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SOLUTIONS TO THE PROBLEM OF THERAPEUTIC ANTIBODY GENUS CLAIMS

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 I wish to thank my partners and colleagues Carla Kim and Eric Steffe for their insightful comments and critiques. They alerted me to several issues they have encountered in the trenches, when prosecuting and litigating patents with antibody claims. The views and opinions expressed here are solely mine and are not to be attributed to my law firm or my firm's clients.

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I. INTRODUCTION

Antibody-based therapies have revolutionized modern medicine and have led to unprecedented success in treating various cancers, autoimmune diseases, and other conditions, many of which previously had no known treatment.[1] Because they target disease-causing mechanisms better than previous small-molecule therapies, therapeutic antibodies also offer the promise of fewer and more manageable side effects.[2]

The first step in developing a therapeutic antibody is to discover in the body the underlying molecular target to which an antibody may bind, the connection between the target and the disease, and the pathways that an antibody may activate or inhibit.[3] Common targets may include membrane-bound molecules, such as PD-1 (which appears on the membranes of immune cells) or its ligand, PDL-1 (which appears on the membranes of cancer cells).[4] The binding of an antibody, such as Keytruda® to PD-1 or Tecentriq® to PDL-1, blocks the attachment of one to the other and activates the immune system to attack cancer cells.[5] These two antibodies are amongst the most advanced and powerful anticancer drugs of our time.[6] Targets may also include free-in-the-cytoplasm molecules, such as PCSK9, an enzyme.[7] When Repatha®, an antibody developed against PCSK9 *binds* to it, PCSK9 is *blocked* from binding to certain

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1 Hashem O. Alsaab et al., *PD-1 and PD-L1 Checkpoint Signaling Inhibition for Cancer Immunotherapy: Mechanism, Combinations, and Clinical Outcome*, FRONTIERS IN PHARMACOLOGY, Aug. 23, 2017, at 1.

2 *Id.* at 5.

3 *See id.* at 1.

4 *Id.* at 2, 5.

5 *See id.* at 2.

6 *Pembrolizumab*, WIKIPEDIA, https://en.wikipedia.org/wiki/Pembrolizumab [https://perma.cc/9BPW-YKTU] (Pembrolizumab is the generic name for Keytruda.); *Atezolizumab*, WIKIPEDIA, https://en.wikipedia.org/wiki/Atezolizumab [https://perma.cc/B4QW-LVYV] (*Atezolizumab* is the generic name for Tecentriq.); *see also* Am. Soc'y Health-Sys. Pharmacists ("ASHP"), *Pembrolizumab Monograph for Professionals*, DRUGS.COM (Sept. 27, 2023), https://www.drugs.com/monograph/pembrolizumab.html [https://perma.cc/7ZPD-Q3ZS] (describing the use of Keytruda in treating various forms of cancer).

7 Caroline Coppinger et al., *A Comprehensive Review of PCSK9 Inhibitors*, 27 J. CARDIOVASCULAR PHARMACOLOGY & THERAPEUTICS 1, 7 (2022).

lipid receptors.[8] Repatha is therefore an advanced and powerful drug for the treatment of cardiovascular disease.[9]

The underlying targets, connections, and pathways, however, may be considered natural phenomena, which cannot be easily patented under the Supreme Court's cases interpreting 35 U.S.C. § 101. It is therefore important that the discoverers of targets be able to obtain patent protection on the antibodies themselves.

But once the underlying target and pathways to disease have been discovered, and an antibody capable of precisely binding to that target has been generated, it may be routine and conventional, and not necessarily innovative, to manufacture similar antibodies that also precisely bind to that target and treat the same disease. Thus, a patent limited to a *single* antibody (i.e., an antibody defined by a deposit number, or by its specific protein or DNA sequence) may not prevent the commercialization of highly similar products. The patentee has simply provided a blueprint for others who, now aware of the target, can make and sell their own antibodies that avoid the narrow patent. Since the early days of antibody research, and to ensure that breakthrough discoveries in targets are adequately protected, inventors and their counsel have tried to obtain patent claims on a family, a genus, of antibodies that bind to the desired target.

Yet, these days the mood is pessimistic among biotech patent practitioners who try to obtain and enforce genus claims in the field of therapeutic antibodies.[10] The Federal Circuit's non-enablement decision in

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[8] *Id.* I will use the terms "binding" and "blocking" to mean different things in this Article. By "binding" I mean the specific attachment of an antibody to its target, whereas by "blocking" I mean that, as a consequence of the binding, the antibody blocks the signaling pathway involving the target in question. As described, when the antibody Repatha *binds* PCSK9 it then *blocks* the signaling that occurs when PCSK9 binds to the lipid receptor.

[9] *See* Marc S. Sabatine et al., *Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease*, 376 NEW ENG. J. MED. 1713, 1714 (2017) (Evolocumab is the generic name for Repatha.).

[10] *See, e.g.*, Naoko N. Koyano, *Wobbling 35 U.S.C. § 112(a) Standards and Their Impact on Antibody Patents*, 52 AIPLA Q.J. 251 (2024); Mark A. Lemley and Jacob S. Sherkow, *The Antibody Patent Paradox*, 132 YALE L. J. 994 (2023); S. Sean Tu and Christopher M. Holman, *Antibody Claims and the Evolution of the Written Description/Enablement Requirement*, 63 IDEA 84 (2022); Mark A. Lemley et al., *The Death Of The Genus Claim*, 35 HAR. J. L. & TECH. 1–72 (2021).

Amgen v. Sanofi (Fed. Cir. 2021) ("*Amgen* 2021"),[11] which was affirmed by the Supreme Court in *Amgen v. Sanofi* (2023)[12] ("*Amgen* 2023"; both holdings jointly referred to as "*Amgen* 2021/2023")), and the Federal Circuit's written description decision in *Juno v. Kite* (Fed. Cir. 2021),[13] have cast a veil on the ability of inventors and their lawyers to obtain and enforce claims of worthwhile scope in the field.

The Federal Circuit has insisted, in cases such as *Ariad Pharmaceuticals v. Eli Lilly* (Fed. Cir. 2010),[14] that the legal requirements for enablement and for written description are to be considered as distinct portions of 35 U.S.C. § 112(a).[15] Enablement of an antibody genus claim requires evidence that, at the desired priority date, a person of skill in the art could achieve the full scope of the claim "without undue experimentation."[16] In contrast, written description requires evidence that, at the desired priority date, the inventor had "possession" of the full scope of the claim.[17]

A practitioner who wishes to obtain antibody genus claims cannot rest by meeting the enablement requirements alone or the written description requirements alone. While the underpinning factual analyses used for the two portions of the statute have become increasingly similar, the legal requirements are not identical. A genus claim must comply with both.

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[11] Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1081 (Fed. Cir. 2021), *aff'd sub nom.* Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023).

[12] Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023).

[13] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021).

[14] Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1344 (Fed. Cir. 2010).

[15] 35 U.S.C. § 112(a)

> (The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.).

[16] *In re* Wands, 858 F.2d 731, 740 (Fed. Cir. 1988).

[17] *See Ariad*, 598 F.3d at 1351.

Whether the claims are to a genus of antibodies or to a method of using such a genus, the development of the case law interpreting 35 U.S.C. § 112(a) has brought us to a difficult spot. It is increasingly problematic to get genus claims that include more than one or a few specific antibodies. If a genus claim also contains any semblance of "function" (a concept interpreted broadly by the courts to mean little more than a claim requirement), the need for an understanding of structure-function correlation rears its head. The head can be seen in the analysis of both full scope enablement and full scope written description.

In Section II of this Article, I will discuss the present state of the case law dealing with the enablement[18] and in Section III and IV, I will discuss written description[19] aspects of 35 U.S.C. § 112(a) when applied to a genus claim of antibodies. Also in Section III, I will analyze how the Court of Appeals for the Federal Circuit has analyzed claims of different formats.[20] In Section V.C., I will draw some conclusions as to whether and which of the existing formats may still yield enforceable genus claims.[21] In Section V.C.3., I will also analyze additional formats not yet evaluated by the courts, such as claims written in mean-plus-function format.[22]

II. ENABLEMENT: FROM *WANDS* (1988) TO *BAXALTA* (2023)

Let me start with enablement. Over the last thirty years, antibody genus claims went from the relatively relaxed enablement analysis of *In re Wands* (Fed. Cir. 1988),[23] to the rigorous requirements of *Amgen* 2021/2023, and their progeny, *Baxalta v. Genentech* (Fed. Cir. 2023).[24]

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18 *See infra* Part II.

19 *See infra* Part III.

20 *See infra* Part III.

21 *See infra* Section V.C.

22 *See infra* Section V.C.V.3.

23 *See In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

24 Baxalta Inc. v. Genentech, Inc., 81 F.4th 1362, 1367 (Fed. Cir. 2023).

The path from 1988 to 2023 goes through classical chemical patent law. The road went through a trio of chemical cases from 2013 to 2019, *Wyeth v. Abbott* (Fed. Cir. 2013),[25] *Enzo Life Sciences v. Roche* (Fed. Cir. 2019),[26] and *Idenix v. Gilead* (Fed. Cir. 2019).[27] I will call these three cases, "The Chemical Triad."

A. ENABLEMENT ANALYSES BEFORE THE CHEMICAL TRIAD

The basic framework for how to evaluate the proper enablement of a genus of antibodies was set forth in 1988 in the seminal case of *In re Wands*.[28] It was this case that established the eponymous eight "*Wands* factors," by which to measure claim enablement (or lack thereof) in view of a specification, when considered in the context of the state of the art at the time of filing. The *Wands* factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and, (8) the breadth of the claims.[29]

Some of the claims in the *Wands* case itself are to monoclonal antibodies *per se* and other claims are to their use in immunoassays.[30] Claim 7 is an example of a genus of antibodies per se with two requirements (the ellipses relate to the requirement of coupling to an insoluble solid phase, which is immaterial for this analysis):

> **Claim 7.** "Monoclonal high affinity"
>
> **[(1) Structure of the antibody:]** "IgM antibodies"
>
> **[Binding definition:]** "immunoreactive with HBsAg determinants . . . wherein"

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[25] Wyeth & Cordis Corp. v. Abbott Lab'ys, 720 F.3d 1380 (Fed. Cir. 2013).

[26] Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc., 928 F.3d 1340 (Fed. Cir. 2019).

[27] Idenix Pharms. LLC v. Gilead Scis. Inc., 941 F.3d 1149 (Fed. Cir. 2019).

[28] *See In re Wands*, 858 F.2d at 737.

[29] *Id.*

[30] *Id.* at 734; U.S. Patent No. 4,879,219 cols. 16–18.

> **[(2) Binding strength:]** "the binding affinity constant of said antibodies for said HBsAg determinants is at least 10^9 M^{-1} ."[31]

The basic definition of the antibody, which I will call the "binding definition," is that the antibody binds to hepatitis B surface antigen (HBsAg) determinants. Beyond that the claim has two requirements: (1) that the antibody be IgM; and (2) that it be of high affinity with a threshold binding strength of 10^9 M^{-1}. While the structure of the antibody (1) must be IgM, this does not refer to the structure or sequence *at the antigen binding site* but to the requirement that the antibody be a pentamer of antibody units. The second requirement in claim 7 is that (2) the binding occur with a minimum threshold of what I will call the "binding strength."

Wands claim 7 does not include sequence structure of either the antibody or the HBsAg antigen to which it binds. In addition, the claim does not require that the binding of antibody to antigen lead to some molecular blocking or biological effect; in other words, there are in *Wands* claim 7 no biological requirements. Other than the binding definition and the overall pentameric structure, antibody claim 7 requires only a minimum binding strength.

The court held that product *per se* claim 7 was enabled by the description of a routine set of screening assays. These assays would allow a person of skill to quickly determine which antibodies in a mixture were reactive with HBsAg, which ones were IgMs, and which ones had the required binding strength.

There were also in *Wands* immunoassay claims, such as claim 1:

> **Claim 1. [(1) Immunoassay function:]** "An immunoassay method utilizing"
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> **[Binding definition:] "**an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:
>
> > contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and
> >
> > determining the presence of said substance in said sample;

[31] U.S. Patent No. 4,879,219 col. 18 ll. 6–10.

> wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}."[32]

In addition to the binding definition, the overall IgM structure and the binding strength present in claim 7, claim 1 has a functional use requirement (1): the antibody is used in an immunoassay. Because of the inclusion of a function, I will come back to claim 1 after I discuss the Chemical Triad, *Amgen* 2021/2023, and *Baxalta v. Genentech*. These cases may have an impact on the patentability of immunoassay claims.

The immediate consequence of *Wands* was that in the unpredictable science of immunology, it was possible to enable a genus of antibodies by a relatively straightforward set of screening tests. As long as the tests could determine the structure of the antibody as IgM, that it bound to HBsAg, and that it had the required binding strength, the experimentation was not undue. The court stressed this point in strong language: "'The key word is "undue," not "experimentation."'"[33] Remember this when I later discuss modern immunoassays run by computerized robots.

After *Wands*, practitioners in the antibody field felt comfortable filing and defending claims to a genus of antibodies enabled by the description of routine screening assays in the specification. *Johns Hopkins University v. CellPro, Inc.* (Fed. Cir. 1998) is a particularly noteworthy success story in the enablement of a genus of antibodies by screening.[34] Claim 1 of Hopkins's '204 patent, which survived a challenge for lack of enablement, is as follows:

> **Claim 1.** "A monoclonal antibody which"
>
> **[Binding definition:]** "specifically binds to an antigen on nonmalignant, immature human marrow cells, *wherein* said antigen is stage specific and not lineage dependent, and *said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483.*"[35]

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[32] *Id.* cols. 16–17.

[33] *In re Wands*, 858 F.2d at 737 (quoting *In re* Angstadt, 537 F.2d 498, 504 (C.C.P.A. 1976)).

[34] *See generally* Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342 (Fed. Cir. 1998).

[35] *Id.* at 1347 (emphasis in the original).

In this claim, the binding definition is at the center of its breadth and ultimate survival. The genus of antibodies in Hopkins's claim 1 is defined by a reference antibody from a cell source on deposit at the American Type Culture Collection (ATCC HB-8483).[36] The reference antibody binds to an antigen known as CD-34. The antigen is not mentioned in the claim but the reference antibody that binds to it is: it is otherwise known as "anti-my-10." The claim extends to the genus of all antibodies that compete with anti-my-10 for binding to CD-34. That is the binding definition; the claim has no biological requirement beyond it.

CellPro challenged the claim for lack of enablement of the full scope. It argued that the Hopkins specification did not teach one skilled in the art to routinely make antibodies which bind to the CD-34 antigen other than the specific HB-8483 reference. Accordingly, contended CellPro, the "full breadth" of the asserted claim was not enabled under 35 U.S.C. § 112(a).

The lower court, in granting Hopkins's motion for a new trial[37] and then on Hopkins's motion for summary judgment,[38] evaluated several items of evidence supporting CellPro's view that making anti-CD-34 antibodies and finding others that compete with the reference antibody HB-8483 entailed undue experimentation.[39] However, taking into account the state of the art at filing, the court dismissed CellPro's evidence as insufficient.[40] The court granted summary judgment in favor of Hopkins, and the Federal Circuit affirmed.[41] In its affirmance, the Federal Circuit said:

> The [lower] court concluded that "experts" to whom CellPro referred in support of its argument either were not experts, did not follow the teachings of the patent, or otherwise did not engage in undue experimentation. As to those experts that only had success in producing a suitable antibody after several attempts, the [lower] court concluded that "[r]outine repetition

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36 *Id.*

37 *See* Johns Hopkins Univ. v. CellPro, 931 F. Supp. 303, 322–24 (D. Del. 1996), *aff'd in part, vacated in part sub nom.* Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342 (Fed. Cir. 1998).

38 *See Johns Hopkins Univ.*, 152 F.3d at 1351–52 (citing Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Feb. 24, 1997)).

39 *See id.*

40 *See id*.

41 *Johns Hopkins Univ.*, 152 F.3d at 1361.

> of a patent's specification to achieve a desired experimental result does not constitute undue experimentation."[42]

I recognize two possible critiques of *Hopkins v. CellPro.* One is that the case needs to be interpreted in the context of its facts, especially the dubious nature of the "experts" and the poor experiments they carried out. Perhaps with different experts, the case would have gone the other way. A second critique is that *Hopkins* is a decision from 1998, years before Chemical Triad and *Amgen* 2021/2023. I will address both critiques in detail below. Because *Hopkins v. CellPro* takes advantage of what I consider easier-to-defend immunoassay formats, I will focus more attention on the case when I propose formats for protecting antibody genus claims.

Another pre-Triad and pre-*Amgen* 2021/2023 case where a challenge to enablement was ultimately overcome is *Chiron Corp. v. Genentech* (Fed. Cir. 2004).[43] The Federal Circuit there analyzed the enablement of claim 19 drawn to a genus of antibodies:

> **Claim 19**. "A monoclonal antibody that binds to human c-erbB-2 antigen."[44]

As the claim in *Hopkins v. CellPro*, the claim in *Chiron* is based on nothing beyond a binding definition: that the antibody bind to human c-erbB-2. As demonstrated by the district court holding, Genentech's accused antibody Humira® also binds to human c-erbB-2.

Before trial, the district court broadly construed claim 19 to embrace chimeric and humanized antibodies in addition to the exemplified murine antibodies that bind to c-erbB-2.[45] The district court subsequently granted Chiron's motion for partial summary judgment of infringement.[46] Also before trial, the parties stipulated that claim 19 would be invalid under § 102 based on intervening prior art if the patent were not entitled to claim priority to the filing date of any one of the 1984, 1985, and 1986 applications. With this stipulation in

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42 *Id.* at 1352.

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

44 *Id.* at 1250.

45 *See* Chiron Corp. v. Genentech, Inc., 266 F.Supp.2d 1172 (E.D. Cal. 2002).

46 *See* Chiron Corp. v. Genentech, Inc., No. Civ. S-00-1252 WBS GGH, 2002 U.S. Dist. LEXIS 19126, 2002 WL 32123930 (E.D. Cal. June 24, 2002).

hand, Genentech argued that at Chiron's earliest filing date (1984), the claim was not enabled for the full scope of these three embodiments.[47]

The court agreed with Genentech and held that the claim was fully enabled as of Chiron's last priority date (1995), but not as of any earlier filing dates.[48] The court reasoned that only by 1995, eleven years after the first priority date, the state of the art fully enabled chimeric and humanized antibodies.[49] Before then, chimerization and humanization of antibodies were nascent technologies and Chiron could not rely on the state of the art for full scope enablement. Nascent technology had to be in the specification itself and it was not. Neither the art nor the specification enabled these embodiments at any earlier time than that of the last filing. Ironically, and precisely because claim 19 was not enabled on earlier dates for the full scope, the claim was anticipated by Chiron's own intervening published patent application in 1985 disclosing murine antibodies. Therefore, the holding in *Chiron*, while based on lack of full scope enablement until late in the filing process, was based on lack of novelty.

While *Wands, Hopkins,* and *Chiron* are illustrations of claim formats that overcame challenges for lack of enablement, the three decisions preceded the Chemical Triad by several years. As noted, I will come back to the all-important question as to whether the claim formats and principles of these cases have survived the Triad and its consequences in the antibody field.

B. THE CHEMICAL TRIAD

The trouble for the enablement of antibody genus claims by screening arose from 2013 to 2019, when the Federal Circuit decided three chemical cases: *Wyeth v. Abbott* (Fed. Cir. 2013),[50] *Enzo Life Sciences v. Roche* (Fed. Cir. 2019),[51] and *Idenix v. Gilead* (Fed. Cir. 2019).[52] The Triad was not about antibodies: it was about chemical compounds. The three cases had claims that included structural as well as functional limitations.

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47 *See Chiron Corp.*, 363 F.3d at 1252.

48 *See id.* at 1253.

49 *See id.* at 1256–57.

50 Wyeth & Cordis Corp. v. Abbott Lab'ys, 720 F.3d 1380 (Fed. Cir. 2013).

51 Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc., 928 F.3d 1340 (Fed. Cir. 2019).

52 Idenix Pharms. LLC v. Gilead Scis. Inc., 941 F.3d 1149 (Fed. Cir. 2019).

Claim 1 in *Wyeth* is drawn to a method of treating or preventing "restenosis in a mammal . . . which comprises administering an antirestenosis effective amount of rapamycin to said mammal."[53] The word "rapamycin" describes a large genus of chemical compounds with a common core structure.[54] The functional limitation is that the genus of rapamycins prevents restenosis.[55]

Claim 1 in *Enzo* is to an oligo- or polynucleotide which is complementary to a nucleic acid of interest. The oligo or polynucleotide is claimed by a structural formula defined as "Sig-PM-SM-BASE." The claim then includes several functional limitations, one of which is that the structure ". . . not substantially interfere with double helix formation or nucleic acid hybridization . . . "[56]

Claim 1 in *Idenix* is drawn to a method of treatment, this time of a hepatitis C virus infection. That is the functional limitation. The claim comprises administering " . . . a purine or pyrimidine ß-D-2'-methyl-ribofuranosyl nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester thereof."[57] That is the chemical structure.

In the three cases, the Federal Circuit held that full scope enablement was missing. The court described the claims in the Chemical Triad as encompassing a large genus of chemical compounds defined structurally (*Wyeth*: "rapamycin," *Enzo*: "purine or pyrimidine," *Idenix*: "Sig-PM-SM-Base").[58] It then noted that all compounds encompassed by such large genera must also meet the requirement of performing a claimed therapeutic or biochemical function ("preventing restenosis," "not substantially [interfering] with double helix formation," and "treating hepatitis C," respectively).[59]

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53 *Wyeth*, 720 F.3d at 1382.

54 *Id.* at 1382.

55 *See, e.g.*, *id.* at 1386.

56 *Enzo Life Scis.*, 928 F.3d at 1343–44.

57 *Idenix Pharms.*, 941 F.3d at 1155. This and the next five citations refer to *Idenix Pharms.* as representative of the reasoning and holdings of the three cases in the Chemical Triad.

58 *See, e.g.*, *id.* at 1162.

59 *See, e.g.*, *id.* at 1163.

The court applied the *Wands* factors to the chemical claims in the Triad. *Wands* factor (7) led the court to conclude that the fields of work and development in the Triad were unpredictable.[60] *Wands* factor (8) led the court to find that the Triad claims were broad.[61] And, applying *Wands* factor (1) to the Triad, the court concluded that achieving full scope enablement of broad claims in these unpredictable biological areas required too much experimentation.[62] The claims could not be enabled by routine screening a la *Wands*.

The conclusion we can reach from the holdings in the Chemical Triad is that full scope enablement in unpredictable technologies cannot be achieved unless there is sufficient guidance in the state of the art or in the specification as to what unique structure in a large number of claimed chemical compounds will result in a claimed function. It is not enough to synthesize a myriad compounds and screen them to determine which ones perform the function and which ones do not.

C. ENABLEMENT ANALYSES AFTER THE CHEMICAL TRIAD

In *Amgen* 2021, the Federal Circuit applied the lessons of the Chemical Triad to an antibody case. The particular format of the claims, which I will call "quasi-chemical" because it included specific chemical structures, was the perfect setting for application of the Triad.

The claims in *Amgen* 2021 are to monoclonal antibodies defined three ways: by a binding definition, by specific binding structure, and by a blocking function. Claim 1 of Amgen's '165 patent is illustrative:

> **Claim 1**. "An isolated monoclonal antibody . . . wherein"
>
> **[Binding definition:]** "when bound to PCSK9,"
>
> **[(1) Specific binding structure:]** "the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and"

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60 *See, e.g.*, *id.* at 1161.

61 *See, e.g.*, *id.* at 1162.

62 *See, e.g.*, *id.* at 1156–57.

> **[(2) Blocking function:]** "wherein the monoclonal antibody blocks binding of PCSK9 to LDLR."[63]

Claim 1 in *Amgen* 2021 and claim 7 in *Wands* are both antibody *per se* claims. But claim 1 in *Amgen* 2021 is different from claim 7 in *Wands*. There is a binding definition in both: the antibodies in *Amgen* 2021 have to bind to PCSK9, and the antibodies in *Wands* have to bind HBsAg. That, however, is where the similarities end. The claim in *Amgen* 2021 has several differences from that in *Wands;* the *Amgen* 2021 claim does not have a requirement of binding strength, as the one in *Wands*. Most importantly, the claim in *Amgen* 2021 requires the binding to be to: (1) specific target structures; and requires (2) a blocking function.

