

ANTIBODY PATENTS: USE OF THE WRITTEN DESCRIPTION AND ENABLEMENT REQUIREMENTS AT THE PATENT & TRADEMARK OFFICE

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ABSTRACT

Antibody patents form the basis of some of the most valuable biotechnology products on the market. In 2020 alone, sales of the top three drugs exceeded \$49.5 billion dollars. Two of those three drugs are monoclonal antibodies (Humira and Keytruda). In the past, patent law offered broad protection for monoclonal antibodies. As time has progressed, however, courts have narrowed the scope of antibody patents. Yet, very little research has been done to see how patent examiners are applying the rules of patentability to these valuable antibody patents.

We examine approximately two decades worth of antibody patents to determine how the US Patent Office has dealt with them. Specifically, we examine a sample of every patent directed to an antibody composition of matter from 2001–present. We find that patent examiners have steadily increased the use of 35 U.S.C. § 112(a) enablement and written description rejections while slightly decreasing the use of anticipation and obviousness rejections. These data suggest that § 112(a) plays a greater role in policing claim scope than prior art rejections, which is the most frequently used rejection type for every other technology center. Correspondingly, patent applicants have also adjusted their claim drafting, moving from broad claims based only on function to narrow claims based on antibody structure.

We also find that the number of antibody composition patents has dramatically increased, while the number of claims per patent has decreased. Additionally, the number of words in each independent claim has increased threefold. These data present an interesting evolution for antibody patents that mirrors the changing nature of antibody technology and offers some insights for improving antibody patent prosecution.

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I. INTRODUCTION

Antibody patents are associated with some of the most valuable drugs in the world. In 2021, two of the top three highest-selling drugs were monoclonal antibodies (Humira and Keytruda), bringing in billions of dollars in sales. During the same year, four of the top six drugs were monoclonal antibodies, taking home a staggering \$54.4 billion.¹ As biologics overtake small molecules² as the world’s most valuable drugs, antibody patents play an increasingly important role for drug companies, health insurance companies, and consumers.

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

This shift in scope has been shown by courts recently invalidating claims with broad scope. For example, the Federal Circuit recently overturned a \$1.2 billion jury verdict on a biotechnology patent based on antibody type technology, finding the asserted claims too broad and thus invalid under the written description requirement.³ This narrowing of antibody claims is likely not due to obviousness or anticipation rejections because courts and the United States Patent and Trademark Office (USPTO) do not use 35 U.S.C.

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

2. Small molecules are chemical compounds that have low molecular weights. Small molecules typically contain only 20–100 atoms. Examples of small molecules include aspirin, penicillin, or esomeprazole. In contrast biological drugs are large, complex drug molecules that are manufactured from living organisms. Biologics are typically larger in size with a single molecule consisting of 200–50,000 atoms. Examples of biologics include insulin, vaccines, and monoclonal antibodies.

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

§ 102 or § 103 rejections⁴ to invalidate or prevent antibody patents from issuing.⁵ This is interesting because for all other technology centers, we see that § 102 and § 103 are the primary mechanisms that examiners use to reject subject-matter eligible patents⁶ and also the primary mechanism that courts use to invalidate patents.⁷

Changes in technology always move faster than changes to the law. Courts are constantly playing a game of catch up to new technological developments. In the patent realm there is an added layer of review by the USPTO. Changes to USPTO policy occur even slower than courts because the USPTO must respond to court decisions, usually in the form of guidance documents and/or examiner training materials. Accordingly, changes to patent policy at the prosecution level should, in theory, lag behind changes in the law.

Surprisingly, our data show that patent examiners at the USPTO have been independently applying a higher standard of review for antibody patents even before the USPTO put out specific guidance and far before current Federal Circuit caselaw. Specifically, patent examiners were increasingly using the enablement and written description requirements for biotechnology patents long before courts began applying an enhanced 35 U.S.C. § 112(a) requirement.

For most areas of technology, prior art rejections are the most difficult hurdles that applicants must overcome to obtain a patent. However, antibody patents face a very different challenge. Specifically, lack of enablement and not meeting the written description requirement seem to be the most difficult hurdles to overcome for antibody composition of matter claims.⁸ These types

4. 35 U.S.C. § 102 is the novelty requirement and is based on the idea that a patent applicant cannot receive a patent to an invention that has already been disclosed in the prior art. 35 U.S.C. § 102 requires that each and every element of the claim be disclosed in only one prior art reference. In contrast, 35 U.S.C. § 103 is based on the idea that obvious variations to an invention should also not be patentable. 35 U.S.C. § 103 allows multiple references to be combined to disclose each and every element of the patented invention. *See* S. Sean Tu, *Patenting Fast and Slow: Examiner and Applicant Use of Prior Art*, 38 CARDOZO ARTS & ENT. L.J. 391 (2020).

5. *See infra* Figure 4.

6. *See infra* Figure 4.

7. *See generally* S. Sean Tu, *Patent Examiners and Litigation Outcomes*, 17 STAN. TECH. L. REV. 507 (2014); *see also* S. Sean Tu, *Invalidated Patents and Associated Patent Examiners*, 18 VAND. J. ENT. & TECH. 135, 159 (2015).

8. 35 U.S.C. § 112(a) encompasses both the “written description” and enablement requirements. Before the America Invents Act, § 112(a) was referred to as “§ 112 first paragraph.” 35 U.S.C. § 112(a) requires that an inventor’s disclosure in the specification of the application must be sufficiently complete to enable a “person having ordinary skill in the art” to make and use the invention without having to engage in an undue amount of experimentation. These two standards are distinct, but closely related. *See* Ariad Pharms., Inc.

of challenges that are rare in most other technology areas are common for antibody technologies.

We argue that the enhanced § 112(a) standard applied by examiners is keyed more towards changes in antibody technology and less towards changes in the law. As antibody technology changed from being primarily used as a diagnostic tool to a therapeutic drug, patent examiners quickly adjusted to the technology by rejecting those broad antibody claims for lack of enablement and/or the necessary written description requirements.

Most USPTO examiners do not have a legal background, but all examiners are required to have a technical background. These data support the idea that patent examiners were able to respond to changes in technology well ahead of any formal guidance from the USPTO and the courts. In fact, for a long period of time, examiners seem to have been applying a stricter standard than that set forth in Federal Circuit precedent. By applying this stricter standard for written description and enablement *in response to changes in the technology*, patent examiners narrowed antibody claims to give exclusive rights to only those narrow claims that are supported by the disclosure of the specification. In this way, although the claims are narrower, they avoid invalidation via anticipation and obviousness arguments.

II. ANTIBODY TECHNOLOGY

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

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

v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010) (en banc). The quid pro quo behind patent law requires that the inventor notify the public of the metes and bounds of the property interest by writing “claims” that notify the public of the exact contours of the property interest covered by the patent. *See* John R. Allison & Lisa Larrimore Ouellette, *How Courts Adjudicate Patent Definiteness and Disclosure*, 65 DUKE L.J. 609, 617 (2016).

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

In Part III, we discuss the databases that were created for this study. In Part IV we present our results. In Part V we present how these results fit within § 112(a) jurisprudence. Finally, in Part VI, Professor Tu offers policy recommendations and critiques the current state of antibody patents based on our findings.⁹

III. THE DATASETS

We created three unique datasets for this study.¹⁰ The goal of this study was to determine whether antibody claims experience a different prosecution history compared to other biotechnology patents.

A. THE ANTIBODY DATASET

The first dataset comprises of over 6,000 patents containing antibody composition of matter patents (hereinafter *antibody dataset*). These patents had filing dates ranging from November 29, 2000 to June 1, 2021 and issue dates from June 18, 2002 to August 3, 2021.¹¹ These data were obtained from the USPTO's Public Web-based Examiner's Search Tool (PubWEST) through the Patent and Trademark Resource Center (PTRC).

Our initial search included every patent with the term “antibody” within the claim (over 46,000 patents). However, after reviewing the claims of numerous patents, we determined that the dataset was too broad for our purposes and included many patents that were only tangentially related to antibodies. Accordingly, we used a title search using the term “antibod\$” which resulted in 15,285 patents. We then reviewed the titles of these patents to determine if the patents truly represented antibody composition of matter

9. S. Sean Tu is the sole author of Part VI and all opinions in Part VI should be solely attributed to him.

10. S. Sean Tu's pertinent credentials are: B.S. in Microbiology and B.S. in Chemistry, University of Florida; Ph.D. in Pharmacology, Cornell University; Post-Doctoral Fellow, La Jolla Institute for Allergy and Immunology; Associate with Foley & Lardner (Chemical, Biotechnology & Pharmaceutical Practice/Life Science and Nanotechnology Industry Team). Christopher Holman's pertinent credentials are: B.A. in Chemistry, California State University, Hayward; Ph.D. in Biochemistry and Molecular Biology, University of California, Davis; Post-Doctoral Fellow, Syntex Research/Roche Bioscience; Patent Agent with Flehr Hohbach, LLP; Associate with Pennie & Edmonds, LLP; Associate Patent Counsel with Transgenomic, Inc.; Patent Counsel with Maxygen, Inc.; Vice-President, Intellectual Property with PhyNexus, Inc.

11. These filing dates correspond to the instant patents and do not represent the “earliest priority date” of the patents. However, as shown in Table 1 *infra*, approximately half of these patents were original patents, and thus the filing date for approximately half of the patents also represents the earliest filing date.

type subject matter. After liberally removing those patents not related to antibody composition of matter claims, we were left with 6,407 patents. To ensure consistent coding, a sample of 400 random patents were taken and reviewed by both authors. Review of the 400 random patents resulted in over 90% consistency in classification coding (inclusion or exclusion of non-composition of matter claims). The claims of these 400 random patents were also reviewed to confirm that they were antibody composition of matter claims. Our goal was not to identify every antibody composition of matter patent, but simply to create a dataset that was mostly limited to antibody composition of matter claims.¹²

The antibody dataset consists of mainly antibody composition of matter claims. Specifically, we attempted to eliminate those patents with only claims directed to drug conjugates, pharmaceutical compositions, methods of use, treatment claims, antibody libraries, polyclonal antibodies, transgenic mice used to produce antibodies, kits with antibodies, and expression vectors. We retained patents directed towards antibodies of any isotype (IgE, IgA, IgD, etc.), humanized and chimeric antibodies, bispecific antibodies, antibody fragments, nucleic acids encoding specific antibodies, neutralizing antibodies, engineered antibodies, and recombinant antibodies.

All the data have been grouped by the *first office action date*. This metric is more accurate than the filing date because prosecution dates can change dependent on the examiner's docket and the backlog of patents at the patent office. Accordingly, filing dates can be deceptive because examiners may not pick up the application for long periods after the PTO receives the application. For example, U.S. Patent No. 6,770,466 has a filing date of July 18, 2001.¹³ However, the first office action did not occur until June 12, 2003, about two years after the filing date. Therefore, using the first office action date better reflects the state of the law at the time the application was under review by the PTO.

B. THE 1650 CONTROL GROUP DATASET

A second data set was generated to act as a control group (hereinafter *1650 control group*). The 1650 control group includes patents directed towards

12. Several other search strategies failed to result in a dataset of enriched antibody composition of matter claims. Failed searches were based on similar searches directed towards the abstract, summary of the invention, claims, as well as CPC codes.

13. U.S. Patent No. 6,770,446 (issued Aug. 3, 2004).

“fermentation, microbiology, isolated and recombinant proteins/enzymes.” This dataset consisted of over 92,000 patents from Workgroup 1650.¹⁴

Workgroup 1650 was chosen as a control because many of the characteristics of the patents found in workgroup 1640 (the workgroup associated with most antibody patents) could also be found in workgroup 1650. Specifically, many of the traits found in recombinant proteins and recombinant enzymes are similar for antibody claims. For example, recombinant enzymes exhibit functional attributes that are tied to specific structural elements. Similarly, therapeutic antibodies exhibit functional characteristics based on the specific antibody Complementarity Determining Regions (CDRs).¹⁵ Additionally, only nine of the 6,408 antibody patents were found in workgroup 1650, so the overlap between these two datasets is minimal.

Similar to the antibody dataset, the 1650 control group was organized chronologically by the first office action date.

C. THE CLAIM TYPE DATASET

A third data set was generated to examine claim type (hereinafter *claim type dataset*). We randomly sampled 340 independent patent claims from the antibody dataset. We reviewed 20 independent antibody claims (“Claim 1”) from each year from 2002-2018. We determined if the antibody claim type was directed to an antibody as described: (1) by binding to a specific antigen (and giving the antigen description/epitope) or (2) structurally by its binding site or specific heavy chain/light chain sequences. Structural limitations were most frequently described as specific sequence identification numbers (“SEQ ID”). These SEQ ID numbers corresponded to either specific amino acid sequences or specific nucleotide sequences, usually corresponding to specific CDR regions.

Antibody claims can be very broad (based only on the description of the antigen) to fairly narrow (based on specific binding regions of the antibody along with a description of the antibody’s function or an antibody generated by a specific hybridoma cell line). In general, antibodies can be defined by: (1) reference to the target antigen; (2) the epitope; (3) target antigen and further antibody functional features; (4) antibody and structural features; (5) their own

14. As shown in Section III.C, *infra*, most antibody patents come from Workgroup 1640. Workgroup 1650 was chosen as a control group because this workgroup encompasses patents directed to “Fermentation, Microbiology, Isolated and Recombinant Proteins/Enzymes.” Workgroup 1650 contains many of the same types of issues present in Workgroup 1640, which is directed to “Immunology, Receptor/Ligands, Cytokines Recombinant Hormones, and Molecular Biology.”

15. For a deeper discussion of CDRs, see *infra* Appendix 1.

structure (amino acid sequences); (6) antibody nucleic acid sequences encoding the antibody; (7) the antibody production process; and/or (8) the hybridoma producing the antibody. In general, this list is ordered from the broadest to the narrowest type of antibody claims.

The broadest patents usually claim antibodies by only referencing the target antigen, without reciting any structural elements for the antibody.¹⁶ In contrast, the narrowest claims reference only the hybridoma that is used to produce the specific antibody, thus giving the complete antibody structure and the means to produce the antibody.¹⁷ In the claim type dataset, we consolidate antibody definitions 1–3 together (antibody defined by antigen structure and no antibody structure) and 4–7 together (antibody defined by its own structure).

