at *18.
319. *See id.* at *19, *4; U.S. Patent No. 8,586,045 col. 100 ll. 8–14 ("[A]n antibody having a CDR H1 as set forth in [listing multiple CDR sequences].").
320. *See Teva*, 2022 WL 4824318 at *19.
321. *Id.* at *17.
322. *Id.*
323. *Id.*
324. *Id.*
325. *See id.* at *18–*19.
326. *Id.* at *18.
327. *Id.* at *19.
328. *Id.*

analysis of equivalence between accused antibodies and patented amino acid sequences provides clear notice to competitors, conforms with the all-elements rule, and adequately prevents application of the DoE from becoming unmoored from patent claims. It also aids in administrability. In *Teva*, the court, exasperated with the parties,[329] provided no other context of its finding of nonequivalence other than the numerical percental differences between the amino acid sequences.[330]

On the other hand, the antibodies' respective clinical properties paint a different picture. Despite possessing only 29.9% to 64.5% sequence homology (depending on the length of the analyzed sequence) the two antibodies in *Teva* have strikingly similar clinical properties. Both antibodies bind to the same target, CGRP, with high specificity.[331] They are used for the exact same purpose: the "preventive treatment of migraine in adults."[332] They are both degraded and cleared by the same processes.[333] Notably, unlike many other drugs, neither is metabolized and excreted via the liver or kidneys.[334] Neither crosses the blood-brain barrier; therefore, they both exert minimal direct effects on the central nervous system.[335] Both medications are administered by subcutaneous injection, on a monthly basis, via a similar injection device.[336] And perhaps most importantly, expert neurologists—even those who specialize in migraine treatment—do not differentiate between the two antibodies when deciding *which* medication to prescribe to patients.[337] The latest clinical guidelines outlining the preeminent expert consensus of migraine treatment recommend neither medication over the other.[338] This indifference holds true for all patient populations (e.g., diabetics, pregnant women, or patients who suffer from the most severe migraines).[339]

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329. *See id.* at *19, *1 ("Together the parties have filed far in excess of 1,000 pages . . . that improperly contain legal arguments." "After weeding through . . . more than 1,296 pages of asserted facts and responses . . . .").

330. *See id.* at *19.

331. *Compare* TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION § 11 (2022), *with* ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION § 11 (2021).

332. *Compare* TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION § 1.1 (2022), *with* ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION § 1.1 (2021).

333. *Compare* TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION § 12.3 (2022), *with* ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION § 12.3 (2021).

334. Both drugs, like all antibodies, are degraded by enzymatic proteolysis. *Compare* TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION § 12.3 (2022), *with* ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION § 12.3 (2021).

335. *Compare* TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION § 6 (2022), *with* ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION § 6 (2021). Neither medication reports neurological adverse reactions, and large molecules like antibodies are restricted from crossing the blood-brain barrier. Peng Zhao, Ningyan Zhang & Zhiqiang An, *Engineering Antibody and Protein Therapeutics to Cross the Blood–Brain Barrier*, 5 ANTIBODY THERAPEUTICS 311, 311–12 (2022).

336. *Compare* TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION § 2.2 (2022), *with* ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION § 2.3 (2021).

337. *See* Ailani et al., *supra* note 295 at 1027–28.

338. *Id.* at 1027.

339. *See id.*

Does this seem right? Experts in the field consider the two antibodies interchangeable.[340] That fact is not dispositive, but it is "one of the hallmarks of an equivalent."[341] Yet the *Teva* court sidestepped the question and relied on a cursory analysis of percental sequence identity.[342] Future courts may take this shortcut too. Like in *Teva*, courts may define antibody sequence homology as the end-all-be-all of equivalence without considering "meaningful real-world biological differences" between the two drugs.[343] To be sure, a large part of the equivalence analysis is a claims-drafting issue, and thus, inherently guided by claim construction. *Teva*'s analysis was soundly reasoned and fundamentally grounded in claim language. But the analysis still misses the mark. That is because the court put too much emphasis on antibody structure in its analysis and too little emphasis on the antibodies' respective clinical properties.[344] This misplaced structural emphasis in turn misapplies DoE principles and incorrectly sidelines empirical data as inapplicable evidence of equivalence.

It is axiomatic that the doctrine of equivalents is invoked when "the nature of language makes it impossible to capture the essence of a thing in a patent application."[345] Such is the case here. It is "impossible" or, at a bare minimum, highly impracticable, to ask an inventor to disclose every possible amino acid sequence conceivable of binding to a particular antigen to treat a certain disease in a certain way.[346] In the field of therapeutic monoclonal antibodies, "the essence" of the invention, especially when method of treatment claims are at issue, is in the name: the treatment of a disease—the alleviation of human suffering. Thus, in the context of therapeutic antibodies, the true "invention"—what the patent attempts to claim but which is thwarted in part by the limits of English itself—is all antibodies, and pharmaceutical compositions thereof, which treat the claimed disease and achieve the same clinical treatment effects of that disease in all ways which are insubstantially different from the analogous properties of the claimed antibody.[347]

In essence, the antibody *sequence itself*, when it is claimed as a human therapeutic, claims, through application of the DoE, all other antibodies which have substantially the same clinical properties. This all might sound familiar, as it is a doppelganger of the argument Teva put forth regarding "meaningful real-world biological differences."[348] The court rejected that argument as reading a limitation

340. *See id.* at 1029 tbl.7 (detailing and not distinguishing "[c]riteria for initiating treatment with [any of the four FDA-approved] monoclonal antibodies to calcitonin gene-related peptide or its receptor").

