LEGAL UPDATE

THERAPEUTIC ANTIBODY PATENT INFRINGEMENT LITIGATION: UNTESTED AND UNCERTAIN LITIGATION STRATEGIES UNDERPIN PATENTS PROTECTING MULTIBILLION-DOLLAR PHARMACEUTICALS

Douglas G. Metcalf, Ph.D.[*]

ABSTRACT

Federal Circuit opinions have long espoused the maxim that patents can claim genera of antibodies, only to invalidate two such patents in *Chiron Corp. v. Genentech, Inc.* and *Centocor Ortho Biotech, Inc. v. Abbott Laboratories*, disputes over rights to multibillion-dollar pharmaceuticals. This Update resolves the intra-circuit split by characterizing an implicit distinction in Federal Circuit precedent: method-of-use patents may claim genera of antibodies while composition patents enjoy less freedom to make broad claims. This distinction fostered two new patenting strategies. A conservative approach claims specific antibodies rather than genera and threatens enforcement pursuant to the doctrine of equivalents, which cedes the patent's fate to the jury. An aggressive approach claims genera of antibodies in method-of-use patents, but risks patent invalidation should the Federal Circuit extend *Chiron* and *Centocor* to method-of-use patents. Both strategies, however, remain untested in the courts.

I. INTRODUCTION

On February 23, 2011, the Court of Appeals for the Federal Circuit (the "Federal Circuit") vacated a $1.67 billion jury verdict, the largest patent infringement award in U.S. history, because the patent claims overreached the scope of the invention.[1] The disputed patent protected Centocor's drug Remicade.[2] Centocor alleged that Abbott's drug Humira infringed Remicade's patent.[3] Both Remicade and Humira are therapeutic antibodies administered to treat rheumatoid arthritis, among other conditions, and their combined annual sales exceed $16 billion.[4] Financial analysts predict that Humira's lifetime

[*] J.D. Candidate, Boston University School of Law, Class of 2013; Ph.D., Biochemistry and Molecular Biophysics, University of Pennsylvania School of Medicine, 2009.

[1] Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1353 (Fed. Cir. 2011).

[2] Susan Decker, *Court Reverses Ruling on Arthritis Drug Patent*, BOSTON GLOBE, Feb. 24, 2011, http://www.boston.com/lifestyle/health/articles/2011/02/24/court_reverses_ruling_on_arthritis_drug_patent/.

[3] *Centocor*, 636 F.3d at 1353; Decker, *supra* note 2.

[4] Abbott Labs., Annual Report (Form 10-K) 28 (Feb. 21, 2012) (reporting that Humira

sales could exceed $130 billion, which would make Humira the world's highest grossing drug ever.[5] Despite Centocor's spectacular loss, several patent holders are aggressively litigating the alleged infringement of identically-styled patent claims, suggesting that a subtle distinction will allow their patents to survive where Centocor's patent failed.[6]

Therapeutic antibodies constitute the fastest growing class of drugs.[7] Dozens of investigational therapeutic antibodies are in Phase III clinical trials, and over a hundred are in other stages of clinical development.[8] Of the world's twelve largest pharmaceutical companies, only Pfizer currently lacks a commercial therapeutic antibody, and it has fourteen investigational therapeutic antibodies in clinical trials.[9]

The patents shielding Big Pharma's investments face an uncertain future against a sparse backdrop of amorphous case law: "U.S. patent law was first

sales totaled $7.9 billion in 2011); Johnson & Johnson, Annual Report (Form 10-K) 28 (Feb. 23, 2012) (reporting that Remicade sales totaled $5.5 billion in 2011); Merck & Co., Inc., Annual Report (Form 10-K) 4 (Feb. 28, 2012) (reporting that Merck licenses Remicade from Johnson & Johnson and its sales totaled close to $2.7 billion in 2011).

[5] Randsdell Pierson & Bill Berkot, *Analysis: Lipitor, Legendary Cash Cow, Prepares for Fadeout*, REUTERS, Nov. 6, 2011, *available at* http://www.reuters.com/article/2011/11/06/us-lipitor-idUSTRE7A51R520111106 (predicting that sales of Humira could exceed Lipitor's $130 billion lifetime sales).