D. DATA LIMITATIONS

Because we are working with issued patents, there is a selection issue for recently granted patents with first office action dates of 2019, 2020, or 2021. Specifically, recently filed patents will always have much shorter prosecution histories simply because they have been reviewed by the USPTO and issued very recently. Thus, many of these more recent patents have prosecution histories that are not representative of most patents. Specifically, these patents usually come from large patent families which exhibit anomalous prosecution histories. To minimize this selection effect, we excluded all patents with first actions that occurred after 2019.

IV. RESULTS

First, we find that antibody patents experience many more § 112(a) rejections compared to similar technology. Second, we find that antibody claims have shifted from broad functional claims defined by the antigen to narrower claims defined by the antibody structure. Third, there was a fivefold increase in the number antibody patents granted with a significant decrease in the number of independent claims per patent. Finally, the number of words

16. An example of this broad claim would be, “An antibody that specifically binds X.” *See, e.g.*, U.S. Patent No. 7,060,800 col. 185 (issued June 13, 2006).

17. An example of this narrow claim would be, “A hybridoma cell line deposited as ATCC Accession Number X.” *See, e.g.*, U.S. Patent No. 7,547,544 col. 62 (issued June 16, 2009). The hybridoma cell line claims are usually the least valuable to firms because they are relatively easy to design around. Specifically, if a competitor develops an independent hybridoma cell line, even if the competitor’s hybridoma cell line produces a very similar mAb to the patented hybridoma cell line, it will not infringe the patented cell line.

per independent claim increased from 2002–2018, which also suggests a narrowing of antibody claims over time.

A. CHANGES IN ANTIBODY CLAIMS

Antibody claims and the rejections that patent examiners apply to allow those claims have shifted dramatically from 2002–2018. Three areas of greatest changes are: (1) increased use of § 112(a) rejections, (2) applicants responding by narrowing their claims by adding structural elements that define the antibody, thus changing the type of antibody claims from functional to structural claims, and (3) increased number of words necessary to claim the invention.

1. *Increased Number of Written Description/Enablement Rejections*

Patent examiners for antibody technology have dramatically increased their use of the written description and enablement rejection. Figure 1¹⁸ shows that from 2003–2006 antibody patents initially received 112(a) rejections only about 20% of the time, almost doubling to 40% by 2018.¹⁹

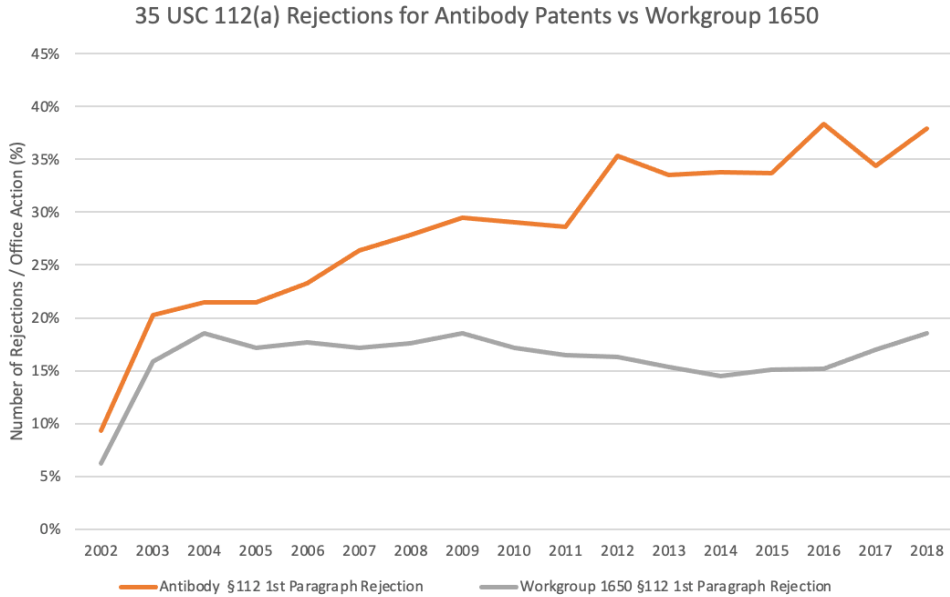
A 10-20% rejection rate based on 112(a) is typical of biotechnology patents.²⁰ As shown in Figure 1B, the 1650 control group does not show a discernible increase in § 112(a) rejections over the same time period. Accordingly, examiners in the 1650 control group only used § 112(a) rejections in the 1650 control group about 20% throughout 2002–2018.

18. These data have been segmented to show the percentage of first office actions with 35 U.S.C. § 112(a) rejections. However, these data are representative of both non-final and final office actions. *See* Appendix 2A and 2B.

19. 35 U.S.C. § 112(a) rejections include both written description and enablement rejections. These two rejections have been cojoined because examiners and applicants often confuse/conflate these two doctrines even though they are separate and distinct requirements. *See, e.g.*, Ex Parte Kim stating, “To the extent the Examiner’s rejection implicates the *enablement* requirement of that statute, we decline to speculate in that regard here, for the rejection is based solely on the claimed invention’s failure to comply with *the written description* requirement, not the *enablement* requirement which is a separate and distinct requirement under § 112.” U.S. Patent Application 15/369,177 BPAI opinion dated April 21, 2022 (emphasis in original); *see also* Ex Parte Palmer stating, “§ 112, first paragraph, contains a *written description requirement separate from enablement*. . . the rejection here, however, is for lack of adequate written description, *not* lack of enablement.” U.S. Patent Application 15/790,961 BPAI opinion dated April 4, 2022 (emphasis in original); *see also* Dennis Crouch, *Enablement at the USPTO*, PATENTLYO (Apr. 25, 2022), <https://patentlyo.com/patent/2022/04/enablement-the-uspto.html>; *see also* Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010).

20. *See infra* Figure 4 showing that rate of 112(a) rejections for all technology types is typically below 10%; *see also infra* Figure 1 showing that patents from Workgroup 1650 examiners typically use 112(a) in approximately 20% of their office actions.

Figure 1



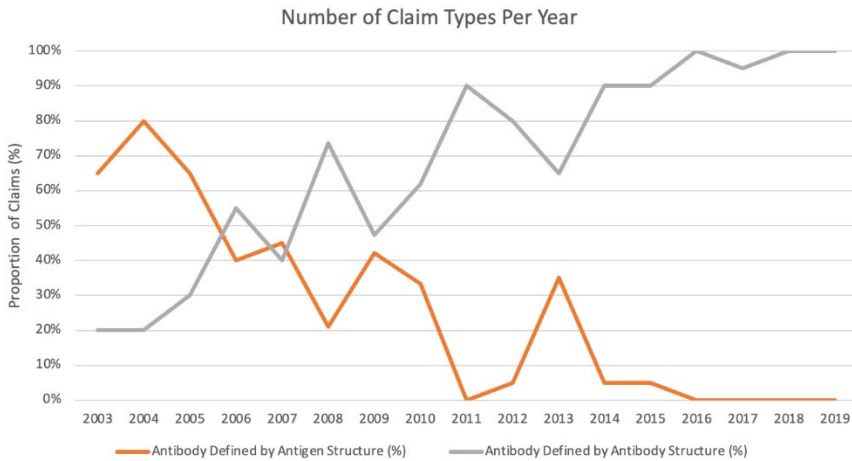
2. *Change in Type of Claims*

The way antibody claims are drafted has also dramatically changed from 2003 to 2019.²¹ As shown in Figure 2, in the early 2000s, approximately 70% of the claims were directed to antibodies that were defined only by their antigen or epitope, while about only 30% were defined by structural elements (usually given by the exact amino acid sequence of the six CDRs or the full light chain/heavy chain sequence). By 2011, we saw almost a complete switch. In 2011, almost no antibody claims were characterized only by their antigen binding site, and by the late 2010s, almost 100% of the claims were completely defined by their structural elements.²²

21. These data were based on the 340 patents from the Claim Type Dataset described *supra* in Section III.B.

22. See Examples 1, 2 and 3 *infra* in Section V.A for examples of claim language evolution.

Figure 2



This change in the types of antibody claims allowed by examiners mirrors the increase in the number of words in each claim²³ as well as the increased use of § 112(a) rejections.²⁴ That is, we see a shift from broad antigen-based functional claims to narrow structural claims in the same time frame in which applicants increase the number of words in their independent claims as well as an increase in the examiner's use of § 112(a) rejections.

Currently patent examiners do not allow broad antibody claims described only by the antigen. Thus, antibody patents are much narrower because applicants must describe specific structures that correspond to the antibody they are attempting to claim and can no longer claim antibodies based solely on their function (binding to their specific antigen).

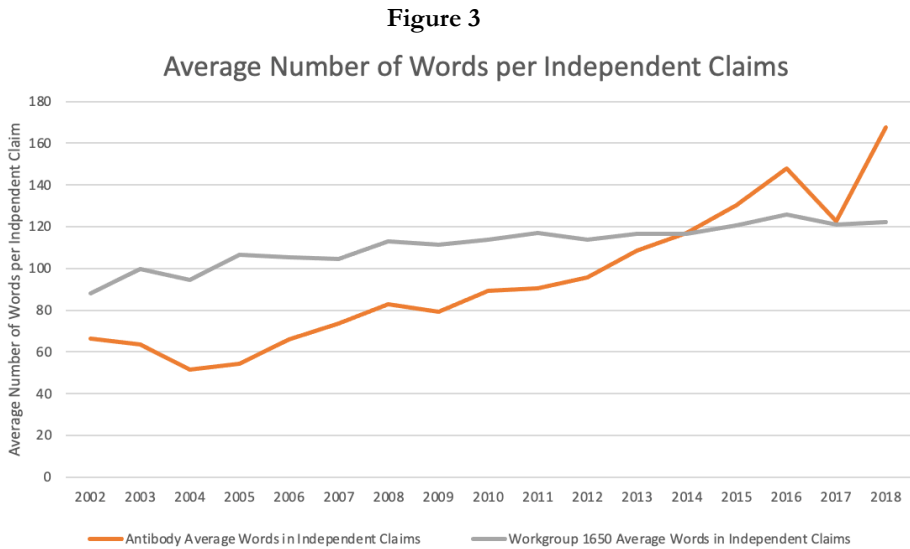
3. *Increase in the Number of Words Per Independent Claim*

In response to the increase in § 112(a) rejections, applicants have been adding more words to their claims. As shown in Figure 3 (orange line), the number of words in each independent antibody claim has almost tripled from 2002 to 2018.²⁵

23. *See supra* Section IV.A.3.

24. *See supra* Section IV.A.1.

25. These data were based on the 6,407 patents from the Antibody Dataset described in Section III.A.



B. ANTIBODY PATENT REJECTIONS

Antibody patents differ not only from other patents in Technology Center 1600 (TC 1600), but also from many other technology types. We compare antibodies against all other technology centers. Additionally, we review how examiners use prior art rejections against antibody patents.

1. *Antibody Claims in Comparison to Other Technologies*

The prosecution histories and rejections used for antibody claims are different from almost every other Technology Center.²⁶ We compared antibody patents with a first office action in 2018 against patents from all other technology centers. Figure 4 shows that antibody patents do not receive many anticipation (35 U.S.C. § 102) or obviousness (35 U.S.C. § 103) rejections compared to any other Technology Centers (TC).²⁷ Furthermore, antibody

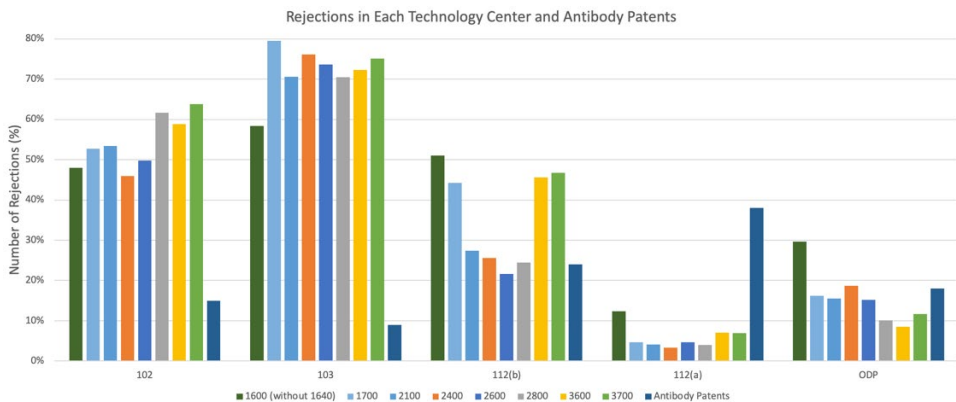
26. Technology Center 1600 includes all patents except those from Workgroup 1640. Workgroup 1640 was excluded out because most antibody patents come from Workgroup 1640, which significantly skewed the results. Workgroup 1640 is the workgroup that contains almost all antibody composition of matter claims, and thus are largely captured in the “antibody patent” segmented data. *See infra* Part II (Figure 7, showing the distribution of all antibody composition of matter patents). For example, Workgroup 1640 alone represents 24% of all 35 U.S.C. § 112(a) rejections from Technology Center 1600 (Figure 4).

27. This includes TC 1600 Biotechnology and Organic Chemistry; TC 1700: Chemical and Materials Engineering; TC 2100 Computer Architecture, Software, and Information Security; TC 2400 Computer Networks, Multiplex Communication, Video Distribution and Security; TC 2600 Communications; TC 2800 Semiconductors, Electrical and Optical Systems and Components; TC 3600 Transportation, Construction, Electronic Commerce, Agriculture,

patents receive fewer indefiniteness rejections (§ 112(b)) compared to TC 1600 (without 1640), 1700, 3600, and 3700. Also, antibody patents receive about the same percentage of Obviousness Type Double Patenting (ODP) rejections. Finally, antibody patents receive the highest number of enablement and written description rejections (§ 112(a)) with about four times as many rejections as the next highest TC.

These data show that § 112(a) is the biggest hurdle to overcome antibody patents. This is surprising because for every other technology group, obviousness is the principal obstacle to receiving a patent.