341. Overhead Door Corp. v. Chamberlain Grp., Inc., 194 F.3d 1261, 1270 (Fed. Cir. 1999).

342. Teva Pharms. Int'l GmbH v. Eli Lilly and Co., No. 18-cv-12029-ADV 2022 WL 4824318 at *19 (D. Mass. Oct. 3, 2022).

343. *Id.* at *18.

344. See also Mylan Institutional LLC v. Aurobindo Pharma Ltd., 857 F.3d 858, 868–70 (Fed. Cir. 2017) (Lourie, J.) to see the Federal Circuit emphasizing structural primacy of chemical equivalents.

345. Festo Corp. v. Shoketsu Kinzoku Kobyo Kabushiki Co., Ltd., 535 U.S. 722, 731 (2002).

346. *See* discussion *supra* Section I.B.

347. This holds true whether the claim is directed to the antibody itself, a pharmaceutical composition thereof, or as an element of a method of treatment claim.

348. *Teva*, 2022 WL 4824318 at *18.

out of the asserted claims.[349] That may be a correct analysis of those facts and those claims. But assuming the claim contemplates the entire antibody sequence, the refusal to engage in that analysis was flawed. By only considering structural homology and eschewing clinical data, *Teva*'s analysis undermines the policy of the DoE. The deification of antibody molecular structure forewarns innovators that competitors can avoid infringement if they only reduce sequence homology to below some arbitrary percentage. Excluding clinical data from the equivalents analysis permits competitors to utterly disregard whether their categorically noninfringing antibody treats the same disease (function) by binding to the same target (way) to alleviate the same symptoms to the same degree (result).[350]

The difficulty of injecting clinical nuance into the antibody equivalence analysis does not represent its inaptness. Antibodies are the epitome of a biological class of molecules that have nearly unlimited structural possibilities.[351] Their therapeutic potential is limited only by the range of natural antigens to be targeted. But patent applicants cannot enable classes of antibodies because patents, by their nature, are at the "mercy of verbalism,"[352] and antibodies, by their nature, are at the mercy of their unlimited potentiality restrained by the limits of human cognition. Instead of trying to fit the science into the patent laws, our patent laws should mold to the requirements of science, technology, and "Progress."[353] The DoE is one way patent law recognizes the limitations of human language. The doctrine confronts humanity where it is and explicitly accounts for its shortcomings.[354] Instead of skirting the question of clinical equivalence by engaging in incomplete analyses based in structural primacy, courts should recognize that rules, especially common

349. *Id.* at *19.

350. Like Judge Lourie explained in Mylan Institutional LLC v. Aurobindo Pharma Ltd., 857 F.3d 858, 868–70 (Fed. Cir. 2017), perhaps the tripartite test is not the best suited to therapeutic analyses. I do not suggest that what is the "function," "way," or "result" is categorically equivalent to "disease," "target," and "alleviation," respectively. An invention's function, way, and result are claim dependent determinations. But Judge Lourie suggests that aspirin and ibuprofen are, *a priori*, inequivalent, and yet, could be found equivalent under a tripartite analysis and the opposite under an "insubstantial differences" analysis. Here too, absolute dependence on structural primacy, for its own sake, is misplaced. I agree the two drugs are inequivalent as a matter of law based on structure alone. But hypothetically, if they were large enough molecules such that minor structural differences did not predictably clinically manifest, the question in an equivalence analysis should not be based on structural similarity, but *clinical* similarity in terms of the drugs' functions, ways to perform those functions, and the results evoked. For example, under the same hypothetical, aspirin would be inequivalent to ibuprofen, not because of its different structure from ibuprofen (because in this hypothetical they are macromolecules), but because it, for one, possesses greater platelet inhibitory effects than ibuprofen, which leads to higher risk of gastrointestinal bleeding but greater therapeutic antithrombotic effects. When the Supreme Court dictates that the tests are two sides of the same coin, differing results under either test indicates a fault in the application, rather than the choice of analysis.

351. ALBERTS, *supra* note 24, at 1320.

352. Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co., 339 U.S. 605, 607 (1950).

353. *See* Burk & Lemley, *supra* note 90 (explaining how patent law doctrines may be used as "policy levers" to tailor patents of specific industries in a "unitary patent system to the more complex realities of the world").

354. *See* Festo Corp. v. Shoketsu Kinzoku Kobyo Kabushiki Co., Ltd., 535 U.S. 722, 731 (2002).

law rules like the DoE, are "measures to be judged against their purposes."[355]

> But once called into being, they are also limitations on effectuation of any purposes which do not fit the actual form and nature of the rules. . . . Though the purpose-means pattern of idea is simple, the pattern of the weaving is bafflingly complex. Yet there results, in any rule or body of inter-related rules, a type of to All-of-us, a type of net purpose which must be figured out if the rule is to have meaning beyond the flat fiat or fact that "Thus it is."[356]

Laws are made by humans, for humans. Perhaps we should not allow our patent laws to stranglehold innovation. After all, "[w]e grant patents in order to promote innovation, and so we should grant [and enforce] patents . . . to the extent necessary to encourage such innovation."[357]

IV. CLINICAL DATA DEFINES ANTIBODY EQUIVALENCE

An antibody's clinical properties, buttressed by scientific data, ought to be the driving force of how courts analyze equivalence between two therapeutic antibody *structures*. That is not to say a patentee can claim dominion over that which it has not invented. Under this "biological" or "clinical" analysis, a patentee would *not* be entitled to a finding of infringement by equivalents against all antibodies which bind to the same antigen or epitope as the claimed antibody.[358] Instead, a biological analysis of therapeutic antibody equivalents only finds infringement when an accused antibody exhibits all the same insubstantially different clinical properties as the claimed antibody. Infringement is therefore limited to those instances when a patentee can demonstrate, through clinical data, that every relevant clinical property reasonably derives from the antibody composition itself.[359] This analysis complies with DoE precedent[360] and is no less administrable than other equivalents analyses