[6] Genentech, Inc. v. Trs. of Univ. of Pa., No. 10-02037 (N.D. Cal. filed May 11, 2010); Biogen Idec, Inc. v. GlaxoSmithKline LLC, No. 10-00608 (S.D. Cal. filed Mar. 24, 2010); *see infra* Part IV.B–C.

[7] *Fast Growth MAb Market to Offer Great Rewards to a Select Few Over 2009-15*, DATAMONITOR (Nov. 1, 2010), *available at* http://www.datamonitor.com/store/News/?productid=A31659B5-E3F6-4C49-8C5B-DF524E8EB770 ("The MAb [antibody] sector will provide the highest growth across the entire [pharmaceutical] industry.").

[8] Janice M. Reichert, *Antibody-based Therapeutics to Watch in 2011*, 3 MABS 76, 76 (2011).

[9] Pfizer lacks a commercial therapeutic antibody, but it has at least fourteen investigational therapeutic antibodies in clinical trials. *See Pfizer Pipeline*, PFIZER, 5–11 (Feb. 28, 2012), http://www.pfizer.com/files/research/pipeline/2012_0228/pipeline_2012_0228.pdf (noting that Pfizer's investigational therapeutic antibodies include: RN316, CVX 096, PF-04840082, SBI-087, anrukinzumab, PF-00547659, PF-04236921, bapineuzumab, tanezumab, AAB-003, inotuzumab ozogamicin, CVX 060, PF-05082566, RN6G). The remaining 11 largest pharmaceutical companies market therapeutic antibodies as follows: Johnson & Johnson (Remicade, Simponi, Orthoclone, Stelara); Novartis (Xolair, Simulect, Ilaris, Lucentis); Roche (Avastin, Rituxan, Herceptin, others); Bayer (Zevalin); GlaxoSmithKline (Arzerra, Benlysta, Bexxar); Merck (Remicade, Erbitux, Simponi); Sanofi (Campath); Abbott (Humira); AstraZeneca (Synagis); Eli Lilly (ReoPro); Bristol-Myers Squibb (Erbitux; Yervoy). *See generally Pharmaceuticals & Biotech Industry Global Report*, IMAP, Appendix (2011), http://www.imap.com/imap/media/resources/IMAP_PharmaReport_8_272B8752E0FB3.pdf (ranking pharmaceutical companies by 2010 sales).

written in 1790, and its principal author, Thomas Jefferson, didn't have much to say about monoclonal antibodies . . . ."[10] *Centocor* highlights some of the challenges attorneys face when drafting therapeutic antibody patents. This Update identifies questions raised by *Centocor* that remain ripe for litigation, a second wave of lawsuits aimed at circumventing those issues, and other tactics that protect therapeutic antibodies but remain untested in court.

The *Centocor* opinion invalidated a composition patent because it claimed a group of antibodies, called a genus, without adequately describing it.[11] Despite Centocor's loss, several patent infringement cases are proceeding with identically-styled claims in method-of-use patents.[12] This Update proposes that patents claiming methods of using antibodies can validly claim genera of antibodies, while composition patents enjoy less freedom to make genus claims—and if Centocor had asserted a method-of-use patent, its $1.67 billion jury verdict might have survived. This Update addresses this central thesis and related issues. Part III identifies two recent court battles that failed in attempting to enforce composition patents against multibillion-dollar therapeutics. Part IV identifies an increasing reliance on the doctrine of equivalents to protect therapeutic antibodies, a tactic that remains untested in the courts.[13] Finally, Part V assesses the probability that the current trend toward enforcing method-of-use patents will succeed where composition patents have failed.

---

[10] Rick Weiss, *How Do You Patent a New Elephant*, WASH. POST, Sept. 20, 1987, at C3.

[11] Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1352–53 (Fed. Cir. 2011).

