Monoclonal Antibody Patents: Evolving Law & Strategies

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The United States Supreme Court's denial of Janssen's cert petition finally put to rest the epic litigation first known as *Centocor v. Abbott*. The case had produced the largest patent verdict in history, followed by the vacating of that verdict, as well as the patent itself, by the Court of Appeals for the Federal Circuit. The Federal Circuit opinion — applauded by some, and criticized by others — is the most important development in patent law, as far as monoclonal antibody patents are concerned, in many years.

What new strategies, if any, should companies with pending therapeutic monoclonal antibody patent applications take into consideration? What about all the monoclonal antibody patents that have been issued over the years under the USPTO's "antibody exception" and therefore could, in theory, lack written description support? What about monoclonal antibody patent licensees when their licenses expire? And how might aspiring biosimilar drug manufacturers look at these developments? Since monoclonal antibodies represent the single-most successful part of the biotechnology business to date, these are not small questions.

In this article we will give an overview of monoclonal antibody patenting, briefly review the Janssen case, discuss the "antibody exception," and then provide some possible strategic directions for antibody patenting going forward, focusing on the critical issue of the interplay between the post-Janssen antibody exception and the recently enacted America Invents Act.

Patents and the Historical Development of Monoclonal Antibodies

Biotechnology patenting and patent strategy have always been markedly different than that of the pharmaceutical industry. Biotechnology, dealing with chemical complexity orders of magnitude larger than small-molecule pharmaceuticals, generally requires more than one patent to cover any given therapeutic entity, and may potentially require dozens. In general, small-molecule pharmaceutical companies rely on one or two key patents per therapeutic molecule and rarely, if ever, have to license manufacturing-related technology.

Another important area of difference between pharma and biotech, when it comes to patents, is the latter's more frequent reliance on outside and university research.

New biological entities may frequently involve a critical discovery that originated in a university or publicly supported lab or research institution, and is being commercialized via tech transfer. The original patenting, and thus the approach to claim drafting and scope, is often not under the control of the commercializing company. In pharma, traditionally, the molecules are developed in-house, with in-house counsel often playing a critical role in the claims drafting and patent prosecution.

Small-molecule pharma manufacturing processes are also, generally, straightforward matters of standard chemical manufacturing, widely accepted and known and not covered by patents. With protein products, in contrast, much of the very difficult (and expensive) work comes from developing the techniques and tools for producing the products in ways that are suitable for human therapeutic use, and in sufficient volumes. These processes can be protected by trade secret or patent, and, in either instance, may sometimes require licensing of antibody-engineering patents from others.

Within the very large universe of biotechnology, we can define a narrower world of protein products. Protein products range from the relatively simple — hormones, for example — to the highly complex

— such as some monoclonal antibodies. Likewise, the complexity of protein drug patenting may range widely across the entire family of protein products. For example, a relatively simple protein — a peptide, for example — can be encoded by a relatively short genetic sequence. As far back as 1996, Genetics Institute claimed to have found 5,000 proteins and the respective genes that encode them. The creation of a monoclonal antibody, on the other hand, especially one that will be used in humans, is never as straightforward.

Although monoclonal antibodies are protein products, not all protein products are antibodies. And while there is a special USPTO policy with regard to monoclonal antibodies (discussed below), there is no similar special policy for the entirety of protein products.

The straightforward and generally accepted definition for monoclonal antibodies states (this from Wikipedia), "Given almost any substance, it is possible to produce monoclonal antibodies that specifically bind to that substance; they can then serve to detect or purify that substance."

Antibodies are the part of the immune system that mark a substance — an antigen — for action by other parts of the immune system, usually removal from the system. Monoclonal antibodies, which we'll henceforth refer to as "mAbs," are antibodies that are all identical because they are made by cloned immune cells.

Development of the first method of mAb production is generally credited to Kohler and Milstein in 1975. They fused cancer cells with antibody-secreting B-cells from a mouse that had been immunized so as to secrete the desired antibody. This fusion created an antibody-secreting "hybridoma" cell.