355. KARL N. LLEWELLYN, THE THEORY OF RULES 43 (2011).

356. *Id.*

357. Burk & Lemley, *supra* note 90, at 1599.

358. Thus, clinical antibody equivalents analyses would not undermine *Amgen*'s holding via a backdoor.

359. The clinical analysis only applies to the DoE context. However, 42 U.S.C. §262(i)(2) (emphases added) defines a "biosimilar" as a "biological product [that] is highly similar to [a] reference [biological] product notwithstanding minor differences in *clinically inactive components*; and there are no *clinically meaningful* differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." So the application of clinical data to the equivalents analysis would be consistent with Congress' acknowledgement that the complexity of large macromolecules requires this type of analysis precisely because of how unwieldy their structures are to precisely describe.

360. *See* Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555, 1567 (Fed. Cir. 1994). In *Genentech*, the Federal Circuit construed "human tissue plasminogen activator" to mean a "narrow structural definition" of only the exact structure of natural tissue plasminogen activator (t-PA), a protein. *Id.* at 1564. Yet, it entertained the idea, despite its mootness, *see id.* at 1567 n.36, that FE1X, an accused protein, could infringe by equivalents under the tripartite analysis despite being "structurally distinct from natural t-PA." *Id.* at 1559. In fact, FE1X was devoid of one of the five "regions" of natural t-PA and "most" of another region. *Id.* at 1559 n.4. The court, however, looked to t-PA's function "in a therapeutic sense," i.e., "reduc[ing] the risk of hemorrhaging." *Id.* at 1568. Judge Lourie concurred in

of complex technologies. Clinical analysis also offsets the innovation deterrents caused by *Amgen*'s antibody patent singularity.[361] Focusing the analysis on clinical properties enables innovators and patentees to confidently invest R&D funds into groundbreaking discoveries rather than "impractical" and "wasteful" experiments to insure against the unscrupulous copyist.[362] Clinical analysis therefore assuages concerns of the ever-looming risk of conservative replacement while simultaneously reserving the option to potentially patent structures that exhibit "unexpected results."[363] It achieves this harmonization whilst promoting information disclosure and product differentiation in the marketplace.[364] In addition, the structure and associated costs of clinical trials gives notice to all players of the boundaries of their freedom to operate at inherent stepwise intervals of clinical development, giving firms ample opportunity to evaluate whether to forge on in the development process, pivot, or abandon their inventions entirely.[365] For these reasons, the clinical properties of therapeutic antibodies should not just be included in an equivalents analysis; they should be its primary thrust.[366]

A. Pertinent Clinical Properties

For the purposes of clinical antibody equivalence analysis, each considered antibody property should be reasonably derived from the antibody composition itself. A clinical property must also be relevant to whether the antibodies in question are known clinical substitutes or insubstantially different according to the PHOSITA. Structural differences, even clearly delineated and articulated ones, should be disregarded or minimized unless the party asserting the importance of structural equivalence can show how the specific molecular structural difference causes the observed effect in clinical outcomes. Of course, molecular structural differences are assumed to manifest themselves in biological systems. But under this analysis, those manifestations—observed clinical differences—are sufficient and necessary to demonstrate inequivalence between two therapeutic antibody structures.[367]

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the judgment but disagreed with that portion of the analysis. Like in Mylan Institutional LLC v. Aurobindo Phama Ltd., 857 F.3d 858 (2017), he emphasized self-evident structural differences as dispositive. "The accused compound in this case consists of a protein that contains 446 amino acids, 15% fewer than the t-PA referred to in the claims. This is not an insubstantial change, but a substantial one." *Genentech*, 29 F.3d at 1570 (Lourie, J., concurring). Notably, Judge Lourie failed to cite what exact percentage would, in his view, differentiate "substantial" from "insubstantial."

361. *See supra* Part II.

362. GSK Brief, *supra* note 3, at 7.

363. *See generally* Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc., 752 F.3d 967, 976–79 (Fed. Cir. 2014) (discussing the role of "unexpected results" in relation to nonobviousness).

364. *See infra* Section IV.D.

365. *See infra* Section IV.D.

366. *See supra* note 290 and discussion therein. The analysis does not apply under the BPCIA but may apply to all macromolecules in addition to antibodies.

367. Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 40 (1997) (The "essential inquiry" is whether the accused product "contain[s] elements identical or equivalent to each claimed element of the patented invention.").

1. Clinical Equivalence Generally

Pertinent clinical properties are certainly the drug's indications and contraindications, the frequency and route of administration, side effects, and the rate and level of efficacy observed in clinical trials. On the other hand, a drug's recommended dose, in absolute terms, is not intrinsically a strong indicator of substantial clinical difference. This is because recommended doses of FDA-approved drugs represent a point on a spectrum of all possible doses that could have been selected by the drugmaker to market in interstate commerce.[368] The finalized dose is the actualization of a compromise between two fundamentally competing risks: more frequent and severe side effects and lack of efficacy.[369] An antibody's mechanism of action also imports a notable caveat. To the extent that two antibodies may have substantially the same clinical properties yet different mechanisms of action (i.e., they bind to different antigens) those antibodies are fundamentally inequivalent.[370] This notion represents a calibration of how much molecular structure should determine antibody equivalence. Structural considerations are therefore subordinated to clinical data except in only the most clear and delineated circumstances. In any event, two antibodies that bind to different targets are likely structurally different enough to warrant this bright-line rule. In the case they are not, they would still be categorically inequivalent because they perform different functions.[371]