[12] *See infra* Part IV.B–C; Genentech, Inc. v. Trs. of Univ. of Pa., No. 10-02037 (N.D. Cal. filed May 11, 2010); Biogen Idec, Inc. v. GlaxoSmithKline LLC, No. 10-00608 (S.D. Cal. filed Mar. 24, 2010). Inventors may patent either the composition of a drug or a method of using the drug, and the two types of patents contain subtle differences. *See generally* Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1385–86 (Fed. Cir. 2003) (citing *In re* Byck, 48 F.2d 665, 666 (1931)) (allowing either a composition or method patent for the same drug, but not both).

[13] *See, e.g.*, U.S. Patent No. 8,048,420 col.30–31 (filed June 12, 2008) (claiming a single antibody, but declaring rights to any "functionally equivalent antibody"); U.S. Patent No. 8,034,904 col.10 l.36–56 (filed Dec. 8, 2003) (claiming a single antibody, but declaring "[t]he invention also includes functional equivalents of the antibodies described in this specification"); U.S. Patent No. 8,008,448 col.10 l.38–42 (filed Mar. 8, 2008) ("Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention specifically described herein. Such equivalents are intended to be encompassed in the scope of the claims."). *See also* Goldenberg v. Cytogen, Inc., 373 F.3d 1158, 1168–69 (Fed. Cir. 2004) (preserving infringement claims pursuant to the doctrine of equivalents for antibodies).

II. THERAPEUTIC ANTIBODIES ARE THE BASIS FOR A NEW GENERATION OF DRUGS.

In 1984, Georges Köhler and César Milstein won the Nobel Prize for discovering monoclonal antibodies, perhaps the most important discovery in modern medicine.[14] Doctors previously knew they could elicit an immune response by injecting patients with foreign material, the basis for vaccination.[15] The immune response fosters the production of antibodies that recognize, bind, and neutralize the foreign material.[16] Scientists then discovered they could take advantage of the immune response to produce antibodies that target a specific molecule, called an antigen.[17] To do so, a researcher injects the target molecule into an animal and later draws the animal's blood to harvest its antibodies.[18] Köhler and Milstein recognized they could harvest antibody-producing cells, and they hybridized these cells with immortal cell lines to create hybrid cell lines, called hybridomas.[19] A hybridoma secretes a single antibody, called a monoclonal antibody, which can bind and identify its target molecule.[20] Monoclonal antibodies fostered a multibillion-dollar industry comprising various diagnostic tests, such as the pregnancy and HIV tests which rely on antibodies to bind and identify a target molecule in a patient's blood or urine.[21] Additionally, doctors can administer monoclonal antibodies as drugs, called therapeutic antibodies, to alter a molecule's function in a patient.[22] In many cancer applications, therapeutic antibodies simply kill

---

[14] Johathon W. Uhr, *The 1984 Nobel Prize in Medicine*, 226 SCIENCE 1025, 1025 (1984); *see also* Benjamin Yang, *Cesar Milstein*, DISCOVERY MED., May 15, 2009, *available at* ://www.discoverymedicine.com/Benjamin-Yang/2009/05/15/news-and-quotes-cesar-milstein/ ("Cesar Milstein's contributions to science and medicine were among the most important ever made.").

[15] Stanley A. Plotkin, *Vaccines, Vaccination, and Vaccinology*, 187 J. INFECTIOUS DISEASES 1349, 1349 (2003).

[16] CHARLES A. JANEWAY, JR. ET AL., IMMUNOBIOLOGY, glossary (5th ed. 2001) ("antibody" definition).

[17] Uhr, *supra* note 14, at 1025.

[18] *Id*.

[19] *Id*. at 1025–26; Georges Köhler & César Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 NATURE 495, 495–97 (1975).

[20] Uhr, *supra* note 14, at 1026; Köhler & Milstein, *supra* note 19, at 495–97.

[21] Hybritech pioneered the antibody-based diagnostics industry. *See* Penni Crabtree, *A Magical Place*, SAN DIEGO UNION-TRIBUNE, Sept. 14, 2003, at H-1. Analysts estimate that antibody-based diagnostics earned $8 billion in 2009. *2009 Antibody Report Market Overview and Industry Survey Executive Summary*, BIOCOMPARE, 4–5 (Mar. 24, 2009), http://www.biocompare.com/Documents/surveys_files/ExecSumm/Antibodies_2009_ExecSumm.pdf.