Figure 4²⁸



2. Other Substantive Rejections and Antibody Patents

Figures 4 and 5 show that antibody patents do not regularly encounter prior art rejections.²⁹ When compared to other patents from other technologies, antibody patents face substantially fewer prior art rejections. Other patents in Technology Center 1600, which examines patent applications in the fields of biotechnology and organic chemistry, face obviousness

National Security and License & Review; TC 3700 Mechanical Engineering, Manufacturing, Products; TC 4000 Training Academy.

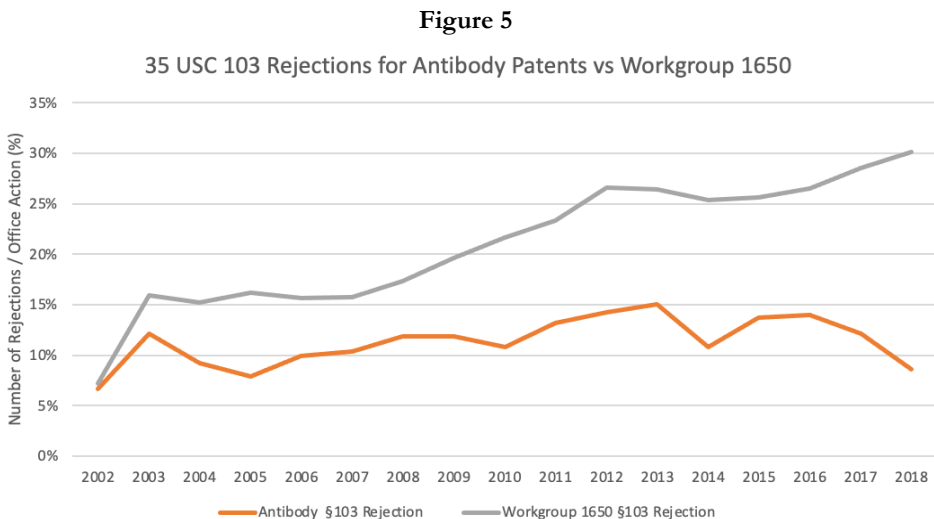
28. Technology Center 1600 includes all patents except those from Workgroup 1640. Workgroup 1640 was excluded out because most antibody patents come from Workgroup 1640, which significantly skewed the results. Workgroup 1640 is the workgroup that contains almost all antibody composition of matter claims, and thus is largely captured in the “antibody patent” segmented data.

29. Figure 5 data have been segmented to show the percentage of first office actions with 35 U.S.C. § 103 rejections. However, these data are representative of both non-final and final office actions. *See infra* Appendix 3A and 3B.

rejections approximately five times more frequently than antibody patents (Figure 4). This is significant because obviousness prior art rejections are usually the most difficult rejections to overcome during prosecution and litigation.³⁰

Additionally, as shown in Figure 5, the number of obviousness rejections (§ 103) in the 1650 control group steadily increases to about twice the number (25–30%) found in the antibody group, which stays at around 10–15%. This is interesting because most of the time when a technology type evolves, the art becomes more crowded and more inventions in the same technology group become obvious over prior art. This is not true for antibody patents, which seem to have a steady state for obviousness rejections. In contrast, the 1650 control group does follow the expected trend of increased obviousness rejections as we move through time.

This trend for obviousness rejections (§ 103), however, does not translate to novelty rejections (§ 102). Both the antibody group and the 1650 control group experience approximately a 20% rejection rate based on § 102.³¹



Antibody patents and the 1650 control group encounter indefiniteness (§ 112(b)) and obviousness-type double patenting (ODP) rejections (35 U.S.C.

30. See S. Sean Tu, *supra* note 4; see also S. Sean Tu & Mark A. Lemley, *What Litigators Can Teach the Patent Office About Pharmaceutical Patents*, 99 WASH. U. L. REV. 1673 (2022) (Figure 6 showing that when an Orange Book patent is invalidated, it is usually done based on obviousness arguments.).

31. See *infra* Appendix 4.

§ 101) at approximately the same rates.³² These data are unsurprising because both antibody patents and 1650 control patents have fewer claims with an increasing number of patents filed per year (Figure 8 and Figure 9). The ODP rejection data suggest that applicants are filing more patents relating to the same product, which seems to be a common strategy in this sector.³³

3. *Allowance Rates of Antibody Patents*

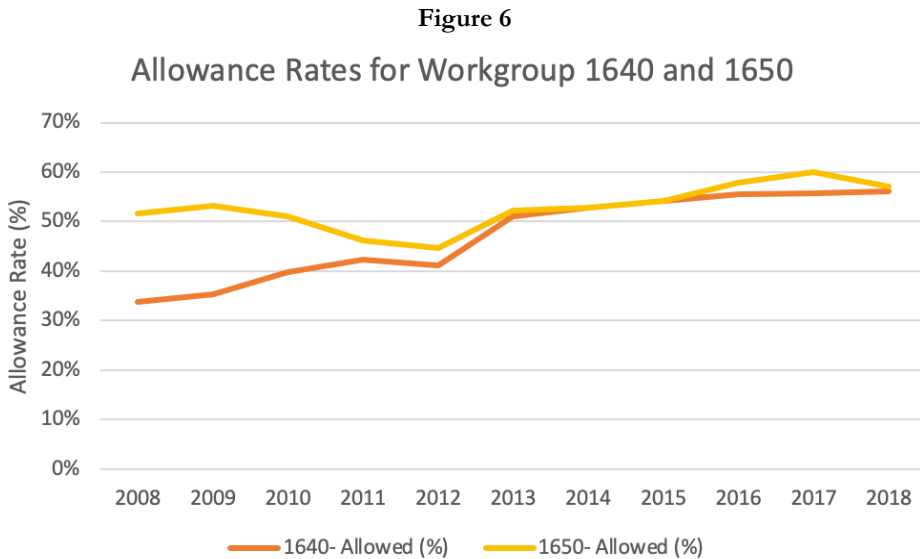
As shown in Figure 6, from 2008–2010, there was a lower allowance rate (32% as compared to 52%) for Workgroup 1640 patents compared to Workgroup 1650.³⁴ However, that difference quickly diminished from 2011–present. Currently, the overall allowance rates of patents from Workgroup 1640 do not differ dramatically from Workgroup 1650. These allowance rates correspond with the increased use of § 112(a) rejections as well as the change in antibody claims from claims based on antigen structure to claims based on antibody structure.³⁵

32. See *infra* Appendix 5 and 6 for comparison of antibody versus 1650 control 35 U.S.C. § 112(b) and ODP rejections respectively.

33. Tu & Lemley, *supra* note 30, at 1702 (showing that, for litigated Orange Book patents, pharmaceutical firms file numerous “secondary” patents directed towards the same product, and that the obviousness-type double patenting rejection is one of the most common rejections found for these types of patents); see also Robin Feldman, *May Your Drug Price be Evergreen*, J.L. & BIOSCIS. 590 (2018).

34. We used Workgroup 1640 as a proxy for antibody patents because most antibody patents come from this workgroup. Additionally, because the antibody patent dataset contains only allowed antibody patents, our dataset did not include those antibody applications that did not mature to patents.

35. See *supra* Figures 1 and 2.



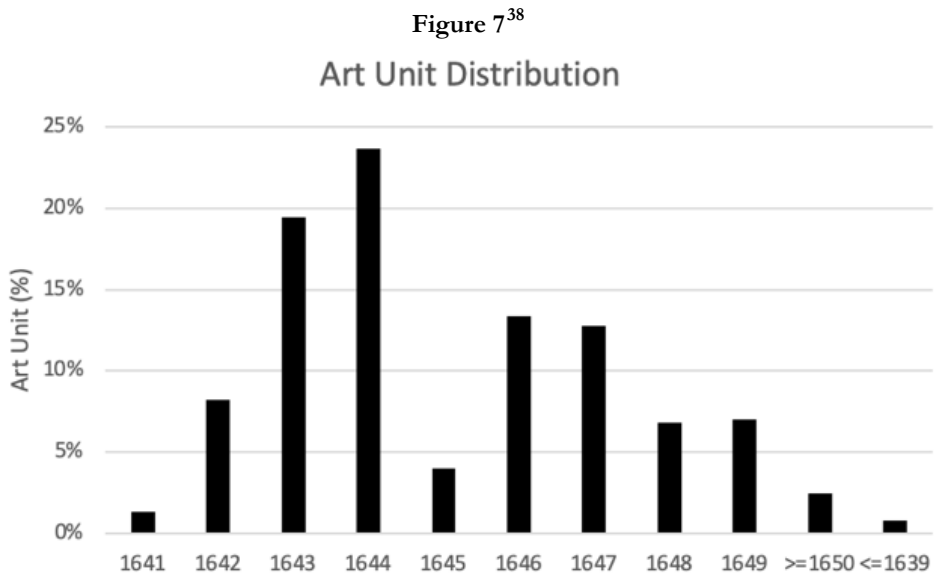
C. CHANGES IN ANTIBODY PATENT PROSECUTION PRACTICE

There have also been several important changes in prosecution practice that have also evolved in the past two decades. First, applicants have increased the number of antibody patents they file over time. Second, there has been a decrease in the number independent claims per patent over time. Finally, antibody patents are going through prosecution faster than their older counterparts.³⁶

As an initial matter, 98% of the antibody patents were found in Workgroup 1640. Specifically, Figure 7 shows that Art Units 1643 and 1644 contained the lion’s share of antibody patents. Patents in Workgroup 1640 are directed to “Immunology, Receptor/Ligands, Cytokines Recombinant Hormones, and Molecular Biology.” Art Units 1643 and 1644 include inventions directed to “peptides or proteins, lignins or reaction products thereof” and “drug, bio-affecting and body treating compositions.”³⁷

36. This shorted prosecution time is not due to the backlog of examined patents. This is because we start our measurement from the date of the first office action and not the filing date.

37. USPTO, CLASSES ARRANGED BY ART UNIT (NOV. 2022), <https://www.uspto.gov/sites/default/files/documents/caau.pdf>.



1. Increasing Number of Antibody Patents

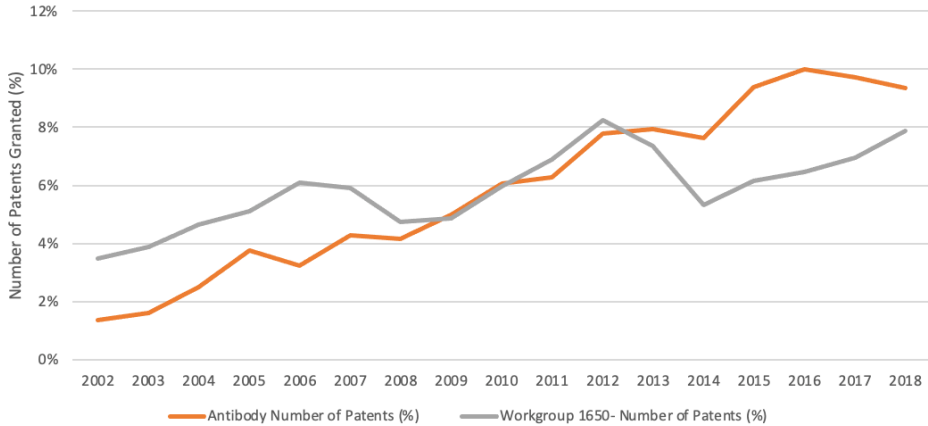
Figure 8 shows that the number of antibody composition of matter patents has steadily risen from only 75 granted (1% of total) with a first office action date in 2002 to a steady state of over approximately 500 antibody patents (10% of total) in 2018.³⁹ Unsurprisingly, as antibodies became increasingly used as therapeutics, and therefore more valuable, more firms moved towards the patent system to protect their inventions. There is a similar increase in the absolute number of patents in the 1650 control group. However, in the 1650 control group, we only see a twofold increase in the number of patents, while there is a fivefold increase in the antibody group.

38. Art Unit (AU) 1641 includes “Peptide or Protein Sequence”; AU 1642 includes “Drug, Bio-Affecting and Body Treating Compositions”; AU 1643 and 1644 include “Drug, Bio-Affecting and Body Treating Compositions” and “Chemistry: Natural Resins or Derivatives; Peptides or Proteins; Lignins or Reaction Products Thereof”; AU 1645 includes “Drug, Bio-Affecting and Body Treating Compositions” and “Chemistry: Molecular Biology and Microbiology”; AU 1646 includes “Drug, Bio-Affecting and Body Treating Compositions” and “Peptide or Protein Sequence”; AU 1647 includes “Drug, Bio-Affecting and Body Treating Compositions”; AU 1648 includes Drug, Bio-Affecting and Body Treating Compositions” and “Chemistry: Molecular Biology and Microbiology”; and AU 1649 includes “Drug, Bio-Affecting and Body Treating Compositions” and “Multicellular Living Organisms and Unmodified Parts Thereof and Related Processes.” <https://www.uspto.gov/sites/default/files/documents/caau.pdf> (last visited March 19, 2023).

39. These data were based on the 6,407 patents from the Antibody Dataset described *supra* Section III.A.

Figure 8

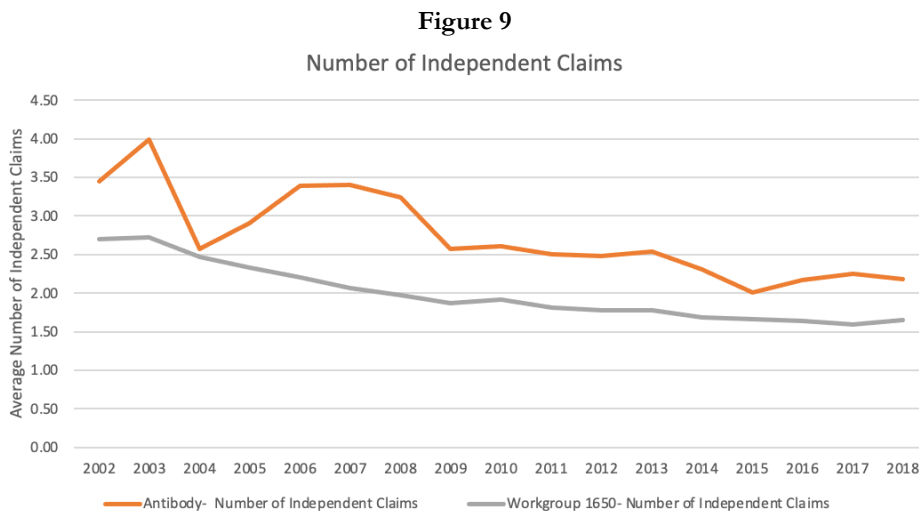
Number of Patents Granted



2. Fewer Claims Over Time

As shown in Figure 9, the number of independent claims in antibody patents has decreased from an average of about 3.5 claims in 2002 to just over two claims in 2018.⁴⁰ Thus, currently, more patents are being granted with fewer independent claims. Figure 9 also shows that the number of independent claims is reduced in the 1650 control group. However, the magnitude of the change is less dramatic, moving from approximately 2.5 independent claims in 2002 to just over 1.5 independent claims in 2018.