From that point on, the mAb industry took off, with successive teams coming up with better production methods. The original hybridomas were not ideal for human use because, being foreign proteins, they were attacked by the human immune system. The history of mAb patents (and patent litigation) from the first hybridoma onward is the history of the successive improvements in mAb production: better specificity, reduced immunogenicity, improved bioavailability, and so forth.

The most famous mAb patents — perhaps because they were the subject of high-profile lawsuits, re-exams and interference proceedings — are the Genentech "Cabilly" patents. Another famous group of mAb patents are the "Queen" patents, named after their inventor, and likewise the subject of litigation.

Litigation over mAbs is the most expensive and high-profile in all of biotech. Why? The numbers speak for themselves. In 2008, the top 10 therapeutic mAbs together accounted for just under $40 billion in sales. In 2012, that number was closer to $120 billion and still growing rapidly. In 2008, the top five mAbs generated $20 billion, but in 2012, just one antibody, Humira, alone generated that number.

And that one drug, Humira, manufactured by Abbott, with its strong market position vis-a-vis new competitors, was the subject of the seminal monoclonal antibody patent dispute of the past decade: *Janssen v. Abbott*.

The Janssen Case (text from a previous Fenwick alert)

On February 21, 2012, the United States Supreme Court denied certiorari in *Janssen v. Abbott*.

Janssen (a J&J subsidiary formerly known as Centocor) filed the cert petition last autumn in an effort to restore the massive $1.6 billion verdict the company won at trial in the Eastern District of Texas. The jury had found that Abbott's blockbuster rheumatoid arthritis drug Humira® infringed on Janssen's U.S. Patent No. 7,070,775 (the '775 patent). In February 2011, the Court of Appeals for the Federal Circuit found the '775 patent invalid for lack of sufficient written description, and accordingly threw out the jury verdict. The Supreme Court's denial of the cert petition without comment allows the Federal Circuit decision to stand and eliminates Janssen's last opportunity to restore the jury verdict.

In its cert petition, Janssen argued that the written description requirement in patent law operates

unfairly in the biotechnology context. Janssen claimed that the requirement effectively forces biotechnology patents to be reduced to practice before they can be patented. Abbott responded that the Federal Circuit correctly applied written description law to bar patent claims to inventions that the applicant does not possess.

The Abbott case concerns therapeutic antibodies targeting human tumor necrosis factor alpha (TNF-α), a protein implicated in autoimmune diseases such as rheumatoid arthritis. Indeed, the commercial backdrop to the case was a battle for dominance in the rheumatoid arthritis drug market, where Abbott's accused antibody product, Humira, dominates.

For many years before Janssen applied for its '775 patent, researchers had been able to produce antibodies to human TNF-α. These antibodies, however, were typically produced in mice and were not suitable for use in human patients. By combining portions of mouse and human antibodies — specifically, the "variable" region of a mouse anti-TNF-α antibody with the "constant" region of a human antibody — Janssen was able to develop so-called "chimeric" antibodies that are both more effective for treatment of conditions (such as rheumatoid arthritis) resulting from TNF-α overproduction, and also less likely to provoke an adverse immune response in patients.

In its '775 patent, however, Janssen also included claims to anti-TNF-α antibodies wherein *both* the variable and constant regions were derived from human antibodies. In 2006, Janssen asserted these claims against Humira, a fully human anti-TNF-α antibody (i.e., an anti-TNF-α antibody possessing a human variable region and a human constant region) developed by Abbott.

The key legal question in the case was whether Janssen was "in possession" of the invention — that is, in possession of a fully human anti-TNF-α antibody — before Abbott. The jury found that Janssen was first in possession of the invention, and therefore its patent was valid and Abbott's Humira drug infringed the patent.

The Federal Circuit disagreed. After undertaking "an objective inquiry into the four corners of the specification" from the perspective of a person of ordinary skill in the art, the appellate court concluded, "There is nothing in the specification that conveys to one of skill in the art that [Janssen] possessed fully human antibodies or human variable regions that fall within the boundaries of the asserted claims." The appellate court noted that the specification of the '775 patent "does not disclose any relevant identifying characteristics for such fully human antibodies or even a single human variable region. Nor does it disclose any relationship between the human TNF-α protein, the known mouse variable region that satisfies the critical claim limitations, and potential human variable regions that will satisfy the claim limitations." In short, the Federal Circuit found no evidence in the specification that Janssen possessed anything but a plan for making fully human antibodies.