Let us look at the "specific binding structure" requirement (1). This is what makes the *Amgen* 2021 claim quasi-chemical. The antibody must bind to one of fifteen specific residues in PCSK9. While the claim does not recite any residues of the *antibody*, it requires binding to specifically numbered residues of the *complementary* molecule, PCSK9 (e.g., S153, I154, etc.) Reading the claim, one has the impression of confronting a classical *Markush* claim from chemical cases, although written in a complementary way. However, in contrast to most *Markush* claims, which are structure only, this *Markush*-type claim also includes a required molecular function (2): blocking the binding of PCSK9 to the LDL receptor. This blocking ultimately results in lowering bad cholesterol.[64]

The Federal Circuit found this claim not enabled due to what it called the "double function" requirement.[65] Beyond the definition of the antibody binding to PCSK9, the two functions the court refers to are (1) the binding to specific amino acid residues on the PCSK9 antigen and (2) the molecular blocking of PCSK9 to LDLR.[66] The court held that the correlation between amino acid residues at the antibody-binding site and the two "functions" was highly unpredictable.[67] Citing the Chemical Triad, it explained that finding antibodies other than those exemplified, which complied with the two broad functions posed "high hurdles in fulfilling the enablement requirement."[68] The lack of a

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[63] Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1083 (Fed. Cir. 2021), *aff'd sub nom.* Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023).

[64] *Id*.

[65] *Id.* at 1087.

[66] *Id.* at 1083.

[67] *Id.* at 1087.

[68] *Id.*

clear structure-function correlation proved fatal to full scope enablement. Too much screening was required to make and test every possible antibody variant. It was undue experimentation under *Wands* factor (1).

In explaining why the experimentation was undue in *Amgen* 2021, while not undue in *Wands*, the court said:

> The holding in *Wands* was based on the facts of that case and the evidence presented there. Here, the evidence showed that the scope of the claims encompasses millions of candidates claimed with respect to multiple specific functions, and that it would be necessary to first generate and then screen each candidate antibody to determine whether it meets the double-function claim limitations . . . The facts of this case are thus more analogous to those in *Enzo, Wyeth,* and *Idenix* [the Chemical Triad], where we concluded a lack of enablement.[69]

One of the important factual distinctions mentioned by the court is that the claims in the two cases are different. The *Wands* claims do not have what the court calls the "double-function" of the *Amgen* claims: first, binding to specific chemical residues and as a consequence, blocking the binding of PCSK9 to the LDL receptor. Additionally, the *Wands* claims are not quasi-chemical in nature: they require neither specific structural sequences nor blocking requirements. The presence of these extra claim requirements in *Amgen* 2021 proved fatal to full scope enablement. Because of the presence of the specific binding structure of the target PCSK9, the court treated the claim as though it was a chemical claim. And the lack of predictability of how to achieve antibodies that bound to the specific target amino acids and that also led to blocking compounded the problem.

The *Amgen* 2021 case with its quasi-chemical claim then went up to the Supreme Court. In *Amgen* 2023, the court affirmed the Federal Circuit's holding and added a twist of its own.[70] It concluded that neither the specification nor the state of the art at the filing date showed any understanding of which of the myriad structures of the *Amgen* antibody would lead to the required function of binding to specific PCSK9 residues and the molecular function of blocking the LDL receptor.[71]

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[69] *Id.* at 1088.

[70] *See generally* Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023).

[71] *Id.* at 1256.

As it has done several times when reviewing decisions of the Federal Circuit, the Supreme Court in *Amgen* 2023 added another element: the need to set forth the existence and understanding of a "general quality common" to all members of the genus that would perform the required double function of specific binding and blocking.[72] I will call this the "common quality" test.

The Supreme Court in *Amgen* 2023 did not mention the eight *Wands* factors, but it also did not negate or critique them. It appears that thirty-eight years after their appearance, the *Wands* factors are still alive and well.[73] They will continue being used whenever the issue of enablement comes up, and in many areas of technology. In early 2024, the United States Patent and Trademark Office (USPTO) announced that the examining corps should continue using the *Wands* factors in their review of pending patent applications.[74]

D. THE POST-*AMGEN* 2021/2023 LANDSCAPE

After the decisions in *Amgen* 2021/2023, there remained the question – at least to me - as to which of the two differences between claim 7 in *Wands* and claim 1 in *Amgen* 2021/2023 led to enablement in *Wands* but no enablement in *Amgen* 2021/2023. Was it the presence in the *Amgen* claims of specific structural requirements of the target PCSK9 (1), or was it the presence of a molecular/biological blocking function (2), or was it both?

Baxalta Inc. v. Genentech, Inc. (Fed. Cir. 2023),[75] a post-*Amgen* 2021/2023 case, provided some clarity. *Baxalta* is an example of a claim that focuses the inquiry squarely on the biological function. Claim 1 in *Baxalta* is to an antibody genus with a binding definition and one biological function requirement. The *Baxalta* claim contains neither specific antibody nor antigen binding structures: i.e., it is not "quasi-chemical" in nature:

"1. An isolated antibody or antibody fragment thereof"

[Binding definition:] "that binds Factor IX or Factor IXa and"

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72 *Id.* at 1253–54, 1256.

73 The so-called *Wands* factors first appeared in *Ex parte Forman*, No. 602-90, 1986 WL 83597, at *2 (B.P.A.I. Apr. 22, 1986).

74 *See* Guidelines for Assessing Enablement in Utility Applications and Patents in View of the Supreme Court Decision in Amgen Inc. et al. v. Sanofi et al., 89 Fed. Reg. 1563, 1563 (Jan. 10, 2024).

75 Baxalta Inc. v. Genentech, Inc., 81 F.4th 1362 (Fed. Cir. 2023).

> **[(1) Biological function:]** "increases the procoagulant activity of Factor IXa."[76]

Other than the binding definition, this claim has one required biological function: to "[increase] the procoagulant activity of Factor IXa."[77] The court held the claim not enabled even though it is *not* quasi-chemical: it does not include an express chemical binding structure of either antibody or antigen as in *Amgen* 2021/2023. The claim in *Baxalta* is purely functional.

Given this analysis, it is safe to conclude that the presence of a biological requirement doomed claim 1 in *Baxalta*. Because claim 7 in *Wands* does not have a biological function, I believe that, in a well-briefed case, it would survive *Amgen* 2021/2023 and *Baxalta*. As I will demonstrate below, this conclusion is part of my proposal of how to reframe antibody genus claims so that they avoid blocking or biological requirements and instead rely on immunoassays.

The *Amgen* 2021 decision, its affirmance in *Amgen* 2023, and its application in *Baxalta* closed the circuit that had started with *Wands* in 1988:

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[76] *Id.* at 1363.

[77] *Id.* In *Amgen* (2021) the court did not use the term "function" to refer to the general binding of the antibody to PCSK9, i.e. what I call its "binding definition," but called only the LDL blocking and the binding to specific residues in PCSK9 its "double function." *See* Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1087 (Fed. Cir. 2021), *aff'd sub nom.* Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023). In contrast, in *Baxalta*, the court calls the general binding to Factor IX/IXa a "function." *See Baxalta*, 81 F.4th at 1363. It remains to be seen if this usage is purposeful or inadvertent. In my opinion, the biological or molecular blocking requirements are better seen as *functions* performed by an antibody that generally *binds* to an antigen. This distinction in nomenclature is consistent with the rationale of the courts in asking which of the many antibodies that *bind* to an antigen perform the claimed *blocking or biological function.*

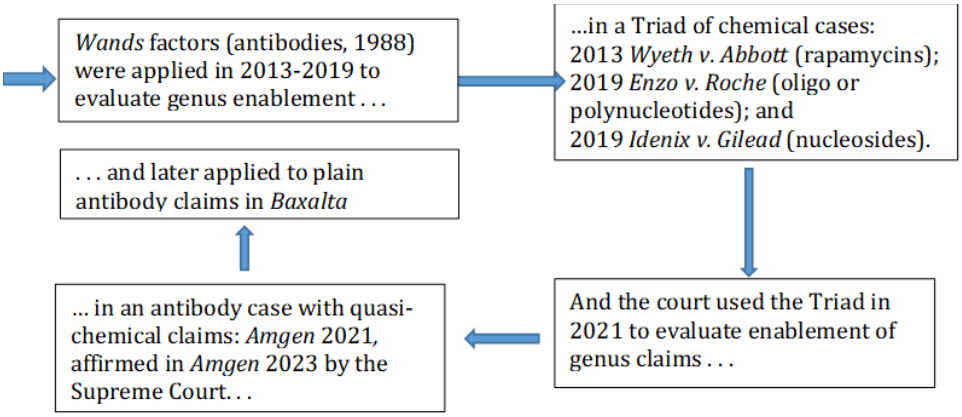

Chart 1. From Antibodies to Antibodies Passing through the Chemical Triad

We have gone from *Wands*, where full scope enablement of antibody genus claims could be demonstrated by routine screening, through the Chemical Triad, to *Amgen* 2021, its affirmance in *Amgen* 2023 with its need for an understood structure-function correlation, or a "common quality," and application to a non-quasi chemical claim in *Baxalta*. Antibody genus claims are to be treated no differently than chemical genus claims.

Before I confidently conclude that an antibody genus claim with no biological or blocking function such as Claim 7 in *Wands* is more likely to survive an enablement challenge than claims that include such function, as those in *Amgen* 2021/2023 or *Baxalta*, let us re-examine the other set of claims in *Wands,* such as claim 1 to a method of use. The question I want to ask is whether such a claim would survive the post-*Amgen* 2021/2023 world. Methods of using antibodies such as claim 1 of *Wands* are similar to product *per se* claims that include blocking or biological functions. Method claims as well as product *per se* claims with blocking or biological requirements will, after *Amgen* 2021/2023 and *Baxalta*, receive more scrutiny than claims without such requirements.

An argument can credibly be made, however, that the enablement requirements of 35 U.S.C. § 112(a) for immunoassay uses are more readily met than the same requirements for claims with blocking or biological requirements. After all, if the *Wands* antibodies are *a priori* selected for their general binding to HBsAg, using them to bind to HBsAg in an immunoassay without further requirements is a natural consequence of their selection process. Blocking a receptor such as LDLR in *Amgen* 2021/2023 or increasing pro-coagulant activity of Factor IXa in *Baxalta*, however, are not necessarily the natural consequences of selecting antibodies to PCSK9 or Factor IXa. In these two cases, the relation between binding and blocking is still in the area of uncertainty.

It is logical to infer that genus claims to immunoassay methods are less vulnerable to challenge than genus claims to methods of therapy or blocking, or to products *per se* with blocking or biological requirements. Therefore, I conclude that *Wands*'s immunoassay claim 1 would survive *Amgen* 2021/2023 and *Baxalta*. This is an important reading of the case law to which I return later.

You would be correct if you surmise from my stressing the differences in claim format between *Wands, Hopkins,* and *Chiron* on the one hand, and *Amgen* 2021/2023 and *Baxalta* on the other, that these differences may be fruitful ground for legal exploration of 35 U.S.C. § 112(a) on the patentability of antibody genus claims. Yet before I dig deeper into the role of claim formats, we must first delve into the other aspect of the statute: the written description requirement for an antibody genus claim. This area of the law is treacherous: it is carpeted in quicksand.

III. WRITTEN DESCRIPTION: FROM *REGENTS* (1997) TO *JUNO* (2021)

In 1997, the written description requirement for a genus of biomolecules went through an upheaval. In *Regents of U. California v. Eli Lilly* (Fed. Cir. 1997), the court held that to meet the written description for a genus of insulin DNAs, the specification, when taken together with the state of the art at the filing date, had to set forth either of two alternatives.[78] The first alternative was to describe a representative number of insulin species encompassed by the genus.[79] The second one was to establish a common structure-function correlation between insulin structure and its function: to regulate glucose levels in the bloodstream.[80] Either one of these two requirements would show to a person of skill that the inventor had "possession" of the whole genus of insulin genes at the filing date. All of the genus claims of the '525 patent in *Regents* failed both tests.[81] The tests, however, are now the law of the land.

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[78] Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997).

[79] *Id*.

[80] *Id*.