[22] *See, e.g*., Dale L. Ludwig et al., *Monoclonal Antibody Therapeutics and Apoptosis*, 22 ONCOGENE 9097, 9097–98 (2003).

cancer cells.[23]

In most applications, therapeutic antibodies must emulate human antibodies; otherwise they would elicit an immune response of their own.[24] Researchers produced early therapeutic antibodies from mouse antibodies by altering them to mask portions of the antibody that would trigger an immune response.[25] For example, Centocor created Remicade by converting a mouse antibody into a chimeric mouse/human antibody.[26] Using a different approach, Genentech "humanized" a mouse antibody to invent Herceptin by converting nearly the entire mouse antibody into its human counterpart.[27] Researchers can now create fully-human antibodies that bind a desired target, bypassing the need to change an antibody to avoid a patient's immune response.[28] Different strategies for producing antibodies can create dozens of different drug candidates that could each be useful in treating the same disease.[29] Consequently, patents claiming single antibodies have little value insofar as they exclude competitors from marketing identical antibodies. Instead, attorneys must craft patents that cover antibodies the inventor did not create.

III. COMPOSITION PATENTS I: COMPOSITION PATENTS CLAIMING GENERA OF ANTIBODIES RISK INVALIDATION FOR FAILING TO ENABLE THE FULL SCOPE OF THEIR CLAIMS.

Patents claiming single antibodies have little value to the extent that they create monopolies on individual antibodies because any number of similar yet chemically distinct antibodies can perform equivalent functions. Instead, many antibody patents claim genera of antibodies, a strategy that relies on tenuous Federal Circuit precedent.[30]

---

[23] *Id*. at 9101–02.

[24] Lutz Riechmann et al., *Reshaping Human Antibodies for Therapy*, 332 NATURE 323, 323 (1988) ("The foreign immunoglobulin [antibody], however, can elicit an anti-globulin response [immune response] which may interfere with therapy or cause allergic or immune complex hypersensitivity. Thus, ideally human antibodies would be used." (citations omitted)).

[25] Aaron L. Nelson et al., *Development Trends for Human Monoclonal Antibody Therapeutics*, 9 NATURE REV'S DRUG DISCOVERY 767, 767 (2010).

[26] David M. Knight et al., Construction and Initial Characterization of a Mouse-human Chimeric Anti-TNF Antibody, 30 MOLECULAR IMMUNOLOGY 1443 (1993).

[27] Paul Carter, *Humanization of an Anti-p185^{HER2} Antibody for Human Cancer Therapy*, 89 PROC. NAT'L ACAD. SCI. USA 4285, 4285–87 (1992).

[28] Ludwig, *supra* note 22, at 9097 ("[T]he isolation of high-affinity fully human monoclonal antibodies is now commonplace.").

[29] *See, e.g.*, C. Lloyd et al., *Modelling the Human Immune Response: Performance of a 10^{11} Human Antibody Repertoire Against a Broad Panel of Therapeutically Relevant Antigens*, 22 PROTEIN ENGINEERING, DESIGN & SELECTION 159, 163 (2009).

[30] *See, e.g.*, Noelle v. Lederman, 355 F.3d 1343, 1349–50 (Fed. Cir. 2004); *accord*

Several Federal Circuit opinions propagate the maxim that patents can claim genera, but no Federal Circuit opinion upholds a claim to a genus of antibodies that was challenged for failing to enable the claim's full scope.[31] Invalidation reflects two issues. First, patent attorneys generally attempt to secure the broadest allowable claims for their clients.[32] Second, the U.S. Patent & Trademark Office ("USPTO") frequently allows broad claims in antibody patents.[33] The drafting and allowance of broad claims relies on three Federal Circuit opinions, discussed in Part III.A–B, but two subsequent opinions curb genus claims, discussed in Part III.C.