Patent prosecutors who had been working with mAbs noticed that the Federal Circuit opinion seriously eroded the "antibody exception" that many had been relying on for years.

The "Antibody Exception" as Traditionally Understood

The USPTO written description guidelines, found in the 2008 Written Description Training Materials, provide that a claim reciting an isolated antibody capable of binding to protein X is adequately described when the specification fully characterizes protein X, even if there are no working examples of actual antibodies that bind to protein X.

The traditional interpretation of written description law would have required more; that is to say, more specific characterization of the antibody. But under this "antibody exception," if the applicant is in possession of an antigen — can fully characterize its structure — he can claim an antibody against it.

The doctrine envisions the antibody-antigen relationship as a lock and key, and that metaphor has been used by others to describe the antibody exception doctrine. The presumption seemed to be that, where an antigen can be characterized to the necessary level of detail, then creating an antibody to bind to it would be straightforward.

Further, the antibody exception found support in case law. The Noelle case — *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004) — cites the antibody exception and has been viewed by some commentators as essentially approving the doctrine.

It is estimated that 45 percent of patents with antibody claims are not supported by examples of antibody production.[1]

The "Antibody Exception" after *Janssen v. Abbott*

Where does the antibody exception stand now?

Centocor (Janssen) argued that the "antigen exception" to written description, and the Noelle case, should apply because the human TNF-α protein was adequately described in their specification. But the Federal Circuit did not agree.

"Centocor suggests that our decision in Noelle and the PTO written description guidelines support the view that fully disclosing the human TNF-α protein provides adequate written description for any antibody that binds to human TNF-α. That suggestion is based on an unduly broad characterization of the guidelines and our precedent."

By carefully distinguishing Noelle, the Federal Circuit kept the antibody exception alive. But how? Centocor was clearly "in possession" of the antigen (tumor necrosis factor alpha) and yet it was not in possession, according to the CAFC, of the antibody that binds to that antigen.

The Federal Circuit distinguished the situation thus:

"The antibody example presumes that the applicant is disclosing a novel protein and then claiming both the protein and an antibody that binds to it.

"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."

Thus the antibody exception can be used only in the case of a *novel* antigen, and only if nothing more than "routine methods" are needed to generate an antibody. Since TNF-α was well known to science it was not a novel antigen. And while arguable routine methods would have been sufficient to create an antibody to bind to that antigen, something far more than routine methods were required to create a fully human antibody to bind to that antigen.

At this point some owners of mAb patents granted under the prior understanding of the antibody exception may be pausing to wonder about the validity of their patents. Clearly different inventors may very plausibly create different antibodies (with different variable regions or other distinguishing structural characteristics) to the same antigen. Some mAb patents, or claims, may not have quite the scope that the original applicants had hoped for. But this remains to be seen. And regardless, what is left of the antibody exception still provides opportunities for applicants. The discovery of novel antigens, when the generation of their antibodies can occur through industry-standard accepted methods, are patentable.[2]

The question then arises: when is the applicant "in possession" of the novel antigen? This may prove critical because, under the new patent law, what matters is not who is "first to invent" but "first to file."

The America Invents Act and "First to File"

Currently, two competing monoclonal patent applicants may find themselves in interference proceedings at the USPTO to determine which of the two parties has priority (i.e. who invented first, and thus who gets the patent). However, on March 16, 2013, the "first to file" rule, which is the core provision and most significant change embodied in the American Invents Act (aka "patent reform") takes

1 Hashimoto and Aida, Antibody patenting without antibodies: a global trend. Nature Biotechnology 26:1341 (2008).

2 After the Supreme Court denied cert in Janssen, another *Centocor v. Abbott* case, this one featuring the IL-12 antibody Stelara, was wending its way through the courts. On March 9, 2012, the District of Massachusetts ruled that the question of sufficient written description was a matter to be put before the fact-finder, and thus not susceptible to a ruling on summary judgment. As an aside, with regard to indefiniteness, the court pointed to how much inference can be given to the use of standard assays by those skilled in the art. Of course, since new assay development is occurring on a nearly daily basis, this particular moving target may inform framing language for epitope descriptions in mAbs, as will be discussed below.

effect. Under the AIA, a claimed invention is not novel if it "was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention or (2) was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention."