[81] All the claims asserted against Lilly, 1,2,4,6, and 7, are genus claims and were found invalid for lack of written description; only claim 5, which was not asserted and was drawn to a species, was not held invalid. *See id.* at 1569.

A. FAILING THE TWO-ALTERNATIVE *REGENTS* TEST

The law on written description of a genus of antibodies followed in the footsteps of *Regents v. Lilly*: the only way to fully describe a genus of antibodies calls for the inventor to comply with either one of the two alternative requirements of *Regents*.[82] Indeed, in four post-*Regents* cases dealing with antibodies, the court applied the *Regents* criteria and held the claimed genera not fully described.

One of the earliest decisions applying *Regents* to antibody claims was *In re Alonso* (Fed. Cir. 2008), which had a method of use claim:

> **Claim 92. [(1) Biological function:]** "[a] method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody"
>
> **[Binding definition:]** "idiotypic to the neurofibrosarcoma of said human, ~~wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells~~."[83]

Beyond the binding definition that the antibody is "idiotypic to [a] neurofibrosarcoma," claim 92 has one biological function requirement: treating neurofibrosarcoma.[84] (There is also a product-by-process limitation, but that is immaterial for our discussion, so it is crossed out.) The court held that this claim failed both alternatives of the *Regents* test.[85] The claim was not supported by a sufficient written description of the antibody genus: there was no common structure-function correlation and the one antibody example in the specification was not representative of the full scope.[86]

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[82] There was a thirteen-year period, from 2004 to 2017, when, under *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004), full scope written description for a genus of antibodies could be achieved by setting forth the description of the antibody's "fully characterized" antigen. In 2017, however, the Federal Circuit in *Amgen Inc. v. Sanofi* ("*Amgen* 2017"), 872 F.3d 1367, 1377–78 (Fed. Cir. 2017), overruled *Noelle* and, as of this writing, *Noelle* is no longer the law.

[83] *In re* Alonso, 545 F.3d 1015, 1018 (Fed. Cir. 2008) (strikethrough added).

[84] *Id*.

[85] *Id*. at 1022.

[86] *Id*.

Centocor v. Abbott (Fed. Cir. 2011), is an example of a claim with multiple requirements beyond the binding definition, although none of them are a blocking or biological function. Claim 2 is as follows:

> **Claim 2. [Binding definition:] "**An isolated recombinant anti-TNF-α antibody or antigen-binding fragment thereof, said antibody or antigen-binding fragment comprising"
>
> **[(1) Structure of the antibody:]** "*a human constant region* and *a human variable region*," "wherein said antibody or antigen binding fragment"
>
> **[(2) Competitive binding:]** "(i) competitively inhibits binding of A2" a mouse monoclonal antibody, "(ATCC Accession No. PTA-7045) to human TNF-α, and"
>
> **[(3) Binding specificity:]** "(ii) binds to a neutralizing epitope of human TNF-α in vivo"
>
> **[(4) Binding strength:]** "with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (K_a), as determined by Scatchard analysis."[87]

The binding definition is that the antibody is against TNF-α. There are then four additional requirements: (1) the structure of the antibody is fully human; (2) as a measure of similar binding, the antibody shows competitive inhibition of a reference antibody, A2; (3) the antibody specifically binds to a "neutralizing epitope" of TNF-α; and (4) the antibody has a minimum binding strength of 1 x 10^8 liter/mole.

The Federal Circuit held that this genus claim failed the written description requirement in that, while the claim contains a virtual wish list of requirements, there was not a single example in the specification of an antibody with all of them. In fact, the most egregious deficit was the absence of an example of a fully humanized antibody.

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[87] Centocor Ortho Biotech, Inc. v. Abbott Lab'ys, 636 F.3d 1341, 1346 (Fed. Cir. 2011) (emphasis in original).

Then came *AbbVie Deutschland v. Janssen Biotech* (Fed. Cir. 2014).[88] Claim 29 in *AbbVie* is, like claim 7 in *Wands*, one with a binding strength requirement (1) but no biological function:

> **Claim 29.** "A neutralizing isolated human antibody, or antigen-binding portion thereof"
>
> **[Binding definition:]** "that binds to human IL-12 and"
>
> **[(1) Binding strength:]** "disassociates from human IL-12 with a K_{off} rate constant of $1\times10^{-2}s^{-1}$ or less, as determined by surface plasmon resonance."[89]

The Federal Circuit held that this claim failed the full scope written description requirement not because there was a lack of a common structure-function correlation.[90] The court based its holding on the fact that the specification did not exemplify a representative number of antibodies.[91] The number of *AbbVie* examples was high: there were 300 antibodies that fell within the claim.[92] Yet during litigation, the defendants introduced evidence that the examples were not representative of the full scope of the claim.[93] The accused antibody, which literally infringed, was quite dissimilar from the 300 examples.

The court introduced the image of a real estate field to explain its decision: the 300 antibodies were in a "corner" of the field (the examples) and were not representative of the "whole" field (the claim).[94]

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88 AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285 (Fed. Cir. 2014).

89 *Id*. at 1292.

90 *Id*. at 1302.

91 *Id*. at 1301.

92 *Id*. at 1291.

93 *Id*. at 1300. Introducing, during litigation, evidence of after-arising embodiments that, while claimed were not exemplified at the priority date, is perfectly permissible to undermine or support either enablement or written description at the priority date. *See, e.g., Amgen* 2017, 872 F.3d 1367 (Fed. Cir. 2017).

94 AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1299–1300 (Fed. Cir. 2014). My take on this real estate image is that both the corner and the whole field are blanketed in quicksand.

This line of precedents led to *Juno Therapeutics v. Kite* (Fed. Cir. 2021).[95] Claim 5 in *Juno* is to a fusion of two known DNA sequences (a) and (b) to a third DNA sequence (c) encoding antibody-like molecules capable of binding to a CD19 antigen (the ellipsis relate to details of the nucleic acids that are not material to our analysis):

> **Claim 5.** "A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising
>
> (a) a zeta chain portion . . .
>
> (b) a costimulatory signaling region, and
>
> (c) . . . a single chain antibody . . . that . . . binds to CD19 . . ."[96]

The single chain antibodies of part (c) of the claim, also known as ScFvs (Single chain Fragment variables), are antibody-type binding molecules first described in 1989. Sidestepping the fact that single-chain antibodies had been in the state of the art for more than thirty years, the court found that there was in the *Juno* specification neither a representative number of examples nor a common structure of ScFvs that would bind to the specific target CD19. The court applied the two-alternative test of *Regents* and held that there was no written description for the full scope of the genus of claimed anti-CD19 single chain antibodies.[97]

What is striking about *Juno v. Kite* is that claim 5 is to a multi-component nucleic acid fusion, where only one of the components is the sequence of a single chain antibody. The other components are sequences encoding a zeta chain and a costimulatory region, respectively. This combination of an antibody-like molecule that serves as a recognition site for its complementary target together with other, non-antibody biologically active components is now a common invention strategy. In addition to the fusions of *Juno v. Kite*, examples include antibody-drug conjugates and antibody-nucleic acid conjugates. I conclude that under the holding of *Juno*, inventors cannot build their claims around the novel and nonobvious *combination*, and claim the individually known antibody components in genus form without risking invalidation of the whole claim. Each component is subject to the *Regents* two-alternative test for full scope written

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[95] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021).

[96] *Id.* at 1334.

[97] *Id.* at 1338.

description. This is a greater obstacle than presented for a claim to a stand-alone antibody.

In all four cases, *Alonso, Centocor v. Abbott, AbbVie,* and *Juno v. Kite*, the specifications, when taken together with the state of the art at the filing dates, failed to meet either of the two requirements of *Regents v. Lilly*. As a consequence, their claims did not achieve full scope written description. Notwithstanding these results, I do not want us to conclude that all attempts at complying with full scope written description have been failures. A well-developed state of the art at the priority date helps to overcome the rigors of *Regents*.

B. PASSING THE TWO-ALTERNATIVE *REGENTS* TEST

In addition to the successes of *Wands, Chiron*, and *Hopkins* in the enablement area, there are cases with genus claims for biomolecules where challenges for failure to comply with the written description requirement have been overcome. We will see that, just as the state of the art eventually enabled the claim in *Chiron*, claim survival in the written description cases also depended on enlisting the state of the art at the priority date.

In *Invitrogen v. Clontech* (Fed. Cir. 2005), the claims are to a genus of reverse transcriptase (RT) enzymes with enhanced polymerase activity and reduced RNAse activity:

> **Claim 1.** "An isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, *Neurospora*, *Drosophila*, primates and rodents."[98]

There were only two examples in the specification. However, there were in the state of the art many RT enzymes with high homology to each other. Relying on the state of the art, the court held that full scope written description for the genus was sufficient.

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[98] Invitrogen Corp. v. Clontech Lab'ys, Inc., 429 F.3d 1052, 1072 (Fed. Cir. 2005) (underlined emphasis added, italics in original).

Another case worth noting is *Ajinomoto Co., Inc. v. International Trade Commission* (Fed. Cir. 2019).[99] Claim 9 is as follows:

> **Claim 9.** "A recombinant *Escherichia coli* bacterium, which has the ability to accumulate aromatic L-amino acid in a medium, wherein the aromatic L-amino acid production by said bacterium is enhanced by enhancing activity of a protein in a cell of said bacterium beyond the levels observed in a wild-type of said bacterium, . . . and in which said protein consists of the amino acid sequence of SEQ ID NO: 2; . . . and said protein has the activity to make the bacterium resistant to L-phenylalanine, fluoro-phenylalanine or 5[-]fluoro-DL-tryptophan, . . . wherein the activity of the protein is enhanced by . . . transformation of the bacterium with a DNA encoding the protein to express the protein in the bacterium, . . . by replacing the native promoter which precedes the DNA on the chromosome of the bacterium with a more potent promoter, . . . or by introduction of multiple copies of the DNA encoding said protein into the chromosome of said bacterium to express the protein in said bacterium."[100]

Defendants challenged the phrase "more potent promoter[s]" for lack of written description of the genus of such promoters.[101] Their challenge, however, failed. The specification disclosed four examples of promoters more potent than the native one. It also cited an article disclosing fourteen promoters with potencies relative to each other, as well as a methodology for determining promoter strength in *E.coli* bacteria.[102] The Federal Circuit held that the examples were representative of the genus of more potent promoters and that the state of the art showed that there were structural features common to the genus.[103] Both alternatives of *Regents* were therefore met. Interestingly, since there were common structure-function features in the genus, full scope written description was achieved even though it required some testing to measure the strength of potential promoters.

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[99] Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342 (Fed. Cir. 2019).

[100] *Id.* at 1346–47 (underlined emphasis added, italics in original).

[101] *Id.* at 1358.

[102] *Id.* at 1359.

[103] *Id.*

A third case of interest is *BASF Plant Science, LP v. Commonwealth Scientific and Industrial Research Organisation* (Fed. Cir. 2022).[104] Claim 1 of the '792 patent is to a genus of genetically transformed plant cells of *Brassicus napus* (canola):

> **Claim 1.** "A *Brassica napus*" [canola] "cell, comprising exogenous polynucleotides encoding"
>
> [A first enzyme],
>
> [A second enzyme],
>
> [A third enzyme],
>
> [A fourth enzyme], and
>
> [A fifth enzyme],
>
> "wherein each exogenous polynucleotide is operably linked to a promoter that directs expression of said polynucleotide in the cell."[105]

The claim requires that five exogenous enzymes be expressed in a canola cell. The court evaluated the written description for this claim and held that the genus of engineered canola cells was supported by the state of the art.[106] Even though there was no actual reduction to practice in canola cells, the court concluded that the inventors had sufficient possession of the genus because of the existence in the state of the art of a model system, *Arabidopsis*.[107] This model system was widely accepted by those of ordinary skill in the art as predictive of canola. A broader claim, not limited to canola but drawn to all plant cells, was not supported by the *Arabidopsis* model system. The court held that the broader claim did not meet the full scope written description requirement.[108]

The genus claims in *Invitrogen, Ajinomoto,* and *BASF* have functional requirements: enzymes with decreased RT activity in the first, more potent

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[104] BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Rsch. Org., 28 F.4th 1247, 1264 (Fed. Cir. 2022).

[105] *Id*. at 1257.

[106] *Id.* at 1268.

[107] *Id.* at 1265–66.