40. These data were based on the 6,407 patents from the Antibody Dataset described *supra* Section III.A.



3. Fewer Original Patent Filings Over Time Compared to the 1650 Control

As shown in Figure 10A, fewer “original” patents were granted early (2002–2005), but that number almost doubled over time.⁴¹ An “original” patent is defined as a patent that does not claim priority to another patent. Specifically, in 2002–2005 only approximately 30% of granted patents were original filings. However, by 2009–2018, the number of granted patents that were original filings increased to about 50%. In contrast, both divisional (“DIV”) and continuation (“CON”) patents, for the most part, stayed at approximately 20–25% while continuation-in-part (CIP) patents stayed at around 5% throughout 2006–2018.

In contrast, Figure 10B shows that, for the 1650 control, the number of granted patents that were original filings stayed constant at around 60% through 2002–2018. Additionally, DIVs and CONs stayed at around 15–20% while CIPs also stayed at around 5%.

41. These data were based on the 6,407 patents from the Antibody Dataset described *supra* Part III.A.

Figure 10A

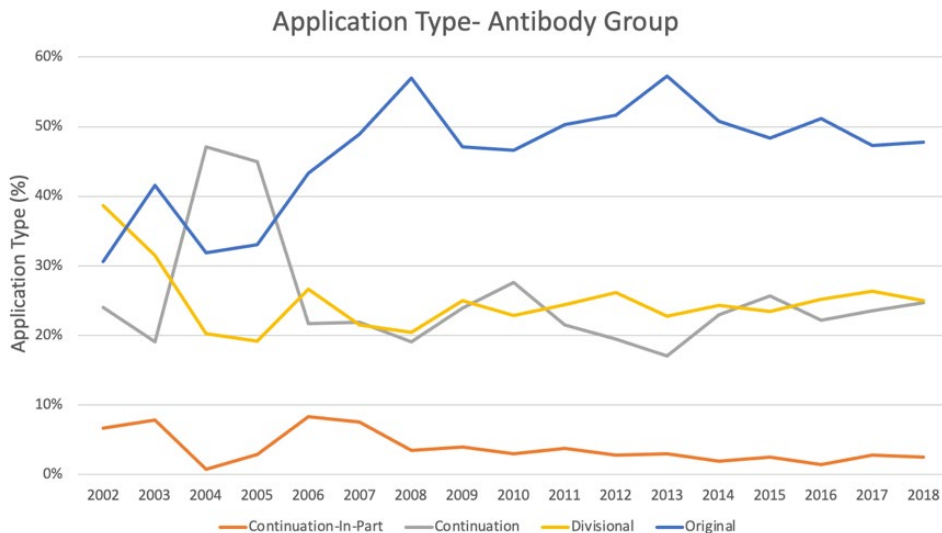


Figure 10B

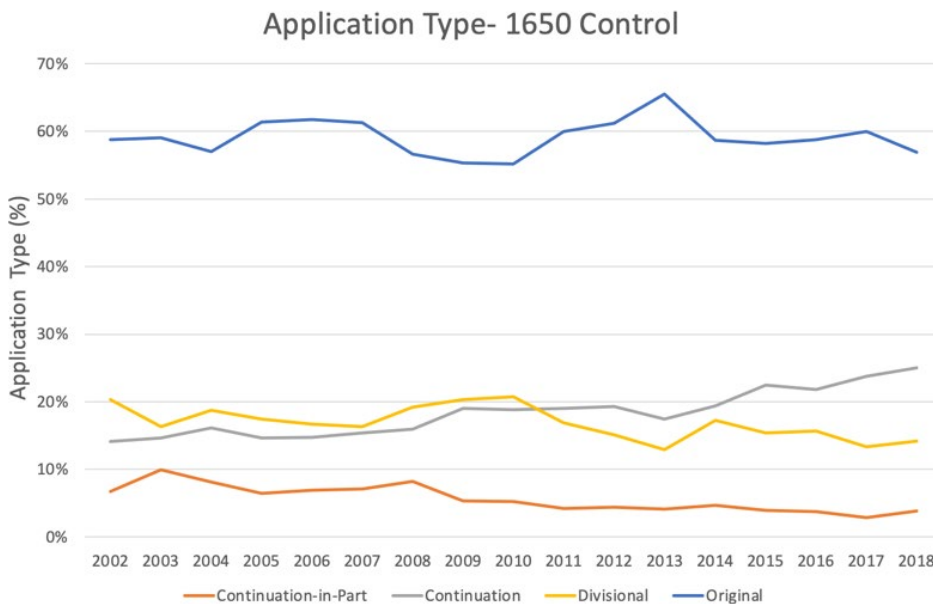


Table 1 shows the overall data where the data is not segmented by year. Additionally, Table 1 includes the percentage of applications with restriction requirements. These data show that antibody patents claim priority to another application and have fewer original patents compared to the 1650 control

group. Although the antibody dataset has more divisional patents, they experience about the same number of restriction requirements as the 1650 control group.

Table 1

	Antibody Dataset	1650 Control
Continuing Applications ⁴²	52%	41%
Continuation-in-Part Patents	3%	5%
Continuation Patents	25%	20%
Divisional Patents	24%	16%
Original Patents	48%	59%
Restriction Requirements	67%	63%

4. *Shorter Patent Prosecution Duration Over Time*

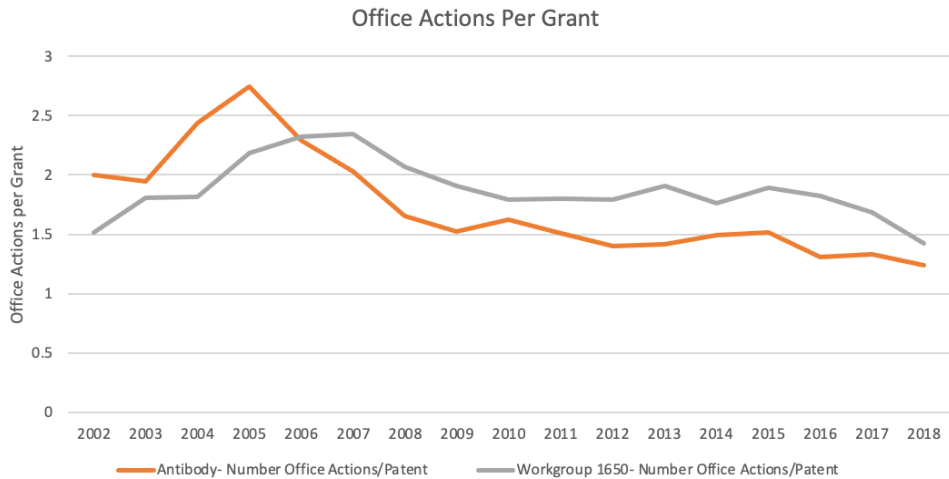
The patent prosecution profile has also changed for antibody patents over time. This shortened patent prosecution time is not due to the decreased backlog of patent applications. Rather, it is because we start measuring the prosecution duration from the date of the first office action and not the filing date of the application.

First, as shown in Figure 11 (orange line), the number of office actions per antibody patent has decreased from approximately 2.5 in the early 2000's to only 1.2 office actions per patent in 2016–2018. In contrast, as shown in Figure 11 (grey line), the number of office actions in the 1650 control group remains relatively steady at 1.8 office actions per patent throughout the 2002–2018 timeframe.⁴³ Thus, the back-and-forth negotiations between the examiner and the applicant for antibody patents are far fewer now than two decades ago.

42. A “continuing application” is a continuation, divisional, or continuation-in-part application. MPEP § 201.02.

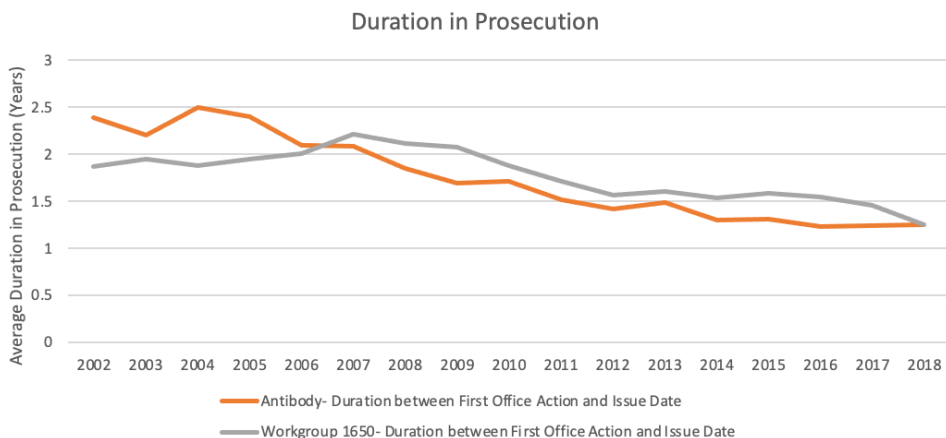
43. The number of Office Actions per Grant corresponds to the Office Action per Grant Ratio (OGR score). See S. Sean Tu, *Three New Metrics for Patent Examiner Activity: Office Action per Grant Ratio (OGR), Office Actions per Disposal Ratio (ODR), and Grant Examiner Ratio (GER)*, 100 J. PAT. & TRADEMARK OFF. SOC'Y 277 (2018); S. Sean Tu, *Bigger and Better Patent Examiner Statistics*, 59 IDEA 309 (2018).

Figure 11



This naturally corresponds to the duration of prosecution. Figure 12 (orange line) shows that in the early 2000's patent prosecution would customarily take about 2.5 years and fell to about only 1.2 years from 2016–2018. There is a similar decrease in patent prosecution duration in the 1650 control group, shown in Figure 12 (grey line). However, the magnitude of this decrease is much smaller for the 1650 control group, moving from about 1.8 years to 1.5 years.

Figure 12



V. DISCUSSION

The caselaw around antibody patents, specifically around the written description and enablement requirements, has evolved in the past two decades.⁴⁴ The PTO has attempted to track the changes in caselaw with their own guidance around antibody patents. In this Section, we interpret the empirical results by placing these results in the context of the time-dependent PTO policy and Federal Circuit caselaw on antibody patents.⁴⁵

A. CHANGE IN CLAIM TYPE

The increase in 112(a) rejections faced during prosecution supports the idea espoused by Judge Lourie, specifically that “[w]hat is new today is not the law, but generic claims to biological materials that are not fully enabled.”⁴⁶ These data are also consistent with findings by other commentators that non-ANDA pharmaceutical patents face higher invalidation rates based on § 112(a) during litigation.⁴⁷

Applicants have changed from broad functional genus claims defined by the antigen alone to narrower claims defined by the antibody’s structure (Figure 2). Below we describe the evolution of these claims and develop a hypothesis of how the changing nature and uses for antibodies resulted in a shift in antibody claiming practice.

44. For a complete discussion of the historical changes in USPTO policy and Federal Circuit jurisprudence on antibody patents, see S. Sean Tu & Christopher Holman, *Antibody Claims and the Evolution of the Written Description and Enablement Requirement*, IDEA (2022).

45. *See id.*

46. *Amgen Inc. v. Sanofi, Aventisub LLC*, 850 F. App’x 794, 795 (Fed. Cir. 2021) (also stating that, “in order to have invented a genus, one needs to have invented species that constitute the genus. Drawing a broad fence around subject matter, without filling in the holes, is not inventing the genus. It in fact discourages invention by others. If one has disclosed or enabled only a small number of invented species, then one has not invented a broad genus. Invention of a genus means to conceive and reduce to practice a reasonable number and distribution of species constituting the genus. Mere statement of a genus does not demonstrate that one has invented a generic concept, without the enablement of constituent species.”)

47. John R. Allison & Lisa Larrimore Ouellette, *How Courts Adjudicate Patent Definiteness and Disclosure*, 65 DUKE L.J. 609, 666 (2016) (Table 7 showing that non-ANDA pharmaceutical patents are the worst performers on written description of any industry); *see also* Jakob S. Sherkow, *Describing Drugs: A Response to Professors Allison and Ouellette*, 65 DUKE L.J. 127, 128 (2016). *But cf.* Dmitry Karshedt, Mark A. Lemley & Sean B. Seymore, *The Death of the Genus Claim*, 35 HARV. J.L. & TECH. 1, 4 (2021) (showing that only a small minority of Federal Circuit decisions have upheld a genus claim in the chemical industry over the past thirty years).

1. *Early Antibody Claims: Functional Antibody Claims Defined by Antigen Structure Only*

During this early period monoclonal antibodies were mainly used as research and diagnostic tools and not as therapeutic agents. These mouse antibodies were only used to determine if an antigen was present. It did not matter where the antibody bound, i.e., what the specific epitope was, nor the type of antibody. It only mattered if the antibody did or did not bind to the antigen.

This binary decision (binding vs. non-binding) was consistent with broad patent protection based on antigen structure alone because, during this time period, the value of the antibody rested primarily in the antibody's ability to bind and detect the antigen. Accordingly, during this early phase in monoclonal antibody development, an applicant could receive a broad functional patent by simply characterizing the antigen (without giving any structural elements of the antibody itself).⁴⁸

As shown in Figure 1, during this early stage, 112(a) was not used frequently to reject antibody patents. Additionally, as shown in Figure 2, during this time period, the majority of these antibodies were claimed by using functional language and only describing the antigen. These genus claims did not define the antibody structurally, but instead by defining the antigen that the antibody could bind to specifically. During this time period, we also see epitope claims (binding to a specific area of the antigen) and epitope claims with specific binding affinity requirements. The patentee was only required to disclose the antigen's structure. The resulting broad scope of antibody claims was logical during this period of antibody development because antibodies were being used primarily as research or diagnostic tools.

