Difficulty in Patenting Improved Antibodies
Courts Increasingly Invalidating Claims for Lacking Written Description

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William L. Warren, Elizabeth A. Lester, Stacy D. Fredrich
Sutherland Asbill & Brennan LLP

In Centocor Ortho Biotech, Inc. v. Abbott Labs. (Feb. 23, 2011), the U.S. Court of Appeals for the Federal Circuit (the Federal Circuit) recently revisited the written description requirement set forth in 35 U.S.C. § 112, first paragraph, and invalidated Centocor's U.S. Patent No. 7,070,775 (the '775 patent), thus clarifying the standard as applied to antibody patent claims. An important decision for the biologics industry, Centocor is the latest in a line of cases in which the Federal Circuit has applied the written description requirement not only to prohibit later claiming of new subject matter, but also as a general disclosure requirement for originally filed claims.

The Federal Circuit heard the case on appeal after the U.S. District Court for the Eastern District of Texas granted Abbott’s motion for judgment as a matter of law on the issue of willfulness and set aside the jury’s finding of damages in the amount of $1.67 billion, but denied Abbott’s motions on the issues of infringement and validity. Reversing the District Court’s denial on the validity issue, the Federal Circuit held that the asserted claims of the '775 patent were invalid for failure to meet the written description requirement.

Antibody Development and Patent Filings

In the early 1990s, Centocor and Abbott both sought to develop therapeutic antibodies for neutralizing tumor necrosis factor α (TNF-α), the overproduction of which can lead to autoimmune conditions such as arthritis. The companies pursued different strategies to produce antibodies to TNF-α that had the desired neutralizing activity, high affinity, and reduced immunogenicity.

Centocor discovered the A2 mouse antibody with high affinity and the desired neutralizing activity and created a chimeric TNF-α antibody from the A2 mouse antibody by exchanging the mouse constant region with a human constant region. This research reduced immunogenicity and served as the basis for developing Centocor’s Remicade® product for the treatment of various inflammation disorders. In 1991, Centocor filed a patent application that disclosed the A2 mouse and chimeric antibodies and described the difficulties associated with making a fully-human antibody (e.g., one with both human variable and constant regions) to a human protein like TNF-α.

Meanwhile, Abbott created a large phage database of human variable regions and, used molecular techniques of guided selection, chain shuffling, and affinity maturation, to create a fully-human antibody with a high TNF-α affinity. This fully-human antibody became the basis for Abbott’s Humira®, for which they filed a patent application in 1996, and received FDA approval in 2002 also for treating inflammatory disorders.
Subsequently, Centocor filed its own patent claims to human variable regions and fully-human TNF-α antibodies as part of a thirteenth application in the still-pending patent family disclosing only the A2 mouse and chimeric antibodies. This thirteenth application, which relied on a series of continuation-in-part (CIP) applications filed in 1994 to pre-date Abbott’s 1996 filing date, issued as the ‘775 patent in 2006. At that time, Centocor sued Abbott asserting that Humira® infringed Claims 2, 3, 14, and 15. Claims 1 and 2 of the ‘775 patent are reproduced below:

1. An isolated recombinant anti-TNF-α antibody or antigen-binding fragment thereof, said antibody comprising a human constant region, wherein said antibody or antigen binding fragment
   (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α, and
   (ii) binds to a neutralizing epitope of human TNF-α in vivo with an affinity of at least $1 \times 10^8$ liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.

2. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment comprises a human constant region and a human variable region.

On appeal from the denial of Abbott's motions for non-infringement and invalidity, the Federal Circuit stated that “for Centocor to prevail, the asserted claims must be supported by adequate written description in the 1994 CIP applications.” Upon considering the four corners of the CIP applications, which described only the A2 mouse and chimeric antibodies, the court invalidated the asserted claims because “while the patent broadly claims a class of antibodies that contain human variable regions, the specification does not describe a single antibody that satisfies the claim limitations.” Furthermore, the court noted, “the mouse variable region sequence does not serve as a stepping stone to identifying a human variable region within the scope of the claims.”

The court explained that Centocor’s reliance on the U.S. Patent and Trademark Office (PTO) Written Description Guidelines (the PTO Guidelines) was based on an unduly broad characterization of the court’s prior decision in Noelle v. Lederman, 355 F.3d 1343 (2004) and the antibody example contained in the PTO Guidelines. Distinguishing the present case, the court stated that “[w]hile our precedent suggests that written description for certain antibody claims can be satisfied by disclosing a well-characterized antigen, that reasoning applies to disclosure of newly characterized antigens where creation of the claimed antibodies is routine.”

By contrast, TNF-α was known in the prior art, and the creation of human antibodies to TNF-α could not be described as routine in 1994, the priority date of the ‘775 patent. Overall, the court reasoned, “the asserted claims to fully-human antibodies ‘merely recite a description of the problem to be solved while claiming all solutions to it’” as well as a “wish list of properties that a fully-human, therapeutic TNF-α antibody should have,” and such a “mere wish or plan” is not sufficient to satisfy the written description requirement.
Evidence of Possession Required

In holding that Centocor’s asserted claims lacked written description, the Federal Circuit reaffirmed that an adequate written description is measured by whether the disclosure contained in the patent application reasonably conveys to one skilled in the art that the inventor possessed the claimed invention as of the filing date. While working examples and actual reduction to practice are not required for sufficiency under the written description requirement, the court stated that one of skill in the art should be able to “visualize or recognize” the claimed invention based on the specification.

As established by past cases, possession of biologics may be demonstrated by reciting precise structural characteristics either explicitly (e.g., by listing the amino acid sequence of the antibody) or implicitly (e.g., by providing a deposit). The written description exemption for antibodies as outlined in the PTO Guidelines, which permits generic claims to antibodies against newly identified antigens, does not extend to claims to antibodies with a specific properties such as minimum binding affinity or human variable region where such species have not been demonstrated to exist.

The decision in Centocor demonstrates the increased willingness of courts to invalidate claims for lacking written description, as a separate requirement from enablement, especially in the biological arts. Thus, patent applications for improved biologics should be drafted with care to meet the current “possession” standard, for example, by explicitly reciting an antibody’s structure or observed activity. Additionally, multiple working examples of sequenced antibodies exhibiting the desired activity may support broader claims to antibodies with a percentage sequence identity or their encoding genes with variable nucleic acid hybridization. Furthermore, companies should consider process, manufacturing, and technology platform patents as additional means to protect their biologics, biosimilars, and bio-better innovations.