[108] *Id.* at 1265.

promoters in the second, and enhanced expression of five enzymes in the third. Notwithstanding this, with help from the state of the art, the three cases achieved full scope written description. It was a combination of descriptions in the specifications *and* in the state of the art that saved the claims from challenge under 35 U.S.C. § 112(a).

While none of these three written description cases is antibody-related, the lessons from them would apply equally to antibody cases: it helps immeasurably if the state of the art is advanced enough to supplement one or both branches of *Regents*. This statement must be tempered by the holding in *Juno v. Kite*, that even well-known state of the art such as the *general* existence of ScFvs is not enough if the descriptions in the patent or application are not sufficiently *specific*.

IV. HOMOGENIZATION OF ANALYSES UNDER § 112 (A)

A. SIMILARITIES IN FACTUAL ANALYSES OF ENABLEMENT & WRITTEN DESCRIPTION

The analysis and application of 35 U.S.C. § 112(a) to a genus of antibodies shows a trend: the factors to be analyzed in evaluating both aspects of the statute are increasingly similar. The most recent evidence of this trend is in *Amgen* 2021/2023. The "common quality" that the Supreme Court required for enablement of the genus of antibodies in *Amgen* 2023 is like the *Regents* requirement of a common structure-function for full scope written description.

Another indication that the factual underpinnings of both full scope enablement and full scope written description of a genus are converging may also be found in the real estate field image first used in 2014 in *AbbVie* for *written description*. A few years later, the field image found its way into enablement law. In *Amgen* 2021, citing to *AbbVie* and using the same image, the court invalidated Amgen's claim to a genus of antibodies for lacking *enablement* of embodiments that were within the claim but not exemplified in the specification.[109] The common focus of the court in the two legally distinct inquiries in *AbbVie* and *Amgen* 2021 was to point out that describing *or* enabling only one corner of a field does not describe or enable the entire field.

The trend toward factual confluence in the law of enablement and written description actually goes further back. In a 2005 decision, *Capon v. Eshhar* (Fed. Cir. 2005), the court enunciated several factors to determine if a

[109] Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1087 (Fed. Cir. 2021), *aff'd sub nom.* Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023).

specification shows sufficient written description to support genus claims.[110] These "*Capon* factors" were expressly defined by the court as

> [A] the nature . . . of the invention at issue; [B] the existing knowledge in the particular field, the extent and content of the prior art; [C] the maturity of the science or technology and . . .the scientific and technologic knowledge already in existence; [D] the predictability of the aspect at issue; [E] scope of the invention at issue; and [F] other considerations appropriate to the subject matter.[111]

In 2008, I published a paper pointing out the similarity between the *Capon* factors and the *Wands* factors.[112] The following table, which is based on my 2008 paper, compares the two set of factors. I have updated the table to consider the more recent pronouncements of the courts.

[110] Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

[111] *Id.*

[112] Jorge A. Goldstein & Blake Coblentz, In re Wands *Turns 20 This Year and is Increasingly Influencing the Written Description Requirement in Biotechnology*, 15 INTELL. PROP. TODAY, Aug. 2008, 10, 11.

Factual Underpinnings for Enablement of a Genus	Factual Underpinnings for Written Description of a Genus
Amgen 2023: Common quality	*Regents* (1997): Common structure-function relationship
Amgen 2021: Must enable the whole field of the genus claim, not just one corner.	*AbbVie Deutschland* (2014): Must describe the whole field of the genus claim, not just one corner.
Wands (1) Quantity of experimentation,	Only when there is a common structure-function relationship is some experimentation permissible.[113]
Wands (2) Amount of direction or guidance,	
Wands (3) Presence or absence of working examples,	*Regents*: Representative number of examples,
Wands (4) Nature of invention,	*Capon* [A] Nature. . .of the invention at issue,
Wands (5) State of art,	*Capon* [B] The existing knowledge in the particular field, the extent and content of the prior art,
Wands (6) Relative skill in art,	*Capon* [C] The maturity of the science or technology and . . . the scientific and technologic knowledge already in existence,
Wands (7) Predictability of the art,	*Capon* [D] The predictability of the aspect at issue,
Wands (8) Breadth of claims	*Capon* [E] Scope of the invention at issue,

[113] Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

	Capon [F] Other considerations appropriate to the subject matter.

Chart 2. Similarities in Factual Analyses of Enablement & Written Description

The first row of the table shows how the structure-function test of *Regents* is similar to the common quality test of *Amgen* 2023. The second row shows the real estate field metaphor that is identically used for both aspects of § 112(a). Next, the table shows that five of the factors to analyze sufficiency of genus enablement expressly mentioned in *Wands* (#s (4) to (8) on the left column of the table) and five of the factors to analyze sufficiency of genus written description expressly mentioned in *Capon* ([A] to [E] on the right column of the table) are also quite similar.

Not all factors, however, are comparable. Factor (1) for enablement, the quantity of experimentation, was equated in *Wands* to correspond to the amount of screening. The court held that it was not undue experimentation to make and screen a pool of antibodies to identify those that were of the IgM type, and which also bound to HBsAg with a threshold strength. The court's comment in *Amgen* 2021 distinguishing (but not overruling) the decision from *Wands*, confirms that, given the right circumstances, it may still be possible to enable a genus of antibodies by routine screening.

Is the same true of written description of a genus? Is it possible to fully describe a genus of antibodies by routine screening?

The answer is no. *Novozymes v. DuPont Nutrition* (Fed. Cir. 2013), makes it clear that while screening for *enablement* of certain enzyme variants may be acceptable, screening to demonstrate *possession* of the variants is not.[114] The court said that the question "is not whether one of ordinary skill in the art presented with the [priority] application would have been enabled to take those final steps [to identify the claimed variants] but whether the . . . application 'discloses the [variants] to him, specifically, as something appellants actually invented.'"[115]

There is one narrow exception to the *Novozymes* court's categorical view that written description by screening is not permitted. In the 2024 non-precedential decision *PureCircle USA Inc., et al v. Sweegen, Inc., et al* (Fed. Cir. 2024), the Federal Circuit stated:

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[114] Novozymes A/S v. DuPont Nutrition Biosciences. APS, 723 F.3d 1336, 1344 (Fed. Cir. 2013).

[115] *Id.* at 1350 (citing *In re* Ruschig, 379 F.2d 990, 995 (C.C.P.A. 1967)).

> [Where] there are structural features common to a genus, the structure-function correlation does not need to be perfect and some testing—appropriate to the knowledge of a POSA—is allowed. [The court added: *Ajinomoto* does not stand for the proposition . . .] that an unknown structure-function correlation along with extensive testing can satisfy written description.[116]

Notice the pre-condition that the court places on written description by screening: *A priori,* there must be an established structure-function correlation a la *Regents*. If there is one, then a small amount of screening is acceptable. Since there was no established common structure-function correlation in *PureCircle*, and the finding of fact was that a person of skill would have to screen close to 9,000 molecules, the Federal Circuit held that the requirements for written description of the genus claim were not met.[117]

Finally, *Wands* factor (2) in the table, the amount of guidance, focuses on enablement and not on written description. The amount of guidance is a marginal inquiry in an analysis of full scope written description. For written description, the court looks at the specification to see what can be visualized in, or inferred from, the words, formulae, or drawings.

In sum, in our post-*Amgen* 2021/2023 world, the conclusion reached by the courts as to compliance with full scope enablement starts with a balancing of the *Wands* factors. It also focuses on the enablement or lack of enablement of claimed but not exemplified embodiments, and on the presence or absence of a "common quality." I will call this updated set of enablement factors, the "*Wands+*" factors.

In turn, the conclusion regarding written description depends on a common structure-function correlation or representative number of examples under *Regents*. It also depends on the description of claimed but not exemplified embodiments, and on a balancing of the *Capon* factors. I will call this updated set of written description factors, the "*Capon+*" factors. Thus, compliance with both aspects of the statute will ultimately depend on a combination of both, i.e., on a proper balance of the "*Wands+/Capon+*" factors.

The Federal Circuit has repeatedly maintained, such as for example in *Ariad,* that 35 U.S.C. § 112(a) needs to be analyzed in two distinct aspects: one

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116 PureCircle USA Inc. v. SweeGen, Inc., No. 2022-1946, slip op. at 12 n.10 (Fed. Cir. Jan. 2, 2024) (citing Ajinomoto Co. v. Int'l Trade Comm., 932 F.3d 1342, 1360 (Fed. Cir. 2019)).

117 *Id.* at 6, 16.

for enablement and one for written description.[118] I hope to have demonstrated that, notwithstanding that the ultimate *legal* tests are different (undue experimentation vs. possession), there is an increasing trend toward homogenizing the underlying *factual* underpinnings for both.

B. THERE IS NO SEPARATE § 112(A) CASE LAW FOR CHEMICAL CLAIMS THAN FOR BIOLOGICAL ONES

While the application of the Chemical Triad's strict requirements of structure-function correlation to a quasi-chemical claim such as claim 1 in *Amgen* 2021 flows directly from their similar claim formats, the ultimate affirmance of the decision by the Supreme Court in *Amgen* 2023 has brought us to the common quality test. *Baxalta* confirms that structure-function correlations and common quality questions will be applied even in the absence of quasi-chemical formats. These developments have also homogenized the case law, this time between different technologies. There is not to be a separate § 112(a) case law for chemical claims than for biological ones.

The confluence of enablement and written description on the one hand and of chemical and biological claims on the other have simplified the law. The focus of antibody claim analyses is now on common tests and questions. However, the overall trend has been the erosion of legal support for genus claims in the antibody field. The factual requirements to achieve full scope enablement and full scope written description of an antibody genus claim, while increasingly similar, have become onerous. These requirements pose serious hurdles for obtaining and defending such claims.

I will next provide some solutions to the situation we find ourselves in. In the section that follows, I will try to demonstrate that not all is lost for those seeking antibody genus claims of meaningful scope.

V. THE FUTURE OF ANTIBODY-RELATED GENUS CLAIMS

My analysis of claim requirements has led to the conclusion that in most instances when the court has examined a genus claim to an antibody *per se* with blocking or biological requirements, or to a method of using an antibody, it has held that the claim lacked either full scope enablement or full scope written description.

In the absence of a common quality or a common structure-function correlation, the inclusion in any claim of a blocking requirement (as in *Amgen* 2021/2023) or a biological requirement (as in *Baxalta*) proved fatal for lack of full

[118] Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1344 (Fed. Cir. 2010).

scope enablement. Yet even in the absence of a blocking or biological requirement, claims can still fail the two-alternative test of *Regents*. These failures include claims with a wish list of requirements (as in *Centocor v. Abbott*); claims based on specifications with no examples at all of ScFvs that bind to a specifically claimed antigen (*Juno v. Kite);* or specifications where even 300 exemplified antibodies were not representative of the full claimed genus, but only of a corner (*AbbVie Deutschland*).

It is this parade of full scope failures that has led to what I coin the "pessimistic mood" among biotech patent practitioners who try to obtain and enforce genus claims in the field of therapeutic antibodies.

It should be obvious that one solution to the problem of achieving full scope enablement lies in avoiding biological or blocking requirements in the claims, as in *Wands* or *Chiron.* Particularly to be avoided are combining in the same claim such requirements with quasi-chemical formats such as those in claim 1 of *Amgen* 2021/2023.

Because I want to rely heavily on the claim formats in *Wands* and *Chiron*, I will first ask whether the enablement analyses behind the holdings in these two cases are still viable after *Amgen* 2021/2023. After that I will ask whether *Wands* would survive a rigorous *Regents* analysis for full scope written description.

A. WOULD *WANDS* & *CHIRON* SURVIVE *AMGEN* 2021/2023?

Let us start with *Wands*. The product *per se* and immunassay genus claims in *Wands* survived challenges for lack of enablement. That, however, was 1988. The question today is: Would they survive scrutiny under *Amgen* 2021/2023 and *Baxalta*? I believe so.

We have seen that product *per se* claim 7 in *Wands* has no blocking or biological requirements and is not in quasi-chemical format. It can thus be distinguished from the claims in *Amgen* 2021/2023 and *Baxalta*. And, while claim 1 in *Wands* is a method of use, it is drawn to a more readily enabled immunoassay method, not to a therapeutic method.