Example 1 is typical of an antibody patent during this timeframe. No antibody structure is given in the '800 patent. The antibody is only defined by the antigen (SEQ ID NO: 9). This claim is relatively short (only eighteen words) because it defines the antibody only by the antigen that it binds.

48. Tu & Holman, *supra* note 44; *see also* USPTO, WRITTEN DESCRIPTION TRAINING MATERIALS 4546 (2008).

Example 1 – US Patent No. 7,060,800⁴⁹

Claim 1: An isolated antibody or antigen binding fragment thereof, which specifically binds to a polypeptide of SEQ ID NO:9.⁵⁰

2. *Replacing Broad Genus Claims: Antibody Claims Defined by Antibody Complementarity Determining Regions (CDRs)*

During this period, monoclonal antibodies began to be used as therapeutic agents. However they faced many issues due to the human anti-mouse antibody (HAMA) response.⁵¹ Accordingly, these early therapeutics suffered major setbacks at the FDA and oftentimes did not work well as human medicines. For example, the mouse monoclonal antibody OKT3 was one of the first antibodies approved for the reversal of acute kidney, cardiac, and liver transplant rejection.⁵² However, OKT3 treatment was severely limited due to the HAMA response and the first dose reaction which caused side effects such as fever, chills, dyspnea, tachycardia, emesis, and diarrhea.⁵³

The USPTO and courts narrowed claims due to the new therapeutic uses for antibodies, as well as the realization that binding to different epitopes could have dramatically different functional effects on the body. Courts began to apply a stricter version of the *Lilly* written description requirement, requiring applicants to describe their antibodies using structure instead of function.⁵⁴ Antibody claims changed as the USPTO and courts began to reject and invalidate claims based only on antigen structure. Accordingly, during this time period, examiners began using § 112(a) more frequently to reject antibody claims that were directed towards functional genus claims and started forcing applicants to define antibody structures.

49. U.S. Patent No. 7,060,800 (issued June 13, 2006).

50. SEQ ID NO:9 is a human TNF-x protein that is 228 amino acids. U.S. Patent No. 7,060,800, col. 57–59 (issued June 13, 2006).

51. These negative effects are based on the fact that the human body recognizes the mouse antibody as foreign; *see also infra* Appendix 1 for deeper discussion of HAMA response.

52. *See* Bohua Li, Hao Wang, Jianxin Dai, Junjie Ji, Weizhu Quian, Dapeng Zhang, Sheng Hou & Yajun Guo, *Construction and Characterization of a Humanized Anti-Human CD3 Monoclonal Antibody 12F6 with Effective Immunoregulation Functions*, 116 IMMUNOLOGY 487, 488 (2005).

53. *See, e.g.*, Nadim Mahmud, Dusko Klipa & Nasimul Ahsan, *Antibody Immunosuppressive Therapy in Solid-Organ Transplant*, 2 MABS. 148, 151–52 (2010) (showing that OKT3's "adverse effects proved to be consistently problematic.").

54. Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1, 18–19 (2007); *see also* Tu, *supra* note 43.

In response to these rejections, applicants drafted and were issued claims that specifically defined the antibody based on structural elements.⁵⁵ These claims usually focused on the CDRs, which are the antibody structural elements that define the binding site of the antibody to the antigen.⁵⁶ There are six CDRs for each antigen receptor that can come into contact with the antigen. Each CDR binding site is usually defined by 3-15 amino acids. Thus, many antibody claims during this time period require at least 50–60 amino acids spread among the six CDRs (usually six individual SEQ IDs).

Example 2 is a typical antibody claim during this timeframe. The antibody CDRs are now given as the key structural elements that define the invention. These CDRs, however, are based on relatively short amino acid sequences. Accordingly, even with defined CDR structural elements, these antibody claims still can be broad.

Example 2 – US Patent No. 9,353,181⁵⁷

Claim 1: An isolated IL-23p19 antibody, comprising a light chain variable region and a heavy chain variable region, said light chain variable region comprising: a complementarity determining region light chain 1 (CDRL1) amino acid sequence of SEQ ID NO:50; a CDRL2 amino acid sequence of SEQ ID NO:56; and a CDRL3 amino acid sequence of SEQ ID NO:73, said heavy chain variable region comprising: a complementarity determining region heavy chain 1 (CDRH1) amino acid sequence of SEQ ID NO:5; a CDRH2 amino acid sequence of SEQ ID NO:28; and a CDRH3 amino acid sequence of SEQ ID NO:44.⁵⁸

3. Narrow Species Claims: Antibody Claims Defined by Complete Antibody Structure

Presently, many antibodies are defined by both their variable and framework (constant) regions. Accordingly, most antibody claims currently include an almost complete description of the entire antibody structure, and not just the CDR regions. It has also helped that technology has advanced so that it is much easier to obtain the protein sequence for larger molecular

55. *See supra* Figure 2.

56. CDRs are the crucial antibody structural elements that confer antibody specificity. *See infra* Appendix 1 for Antibody Technology primer.

57. U.S. Patent No. 9,353,181 (issued May 31, 2016).

58. SEQ ID Nos. 50, 56, 73, 5, 28 and 44 are 14, 7, 11, 5, 17, and 8 amino acids in length, respectively. *See* U.S. Patent No. 9,353,181, col. 93–117 (issued May 31, 2016).

entities such as antibodies. Previously it was time consuming and costly to obtain the primary structure of an antibody.

The current state of monoclonal antibody technology relies on chimeric antibodies and antibody “humanization” to overcome the deleterious effects of the HAMA response. By using recombinant DNA, scientists can now create an antibody that is mostly (or entirely) human. These chimeric and humanized antibodies are used for therapeutic purposes. Thus, for humanized antibodies, both the CDR structure as well as the framework structures are important. Unlike previous antibody iterations, however, the DNA structures are known for humanized antibodies. Accordingly, the primary structure of these antibodies can be well defined.

Example 3 – US Patent No. 10,822,397⁵⁹

Claim 1: An isolated antibody or epitope-binding fragment thereof that specifically binds to at least one conformational (non-linear) epitope of enterovirus 71 (EV71), wherein the antibody comprises at least one variable light chain and at least one variable heavy chain, wherein the variable light chain comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 3, and wherein the variable heavy chain comprises an amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 4 or SEQ ID NO: 5, wherein the antibody or epitope-binding fragment thereof is neutralizing.⁶⁰

Example 3 is a typical antibody claim during this timeframe. The claim contains an almost complete antibody structure. Both the heavy and light chains are structurally defined. Additionally, the amino acid sequences given are between 112–122 amino acids long. Furthermore, this antibody has the functional requirement of being “neutralizing.” Thus, these claims are much narrower because the structure of antibody is defined with much more specificity and includes additional functional requirements.

B. INCREASING USE OF § 112(A)

We find that antibody examiners have increased the use of § 112(a) to reject antibody patents since 2006 (Figure 1A).⁶¹ Additionally, § 112(a) is the

59. U.S. Patent No. 10,822,397 (issued Nov. 3, 2020).

60. SEQ ID Nos. 3, 4 and 5 are 112, 122, and 119 are amino acids in length, respectively. U.S. Patent No. 10,822,397, col. 33–35 (issued Nov. 3, 2020).

61. See *supra* Figure 1 (showing an almost 100% increase in the use of 112(a) from 2006 to 2018).

major hurdle that applicants must overcome before receiving an antibody patent (Figure 4).⁶²

Beginning in 2006, patent examiners were ignoring their own PTO written description guidelines by increasingly applying a more stringent § 112(a) standard.⁶³ Examiners applied this more stringent standard even when courts had specifically upheld the PTO's written description antibody guidelines.⁶⁴

We argue that patent examiners were able to look beyond case law and consider the intent of § 112(a) through the lens of how the technology was being used.⁶⁵ Accordingly, patent examiners from 2006–2018 were applying 112(a) in a manner that was contrary to the USPTO training materials.⁶⁶ Interestingly, both the courts and the USPTO ended up concurring with patent examiners. However, this concurrence took over a decade and came once the issue was squarely before the court.

Why have patent examiners been applying a different standard than what was expected from the USPTO training guidelines and legal precedent? We believe it is because examiners were following the science and advances in antibody technology. Patent examiners are trained scientists and not trained

62. See *supra* Figure 4 (showing that antibody patents experience 10-fold more 112(a) rejections compared with any other technology center and that 112(a) is the major obstacle to obtaining an antibody patent compared with other technology centers where 103 rejections are the primary obstacle).

63. USPTO, *supra* note 48 at 45–46 (Example 13, showing that a claim directed towards “[a]n isolated antibody capable of binding to antigen X” can satisfy the written description requirements of 35 U.S.C. § 112). We note that our data does not distinguish between the written description or enablement guidelines. However, this is consistent with the 2008 written description guidelines put out by the USPTO because it would be illogical to put out a guidance that gives an example that satisfies the written description requirement while simultaneously failing the enablement requirement (without specifically stating that in the guidelines).

64. See *Enzo Biochem v. Gen-Probe, Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) (stating “[w]e are persuaded by the Guidelines on this point and adopt the USPTO’s applicable standard for determining compliance with the written description requirement.”); *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004) (in holding no interference-in-fact “[t]he court adopted the USPTO Guidelines as persuasive authority for the proposition that a claim directed to ‘any antibody which is capable of binding to antigen X’ would have sufficient support in a written description that disclosed ‘fully characterized antigens.’”); *Centorcor Ortho Biotech, Inc. v. Abbott Labs*, 636 F.3d 1341, 1351–52 (2011) (stating that “an applicant can claim an antibody to novel protein X without describing the antibody when (1) the applicant fully discloses the novel protein and (2) generating the claimed antibody is so routine that possessing the protein places the applicant in possession of an antibody.”).

65. Tu & Holman, *supra* note 44.

66. USPTO, *supra* note 48.

lawyers.⁶⁷ We find that in Technology Center 1600, approximately 20% of examiners have masters degrees and approximately 50% have Ph.Ds. in some natural science degree.⁶⁸ In contrast, most examiners do not have a traditional legal education, with only approximately 10% having a J.D. in Technology Center 1600.⁶⁹

By 2018, the USPTO ended up conforming with examiners and repealing its previous guidance stating that, “[Example 13 of the 2008 Written Description Training Materials]...*should not be used* in determining whether there is adequate written description under § 112(a) for a claim drawn to an antibody.”⁷⁰ Although it took over a decade for the courts and USPTO to catch up with patent examiners, both the Federal Circuit and the USPTO now espouse the same standards that patent examiners were applying for over a decade.

C. NARROWING CLAIM SCOPE

The number of words in each claim is important because previous studies have shown that increasing word counts in a claim correlates with narrower scope.⁷¹ We find a threefold increase in the number of words in independent claims for antibody patents. Specifically, there was an increase from 60 to approximately 180 words per independent claim. (Figure 3A) This is unsurprising because the most common ways to traverse a § 112(a) rejection is to simply make claim amendments.⁷² Narrowing claim amendments almost always require the applicant to add words.

67. All examiners are required to have a science degree in their field. Accordingly, 100% of patent examiners will have a Bachelor of Science degree, however, many examiners have also obtained graduate degrees. *See Become a Patent Examiner*, USPTO. <https://www.uspto.gov/jobs/become-patent-examiner> (last visited Nov. 21, 2021).

68. *See* S. Sean Tu, Paul R. Gugliuzza & Amy Semet, *Overqualified and Underrepresented: Gender Inequality in the Pharmaceutical Patent Field*, 48 *BYU L. REV.*, 137, 173 (2022) (Table 1, showing the different education levels of examiners).

69. *See id.* at 155. Examiners are trained extensively in patent law during their first four months in the USPTO training academy.

70. Memorandum from Robert W. Bahr, USPTO Deputy Comm’r for Pat. Examination Pol’y, Clarification of Written Description Guidance for Claims Drawn to Antibodies and Status of 2008 Training Materials (Feb. 22, 2018) (emphasis added).

71. Jeffrey M. Kuhn & Neil Thompson, *How to Measure and Draw Causal Inferences with Patent Scope*, 26 *INT’L J. ECON. BUS.* 5, 6 (2019) (showing that “a patent’s scope can be measured by counting the number of words in its first claim, with more words corresponding to less scope”).

72. S. Sean Tu, *Patenting Fast and Slow: Examiner Rejections and Applicant Traversals to Nonprior Art Rejections*, 2021 *Mich. St. L. Rev.* 411, at 462, Figure 7 (showing the most common response to either a written description or enablement rejection are claim amendments).

These data also match the general trends that we identify where patent examiners initially allowed broad claims in the early development of antibody technology (which requires few words) and then changing to only allow narrow claims as therapeutic antibodies were developed (which requires many more words to describe all six CDRs or the complete heavy and light chains). For instance, Example 1 is relatively short and has only eighteen words. In contrast, Examples 2 (with approximately 50 amino acids described) and Example 3 (with approximately 120 amino acids described) have five times more words with 96 and 97 words respectively. The increase in the number of words combined with the fact that antibodies are now being defined by their structure (instead of their antigen) suggests a much narrower antibody claim today compared to 2002.

We show that applicants are obtaining more and more antibody patents over time, finding a fivefold increase in antibody patents over the course of this seventeen-year period. Of course, this correlates with the ever-increasing importance of biologics as therapeutics. Although applicants are filing more patents, there are fewer claims per patent and those claims are much narrower in scope.

Additionally, we find that more and more of these patents are coming from the same family of patents as outlined by the tenfold increase in ODP rejections, which can only be used for patents within the same family (Appendix 6).⁷³ These data argue that many of these patents are directed to the same antibody product or have relevant family members.

Similar to putting together a jigsaw puzzle with only half the pieces, firms could be cobbling together many narrow patents to try and achieve the same broad patent scope that they were previously able to attain with one genus patent.⁷⁴ See, for example, the Humira family of patents that purportedly

73. Here a patent is determined to be in the “same family” by the presence of an ODP rejection, which requires: (1) a common inventor or owner, (2) the application at issue must be obvious in view of the subject matter claimed, and (3) no restriction requirement that resulted in the subject matter at issue being pursued in a separate divisional application. *See* MPEP § 804.