In some instances, determining if two antibodies share substantially the same clinical properties may often be straightforward. Frequently, those parameters may be identical, according to the primary document disclosing a drug's clinical properties—the prescribing information, also known as the "package insert."[372] For example, fremanezumab, Teva's migraine antibody, and galcanezumab, Lilly's migraine antibody, are both indicated for the exact same purpose: "the preventive treatment of migraine in adults."[373] They are both administered by subcutaneous injection and are only contraindicated in those with allergic reactions to the

368. *See A Framework to Guide Dose & Regimen Strategy for Clinical Drug Development*, 10 CPT PHARMACOMETRICS & SYS. PHARMACOLOGY 1276, 1276 (2021).

369. As Paracelsus famously said: "Solely the dose determines that a thing is not a poison." Philippe Grandjean, *Paracelsus Revisited: The Dose Concept in a Complex World*, 119 BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 126, 126 (2016).

370. *Cf.* Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555, 1568 (Fed. Cir. 1994) (concluding the "function" of human tissue plasminogen activator for purposes of DoE analysis includes "fibrin binding" and therefore, no reasonable jury could have concluded the accused product, FE1X, which exhibited "weak[]" fibrin binding, functions in "substantially the same way with substantially the same results").

371. *See id.*

372. *E.g.*, TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION § 1.1 (2022).

373. *Compare id.*, *with* ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION § 1.1 (2021).

respective drugs.[374] Under a clinical analysis, despite the antibodies' structural differences, those "elements" would be equivalent. Notably, both medications are also administered via a pre-filled syringe, but this property does not reasonably derive from the antibody composition. The injectability requirement is not *inherent* to Teva's antibody vis-à-vis Lilly's accused antibody.[375] This fact, therefore, would be immaterial under a clinical equivalents analysis.

2. Harder Questions

In some instances, particularly when evaluating whether two antibodies are equivalent in terms of safety and efficacy, the answer becomes less absolute. This results, in part, from the truth of the statement adorning every medication's official prescribing information: "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."[376] Outside of rare "head-to-head" trials, when two clinical interventions are pitted against one another, the same notion of the inadequacies of direct comparisons holds when evaluating a drug's efficacy.[377] Still, despite slight methodological differences in clinical trials, it is for the factfinder to determine whether, according to the PHOSITA, the two antibodies are substantially different in those regards.

For example, the PCSK9 inhibitors in *Amgen* were studied in two independent multi-yearlong clinical trials to observe the rate at which each medication reduces the risk of major adverse cardiovascular events, or MACE.[378] These events include death from cardiovascular complications, strokes, heart attacks, and other cardiovascular complications requiring hospitalization.[379] Each trial enrolled over 10,000 patients and assigned half of them to inject a placebo and the others to inject the studied antibody.[380] At the end of the trials, both drugs found the exact same statistically significant reduction in MACE: Both antibodies reduced the risk of MACE compared to placebo by exactly 15%.[381] And the two trials had nearly

374. *Compare* TEVA PHARMACEUTICALS USA, INC., AJOVY FULL PRESCRIBING INFORMATION § 2.1 (2022), *with* ELI LILLY AND COMPANY, EMGALITY FULL PRESCRIBING INFORMATION § 2.1 (2021).

375. To clarify, all monoclonal antibodies must be injected, as the gastrointestinal system would degrade them before they enter the bloodstream. Therefore, injectability does not meaningfully differentiate fremanezumab from galcanezumab.

376. CTR. FOR DRUG EVALUATION AND RESEARCH (CDER), U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ADVERSE REACTIONS SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS — CONTENT AND FORMAT 4 (2006).

377. *See* Candice Estellat & Philippe Ravaud, *Lack of Head-to-head Trials and Fair Control Arms*, 172 ARCHIVES INTERNAL MED. 237, 237 (2012) ("Evidence from indirect comparisons across trials is weaker than evidence from direct randomized head-to-head trials.").

378. Sabatine et al., *supra* note 112; Schwartz et al., *supra* note 112.

379. Sabatine et al., *supra* note 112, at 1714.

380. *E.g.*, *id.* at 1715.

381. *Id.* at 1718 tbl.2; Schwartz et al., *supra* note 112, at 2102.

identical observed absolute incidences of MACE.[382] But the trials differed slightly in their eligibility criteria and the populations studied. On average, one study's population was five years older, had more diabetic patients, and more smokers.[383] All three of these factors increase an individual's risk of cardiovascular complications.[384] These differences raise the issue of whether one drug is more efficacious. When one study population is at a higher baseline risk, and the observed rates of MACE are equivalent, it may seem that the drug studied in the higher risk cohort is more efficacious than the other drug. Yet the latest American clinical guidelines, the gold standard of evidence-based medical decision-making, communicate complete indifference as to *which* PCSK9 inhibitor should be prescribed to any individual patient for the reduction of MACE.[385] Notably, the American Heart Association's guidelines do not quibble over slight variations in the trials' methods or enrolled populations.[386] Despite differences in methodology, people reasonably skilled in the art consider the two medications interchangeable, which the Supreme Court recognizes as an "important factor" of equivalence.[387] Of course, the ultimate determination by the factfinder would depend on the specifics of each case.[388]

B. Clinical Analysis Complies with Doctrine of Equivalents Policy and Precedent

As previously explained, the policy of the doctrine of equivalents stems from the shortcomings of human language and the concordant desire to protect inventors from competitors attempting to "practice fraud on a patent."[389] At the same time, courts must be mindful to give adequate notice of potential competitors as to the

382. MACE was observed in 9.8% and 11.3% of the treated and placebo populations respectively in the evolocumab trial. MACE was observed in 9.5% and 11.1% of the treated and placebo populations respectively in the alirocumab trial. *Compare* Sabatine et al., *supra* note 112, at 1713 *with* Schwartz et al., *supra* note 112, at 2097.