Let us now look at *Chiron*. You may recall that product *per se* claim 19 in *Chiron* is drawn to a genus of antibodies with nothing but a binding definition: "A monoclonal antibody that binds to human c-erbB-2 antigen."[119] The claim has no biological or blocking requirements as do the claims in *Baxalta* or *Amgen* 2021/2023. And, in contrast to the claims in *Amgen* 2021/2023, the *Chiron* claim is not in quasi-chemical format: there is in claim 19 no specific binding structure, whether of the antibody or of the antigen. Claim 19 survived an enablement

[119] Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1250 (Fed. Cir. 2004).

challenge in 2004. It did so, although only on the last filing date and with help from the state of the art. But it survived. This holding was not because only at the latest filing date did Chiron set forth a common structure-function correlation or recognized a "common quality." There is no structure or function in the claim to require such finding.

This success raises a valid question: Is *Chiron* an outlier, a mere legal remnant from earlier and easier times? Remember that by 2004, when *Chiron* was decided, both *Wands* (1988) and *Regents* (1997) were already the controlling precedents on enablement and written description of a genus. Yet the *Chiron* claim was neither challenged for undue experimentation under the *Wands* factors, nor for non-compliance with *Regents.* Since no rigorous challenges were made under *Wands* or *Regents*, we might be justified in thinking that survival of the challenge under § 112(a) in *Chiron* is a fluke.

The reason that I do not believe so is that it is quite possible that defendant Genentech decided to not raise a defense of invalidity under either *Wands* or *Regents.* Both these cases require multipronged approaches to compliance with 35 U.S.C. § 112(a). Instead, Genentech may have decided on a more straightforward analysis: that Chiron failed to describe or enable anything but murine forms until the state of the art came to its rescue. When that happened, however, it was too late to overcome anticipation.

It is equally possible, and in my view likely, that because of the simple form of claim 19, which uses nothing but a binding definition and no further functions or requirements, Genentech concluded that a challenge under either *Wands* or *Regents* might fail. There are few if any hooks on which to attack a claim that contains nothing but a binding definition. Perhaps it is the very simplicity of claim 19 that led to the successful argument that, early on in the priority chain, there was no enablement for anything other than murine forms. This explains my conclusion that *Chiron* is not an outlier. The simple claim format in the case can and ought to be used when the circumstances permit.

B. WOULD *WANDS* SURVIVE THE TWO-ALTERNATIVE *REGENTS* TEST?

Ever since the decision in *Regents v. Lilly*, I have wondered whether the genus claims in *Wands* would survive the rigorous two-alternative test for full scope written description. Because the Federal Circuit decided *Wands* in 1988, nine years before *Regents*, it did not evaluate written description. The court did not look for a common structure-function correlation or a representative number of examples.

Since there are no biological or molecular blocking requirements in *Wands*'s product *per se* claim 7, there is no requirement for a common structure-function correlation under *Regents*. But what about a representative number of

examples? That is where we may run into the quicksand of *AbbVie Deutschland*. As demonstrated by *AbbVie,* challenges for lack of representativeness by introduction of post-filing evidence can become a trap for the unknowing.

There are in the *Wands* patent three examples of monoclonal antibodies within the claims.[120] During prosecution, Wands introduced an affidavit showing a fourth example.[121] Are these four examples representative enough to demonstrate possession of the full scope of claim 7? Was *Wands* unknowingly standing only in the corner of a larger field?

Of course, I cannot tell if a defendant, like the one in *AbbVie Deutschland,* would undermine representativeness of claim 7 by commercializing an IgM antibody that binds to HBsAg with high affinity yet is dissimilar from the four examples. The uncertainty of whether there is a larger field beyond the corner where an inventor is standing is the downside of allowing defendants to introduce after-arising embodiments years after the issuance date. Whether the three examples in the *Wands* specification and the fourth one demonstrated later by declaration would have passed the *Abbvie Deutschland* test of being representative of the full genus is a question that will remain unanswered.

C. PROMISING FORMATS FOR ANTIBODY *PER SE* GENUS CLAIMS

We have seen that the fewer blocking and biological requirements in a genus of antibody-centered claims, and the fewer quasi-chemical elements in such claims, the better the chance of them surviving a challenge under 35 U.S.C. § 112(a). The obvious question then is: How easy is it to avoid *any* requirements, especially biological or molecular blocking requirements, in antibody-based genus claims? How easy is it to limit the claims only to a binding definition? The answer is: Not easy.

The first approach is to avoid method of treatment claims, such as treating a patient with an antibody that affects a specific condition or disease. *A priori,* the inclusion of such a treatment introduces a biological function and leads to *Wands+*/*Capon+* questions about structure-function correlations or "common qualities." If we use method of treatment claims, as we invariably will, we must be aware that such claims are highly vulnerable to challenge.

What then about antibody *per se* genus claims? I will explore this question in terms of different claim formats, some already tested by the courts, others not yet.

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120 *See* U.S. Patent No. 4,879,219 tbl. 1a.

121 *In re* Wands, 858 F.2d 731, 741 (Fed. Cir. 1988).

1. Target is novel: Claim by binding definition only

Whether it is possible to obtain and enforce antibody *per se* claims defined solely by a binding definition, as in *Chiron*, will depend on whether the antigen and antibody are novel or not. If an inventor discovers a novel target X, say, a novel receptor (for example, PD-1) or enzyme (for example, PCSK9), the blocking of which leads to a biological result, the inventor, following *Chiron v. Genentech's* c-erbB-2 example, should present a genus claim to the antibody *per se* with a binding definition only.

Assume that no matter how much our inventor tries, she cannot initially deduce a common quality or common structure-function correlation. Our inventor is then unable to meet the requirements of *Amgen* 2021/2023 or of one of the alternatives of *Regents*. Our inventor should therefore not immediately file for claims, even dependent ones, which include a biological requirement. Yet our inventor should not wait to file an application until she has elucidated a common quality or common structure-function correlation among all members of the genus. She can still obtain a broad *Chiron*-like antibody genus claim with nothing but a binding definition.

For this to work, the specification should include detailed descriptions of two uses for the novel antibody: The first is a diagnostic immunoassay for the target and the second a therapy based on blocking the target.

For the first use the specification should describe non-labeled, labeled, and solid phase-bound forms of the antibody. The labeled and solid-phase-bound antibodies can be used in various types of *in vitro* immunoassays. The specification should also include descriptions of the use of labeled antibodies in *in vivo* diagnostic imaging, such as tissue imaging. The non-labeled antibody should be claimed and described as a useful intermediate that leads to the labeled and solid-phase bound ones utilized in assays. See, for example, *In re Magerlein* (C.C.P.A 1979), where the court held that the usefulness of a final chemical product (in our case the labeled or solid phase-bound antibody), inures to the usefulness of a claimed intermediate (in our case the unlabeled antibody), used in preparing the final product.[122]

As many examples as possible of antibodies that bind the target should be described and exemplified in order to comply with the "representative number" requirement of *Regents*.[123] The inclusion of specific examples will

[122] *In re* Magerlein, 602 F.2d 366, 366 (C.C.P.A 1979).

[123] There is no requirement that the descriptions or examples have actually been reduced to practice. *See*, *e.g.*, Falko-Gunter Falkner v. Inglis, 448 F.3d

improve the chances of our claim over the claim in *Juno v. Kite*, where there was not even one example of a single chain antibody under the claims. To try and preempt an *AbbVie Deutschland* ambush during future litigation, the examples should come from as many different types of antibodies as possible: monoclonal, polyclonal, single chain, murine, chimeric, humanized, fully human, IgG, IgM, IgD, bivalent, from different germlines, antibody fusions, antibody conjugates, and the like. Our inventor can then obtain a genus claim to the new and non-obvious unlabeled antibody claimed as a *per se* product.

For the second use, the specification should also describe the therapeutic function that comes from blocking a pathway involving the novel target X. However, the therapeutic or blocking requirement need not initially be claimed. A broad antibody *per se* claim should still dominate the use of the same antibody for the therapeutic use as well as all future uses.

Dependent claims that include a biological or blocking function should wait to be included until there is a better understanding of a common quality or a common structure-function correlation. If a product *per se* claim that includes molecular or biological function (such as in *Amgen* 2021/2023 or *Baxalta*) or a method of treatment claim (such as in *Alonso*) are initially filed but then dropped in response to a rejection for lack of full scope enablement or written description, there is a risk of an estoppel. In *UCB, Inc. v. Yeda Research and Development Co., Ltd.* (Fed. Cir. 2016), the court held that cancelation of a narrower claim to "chimeric antibody" dependent on a broader independent claim to "monoclonal antibody" caused forfeiture of claim scope.[124] This prevented the broader claim to be later interpreted as encompassing the canceled chimeric embodiments.

It should be kept in mind that including a description of a common quality or correlation in a later follow-on application will likely result in the follow-on receiving a new priority date. Therefore, the inventor should not wait too long to file the follow-on, lest her own published first patent application becomes prior art.[125]

1357, 1366–67 (Fed. Cir. 2006); prophetic examples and descriptions suffice as long as they are sufficiently specific.

124 UCB, Inc. v. Yeda Rsch. & Dev. Co., 837 F.3d 1256, 1260 (Fed. Cir. 2016).

125 The first description of the therapeutic method will publish eighteen months after the initial filing. It will then become prior art as of its initial filing date, anywhere in the world except in the U.S. This will prevent worldwide patent protection for the therapeutic method. In the U.S., inventors get a year of grace for their own publications, so the deadline for filing the follow-on and still obtain patent protection in the U.S. only, is

Of course, if our inventor discovers a novel target X for a pre-existing therapeutic antibody, she may not be able to claim the antibody by just its binding definition as in *Chiron*. Even if the target is novel, that is, it was unknown before the invention, it is likely that the pre-existing antibody claimed by binding only would be inherently anticipated.

A genus claim to a novel and non-obvious method of therapy focused on blocking (or activating) the novel target X should eventually be presented. However, such a claim will *a priori* include a biological or molecular requirement and bring along a full analysis under the *Wands*+/*Capon*+ factors.

2. Target is not novel: Claim by using Markush-type format

Since the 1925 decision in *Ex parte Markush*, the courts have accepted the use of structure-only claims defined by a formula without biological functional requirements.[126] These *Markush* claim formats are routinely used to encompass a genus of small molecule compounds. If a proper utility is spelled out in the specification, and all compounds in the *Markush* group are described as having the same asserted utility, the utility itself does not have to be included in the claim. Therefore, a genus of antibodies could also be claimed without including biological function, in what we may call a "*Markush*-type" format.

Assume that the target X is *not* novel, but the inventor has discovered that blocking the target leads to a heretofore unknown beneficial therapeutic effect. In such a situation, claiming the antibody by a binding definition only, as in *Chiron v. Genentech*, may no longer be possible. Further assume that our inventor has made three specific antibodies (a), (b), and (c), which perform a biological or molecular blocking function when they bind to target X. The three antibodies (a), (b), and (c) are novel; that is, there are no identical antibodies in the prior art.

Now, assume that our inventor deposits three cell lines that are sources for the antibodies at an appropriate depository authority, such as the ATCC. She obtains deposit accession numbers ATCC 123, ATCC 456, and ATCC 789. The inventor also sequences the heavy and light binding regions of her three antibodies (a), (b), and (c). While the sequences of the three antibodies are different, they all have in common the binding of target X.

Claiming the three antibodies by themselves will produce a narrow claim, which can easily be avoided by competitors. Yet with deposits or

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thirty months after the first priority date. *See* 35 U.S.C. §§ 102(a), (b), and (d).

126 *Ex parte* Markush, 1925 Dec. Comm'r Pat. 126, 128–29.

sequence, our inventor can put forth a claim with some scope beyond the three specific antibodies (a), (b), and (c). The claim should include a part (d) with a competitive binding requirement to one of the antibodies claimed by deposit, which, as we have seen from *Hopkins v. CellPro*, is known as the "reference antibody." The claim is in *Markush*-type format:

> An antibody that binds to target X, selected from the group consisting of
>
> > (a) An antibody produced by cells on deposit at the ATCC with accession number ATCC 123;
> >
> > (b) An antibody produced by cells on deposit at the ATCC with accession number ATCC 456;
> >
> > (c) An antibody produced by cells on deposit at the ATCC with accession number ATCC 789; and
> >
> > (d) An antibody that competitively inhibits the binding of antibody (a) to target X.