74. *See, e.g.*, the Humira Patent family with over 100 associated patents. Ryan Knox and Gregory Curfman. The Humira patent thicket, the Noer-Pennington doctrine and antitrust’s patent problem. 40 *Nature Biotechnology* 1761 (2022); *see also* Jeffrey Wu & Claire Wan-Chiung Cheng, *Into the Woods: A Biologic Patent Thicket Analysis*, 19 *CHI. KENT J. INTELL. PROP.* 93, 129 (2021) (describing patent thickets as overlapping patents covering a single technology); Rachel Goode & Bernard Chao, *Biological Patent Thickets and Delayed Market Access to Biosimilars, An American Problem*, *J.L. & BIOSIS.* 1, 4 (2022) (discussing how patent thickets can impede biosimilar commercialization).

contains over 150 patents covering similar products.⁷⁵ Many of these patents contain antibodies that have been defined by different CRDs or by their heavy and light chain framework regions.

Some commentators have expressed concern that large patent thickets have delayed biosimilar market entry.⁷⁶ Others argue that the pendulum has swung too far, and that applicants are now inappropriately being denied genus claims.⁷⁷ It is possible that innovators have responded to the narrowing scope of antibody patents by obtaining a larger number of patents with relatively narrow claims.

Examiners seem to be narrowing the scope of antibody claims, which has allowed examination times to speed up. Patentees have responded by filing more and more patents in an attempt to piece together a larger scope. This has created the unexpected market effect of encouraging and causing the formation of “patent thickets.”⁷⁸ Goode and Chao recently found that nine to twelve times as many patents are asserted against biosimilars in the US compared to Canada and the UK, respectively.⁷⁹ At the same time, biosimilars enter the UK and Canadian markets more quickly than they do in the US. Goode’s data suggest that patent thickets are delaying biosimilar entry in the US.

D. SPEEDING UP PROSECUTION

In 2002, antibody patents took about 30 months to go through prosecution, but that time has been reduced to only 14 months in 2018.⁸⁰ Correspondingly, the number of office actions required to obtain a patent was also cut in half over this seventeen-year period.⁸¹ The overall patent pendency across all technologies at the USPTO has decreased from 31 months to about

75. *See, e.g.*, Humira patents: U.S. 8,414,894 (claim 61, 68, 76, defining both the LCVR and HCVR); U.S. 8,372,401 (claim 1 defining an almost complete heavy and light chain region); *see also* Wu & Cheng, *supra* note 74, at 130 (Table 5, finding more than 154 patents associated with the Humira antibody product); Goode & Chao, *supra* note 74.

76. *See* Goode & Chao, *supra* note 74, at 9. (Figure 2 showing that the US biologic market creates large patent thickets. Where the US asserts 377 patents covering 30 biosimilars, Canada and the United Kingdom only assert 50 and 24, respectively for those same 30 biosimilars); *see also* Wu & Cheng, *supra* note 74 at 109.

77. Karshedt et al., *supra* note 47; Mark A. Lemley & Jacob Sherkow, *The Antibody Paradox* 132 YALE L.J. (forthcoming 2023). *But cf.* Christopher M. Holman, *Is the Chemical Genus Claim Really “Dead” at the Federal Circuit?: Part I*, 41 BIOTECH. L. REP. 4 (2022).

78. Patent thickets are a set of numerous patents with overlapping rights to the same product. These patent thickets are usually used to delay or deter competition. *See* Wu & Cheng, *supra* note 74, at 130; Feldman, *supra* note 33, at 597.

79. Goode & Chao, *supra* note 74, at 3.

80. *See supra* Figure 12.

81. *See supra* Figure 11.

24 months since 2013.⁸² In contrast, there is an increase in pendency from 23 to 27 months for patents in TC 1600 over the past two years.⁸³ Thus, antibody patents seem to be moving through the patent office much faster than other patents.⁸⁴

The back-and-forth negotiations between the examiner and the applicant for antibody patents are far fewer now than two decades ago. This could be because the claims are much narrower and thus require fewer limitations since applicants have already started with antibody claims that have structural limitations and are narrower in scope. Additionally, these data suggest that both applicants and examiners understand what is required to overcome the written description and enablement standards. In contrast, the earlier patents filed in the early 2000s had broad scope and likely needed more rounds of prosecution to narrow the scope of the claims.⁸⁵

These data also show that antibody patents receive fewer anticipation and obviousness rejections.⁸⁶ This is somewhat surprising since usually as a technology develops there is an increase in anticipation and obviousness rejections.⁸⁷ It is likely that we see fewer prior art rejections because these very narrow claims are truly novel and non-obvious over the prior art, especially if they contain both structural and functional requirements. Typically, anticipation and obviousness rejections based on prior art are the most difficult and time consuming to overcome.⁸⁸ Thus, patent claims that do not face these rejections can move through prosecution faster.

VI. IMPROVING ANTIBODY PATENT PROSECUTION⁸⁹

Antibody technology has radically advanced within the last 30 years. Revolutionary changes in antibody technology have moved antibodies from research tools to diagnosis to treatment of diseases. Current antibody

82. See *Patents Pendency Data September 2022*, USPTO (Nov. 14, 2022), <https://www.uspto.gov/dashboard/patents/total-pendency-by-tc.html>.

83. See *id.*

84. We note that the 1650 control group also exhibited a decrease in prosecution time from approximately 24 to 18 months. However, this decrease is significantly less than the 16 month decrease from 30 to 14 months exhibited for antibody patents.

85. See *supra* Figure 2 and Section IV.C.

86. See *infra* Figure 5 (showing that the 1650 control group exhibits more than two fold more obviousness rejections) and Figure 4 (showing that 103 rejections comprise less than 10% of the rejections experienced by antibody patents are obviousness rejections, while most other inventions receive seven times more obviousness rejections).

87. See Lemley & Sherkow, *supra* note 77, at 4–5.

88. Tu, *supra* note 4.

89. S. Sean Tu is the sole author of Part VI and all opinions in this Section should be solely attributed to him.

technology now allows researchers to create consistent and highly specific antibodies that can not only treat diseases, but also treat disease without many of the key side effects previously common to these drugs. While the uses for antibodies have increased, the numbers of patents filed towards antibodies have commensurately increased. Courts, the USPTO administration, and patent examiners have all responded. Interestingly, however, they have not all moved in the same direction at the same pace.

The USPTO administration, patent examiners, and courts have all taken notice of these scientific advances and have significantly limited the scope of these patents by using the written description and enablement requirements, thus forcing applicants to specifically describe their invention by giving structural elements to the claimed antibody. The Federal Circuit is willing to invalidate patents and reverse billion-dollar judgments based on the written description and enablement requirements.⁹⁰ The courts and the USPTO administration, however, have been slow to implement change in response to the changes to antibody technology. In contrast, patent examiners have been actively rejecting patents based on these theories for over a decade.

A. ALLOW SCIENCE TO GUIDE THE LAW

Interestingly, patent examiners applied these enhanced patentability rules for written description and enablement independent of court cases or even in the face of the USPTO written description rules that would otherwise allow broad patent claims. Specifically, patent examiners were forcing applicants to disclose structural features (and not just describing the antigen) before many changes in the caselaw and even after the 2008 USPTO written description guidelines that specifically stated that antibody claims based on antigen structure alone could satisfy the written description requirement.

This phenomenon is most likely because most patent examiners in this technology center are highly educated scientists⁹¹ and although they do apply the legal rules for patentability, they do so through the lens of a scientist. Patent examiners, therefore, are the most in tune with changes in technology.

90. *See Centocor Ortho Biotech, Inc. v. Abbott Lab's*, 636 F.3d 1341 (Fed. Cir. 2011) (where the Federal Circuit overturned a \$1.67 billion dollar verdict and invalidated a set of patents based on the lack of written description); *Juno Therapeutics Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021) (where the Federal Circuit reversed a \$1.2 billion dollar verdict and invalidated a patent based on lack of written description); *Amgen Inc. v. Sanofi*, 987 F.3d 1080 (Fed. Cir. 2021) (where the Federal Circuit affirmed invalidation of a set of patents based on the enablement requirements).

91. Tu et al., *supra* note 68, at 39 (Table 1, showing that over 50% of pharmaceutical patent examiners have a Ph.D.).

Most patent examiners in this technology center, however, do not have a law degree.⁹² Patent examiners are also unlikely to be in tune with the most current changes to patent law jurisprudence. Accordingly, it is somewhat unsurprising that patent examiners have been applying a stricter written description and enablement standard than courts for over a decade. What is surprising is that they have largely ignored the USPTO's own 2008 written description guidelines that specifically allow broad antibody claims based solely on antigen structure.⁹³ In the early days of antibody technology, these broad antigen-defined antibody claims were allowable. After *Lilly*, it looked like antibody patents would be narrowed much like many other biotechnology inventions.⁹⁴ However, the courts and the PTO carved out an exception for antibodies, which allowed them broader scope. The courts, however, have now caught up with what patent examiners have been doing for a decade, which is using the written description requirements to narrow antibody claims.

Ultimately, patent examiners help innovators by denying claims that would subsequently be struck down in court. Rejecting these patents spares investors from spending resources based on them. Additionally, rejecting overly broad claims that would be later invalidated in court creates more certainty, predictability, and confidence for investors.

By allowing narrower claims, patent law strikes a balance between granting exclusive rights to what the inventor disclosed to the public while protecting against overly broad claims that may hinder innovation in the area. Additionally, unlike broad genus type patents, narrow patent rights incentivize competitors to “design around” products to create additional novel therapeutic antibodies (even if they are directed towards the same antigen).

B. REVERSE DOCTRINE OF EQUIVALENTS

Patent law attempts to promote the progress of the useful arts by giving limited exclusive rights to inventors.⁹⁵ This is a delicate balance for the biologics field. On one hand, it may be necessary to provide broader patent protection to motivate firms to take the risk to innovate in this technology, which requires high upfront costs.⁹⁶ On the other hand, giving too much

92. *Id.* (Table 1, showing that the only about 10% of patent examiners in TC1600 have a J.D.).

93. USPTO, *supra* note 48, at 45–46 (Example 13, showing that a claim directed towards “[a]n isolated antibody capable of binding to antigen X” can satisfy the written description requirements of 35 U.S.C. § 112).

94. *See generally* Holman, *supra* note 54.

95. U.S. Const. art. 1, § 8.

96. Olivier J. Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018*, 323 JAMA 844, 848 (2020)

protection can inhibit innovation by preventing important follow-on technology. Some commentators have argued that the pendulum has swung too far, arguing that applicants are now inappropriately being denied genus claims.⁹⁷

One solution to this delicate balance may lie in the rarely used Reverse Doctrine of Equivalents (“reverse DOE”). The reverse DOE allows improvers to capture the value associated with an invention that would literally infringe another’s patent. Accordingly, the reverse DOE could offer a solution to reward improvers even though their improvements would literally infringe on a prior patent.⁹⁸

The rarely used reverse DOE is a mechanism by which a court can find that an invention does not actually infringe on a patent even though it literally falls within the scope of the claims.⁹⁹ The original example of reverse DOE occurred in 1869 when George Westinghouse invented a train brake that used compressed air from a central reservoir to stop the train. In 1887, George Boyden improved on this break by using compressed air from a central reservoir *and* a local reservoir in each brake cylinder. The Supreme Court found that, the new invention “has so far changed the principle of the device that the claims of the patent, literally construed, have ceased to represent his actual invention.”¹⁰⁰ Similarly, the Court in *Graver Tank* stated that:

[W]here a device is so far changed in principle from a patented article that it performs the same or similar function in a substantially different way, but nevertheless falls within the literal words of the claim, the [reverse] doctrine of equivalents may be used to restrict the claim and defeat the patentee’s action for infringement.¹⁰¹

(showing that the median capitalized research and development investment to bring a new drug to market was estimated at \$985 million).

97. Karshtedt et al., *supra* note 47. *But cf.* Holman, *supra* note 77.

98. *See* Scripps Clinic & Rsch. Found. v. Genetech, Inc., 927 F.2d 1565, 1581 (Fed. Cir. 1991) (suggesting that a device may escape liability under the reverse doctrine of equivalents because it is a radical improvement over the patented technology); Atlas Power Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569 (Fed. Cir. 1984); *see also* Robert Merges, *Intellectual Property Rights and Bargaining Breakdown: The Case of Blocking Patents*, 62 TENN. L. REV. 75 (1994); Robert P. Merges, *A Brief Note on Blocking Patents and Reverse Equivalents: Biotechnology as an Example*, 73 J. PAT. & TRADEMARK OFF. SOC’Y 878 (1991) [hereinafter Merges, *Biotechnology as an Example*].

99. Ethyl Molded Prods. Co. v. Betts Package, Inc., 9 U.S.P.Q.2d 1001, 1026 (E.D. Ky. 1988) (stating that, “the reverse doctrine of equivalents, although frequently argued by infringers, has never been applied by the Federal Circuit”); *see also* Merges, *Biotechnology as an Example*, *supra* note 98, at 884.

100. *Westinghouse v. Boyden Power-Break Co.*, 170 U.S. 537, 537 (1898).

101. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608–09 (1950).

As outlined by Merges, reverse DOE may be especially justified when the original patent contributes very little value compared to the improvement.¹⁰² When the improvement greatly increases the value of the original patent, then an inefficient holdup problem may become significant. The social costs of this holdup problem are also significant because the improvement “sits on the shelf for the life of the original patent.”¹⁰³ Reverse DOE avoids this problem by exempting the improver from infringement liability, thus preventing the patentee from exercising their ‘holdup right.’¹⁰⁴

Reverse DOE may be a suitable response to the current situation where courts and the PTO only allow very narrow antibody claims. In calculating the balance between broad and narrow rights, one option could be to default to allowing broad patents and then use reverse DOE to excuse liability for those follow-on inventions that greatly increase the value of the original patent.

This framework creates a system where the USPTO initially grants broad protection for novel inventions based on antibody technology then uses the reverse DOE to exclude follow-on technology that greatly differs from the patented invention. Specifically, courts might use the reverse DOE in a case where a humanized or chimeric antibody recognizes a different epitope or has significantly different functional characteristics from the patented antibody.