383. *Compare* Sabatine et al., *supra* note 112, at 1716 tbl.1, *with* Schwartz et al., *supra* note 112, at 2101 tbl.1.

384. Jennifer L. Rodgers, Jarrod Jones, Samule I. Bolleddu, Sahit Vanthenapalli, Lydia E. Rodgers, Kinjal Shah, Krishna Karia & Siva K. Panguluri., *Cardiovascular Risks Associated with Gender and Aging*, J. CARDIOVASCULAR DEV. DISEASE, Apr. 27, 2019, at 5.

385. Salim S. Virani, Kristin Newby, Suzanne V. Arnold, Vera Bittner, LaPrincess C. Brewer, Susan Halli Demeter, Dave L. Dixon, William F. Fearon, Beverly Hess, Heather M. Johnson, Dhruv S. Kazi, Dhaval Kolte, Dharam J. Kumbhani, Jim LoFaso, Dhruv Mahtta, Daniel B. Mark, Margo Minissian, Ann Marie Navar, Amit R. Patel, Mariann R. Piano, Fatima Rodriguez, Amy W. Talbot, Viviany R. Taqueti, Randal J. Thomas, Sean van Diepen, Barbara Wiggins & Marlene S. Williams, *2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines*, 148 CIRCULATION e9, e37 tbl.4.2.6 (2023) ("In patients with [coronary disease] who are judged to be at very high risk . . . a PCSK9 monoclonal antibody can be beneficial to further reduce the risk of MACE.").

386. *See id.* at e39–e40 (discussing both trials without differentiating recommendations).

387. A defendant, of course, has a right to rebut this evidence and the clinical equivalence inquiry does *not* reduce to simply what published clinical guidelines suggest.

388. Given the facts laid out above, however, I do not see any clinically substantial differences between the two antibodies in *Amgen*.

389. Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co., 339 U.S. 605, 607–08 (1950).

boundaries of patent rights.[390] An accused element is equivalent to a patented one when it performs the same function in the same way to achieve the same result.[391] If that exact verbiage does not aid the inquiry, another way to frame the analysis is to ask whether the elements are "insubstantially different."[392]

Comparing clinical equivalency between therapeutic antibodies to the minimization of pure structural equivalence complies with the policy of the DoE. For starters, language inherently limits an applicant's ability to describe all the possible antibody structures which are clinically equivalent to the claimed invention—those that treat the same disease in the same way to result in the alleviation of suffering from that disease. In *Amgen*, the Court recognized that potentially "millions" of antibodies may bind to a single antigen.[393] Even if the class of clinically equivalent antibodies to evolocumab, Amgen's PCSK9 inhibitor, consists of a small subset of the class of millions, it still would be unreasonable to ask an applicant to include them all in their claims and specification. Instead, the Court instructs us to focus on the invention's "practical purposes."[394] In the case of medications, that requires incorporating clinical data.

Second, employing a clinical analysis prevents inventors from the "unscrupulous copyist."[395] If a competitor derives a new therapeutic antibody from a known primary sequence through conservative replacement, depending on the severity of the change, the antibody will likely qualify as a clinical "equivalent." And to the extent that the new antibody exhibits substantially different "functions," "ways," or "results", it would not literally infringe the patented antibody structure (because conservative replacement by definition modifies the primary structure) *and* not infringe by clinical equivalents. A competitor is therefore free to experiment[396] with conservative replacements and undertake the steep financial risk of exploring the clinical properties of antibodies derived from those replacements, if it is so inclined. Clinical antibody analysis does not change the heart of the equivalents analysis. It merely asks the same question in a new light. It accepts the impracticality of requiring applicants to protect their inventions by reducing to practice and testing all likely equivalents from a single lead molecule. And it encourages courts to "look past the exact wording of the patent claim to the *technological substance* of what it appears the patentee was trying to claim."[397]

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390. *See id.* at 617 (Black, J., dissenting).

391. *Id.* at 608 (majority opinion).

392. Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 39–40 (1997).

393. Amgen Inc. v. Sanofi, 598 U.S. 594, 603 (2023).

394. *Graver Tank*, 339 U.S. at 611 (internal quotation marks omitted).

395. *Id.* at 607.

396. That is, by only creating antibodies that avoid literal infringement (which is easy enough to plan when the patented primary structure is publicly available). A future applicant may also be able to fit actual use of a literally infringing antibody under the BPCIA's "safe harbor" provision, but that seems tenuous if it is for the development of a non-biosimilar product. *See* 35 U.S.C. §271(e)(1).