Part (d) attempts to capture some worthwhile scope that could prevent others from making highly similar antibodies to the ones in (a), (b), and (c) while literally avoiding the original claim. In order to pre-empt a challenge of this claim for indefiniteness under 35 U.S.C. § 112 (b), I strongly suggest including in the specification and perhaps even in part (d) of the claim a detailed description of the specific immunoassay to be used to screen for competitive inhibition against the reference antibody. The description should be specific as to assay conditions, reagents, measurement methods, and evaluation of results. The specificity and distinctness of the assay conditions will not detract from the breadth of the overall claim.

A foreseeable ground of challenge under § 112(a) would be that part (d) of our claim is broader than the disclosure of the three deposited antibodies. The attack on the claim would be that only the deposited antibodies (a), (b), and (c) comply with both requirements of 35 U.S.C § 112(a) but that the genus in part (d) does not.[127]

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[127] A threshold objection by a USPTO examiner to our proposed claim may be that the claim involves an improper *Markush* grouping, in that there is no common sequence core of antibody variable regions in antibodies (a), (b), and (c). Such objection came up in biological *Markush*–type claims in *Ex parte* Narva, No. 2018-006168, at 3–5 (P.T.A.B. Apr. 5, 2019). The

Let us start with enablement. This is where *Hopkins v. CellPro* comes to help.

a. Enablement.

A challenge for lack of full scope enablement of a claim with a similar competitive binding requirement was made and fended off in *Johns Hopkins University v. CellPro, Inc.* (Fed. Cir. 1998).[128] That is a hopeful precedent.

When I first introduced *Hopkins*, I noted that the case might today come under criticism. A challenger may plead that the case should be limited to its facts, in that better evidence than that presented by CellPro might have been more convincing to the lower court and the Federal Circuit. *Hopkins* might also be critiqued as belonging to an earlier era: an era when screening under *Wands* still ruled supreme, before the strict analysis of antibody claims drafted in quasi-chemical format, and before *Amgen* 2023 and its requirement for a common quality. Let me answer each in turn.

i. Evidence.

Maybe there could have been in *Hopkins* better evidence of lack of enablement. This, however, is nothing but a counterfactual hypothesis. Every case is decided on its facts and yet that does not eliminate its value as binding precedent. Of course, it is possible that in the case of *our* proposed claim an opponent might present evidence more convincing than CellPro's. The fact

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Appeals Board in *Narva* held that a grouping of double-stranded RNAs (dsRNAs) with *different* sequences was a proper *Markush* group. *Id.* The dsRNAs could hybridize to their complements for silencing expression of the ROP gene in insects. The PTAB noted that

> the nucleic acid sequences recited in the rejected claims belong to the same recognized chemical class of polyribonucleotides . . . While the individual sequences differ because they are drawn to ROP sequences of different insects . . . or different portions of the ROP sequence . . . all of the sequences share the common use of silencing ROP proteins.

Id. Narva would allay a concern that our proposed claim does not constitute a proper *Markush* group. The three claimed antibodies belong to the same chemical class and they all share a common function: binding to the same target.

128 Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1359–60 (Fed. Cir. 1998).

remains, however, that in *Hopkins*, when the lower court considered the evidence in view of the accepted state of the art of making and screening antibodies for simple competitiveness with the reference antibody, it remained unconvinced that the claim was not enabled for the "full breadth."[129] And the Federal Circuit affirmed.[130] If anything, the state of the art of making and screening antibodies in competitive immunoassays is more advanced today than in 1998.

ii. Competitive binding format.

As far as earlier legal eras: The claim in *Hopkins* is neither in quasi-chemical format nor does it contain any blocking or biological requirement. The claim is to a genus of antibodies defined by nothing but a competitive immunoassay. I believe that immunoassays using antibodies raised against a target are readily enabled for their full scope by routine testing. They are more like the immunoassay claim 1 in *Wands* than the claims in the Chemical Triad, *Amgen* 2021/2023, or *Baxalta.*

Let me discuss the impact of *Amgen* 2023 on *Hopkins v. CellPro*. In *Amgen* 2023, the Supreme Court urged that inventors describe "a quality common" among the elements of a genus claim[131]. The court's coining of this term comes from several historical cases especially that of Edison's invention of a successfully incandescent light bulb. Edison discovered that bamboo fibers (which his emissaries had brought back from Japan after searching the four corners of the world) worked "brilliantly" in incandescent light bulbs.[132] Edison was promptly sued by Sawyer and Man who, based only on their use of carbonized paper, had earlier obtained a broad patent claiming every fibrous or textile material used in incandescence. In *The Incandescent Lamp Patent* (S. Ct. 1895), the Supreme Court held that unless Sawyer and Man disclosed "a quality

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129 Johns Hopkins Univ. v. CellPro, 931 F. Supp. 303, 322–24 (D. Del. 1996), *aff'd in part, vacated in part sub nom.* Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342 (Fed. Cir. 1998); *see also Johns Hopkins Univ.*, 152 F.3d at 1351.

130 *Id.* at 1361.

131 While the genus claim in *Amgen* 2023 includes a specific antigen structure and a blocking requirement, I will presume that the Supreme Court's "common quality" mandate will be interpreted as beyond the claim before it. Amgen Inc. v. Sanofi, 143 S. Ct. 1243, 1246 (2023).

132 The pun is from the contemporary Supreme Court. *See Amgen*, 143 S. Ct. at 1253.

common" that made their incandescent fibers superior, they were not entitled to a genus claim to all fibers beyond those made of carbonized paper.[133]

The "common quality" missing from Sawyer and Man's failed genus of fibers is a much more complicated quality than that in a claim to a genus of antibodies that all bind to the same target as a reference antibody in an immunoassay. There is no requirement other than competitive binding in our proposed claim or that of *Hopkins*. If the antibodies do not compete with the reference, they are not claimed.

A more recent appearance of a competitive binding requirement is in *Immunex Corporation v. Sanofi-Aventis U.S. LLC, et al. and Andrei Iancu, Intervenor* (Fed. Cir. 2020).[134] Claim 1 is as follows:

> **Claim 1.** "An isolated human antibody *that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor*, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO: 10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO: 12."[135]

This claim contains both a competitive binding requirement (italicized) and specific sequences of the light and heavy chains of the reference antibody. The reference antibody is not defined by an ATCC deposit number, but by sequence identity. Since our inventor has sequenced the light and heavy chains of her antibodies, her claims could easily be reframed to amino acid sequences instead of deposit numbers. Indeed, both types of descriptions of reference antibody (a) could be included in her patent application.

There was no challenge in *Immunex* for lack of enablement of the full scope because the case was an appeal from a decision by the Patent Trial and Appeal Board (PTAB) of the USPTO in an *Inter Partes* review. In such IPRs, issues under 35 U.S.C. § 112(a) are not raised unless in the context of attacking a priority date, which did not happen in *Immunex*.[136] *Immunex* is therefore not as

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[133] *See* Consol. Elec. Light Co. v. McKeesport Light Co. ("The Incandescent Lamp Patent"), 159 U.S. 465, 474 (1895).

[134] Immunex Corp. v. Sanofi-Aventis U.S. LLC, 977 F.3d 1212, 1213 (Fed. Cir. 2020).

[135] *Id.* at 1214–15 (emphasis added).

[136] The issue in *Immunex v. Sanofi* was whether to construe the claim term "human" to mean "fully human" or "partially human." In its holding, the

strong an authority as *Hopkins* on the enablement of claims that include a competitive binding requirement. Yet, *Immunex* is a modern illustration that competitive binding against a reference antibody is a common and acceptable format in antibody claims.[137]

iii. Automated screening.

Our proposed claim, as well as the claims in *Hopkins* and *Immunex*, might also be challenged on the basis that some degree of screening will be necessary for full scope enablement. Such a challenge could be overcome by demonstrating that generating other antibodies that compete with reference antibody (a) can be done quickly and routinely; that is, without undue experimentation. In order to evaluate if a new antibody falls or not within claim limitation (d), a person of skill would obtain the reference antibody (a) from the culture collection and run a competitive inhibition test against target X.[138]

While some of the tests may be positive and others not, it is clear from the opinion of the Supreme Court in *Amgen* 2023 that some amount of screening is still permissible to comply with the full scope enablement requirement. The Court said it a few times: "[A] specification [is not] necessarily inadequate just because it leaves the skilled artist to engage in some measure of adaptation or testing";[139] "[A] specification may call for a reasonable amount of

Federal Circuit construed the term to mean "partially human." This interpretation led to invalidity of Immunex's claim for obviousness. *Id*.

137 *See also* Centocor Ortho Biotech, Inc. v. Abbott Lab'ys, 636 F.3d 1341, 1346 (Fed. Cir. 2011)., which included a claim with a competitive binding requirement: the antibody against TNF-α "competitively [inhibits] binding of A2 (ATCC Accession No. PTA-7045) to TNF-α." The Federal Circuit described the competitive binding requirement as the "the ability to bind in the same place as the mouse A2 antibody," calling it the "A2 specificity." *Id.* at 1351–52. While the court held that Centocor's claim was invalid for failure to meet the full scope written description requirement, it did not do so on concerns with the format of the competitive binding requirement, but on the failure to describe any antibody that met the "wish list" of the multiple requirements of the claim.

138 For this to work, the patent specification must enable target X by a complete DNA sequence or a deposit of cells containing the gene for target X and a method for its expression and isolation. Alternatively, since in this discussion the target X is in the prior art, the specification must provide appropriate literature citations.

139 Amgen Inc. v. Sanofi, 143 S. Ct. 1243, 1255 (2023).

experimentation to make and use a patented invention. What is reasonable in any case will depend on the nature of the invention and the underlying art."[140]

Making antibodies to target X and then screening for competition with reference antibody (a) is in the nature of "some measure of adaptation or testing," and "a reasonable amount of experimentation." It is certainly more routine and repetitive than testing multiple and different fibrous materials to find those with superior incandescence as was the case in *Incandescent Light Patent.* It is also more in the nature of routine and repetitive testing than the screening in the Chemical Triad in *Amgen* 2021/2023, or in *Baxalta*. In the Triad cases, a person of skill had to first synthesize molecules (rapamycins; or purine or pyrimidine derivatives; or labeled polynucleotides) and then test them for blocking or biological function. In *Amgen* 2021/2023, or in *Baxalta,* such a person had to first make antibodies that bind to PCSK9 or to Factor X or IXa and then find those that blocked the LDL receptor or increased the procoagulant activity of Factor IXa, respectively; that is, find those with therapeutic activity.

In contrast, the testing in our proposed claim is in the realm of immunoassays, not therapeutics. No testing for biological or blocking function is required. Because of that, the proposed claim presents one of those few situations similar to the one with claim 7 in *Wands*, or claim 1 in *Hopkins*. In both these cases, the amount of screening was not related to biological or blocking functions but to immunoassays, and it was held not to be undue.

Of course, it is possible and perhaps likely that some of the antibodies generated against target X may not compete with reference antibody (a). The case law supports the notion that a genus claim is not invalid for lack of enablement just because it contains some species that do not meet a claim limitation.[141]

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[140] *Id.*

[141] *See*, *e.g.*, Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005) ("It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention."); Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984) ("Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid."); *In re* Dinh-Nguyen, 492 F.2d 856, 858–59 (C.C.P.A 1974) ("It is not a function of the claims to specifically exclude. . .possible inoperative substances. . . ."). *But cf. Atlas Powder Co.,* 750 F. 2d at 1576–77 (Fed. Cir. 1984) ("Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in

I have one last argument for not foregoing the idea of routine screening for enablement analysis of a genus of antibodies: automated high-throughput methods. The time when scientists stood at the bench and manually looked for antibodies that complied with a set of requirements is long gone.[142] Screening for antibodies that bind a target and finding among those the ones that compete with a reference antibody for it are no longer slow and labor intensive. The screening is now done by computerized equipment. Add to that the advent of artificial intelligence and the task is not only faster but also self-improving.[143] There are now assay techniques that can screen for soluble, secreted, full length IgG antibodies against a given target at rates of several thousand clones per second.[144]

Put differently, modern high-throughput screening techniques for the isolation of antibodies with desired requirements, enhanced by artificial intelligence, are in 2024 the state of the art. *Wands* factor (6), the relative skill in the art, and *Capon* factor [C], the maturity of the technology, are now light-years removed from the days of *Wands* and *Hopkins v. CellPro*. In addition, *Wands* factor (1), the quantity of experimentation, which is now in the repetitive arms of robots, while perhaps still lengthy, is today as routine as it can get. Recall the words of the court in *Wands*: "The key word is 'undue' not 'experimentation.'"[145]

Interestingly, in its response to Sanofi's argument that claim 1 in *Amgen* 2021 lacked enablement since, among other things, the quantity of experimentation was very high, Amgen brought up the possibility of high-

order to practice the claimed invention, the claims might indeed be invalid.").