The AIA, having replaced "first to invent" with "first to file," does away with interference proceedings for applications filed on or after March 16, 2013. Although there will now be a "derivation proceeding" to ensure that the first filer of the patent is indeed the inventor, the concept of determining who, among competing inventors, was the first to invent, is moot. The first filer trumps.

It has been argued that "first to file" may act as a starting gun for the life sciences industry to race to the USPTO prematurely, before inventions have reached the patentability stage, betting that deficiencies can be cured over the course of prosecution.

In the mAb context, there could be real tension between the AIA and the written description doctrine. In the case where a novel antigen is discovered, the pressure to instantly file a patent on its antibody will be justified. The risk of insufficient written description may give pause in the context of development of new antibodies to known antigens, but there, too, the first-to-file rule will pressure applicants.

Strategies: The USPTO's "Antibody Exception" in the Context of the AIA's "First to File" Rule

Previous Fenwick & West client alerts have delved into various parts of the America Events Act and provided scenarios on some emerging strategies. For companies dealing with mAbs — developers, licensees, competitors, biosimilar developers, and so forth — the general "first to file" strategies discussed in prior alerts must be viewed in light of the current state of the antibody exception to written description doctrine. To these companies the question must be put directly: how do you balance the risk that that your monoclonal antibody patent will be invalidated for insufficient written description versus the risk that you will be beaten to the patent office by a competitor or potential investor?

This question can only be answered on a case-by-case basis. However, in limited situations, the use of the one-year provisional patent application window in combination with the antibody exception doctrine may be warranted. For example, a start-up company may only have an idea in hand for making a new antibody to a particular antigen, but lack the financial resources to actually create the antibody itself. In order to gain the necessary financial resources to actually make the antibody, the start-up company will likely need to go out into the investor community and pitch the idea in exchange for the monetary funds needed to create the antibody. In such a case, it may make sense for the company to first file a provisional patent application that describes the particular antigen in a way that highlights its novel characteristics (and an antibody that binds to that "novel" antigen), thus increasing the chances that later invocation of the antibody exception doctrine will be enough to meet the U.S. written description requirement for claims directed to the new antibody.

Creative ways to characterize an antigen or epitope will become increasingly important, as truly "novel" antigens become rarer in the age of widespread genomic sequencing. During the one-year window that follows the provisional application filing date, the start-up company would be well advised to work diligently toward the creation and characterization of an antibody based on the original idea. At the conclusion of the one-year window, all of the sequence information and data ultimately generated with the new antibody can then be included within the converted patent application(s), providing further written description support for the various claims covering the antibody.

Scientists may be prompted at this point to ask exactly how much sequence information and data would be sufficient to characterize an antibody and its binding epitope(s). This, too, can only be answered

on a case-by-case basis. But we can be certain that, as tools and techniques for sequencing and epitope mapping rapidly improve, patent applicants will be presented with important tactical choices. These may be particularly thorny in the case of start-ups with limited funds. For example, should a start-up with limited funds expend the time and energy to perform X-ray crystallography in order to better characterize its newly discovered antigen before filing its application?

These strategic choices must take into consideration not only patent law and USPTO practice but the applicant's competitive landscape and the likelihood of a competitor's earlier filing. Discussions with counsel from the earliest possible instance may prove critical.

We can be sure that, whatever happens with the details of patent law, the development of therapeutic mAbs will continue unabated for the foreseeable future.

Indeed, one of the most exciting trends in mAbs at the moment is the antibody-drug conjugate, which is the fusion of an antibody with a therapeutic agent, such as chemotherapy, to both target the antigen-expressing cell for elimination by the immune system as well as kill the cell directly via the chemotherapy agent. Scientific developments such as these will present new and interesting patenting challenges. We can be sure that the law will evolve alongside the industry.

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