A. The In re Wands *opinion propagated the precept that patents can claim genera of antibodies by merely disclosing a target molecule.*

In 1988, the *In re Wands* court held that a patent application sufficiently enabled claims to a genus of antibodies.[34] Wands and his co-inventors developed a diagnostic test for Hepatitis B that relied on an antibody to detect it.[35] The test could employ any number of different antibodies to identify Hepatitis B; thus, the patent application validly claimed a genus of antibodies. In fact, this claim was narrow relative to a related patent: Hybritech patented its pioneering "sandwich assay" in 1983, claiming an antibody-based diagnostic test that encompassed virtually every antibody regardless of its target or origin.[36]

Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d at 1351–52.

[31] *See, e.g.*, *Centocor*, 636 F.3d at 1351–52; *Noelle*, 355 F.3d. at 1349. The *In re Wands* court came closest to addressing the scope of enablement issue as applied to an antibody. *See infra* Part III.A; *In re Wands*, 858 F.2d 731, 740–42 (Fed. Cir. 1988) (Newman, J., dissenting in part).

[32] Jerome D. Drabiak, *Patents, Copyrights, and Trademarks: A Primer on Protecting Intellectual Work Product*, 11 S. ILL. U. L.J. 1, 9 (1986) ("Broadly worded claims are preferred over narrow claims.").

[33] U.S. PATENT & TRADEMARK OFFICE, WRITTEN DESCRIPTION TRAINING MATERIALS 45–46 (Mar. 25, 2008), *available at* http://www.uspto.gov/web/menu/written.pdf; *see also Noelle*, 355 F.3d at 1349 (applying the USPTO's guidelines); Ex parte Griffiths, No. 2004-1660, 2004 WL 4983380, at *2–3 (B.P.A.I. Dec. 9, 2004) (holding that an inventor can claim a genus of antibodies by disclosing a single antibody). *See, e.g.*, U.S. Patent No. 6,733,752 col. 8–10 (filed Nov. 20, 1995).

[34] *In re Wands*, 858 F.2d at 736–40. The patent application claimed methods of using antibodies, but it provided precedent for genus claims in composition patents, discussed in Part II.B, *infra*.

[35] U.S. Patent No. 4,879,219 col.15 l.52–65 (filed Sept. 19, 1980); Jack R. Wands et al., *Immunodiagnosis of Hepatitis B with High-Affinity IgM Monoclonal Antibodies*, 78 PROC. NAT'L ACAD. SCI. U.S.A. 1214, 1214–17 (1981).

[36] U.S. Patent No. 4,376,110 col.9 l.15–51 (filed Aug. 4, 1980). Prior to *In re Wands*, the *Hybritech* opinion held Hybritech's patent valid. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385 (Fed. Cir. 1986).

In the decade preceding *In re Wands*, the USPTO allowed dozens of patents claiming genera of antibodies.[37] Allowance was rational because the laboratory protocols required to produce antibodies were routine relative to purification methods for target molecules; thus, an inventor who could make an individual monoclonal antibody could presumably make more.[38] Additionally, scientists lacked technology to adequately distinguish antibodies. For example, in the early 1990's, it would have cost over $100,000 to sequence the DNA of ReoPro, a therapeutic antibody.[39] Further, even if scientists could economically distinguish different antibodies, patents claiming individual antibodies would have trivial value.[40] Consequently, the *In re Wands* court could not invalidate genus claims without both invalidating scores of patents and depriving inventors of an economical means to obtain patent protection for antibodies.

In re Wands remains good law. Subsequent opinions, however, curtailed its reach.[41] Prophetically, Judge Pauline Newman dissented because she believed the application's disclosure lacked adequate support for genus claims.[42] Few

[37] *USPTO Patent Full-Text and Image Database*, U.S. PATENT & TRADEMARK OFFICE, http://patft.uspto.gov/netahtml/PTO/search-adv.htm (search for "TTL/(antibody or antibodies) AND ISD/3/20/1979->9/30/1988"). The USPTO first allowed patents claiming genera of antibodies in 1982. *See, e.g.*, U.S. Patent No. 4,363,799 col.13 l.19–36 (filed Mar. 20, 1979).