142 *See* Robert P. Hertzberg & Andrew J. Pope, *High-Throughput Screening: New Technology for the 21st Century*, 4 CURRENT OP. CHEM. BIOLOGY 445, 445 (2000) ("New technologies in high-throughput screening have significantly increased throughput and reduced assay volumes."); Simon Tickle et al., *High-Throughput Screening for High Affinity Antibodies*, 14 J. ASS'N LAB'Y AUTOMATION 303, 306 (2009) (using automation, it took the authors three months to go from close to 260,000 cells to one humanized variable region selected as therapeutic).

143 Jonathan Parkinson et al., *The RESP AI Model Accelerates the Identification of Tight-Binding Antibodies*, 14 NATURE COMMC'NS 454, 455 (2023).

144 Yongliang Fang et al., *Going Native: Direct High Throughput Screening of Secreted Full-Length IgG Antibodies Against Cell Membrane Proteins*, 9 MABS 1253, 1253 (2017).

145 *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

throughput screening.[146] Pointing to expert testimony that "automated high-throughput techniques existed [at the priority date] for testing a large number of antibodies to determine whether they fall within the scope of the claims quickly, efficiently, and cheaply," Amgen argued that the quantity of experimentation required to make the full scope of its claims was low."[147] The district court, however, dismissed Amgen's argument as "largely conclusory." It held that such conclusory expert testimony was insufficient to support a factual conclusion that the time and effort required to enable the full scope of the claims was minimal.[148]

We should advise our inventor that whatever screening she needs to do to find antibodies with the right binding definition and the right competitive inhibition against a reference antibody should be carried out by high-throughput screening, possibly assisted by artificial intelligence. If the equipment is not readily available, we should at least describe at great length in the specification how screening is to be done by such modern techniques. Based on how routine robot-assisted antibody screening has become in the 21st century we will then be able to point to the very advanced state of the art and to the very high level of skill. This will allow us to go from the largely conclusory expert statements in *Amgen* 2019, to what real world screening actually looks like in this day and age.

b. Conclusion as to *Markush*-type formats.

The use of a *Markush*-type format with a competitive binding limitation against a reference antibody essentially turns an antibody genus claim with biological or blocking requirements having therapeutic consequences, as in *Amgen* 2021/2023 or *Baxalta*, into an immunoassay claim a la *Wands* or *Hopkins*.

It is always possible that even a routinely and quickly obtained antibody that successfully competes with reference antibody (a) will not exhibit the described *but not claimed* biological function of therapy or molecular blocking. But, since the claim itself does not require a biological or blocking function, that should not doom it to invalidity under § 112(a). The only question with our proposed claim is whether it is undue experimentation to screen for antibodies that compete with the reference antibody (a).

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146 Amgen Inc. v. Sanofi ("Amgen 2019"), No. CV 14-1317-RGA, 2019 WL 4058927, at *10 (D. Del. Aug. 28, 2019).

147 *Id*.

148 *Id*.

Ultimately, the question of whether screening for competitive binding with a reference antibody is or not undue experimentation in this very advanced state of the art in which we find ourselves or, further, whether the claimed antibodies need to exhibit *unclaimed* biological or molecular blocking will have to be answered by the Federal Circuit.

Let us now turn to the written description requirement of our *Markush*-type claim.

c. Written Description.

We have seen that screening, no matter how high-tech, is not a proper method to comply with full scope written description.[149] Therefore, our arguments about the enablement of a claim that includes a binding definition plus competitive binding requirement do not apply to written description.

One possibility to comply with the full scope written description requirement for a claim based on multiple deposits is provided by *Enzo Biochem v. Gen-Probe* (Fed. Cir. 2002).[150] The court in *Enzo Biochem* held that the deposit of three microbial strains at the ATCC inherently described the sequences of the individual DNAs in each strain.[151] But it remanded to the lower court to decide if the three deposits were representative of the full scope of a broader genus claim.[152] Similarly, our inventor could try to demonstrate that her three deposited cell lines, which are the source for the three specific antibodies (a), (b), and (c), are representative of the full genus claim, including the antibodies of part (d).

Another possibility to comply with full scope written description under *Regents* for part (d) of her claim is to provide multiple examples of additional antibodies beyond the three claimed ones (a), (b), and (c), and show that they bind competitively to reference antibody (a). The inclusion of multiple, and hopefully representative, examples of antibodies will distinguish *Juno v. Kite* (where there was not even one example of ScFvs binding to CD19) or *AbbVie Deutschland* (where even 300 examples were not representative).

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149 Novozymes A/S v. DuPont Nutrition Biosciences. APS, 723 F.3d 1336, 1347 (Fed. Cir. 2013); Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1352 (Fed. Cir. 2019); PureCircle USA Inc. v. SweeGen, Inc., No. 2022-1946, slip op. at 6, 11–13 (Fed. Cir. Jan. 2, 2024).

150 Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 970 (Fed. Cir. 2002).

151 *Id*. at 964–65.

152 *Id*. at 966–67.

3. Target novel or not: Claim by using Means-Plus-Function format

Even before *Amgen* 2021/2023, several commentators had speculated on alternatives for drafting genus claims to biomolecules using so-called "means-plus-function" claims.[153] The means-plus-function format arises out of 35 U.S.C. § 112(f), which states (emphasis added):

> An element in a *claim for a combination* may be expressed as a means or step for performing a specified function *without the recital of structure*, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification *and equivalents thereof*.[154]

By its terms, the statute allows "a claim for a combination" to use functional language "without the recital of structure." In accordance with the statute, we might re-draft antibody *per se* claim 1 in *Amgen* 2021/2023 as follows:

> In combination, (a) means for binding a molecular epitope in PCSK9 such that the binding of PCSK9 to the LDL receptor is blocked, together with (b) a pharmaceutically acceptable carrier.[155]

Note that, as required by the statute, the claim is a combination of the means for binding and a carrier. Note also that the claim does not contain any structure of the "means for binding," such as whether it is an antibody, a receptor, or any other such molecule. It also does not include any of the one or more fifteen amino acid residues in the PCSK9 antigen that are part of the claim in *Amgen* 2021/2023.

Yet the claim contains a functional requirement: ". . . such that the binding of PCSK9 to the LDL receptor is blocked." The case law on mean-plus-

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153 Jorge A. Goldstein, *Capturing After-Discovered Embodiments in Biotechnology Patents*, 25 FED. CIR. BAR J. 401, 442–43 (2016); *see* Lemley & Sherkow, *supra* note 10 (Professors Lemley and Sherkow in their Article" The Antibody Patent Paradox," developed the idea more fully and applied it to antibody genus claims).

154 35 U.S.C. § 112(f) (emphasis added).

155 *Amgen 2019*, 2019 WL 4058927, at *2.

function claims suggests that such claims should not include any structure *whatsoever*; thus, there is no mention of an "antibody" in the proposed claim.[156]

As of this writing the fate of means-plus-function claims for antibodies is being tested in *In re Xencor* (Fed. Cir. 2024)[157] and its sequelae. *Xencor* is a case in which the PTAB initially rejected the use of such formats for antibody genus claims.[158] That decision was appealed to the Federal Circuit, but before the court had a chance to act, the USPTO requested that the appeal be withdrawn.[159] The court then remanded it to the agency to reanalyze its earlier grounds of rejection.[160] Four months later, in *Ex Parte Aaron Keith Chamberlain, et al*., (Pat. Trial and App. Bd. 2024) the USPTO did just that. It decided that means plus function formats are acceptable for antibody genus claims.[161] It also interpreted 35 U.S.C. § 112(f) to require that the specification need describe no more than one structure.[162]

Following the guidance of *Chamberlain*, the specification in our case need not describe more than one example of an antibody that binds to target X. However, it would be good practice to include as lengthy a description as possible of the many distinct "means" to carry out the claimed binding function: for example, antibodies of different types, i.e., IgG, IgE, IgD, IgM, single chain variables (ScFv), minibodies, nanobodies, chimeric, humanized, fully human, bivalent, fusions of antibodies, receptors, fusions of receptors, antibodies from different germ lines, and the like. While there is no need to list all of these to meet the terms of § 112(f), including several will provide as extensive a list of the "equivalents thereof" mentioned in the statute. This will assist during enforcement of the claim in litigation.

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156 *See*, *e.g.*, MANUAL OF PATENT EXAMINING PROCEDURE § 2181 (9th ed. Rev. 07.2022); Gene Quinn, *A Primer on Indefiniteness and Means Plus Function*, IP WATCHDOG (Nov. 15, 2017, 5:15 AM), https://ipwatchdog.com/2017/11/15/primer-indefiniteness-means-plus-function/id=89708 [https://perma.cc/8DL8-JYDY].

157 *In re* Xencor, Inc., No. 23-2048, slip op. at 1 (Fed. Cir. Jan. 23, 2024).

158 *Ex parte* Chamberlain ("Chamberlain I"), No. 2022-001944, at 28–30 (P.T.A.B. Jan. 10, 2023).

159 *Xencor*, slip op. at 1.

160 *Id*. at 2.

161 *Ex parte* Chamberlain ("Chamberlain II"), No. 2022-001944, at 1 (P.T.A.B. May 21, 2024).

162 *Id*. at 31–33.

VI. CONCLUSION

I am not concluding that it is only possible to achieve full scope enablement and full scope written description in the unique situation of *Chiron v. Genentech;* that is, after the discovery of a novel and unbeknownst biological target not yet in the prior art. When a new target is discovered, it should be possible under *Chiron* to put forth a *per se* antibody genus claim with no requirements other than a binding definition. The chances of survival of such a genus claim are higher than if the claim has blocking or biological requirements, such as in *Amgen* 2021/2023, *Baxalta,* or *Alonso.*

But even if a *Chiron*-like situation is narrow, the discovery of a new target and its applications are precisely the kind of circumstances that I discussed in the introduction. A new target is a major contribution to medicine and should be rewarded by more than a patent drawn to one or a few narrowly claimed specific antibodies.

If a discovery is made that blocking a known target leads to a heretofore unbeknownst new method of therapy, then, following the formats in *Hopkins v. Cellpro* and *Immunex v. Sanofi,* antibodies can still be claimed in *per se* form using a *Markush*-type format. The claims should include a binding definition plus a competitive binding requirement against a reference antibody. The reference antibody can either be deposited in a cell depository, as in *Hopkins,* or it can be sequenced, as in *Immunex*. Such claims should not include biological or blocking functions. They will therefore be akin to immunoassay claims, which with modern automated screening techniques are more readily enabled than therapy-related claims.

I am also not concluding that a genus claim with multiple requirements such as that in *Centocor v. Abbott* would never pass muster under 35 U.S.C. § 112(a). If such a claim complied with the *Wands*+/*Capon*+ factors, the claim could survive a challenge. It would help if, as in *Invitrogen, Ajinomoto,* and *BASF,* the state of the art is advanced and can be enlisted to demonstrate additional examples or a common structure-function correlation.

Finally, if the scope of the claim is not too large, the skill high, the guidance detailed, the amount of experimentation reasonable, the enablement and written description are of the whole field and not just of a corner, and a common quality can be surmised, then antibody-related genus claims including biological or blocking functions might be obtainable and defendable. If this sounds like a Goldilocks scenario, it is indeed one that appears hard to meet.

Yet the problems with narrow patents have not disappeared: they still allow free-riders to take advantage of fundamental target discovery by others and to avoid such patents by simple design-around. It therefore behooves a

practitioner who wishes to protect target-related discoveries by broad antibody patents to include all sorts of antibody claim formats into their filings. These should include *Markush*–type claims with competitive inhibition requirements, and claims in means-plus-function formats. I also hope that, if possible, our practitioner not stop at the USPTO, but take the case to the Federal Circuit. The times call for being cautiously creative and experimenting with new approaches to antibody-related genus claims.