397. R. CARL MOY, MOY'S WALKER ON PATENTS §13:69 (2020) (emphases added and omitted).

Clinical analysis also gives adequate notice to competitors of their freedom to operate. Because clinical data is published as a required disclosure of drug development and FDA approval, competitors are on notice of what their new antibody medication must not do (or do substantially differently).[398] The clinical data underlying the analysis is reliable. It is subject to strict regulatory safeguards and peer review.[399] So if, as a simplified example, Amgen had only studied evolocumab for the prevention of stroke, Sanofi is provided clear notice that it is free to study alirocumab for the prevention of heart attacks. If empirically proven,[400] then the two treatments would be used for different purposes (i.e., have different functions) and the two antibody *structures* would be inequivalent as a matter of law, even if they shared 99.9% sequence homology.[401]

Finally, clinical equivalents analysis complies, as it must, with *Warner-Jenkinson*'s "all-elements" rule.[402] A therapeutic antibody would only be equivalent to another if *all* clinical properties of the accused antibody are insubstantially different from the claimed antibody. The all-elements rule therefore functions to reserve infringement by clinical equivalents to those competitor antibodies that truly "add[] nothing" to the "storehouse of knowledge and experience."[403] Treating each clinical property as its own "element" for purposes of the all-elements rule prevents the analysis from becoming "unbounded by the patent claims."[404] In the case of therapeutic monoclonal antibodies, the entire scope of an antibody's clinical attributes is its technological substance. Each clinical property may be defined as an element of the antibody structure itself. Of course, whether the PHOSITA considers each element insubstantially different would be a factual issue and would only apply to the structural antibody element of the asserted claim.[405]

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398. FDA requires New Drug Applications (NDAs) to contain an extensive "section describing the clinical investigations of the drug." 21 C.F.R. §314.50(d)(5) (2023). It would be essentially unheard of that a major clinical trial leading to FDA approval of a new drug would go unpublished in a major peer-reviewed medical journal.

399. *See* discussion *supra* note 398.

400. To the point of statistical significance, that is. Of course, that standard is arbitrary and whether something is "empirically proven" would be based on expert testimony, and subsequently an issue for the factfinder.

401. This example omits many important details of reality, not the least of which is the added length and cost clinical trials would incur to be statistically powered to observe such specific outcomes. In addition, a plaintiff may argue that even these different "functions" are "insubstantially different," although that argument seems tenuous in its most favorable light.

402. *See* Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 29 (1997).

403. Graver Tank & Mfg. Co., Inc. v. Linde Air Prods. Co., 339 U.S. 605, 607, 610 (1950).

404. *Warner-Jenkinson*, 520 U.S. at 28–29.

405. And because equivalence is determined at the time of infringement, if either party as a patentee added the indication of the competitor's antibody to its label (or just studied their drug for the treatment of the other indication and found it to be adequate for that purpose too, as FDA-approval is not required for the clinical property to become a clinical element of the antibody), the party conducting that research could assert infringement once it showed the inherent property of its antibody. The less clinically developed antibody would then exhibit all indications of the more clinically developed one, and therefore be equivalent, at least to the indication element.

C. Clinical Analysis Counterbalances Amgen*'s Singularity*

Amgen's reduction of valid antibody patent scope forces innovators of therapeutic antibodies to divert R&D investments into "impractical" and "wasteful" experiments to insure against the unscrupulous copyist, rather than funding groundbreaking medical discoveries.[406] Clinical equivalence reduces this waste and assuages concerns of the ominous risk of conservative replacement while simultaneously adhering to the notion in patent law that a serendipitous discovery is patentable. Under a clinical analysis, a drugmaker-patent holder is not restricted to assert infringement against only those competitors which would create an exact copy of its patented antibody.[407] The analysis therefore expands the scope of antibody structures to which a charge of infringement would be proper under the DoE. At the same time, clinical equivalents are limited by other established rules, such as the all-elements rule, prosecution history estoppel, and ensnarement.

D. Clinical Analysis Incentivizes Innovation

Clinical antibody analysis is additionally limited in scope by its natural effect of promoting information disclosure, inherently leading to clinical innovation. Incentivization to public disclosure is a core tenet of patent law policy.[408] In turn, clinical information fuels clinical innovation. Over time, as the body of clinical data and knowledge expands, clinicians, such as doctors and pharmacists, are better equipped to extrapolate individually optimized clinical decisions from scientific data.

To see the importance of why the DoE should embrace clinical data, consider the history of bloodletting. Bloodletting was an accepted practice for all sorts of ailments prior to the development of the germ theory of disease.[409] When George Washington developed a fever and respiratory distress in December of 1799, Washington himself requested that he be bled, as "he believed that it cured him of past ailments."[410] He eventually succumbed to the illness on December 14, 1799 (assumedly bacterial epiglottitis and associated septic shock) after doctors bled him of nearly two and a half liters over a twelve-hour period.[411] Today, of course, we do not bleed patients with throat infections—we use antibiotics. As many of us may take for granted today, we learned that bloodletting fails to treat the underlying infection. Through sedulous scientific experimentation, Louis Pasteur and Robert Koch invalidated the humoral theory of disease, which postulated that all disease

406. GSK Brief, *supra* note 3, at 7.

407. In any event, that would be a "biosimilar" and is subject to BPCIA litigation.

408. Christopher A. Cotropia, *Physicalism and Patent Theory*, 69 VAND. L. REV. 1543, 1556 (2016).

409. Timothy M. Bell, *A Brief History of Bloodletting*, 11 J. LANCASTER GENERAL HOSPITAL 119, 119 (2016).

410. GEORGE WASHINGTON'S MOUNT VERNON, THE DEATH OF GEORGE WASHINGTON https://www.mountvernon.org/library/digitalhistory/digital-encyclopedia/article/the-death-of-george-washington/ [https://perma.cc/W6PS-FKM7] (last visited Oct. 18, 2024) [hereinafter THE DEATH OF GEORGE WASHINGTON].

