TRENDS AND PRACTICE TIPS IN THERAPEUTIC ANTIBODY PATENTING


BY PEI WU AND JOHN P. IWANICKI

Antibody technologies have evolved side-by-side with the advancement of molecular cloning, DNA sequencing, phage display and transgenic mice techniques. Since the introduction of hybridoma technique by Kohler and Milstein in 1975, therapeutic monoclonal antibodies (mAbs) have become one of the most attractive and fastest-growing classes of therapeutic agents for the treatment of diverse diseases including cancers, autoimmune diseases and infections. Currently, at least 30 therapeutic mAbs achieve multi-billion dollar annual sales in the United States.[1] Because significant time and cost is invested in bringing an antibody therapeutic to market, a sound intellectual property strategy and sufficient patent protection is necessary to ensure commercial success.

PATENTABILITY

Antibodies, also known as immunoglobulins, are proteins used as immune defense or therapeutics. Antibody patent applications are subject to similar standards for patentability as chemical compound inventions. On a basic level, a patent application for an antibody needs to satisfy novelty, nonobviousness, written description and enablement requirements to be patentable.

The novelty requirement is relatively easy to meet, *e.g.*, if the target antigen or epitope to which the antibody binds is new. Compared to novelty, the nonobviousness requirement is becoming increasingly difficult to satisfy. With about 70 mAb products projected to be on the market by 2020,[2] many of the pioneering antibody technologies, including production of chimeric and humanized mAbs (antibodies produced from non-human species with modified protein sequences to be more similar to antibody variants produced naturally in humans), antibody phage display (displaying antibody libraries on a phage for rapid *in vitro* selection and production), transgenic mice (mice engineered to have integrated human immunoglobulin (Ig) loci for the production of human antibodies), Fc engineering (antibodies having engineered constant regions for improved efficacy) and antibody-drug conjugation (antibodies linked to drug molecules), are now becoming routine. Therefore, the mere generation of yet another therapeutic mAb, absent of any improved efficacy or unexpected functional properties, is going to be considered obvious, especially if the target antigen or epitope is already known. Post-*KSR*, the bar for showing that an antibody is nonobvious has been raised, and there is an increased tendency for U.S. Patent and Trademark Office patent examiners to reject an antibody claim on the grounds that it is merely applying a known technique to a known method or product ready for

improvement to yield predictable results; or "obvious to try" — choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.[3]

Written description represents another battleground in antibody patenting. In the 1990s, it was a usual practice for applicants to broadly claim a genus of antibodies by relying on what the USPTO called the "antibody exception," which suggested that disclosure of an antigen alone can satisfy the written description requirement for any antibody that binds to that antigen. However, a few recent Federal Circuit decisions have significantly narrowed the "antibody exception." When the target antigen is novel, the Federal Circuit, in its 2004 decision in *Noelle v. Lederman*, required that a specification discloses a "fully characterized antigen" to support a claim to an antibody defined by its binding affinity to an antigen.[4] In another case where the novel antigen is not characterized, the Federal Circuit, in its 2008 decision *In re Alonso*, held that written description is insufficient for a claim to a method of treating neurofibrosarcoma using human monoclonal antibodies, where the specification taught nothing about the structure, epitope characterization, binding affinity, specificity or pharmacological properties common to the large family of antibodies implicated by the method.[5]

On the other hand, when the antigen is already known, the Federal Circuit, in its

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To survive the obviousness challenge, counsel and inventors must work closely to characterize the antibody therapeutic and related technology as much as possible. For example, is there any data that support unpredictability such as a showing of no reasonable expectation of success to produce claimed antibody therapeutic, or a showing that claimed antibody therapeutic has unexpected or synergistic results with comparative studies? Additionally, does the antibody have unusual structural features or recognize a new epitope? Functional properties such as improved efficacy, prolonged half-life, reduced toxicity, increased affinity or inhibition of a biological process or target, as well as follow up *in vivo* data and clinical observations are useful to support unpredictability. To anticipate rebutting the rejection, counsel can work with inventors post-filing to design experiments for inclusion in expert declarations to further support unpredictability. Finally, secondary indicia of nonobviousness such as commercial success and long-felt unmet need can also be used to rebut obviousness rejections.