One possible application of this solution could be exemplified by the *AbbVie* case.¹⁰⁵ The *AbbVie* court held two AbbVie patents invalid because they lacked adequate written description.¹⁰⁶ These patents were directed to fully human antibodies that bind to and neutralize the activity of human interleukin 12 (IL-12).¹⁰⁷ AbbVie obtained a broad patent directed to fully human anti-IL-12 antibodies.¹⁰⁸ Although the AbbVie patents broadly claimed full human IL-12 antibodies, all the disclosed AbbVie antibodies had: (1) VH3 heavy chains, (2) lambda light chains, (3) at least 90% similarity with Joe-9 in variable regions, and (4) more than 99.5% similarity in variable regions.¹⁰⁹

102. See Merges, *Biotechnology as an Example*, *supra* note 98, at 885.

103. *Id.* at 886.

104. *Id.*

105. *AbbVie Deutschland GMBH & Co, v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014).

106. *Id.*

107. *Id.* at 1291.

108. U.S. Patent No. 6,914,128, col. 386 (issued Jul. 5, 2005) (exemplary claim 29 of the 128 patent reads, “A neutralizing isolated human antibody, or antigen-binding portion thereof that binds to human IL-12 and dissociates from human IL-12 with a K_{off} rate constant of $1 \times 10^{-2} s^{-1}$ or less, as determined by surface plasmon resonance.”).

109. *AbbVie Deutschland GMBH & Co, v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1291 (Fed. Cir. 2014).

Centocor produced Stelara (“ustekinumab”) which was a fully human IL-12 antibody that neutralized the activity of IL-12.¹¹⁰ Stelara literally infringed the AbbVie patent.¹¹¹ However, the Stelara antibody was structurally distinct from Joe and Joe-derived antibodies. Table 2 outlines these key differences.

Table 2

	Stelara	J695	Joe-9
Sequence Similarity	50%	90%	90%
CDR Length	Different	Identical	Identical
Epitope Binding Site	Side Binder	Bottom Binder	Bottom Binder
V _H Family	V _H 5	V _H 3	V _H 3
Light Chain Type	Kappa	Lambda	Lambda

Instead of invalidating the AbbVie patents based on lack of written description, a court could have held the patents valid, but excused Centocor from liability under the reverse DOE. Excusing liability under the reverse DOE in this case is rational because the Stelara antibody improvements changed the principle of the device in a way that no longer represented what AbbVie disclosed in the specification of their patents.

Allowing broad claims while carving out exceptions to those broad claims by using reverse DOE, however, is not a magic bullet. Reverse DOE is an ex post solution applied by courts only after heavy investment in the technology by competitors. Thus, reverse DOE does not address the incentives issue because competitors would not know ex ante if their antibody is “too similar” to the patented antibody.¹¹² Accordingly, a rational competitor might simply avoid the risk of infringing a broad patent by never investing in research on new antibodies in the first place or delaying research until the relevant patents expire.

Additionally, if reverse DOE is applied too narrowly, then it would act identically to the current written description and enablement framework. Specifically, if reverse DOE is interpreted to only grant a scope exactly commensurate with those working examples disclosed in the specification,

110. *Id.*

111. *Id.* at 1293.

112. With that said, a competitor would also not know ex ante if a 35 U.S.C. § 112(a) invalidity argument would succeed. However, allowing both § 112(a) and reverse DOE arguments to move forward might be the best way to maximize social welfare. Doing so would by incentivize truly novel patents by preventing trivial variations while excusing liability for valuable design arounds.

then it is no better than using the current written description and enablement standards. However, reverse DOE is currently better than the current solution, which is to simply invalidate broader antibody patents that may bring new and innovative drugs to market.

C. FUNCTIONAL CLAIMING AND THE DOCTRINE OF EQUIVALENTS

Lemley and Sherkow have recently suggested the use of functional claiming and the Doctrine of Equivalents (DOE) to save these antibody genus claims.¹¹³ Functional claiming through means-plus-function claiming (§ 112 ¶ 6) allows a patentee to claim those antibodies disclosed in the patent's specification and equivalents thereof.¹¹⁴ The difficulty, however, lies in determining which antibodies are "equivalent" to those described in the specification. Accordingly, many of the problems associated with the use of reverse DOE are also present with DOE.

Similar to reverse DOE, the means-plus-function claiming in combination with DOE offers a possible intermediate scope. Use of reverse DOE or functional claiming with DOE would allow patent owners to prevent the development trivial changes to competing technologies that bind the same antigen with the same functional result. However, both doctrines would also leave open the ability for competitors to develop their own antibody that works in a different way, binding to a different epitope and creating a different therapeutic outcome.

The advantage of DOE in combination with means-plus-function claiming is that this broader claim would cover any equivalents covered by the means-plus-function language as well as the DOE (same function, way, and result). Additionally, use of DOE in combination with means-plus-function should avoid written description problems because the functional equivalents would be tethered to the functions disclosed in the specification.

One advantage of using reverse DOE over DOE is placement of the burden of proof. With reverse DOE, the alleged infringer is put on notice of the broader patent. The alleged infringer would be aware *ex ante* that he is infringing the patent. However, the alleged infringer could then argue that their changes to the antibody were significant enough to excuse liability. This would force competitors to base the changes to the antibody on a change in function or a change in epitope.

Using functional claiming with DOE would put the burden of proof on the patentee to show that the alleged infringing antibody is substantially similar

113. Lemley & Sherkow, *supra* note 77.

114. *See In re Hyatt*, 708 F.2d 712, 713–14 (Fed. Cir. 1983).

to the claimed invention. Accordingly, unlike reverse DOE, the burden is placed on the patentee and not the accused infringer. I (S. Sean Tu) believe that the better default rule should be that the alleged tortfeasor bears the burden of showing why his acts are lawful rather than placing the burden on the patentee to show why the alleged infringer's acts are unlawful.

VII. CONCLUSION

Courts, the USPTO administration, and patent examiners have all dealt with antibody patents in slightly different ways. However, it seems that all three arms have now reached a consensus. Each group now uses 112(a) to deny broad claims based only on function and antigen structure. However, narrow claims with antibody structural elements are currently allowed.

This study shows that patent examiners over time have increasingly used § 112(a) rejections to narrow claims. Antibody patents moved from broad functional claims to narrow structurally limited claims. Finally, an increase in the number of words per independent claim and the increased use of continuation practice combined with shorter prosecution durations all suggest that the scope of antibody patents has narrowed over time.

VIII. APPENDIX 1 – ANTIBODY FUNDAMENTALS

A. GENERAL DEFINITIONS

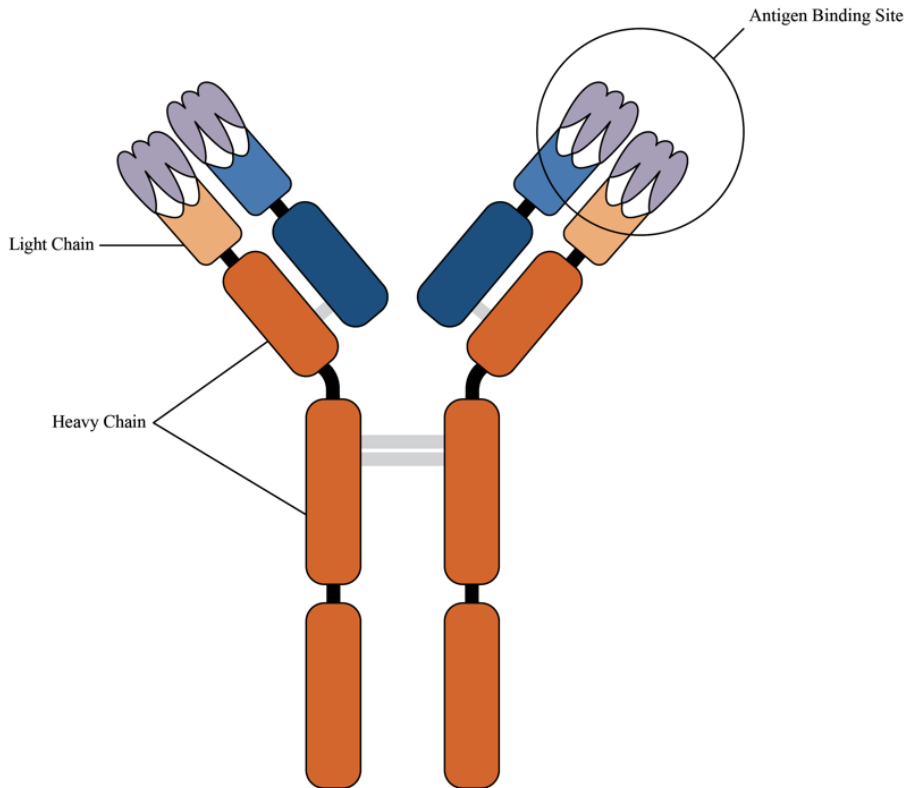
1. Antigen – The target molecule that the antibody binds to.
2. Epitope – The specific region of an antigen that the antibody binds to.
3. Paratope – The region of an antibody that is responsible for binding to the epitope.
4. Complementarity Determining Regions (CDRs) – Six regions on the antibody that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

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

B. ANTIBODY STRUCTURE, FUNCTION AND METHOD OF PRODUCTION

Antibodies, also known as immunoglobulins, are natural products of the body that are secreted by B-cells as part of an immunological response to neutralize antigens such as bacteria and viruses. Figure 1 shows the structure of an antibody. The antibody structure is a classic Y-shaped molecule composed of two heavy chains (connected by a linker) and two light chains (connected to the heavy chains). Each tip of the “Y” contains a paratope which can bind only one epitope on an antigen. This allows the antibody to bind its antigen with precision. There are two main types of antibodies: polyclonal and monoclonal. Monoclonal antibodies are identical and have the same binding specificity and recognize the same epitope. In contrast, polyclonal antibodies against an antigen are a mixture of molecules that have different binding sites, different binding specificities and typically recognize different epitopes on the antigen.

Figure 1



Polyclonal antibodies (pAbs) are a mixture of heterogeneous antibodies which are usually produced by different B-cell lines in the body. Thus, pAbs recognize and bind to many different epitopes of a single antigen. Polyclonal antibodies are usually manufactured by injecting an animal with an antigen. After injection, the animal elicits a primary immune response, and then given a secondary injection (and sometimes a third injection) to boost the immune response. The animal's serum¹¹⁵ can then be collected and polyclonal antibodies to the antigen are isolated using an immobilized antigen.

There are several benefits associated with pAbs. First, is the relative ease and cost of production of pAbs. pAbs are highly stable and can tolerate pH or buffer changes. Additionally, pAbs bind more than one epitope and can help amplify the signal from a target protein even with low expression levels. Accordingly, pAbs are ideal for immunoprecipitation and chromatin immunoprecipitation. Finally, pAbs are less sensitive to antigen changes such

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

as denaturation, polymorphisms, and different glycosylation patterns. One major downside to pAbs, however, is batch to batch variability because each animal mounts a different immune response to the antigen injection.

Polyclonal antibodies have been used as components of antivenom, antitoxin, and transplant antirejection drugs. Importantly, pAbs are also used to *detect* disease in blood or tissue samples. For example, pAbs have been used to detect viruses, cancers, encephalitis, HIV, and Lyme disease.

Monoclonal antibodies (“mAbs”) revolutionized antibody technology. In contrast to pAbs, mAbs are usually not produced in live animals. In 1975, Nobel laureates Köhler and Milstein produced the first mAbs.¹¹⁶ Monoclonal antibodies are generated using hybridoma technology, which is a product of splenocyte and myeloma cell fusions creating an immortalized B-cell-myeloma hybridoma. The hybridomas grow continuously in culture while producing antibodies. These antibodies are then screened for the desired mAbs. Importantly, monoclonal antibodies exhibit *precise and reproducible binding properties*. Monoclonal antibodies bind one specific epitope on an antigen.

Figure 2A describes the different binding specificities of mAbs compared to pAbs. Polyclonal antibodies have the ability to bind different epitopes (triangles and rectangles) on the same antigen. In contrast, mAbs can bind only one specific epitope (triangles) on an antigen. Figure 2B shows that polyclonal antibodies bind to multiple epitopes on the same antigen, while monoclonal antibodies can bind to only one epitope.

116. Georges Köhler & César Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 NATURE 495 (1975). Georges Köhler and César Milstein shared the 1984 Nobel prize in medicine for this breakthrough.

Figure 2A

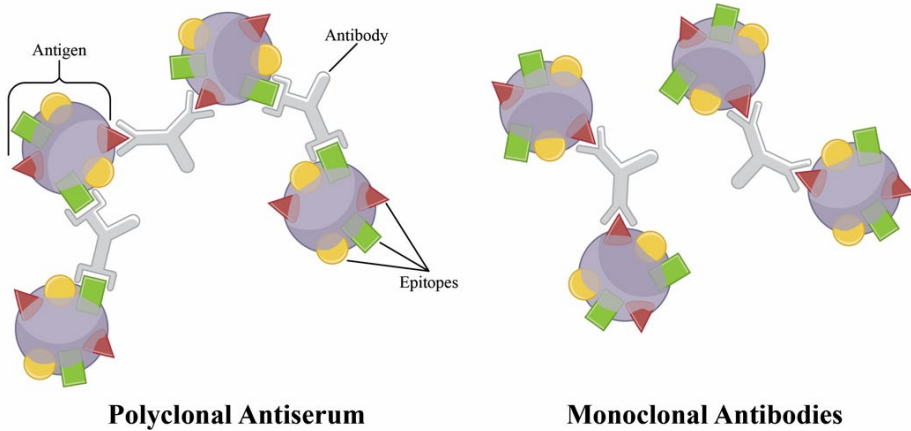
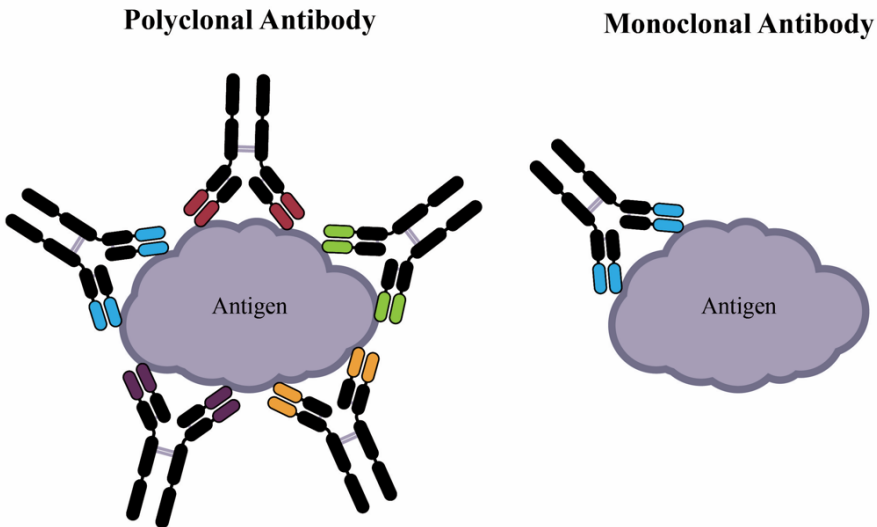


Figure 2B



The benefits of using mAbs cannot be understated. First, mAbs are highly specific and recognize only one epitope of an antigen. Second, once an immortal hybridoma cell line is created, the firm has the ability to produce unlimited quantities of mAb. Because mAbs recognize only one epitope, the results of mAbs are highly consistent with minimal background noise and cross-reactivity. However, the cost and time needed to generate monoclonal antibodies is considerably greater than polyclonal antibodies. Additionally, it

requires highly technical knowledge to create these hybridomas. mAbs are also vulnerable to changes in the epitope and even small changes in antigen conformation may lead to dramatically reduced binding capacity. Due to these consistent results, mAbs are much better suited to be used for therapeutic treatments. Accordingly, mAbs have been used to treat diseases such as rheumatoid arthritis,¹¹⁷ asthma,¹¹⁸ psoriasis,¹¹⁹ and many forms of cancer.¹²⁰

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

Accordingly, additional steps are required for mAbs used to treat disease in humans. Monoclonal antibodies must be “humanized” for human clinical use. Figure 3 shows the humanized and chimeric versions compared to mouse antibodies. Chimeric and humanized antibodies reduce the likelihood of a HAMA response by minimizing the non-human portions of administered antibodies. Because most regions of the chimeric and humanized antibodies are human, these antibodies do not elicit as much of an immune response from the patient. Chimeric and humanized antibodies have the additional benefit of activating secondary human immune responses such as antibody dependent cellular cytotoxicity. Furthermore, these chimeric/humanized antibodies have a much longer serum half-life.