411. Liakat Ali Parapia, *History of Bloodletting by Phlebotomy*, 143 BRITISH J. HAEMATOLOGY 490, 492 (2008).

amounted to an imbalance between blood, yellow bile, black bile, and phlegm.[412] They hypothesized, tested, and discovered that some diseases are caused by bacteria. As a partial result of their discoveries, in 1850, a white man born in Massachusetts could expect to live thirty-eight years.[413] The average American life expectancy is now double that, at seventy-six years.[414]

Today, because of the advent of evidence-based medicine, doctors have more information at hand than ever before. And they harness that information to curate their clinical decision-making. Elevating clinical data as the prime determinant of therapeutic antibody structural equivalence incentivizes innovators to contribute to the clinical storehouse of knowledge. Because equivalence is determined at the time of infringement, clinical analysis incentivizes drugmakers to divulge more information about their medications over time. Infringers, therefore, are only those who exacerbate a state of undifferentiated therapeutic pluralism, whereas noninfringers contribute to the diversity of therapeutic solutions.[415] Moreover, an infringer can remove its product from outside the realm of infringement by investing in scientific inquiry sufficient to show that its therapy performs a different function or performs it in a different way or that it achieves a different result. To be sure, a finding of inequivalence does not require clinical *superiority*, but merely substantial differentiation. A competitor may be "worse" in some aspect (e.g., more severe side effects) and, thus, substantially different. Success in the marketplace is untethered from clinical equivalence. And it is likely that if a new therapy is "worse" in one aspect that it may be "improved" in another, such as increasing the rate of side effects but decreasing the frequency of administration. Of course, superiority would be preferred.[416] In any event, mere clinical differentiation will be sufficient to transform an infringer into a scientific explorer. Clinical analysis therefore incentivizes innovation through disclosure.

The structure of the clinical development process also gives notice to potential competitors of their freedom to operate. Not only that, but the progression through the drug pipeline provides firms with regular stepwise intervals to evaluate next

412. Bell, *supra* note 409, at 120, 122.

413. U.S. CENSUS BUREAU, U.S. DEP'T COMMERCE, HISTORICAL STATISTICS OF THE U.S., 1789–1945, CHAPTER C. VITAL STATISTICS, HEALTH, AND NUTRITION at 45 tbl.6–21 (June 1949).

414. NAT'L CTR. FOR HEALTH STATISTICS, CTRS. FOR DISEASE CONTROL, MORTALITY IN THE U.S., 2021 at 1 (Dec. 2022).

415. *See* Aronson & Green, *supra* note 293, at 2121, 2117 tbl.2 (finding "about 60%" of drugs on the World Health Organization's essential medicines list are "me-too" drugs and citing beneficial rationales of developing "me-too" drugs).

416. Perhaps a recognition by courts of the role of clinical equivalents may lead to the undertaking of more "head-to-head" trials, where two drugs are pitted against one another to see which one performs better. These trials, though, are quite rare in clinical development, because they are fundamentally risky for competitors entering an established space. *See* Estellat & Ravaud, *supra* note 377, at 241 As a result, trials are usually planned to statistically prove "non-inferiority" while superiority is a secondary consideration. *Id.*; *see also id.* at 241–42 (researching and finding only five head-to-head trials out of ninety-one trials found and describing that data as failing to "provide the correct information for making evidence-based decisions").

steps.[417] When screening and selecting potential drug candidates in the earliest stages of development, a company may choose to risk developing an antibody structure that is structurally similar to a patented competitor antibody but not literally infringing. As more preclinical studies are performed, the developer can observe whether the new candidate exhibits significantly different clinical properties than the known medicine. Clinical antibody equivalence, therefore, by its nature, incentivizes competitors to "find" antibodies that either perform different functions, do them in different ways, or achieve different results. It maintains these incentives throughout every stage of clinical development and allows innovators to regulate their strategies according to their individual appetites for risk. Antibodies are inherently unpredictable.[418] In the case a product of conservative replacement shows promise of an exciting clinical lead, that inventor would not be discouraged from continuing to forge ahead in clinical development. In fact, that inventor, if clinical equivalents were the law, would be actively encouraged to do so at the prospect of bringing a new drug to market. Only and until the point at which it becomes clear that the drug is substantially clinically equivalent to another already patented antibody on the market would the risk of infringement arise. At that point, the competitor is incentivized either to explore its compound in new ways, power its clinical trials to discover the antibody's differentiated properties, abandon the project, or wait until patent exclusivity expires. The notice of competitors' freedom to operate therefore comes into focus in congruence with the natural continuation of the drug development process. Clinical analysis therefore promotes innovation without unduly preempting it, putting the onus on potential infringers to either differentiate in an established field or trailblaze. The result is product differentiation backed by rigorous scientific inquiry to the benefit of public health.

In sum, under the doctrine of equivalents, clinical data should be the primary determinant of equivalence between two therapeutic antibody structures. To ignore clinical data reduces the inquiry to arbitrary homological line-drawing and removes all nuance from a field which needs it the most. Clinical data is reliable, peer-reviewed, and subject to intense scientific scrutiny. Its use would comport with all tenets of the doctrine of equivalents. A doctrine of clinical equivalents would also provide a lifeline to those post-*Amgen* antibody patent holders, who out of fear of invalidation for lack of enablement, have narrowed their claims to the lowest possible size. At the same time, the adoption of a clinical equivalents analysis for therapeutic antibody structures organizes innovatory incentives to promote clinical information disclosure and therapeutic differentiation.

417. See HASSAN Z. SHEIKH, CONG. RSCH. SERV., R41983, HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 3–8 (2018) for an overview of the drug development and regulatory process.

418. *See* discussion *supra* Section I.B.