MORE

[**THERAPEUTIC ANTIBODY PATENTING,** FROM PAGE 17]

2011 decision in *Centocor v. Abbott*, found that written description is not sufficient for claimed anti-TNF-alpha antibodies wherein both the variable and constant regions were derived from human antibodies, when the specification only describes a chimeric antibody having the "variable" region of a mouse anti-TNF-alpha antibody with the "constant" region of a human antibody.[6] In another 2014 case, *AbbVie v. Janssen*, the Federal Circuit held AbbVie's written description insufficient to support a claim to a whole genus of human antibodies to interlukin-12 when the specification only describes 300 human VH3/lambda-type antibodies, which are not representative of the VH5/kappa-type of the later-invented Stelara mAb by Janssen.[7]

As a separate requirement, enablement frequently comes up with written description in antibody patenting to challenge the scope of claimed antibody genus. A key distinction from written description is that applicants can use post-filing data to show application enables claim. In a 2017 case in the U.S. Court for the District of Delaware, *Amgen Inc. et al. v. Sanofi et al.*, Amgen's claim to monoclonal antibodies that bind to particular epitope residues on a known protein PCSK9 and block low density lipoprotein receptor (LDLR) signaling for treatment of high cholesterol survived an invalidity challenge for lacking written description and enablement brought by Sanofi and Regeneron.[8] Sanofi and Regeneron had an anti-PCSK9 antibody, which binds an overlapping epitope and blocked binding of PCSK9 to LDLR. Notably, Amgen's patent applications included epitope and competitive binding testing data such as X-ray crystallography, alanine scanning, deletion studies and binning experiments. Pending the appeal outcome, broader epitope and competitive binding claims supported by extensive test data can help expand the scope of protection for antibody therapeutics.

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In view of the changing written description landscape, applicants for antibody patents should rethink antibody drafting and claiming to balance structure/function claiming. In addition to functional claiming such as epitope and competitive binding, antibody claims can include structural features such as sequences including VH, VL or key CDR residues. Further, epitope characterization, binding affinity, target specificity, pharmacological properties, and data linking structure and function are helpful for expanding claim scope.

FREEDOM-TO-OPERATE

When a company is planning to launch a new antibody therapeutic, commercialization may be blocked by a competitor who holds a broader (dominant) patent. Patent infringement litigation can be costly and time consuming. As a preventative measure, many companies seek to secure their "freedom to operate" at an early stage to ensure that the commercial production, marketing and use of their new product or process does not infringe the patent rights of their competitors.

A freedom-to-operate (FTO) analysis is the first step to understanding the competitive patent landscape. The focus of the FTO search is to determine whether claims of issued patents or pending patent applications actually cover contemplated commercialization activity. If the FTO search identifies patents that limit a company's freedom to operate, a few options are available to clear the ground for the commercialization of a new product or technology. For example, holders of a subordinate patent may obtain a license under each dominant patent. If a subordinate/improvement patent is valuable or advantageous, a cross-licensing deal may be sought with potential licensing partners.

Another option is to design around the invention. Prosecution history can be used as a roadmap to design around strategies. A company can steer research or make changes to the product or process to avoid infringing claims.

DEFENSES TO PATENT INFRINGEMENT

In the event that a company is sued for patent infringement, the company can file a declaratory judgment claim at the district court to seek invalidity and/or non-infringement as two principal defenses. An invalidity defense asserts that the granted patent is invalid because the claimed invention failed to satisfy the basic requirements for patentability, such as novelty, nonobviousness, written description and enablement requirements. On the other hand, a non-infringement defense asserts that the accused product or method does not fall within the scope of the invention claimed in the patent.

The defendant may use administrative processes and petition the USPTO to determine the validity of an asserted patent. According to the America Invents Act (AIA) *inter partes* review (IPR) procedure, a petition to the USPTO for IPR may be brought on the grounds that the challenged patent claims are invalid as anticipated or obvious based on patents or printed publications.[9] Another AIA procedure is post-grant review (PGR). A petition to the USPTO to institute a PGR may be based on any grounds that are available to challenge a patent's validity.[10] In choosing between these two options, a petitioner should take into account both the legal considerations, such as the grounds of invalidity attack, the time limit for filing petitions, the threshold requirements for instituting petitions and the scope of estoppel, as well as business considerations. For example, if the goal is to

MORE

[**THERAPEUTIC ANTIBODY PATENTING,** FROM PAGE 19]

obtain greater certainty before investing in product development, PRG may be attractive. If the goal is to remove the blocking patent, IPR may be a good option where prior art patents and printed publications are the most promising grounds of an invalidity attack.

CONCLUSION

The high cost associated with developing and commercializing therapeutic mAbs requires a sound IP strategy. Patent protection for a new antibody biologic is often sought early in the research and development process. The extensive regulatory review can lead to significant loss of patent term by the time the new biologic reaches market. Other follow-up protection methods should be considered to prolong protection beyond the original patents covering the biologic. Second or higher generation antibodies, including antibodies with novel indication, improved efficacy, reduced toxicity and increased half-life, should be protected. Clinical applications can be filed, including disease specific, route of administration, dosage regime, pharmacologic formulations, combination therapy and timing and sequence of co-administration, and mechanism of action. New antibody formats, including chimerized and humanized antibodies, antigen binding fragments (Fab), single chain variable fragments (scFv), receptor-Fc fusion peptides and antibody mimetics, can also be protected by additional patent applications to extend patent term.[11] ■

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9. 35 U.S.C. §§ 311-319, AIA § 6 (2011) and Leahy-Smith America Invents Act: Overview: Inter Partes Review (http://us.practicallaw.com/6-508-1601).
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