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

117. Adalimumab (“Humira”) from Abbvie is a fully human antibody against tumor necrosis factor (TNF) used to treat rheumatoid arthritis.

118. Dupilumab (“Dupixent”) from Regeneron Pharmaceuticals is a fully human antibody against IL4RA used to treat atopic dermatitis and asthma.

119. Infliximab (“Remicade”) from Centocor is a chimeric antibody against TNF that is used to treat Chron’s disease and plaque psoriasis.

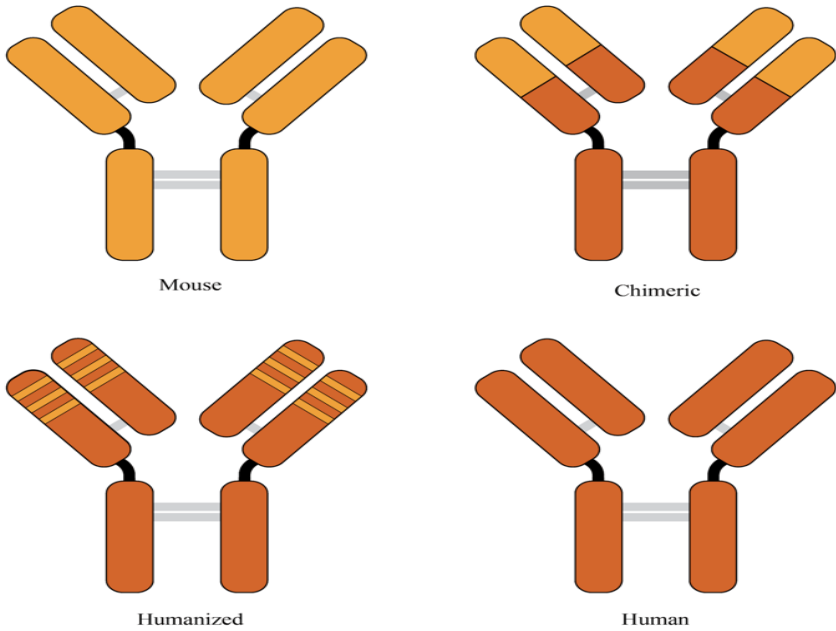
120. Atezolizumab (“Tecentriq”) from Genentech is a humanized antibody against PD-L1 that is used to treat Urothelial carcinoma and metastatic non-small cell lung cancer. Bevacizumab (“Avastin”) from Genentech is a humanized antibody against vEGF used to treat metastatic colorectal cancer. Pembrolizumab (“Keytruda”) from Merck is a humanized antibody against PD-1 that is used to treat metastatic melanoma. Rituximab (“Rituxan”) from Genentech is a chimeric antibody against CD20 that is used to treat B-cell non-Hodgkin’s lymphoma.

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

One of the newest antibody technologies involves the use of a phage display library to artificially construct soluble Fab fragments. These Fab fragments have the ability to penetrate tissues efficiently and do not need to be processed through the endoplasmic reticulum. However, one major drawback to this approach is that a new phage library must be constructed for every antigen, which is a time-consuming process. Additionally, Fabs are not full-length antibodies and lack the C region which is responsible for effector functions. Fabs are produced in bacteria and therefore are not glycosylated, which leads to a much shorter half-life.

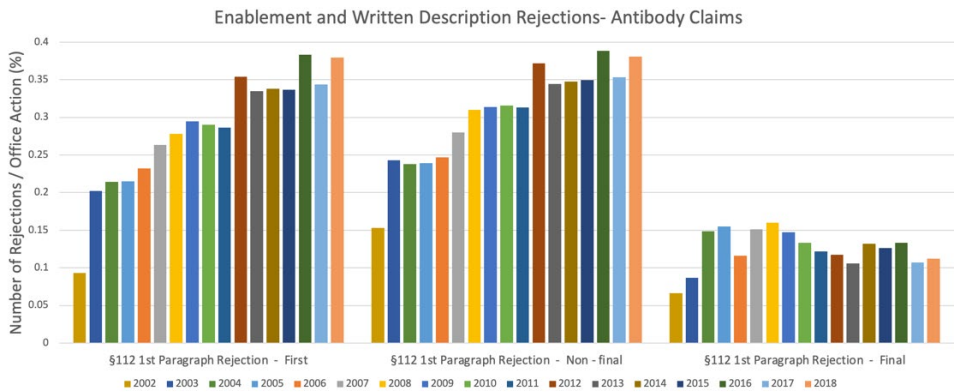
Finally, mAbs are being produced in plants for use in humans. These “plantibodies” are full length antibodies that are glycosylated and thus have a longer half-life in the patient’s body. Plantibodies are generated by creating a transgenic plant that expresses human mAbs without harming their own metabolism.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

Figure 3



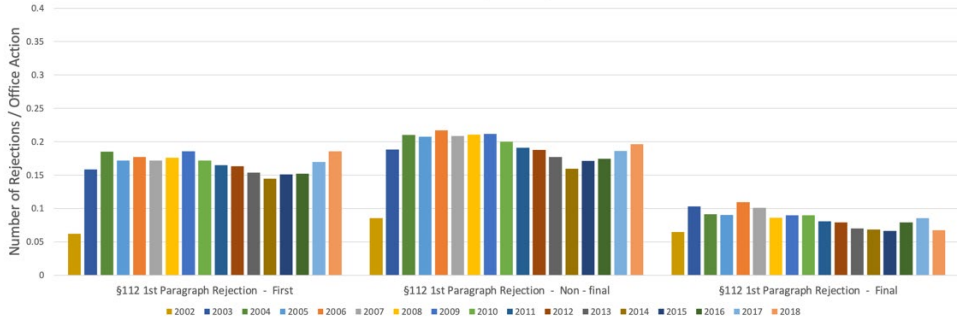
IX. APPENDIX 2

Appendix 2A



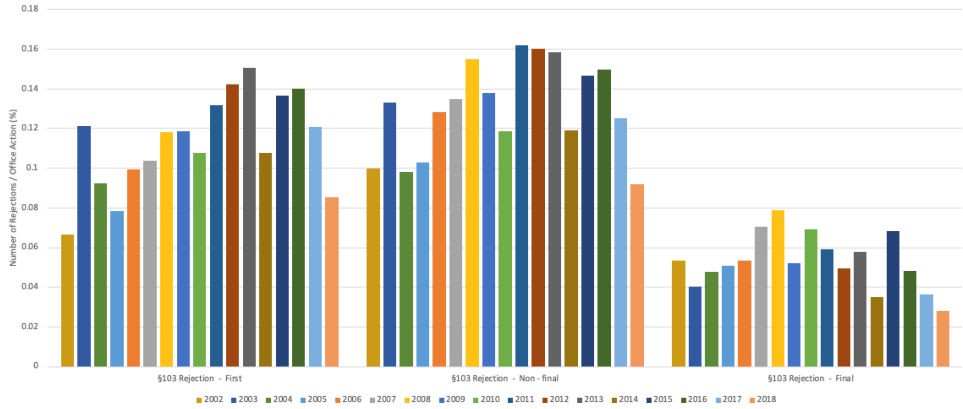
Appendix 2B

Enablement and Written Description Rejections- 1650 Control



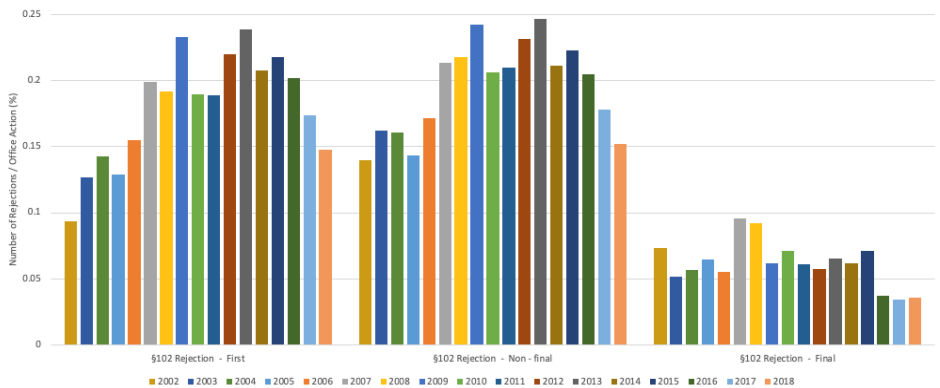
Appendix 3A

35 USC 103 Obviousness Rejections

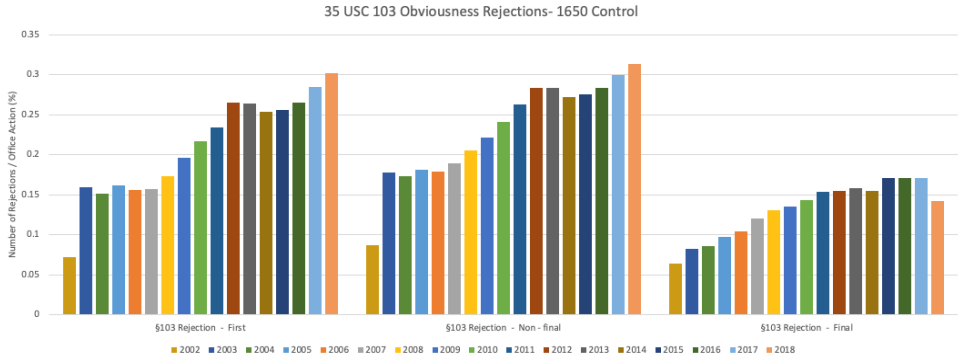


Appendix 3B

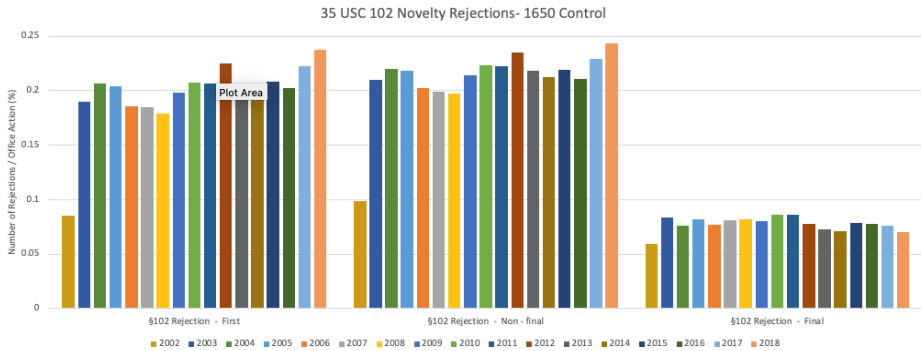
35 USC 102 Novelty Rejections



Appendix 4A

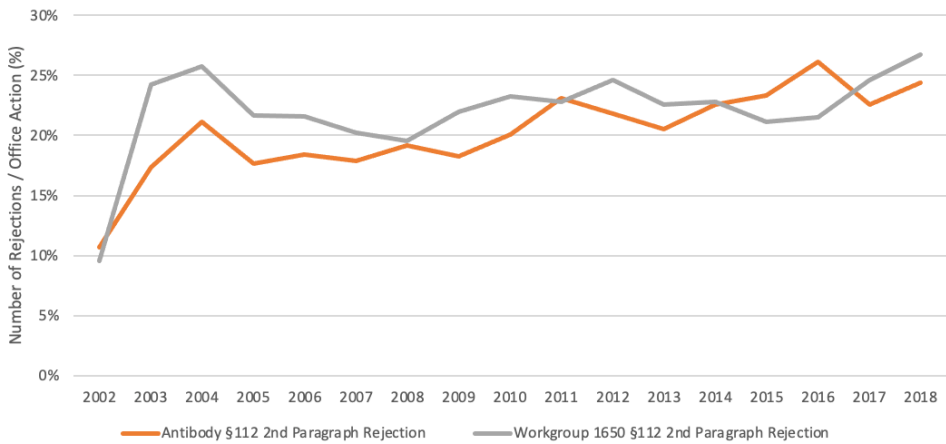


Appendix 4B



Appendix 5

35 USC 112(b) Rejections for Antibody Patents vs Workgroup 1650



Appendix 6

ODP Rejections for Antibody Patents vs Workgroup 1650