CONCLUSION

The Supreme Court's decision in *Amgen*, by limiting the upper boundary of antibody patent scope, may have simultaneously decimated it. But innovation cannot balk. When the only valid claim scope of antibody patents is effectively now an "n of 1" scenario, patentees will naturally turn to the doctrine of equivalents if those patents are to have any more purpose than ceremonial. To date, and to this author's knowledge, no court has accepted the idea that clinical properties of therapeutic antibodies should be imputed to the underlying antibody structure.[419] The district court in *Teva* specifically rejected that theory. To add insult to injury, after *Amgen* was decided in June 2023, the District of Massachusetts, under that precedent, overturned a $176 million jury verdict in favor of Teva because it held as a matter of law that its claim was invalid for lack of enablement.[420]

These holdings underscore the severity of the problem. Antibody patents face an existential crisis in the form of a singularity. When patentees and applicants alike undertake the billion-dollar cost to develop a new therapy while abiding by the rules of enablement that are required of them now, they open themselves up to fast-tracked literally noninfringing competition by those who have done nothing but run-of-the-mill experimentation.[421] Drugmakers face immense hurdles, investing billions in development while adhering to stringent rules. However, without the ability to assert infringement by clinical equivalents, they are subject to the whims of competitors, which, having conducted mere routine experiments, can swiftly compete without bearing the same burden. What results is not "Progress," but sloth. Why innovate and differentiate when you can change a few residues, avoid literal infringement, conduct the *exact* same preclinical and clinical studies, establish noninferiority, and sell?

The doctrine of clinical equivalents harmoniously addresses these concerns without any transgression or transmogrification of DoE principles. In fact, the DoE is tailor-made for precisely this situation.

> Where form and substance are inseparable [as in the case of small molecules], it is enough to look at the form only. Where they are separable; where the whole substance of the invention may be copied in a different form, it is the duty of courts and juries to look through the form for the substance of the invention—for that which entitled the inventor to his patent, and which the patent was

419. *But cf.* Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555, 1567 (Fed. Cir. 1994) (discussing "reduc[ing] risk of hemorrhaging" as related to the "function" of patented human t-PA).

420. Teva Pharms. Int'l GMBH v. Eli Lilly and Co., No. 18-cv-12029-ADB 2023 WL 6282898 at *24 (D. Mass. Sep. 26, 2023), *appeal docketed*, No. 24-1094 (Fed. Cir. Oct. 30, 2023). The appeal, however, does not raise the issue of how to apply the DoE to antibodies, and only appeals the issue of validity under section 112. *See* Appellant's Opening Brief at iv–vi, Teva Pharms. Int'l GmbH v. Eli Lilly and Co., No. 24-1094 (Fed. Cir. Feb. 2, 2024).

421. That clinical experimentation would still be expensive in absolute terms, but not in relative terms. And to reiterate, this applies when two independently approved biologics have come onto the market, not when one is applying to be a biosimilar.

> designed to secure; where that is found, there is an infringement; and it is not a defen[s]e, that it is embodied in a form not described, and in terms claimed by the patentee.[422]

Allowing patentees to assert infringement by clinical equivalents will counteract the singularity that post-*Amgen* antibody patentees now face. As a class of molecules, antibodies are embroiled by the juxtaposition of our precise Promethean knowledge of their primary structure, the absence of language to describe their cosmic range of possible structures, and our ignorance, exemplified by the unpredictability of even the slightest of modifications. Clinical equivalence elevates the discussion of antibodies to a more humanly cognizable plane, while complying with the core tenets and policies of the DoE. If one antibody clinically functions in the same way to achieve the same clinical result, or if all a drug's clinical properties are insubstantially different from another's, it should be determined to be structurally equivalent by clinical equivalents and therefore, infringing. Clinical analysis recalibrates the doctrinal inquiry from the technical to the technological. It incentivizes innovation, information disclosure, and can be applied by courts without an act from Congress.[423]

The United States is the leader in new drug development.[424] Courts should therefore establish a framework for adjudicating these antibody disputes in a way that fosters innovation. The undiscovered antibody panaceas of tomorrow may be discovered before humans solve the antibody structure-function relationship, succinctly describe it in English, and package it nicely in a patent application. But wouldn't we prefer to incentivize progression towards those discoveries despite being unable to adequately describe that relationship to the standard that patents traditionally require?

When his time came, President Washington did not fear death. "Doctor, I die hard; but I am not afraid to go."[425] And yet, it would be most ironic if, in the pursuit of technological "Progress," our patent laws had stalled the very innovation needed to discover a therapy with the potential to save his life. But that is what the exclusion of clinical data in the antibody equivalents analysis effectively achieves in modern times. Even the miraculous successes of the drugs of today will be surpassed by those of tomorrow. However, without the adoption of a clinical equivalents analysis, the incentives to realize them are questionable. Courts should therefore adopt a clinical equivalents analysis in comparing biologic therapies. Faithful to precedent, such an analysis would also provide for a salutary recalibration of innovatory incentives in the pharmaceutical industry. Untapped medicines await discovery. We would be remiss to inadvertently delay their fruition.

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422. Winans v. Denmead, 56 U.S. (15 How.) 330, 343 (1853).

423. *See* Burk & Lemley, *supra* note 90, at 1654–56 (explaining how the doctrine of equivalents may be used as a "policy lever" to tailor patents of specific industries in a "unitary patent system to the more complex realities of the world").

424. Robert Kneller, *The Importance of New Companies for Drug Discovery: Origins of a Decade of New Drugs*, 9 NATURE REVS. DRUG DISCOVERY 867, 871 (2010).

425. THE DEATH OF GEORGE WASHINGTON, *supra* note 410.