[38] *In re Wands*, 858 F.2d at 739–40; U.S. PATENT & TRADEMARK OFFICE, WRITTEN DESCRIPTION TRAINING MATERIALS 46 (Mar. 25, 2008), *available at* http://www.uspto.gov/web/menu/written.pdf ("[P]roduction of antibodies against a well-characterized antigen [is] conventional.").

[39] ReoPro was the second FDA-approved therapeutic antibody, approved in 1992. Its DNA consists of over 9500 base pairs: 3500 base pairs encoding its heavy chain, 6000 base pairs encoding its light chain, and regulatory elements from their expression vectors (*3500 + 6000 = 9500*). *See* U.S. Patent No. 5,877,006 col.9–10 (filed May 17, 1995). In 1990, sequencing cost just over $10 per base pair. *See* Robert F. Service, *The Race for the $1000 Genome*, 311 SCIENCE 1544, 1544 (2006). Thus, conservatively estimating a total length of 10,000 base pairs, it would cost over $100,000 to sequence ReoPro's DNA (*10,000 × $10 = $100,000*). In comparison, the total attorney's fees to obtain global patent protection for an invention cost roughly $13,339 in 1990. *See* AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION, REPORT OF THE ECONOMIC SURVEY 26 (1991).

[40] A patent claiming an individual antibody has trivial value insofar as it excludes competitors from marketing identical antibodies because any number of similar yet chemically distinct antibodies could accomplish the same function. *See supra* Part I.

[41] Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341 (Fed. Cir. 2011); Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1253 (Fed. Cir. 2004); Bernard Chao, *Rethinking Enablement in the Predictable Arts: Fully Scoping the New Rule*, 2009 STAN. TECH. L. REV. 3, ¶16, *available at* http://stlr.stanford.edu/pdf/chao-rethinking-enablement.pdf; *see infra* Part II(C).

[42] *In re Wands*, 858 F.2d at 740–42 (Newman, J., dissenting in part). Judge Newman is the only member of the *In re Wands* court who remains on the Federal Circuit today.

attorneys heeded Judge Newman's warning; otherwise, Centocor might have avoided its $1.67 billion mistake.[43]

B. The Johns Hopkins *and* Noelle *opinions state that patents can claim genera of antibodies in dicta, extending* In re Wands *to composition patents.*

Two subsequent Federal Circuit opinions upheld patents claiming genera of antibodies, extending genus claims to composition patents, but neither opinion ruled on whether the patents enabled the full scope of their claims.[44] First, in *Johns Hopkins University v. CellPro, Inc.*, the court affirmed a motion for summary judgment upholding a patent that claimed a genus of antibodies.[45] The opinion did not address the scope of enablement issue because the issue was not raised in a lower court.[46] Second, in *Noelle v. Lederman*, the court addressed a patent claiming antibody genera including mouse, chimeric, humanized, and fully-human antibodies, but the opinion disposed of the case without addressing the scope of enablement issue.[47]

Both the *Johns Hopkins* and *Noelle* opinions endorsed genus claims in dicta but avoided ruling on whether the disclosure of individual antibodies adequately enabled a genus.[48] In light of these opinions, the USPTO continues to expressly allow claims to antibody genera, reiterating its policy that patents can claim genera of antibodies simply by disclosing a single antibody.[49] Ten weeks after *Noelle*, the *Chiron* opinion rejected similar genus claims without addressing either *Noelle* or *Johns Hopkins*, and the remainder of Part III addresses genus claims that exceed their patent's scope of enablement.

C. The Chiron *and* Centocor *opinions invalidated composition patents claiming genera of antibodies.*

In the two cases that required the Federal Circuit to rule on whether the disclosure of individual antibodies sufficiently enabled the full scope of a

---

[43] *Centocor*, 636 F.3d. at 1341.

[44] Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004); Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342 (Fed. Cir. 1998).

[45] *Johns Hopkins*, 152 F.3d at 1359–61; U.S. Patent No. 4,965,204 col.20–21 (filed June 1, 1987).

[46] *Johns Hopkins*, 152 F.3d at 1361–62.

[47] *Noelle*, 355 F.3d at 1345–46; U.S. Patent No. 5,474,771 col.31 l.5–22 (filed Nov. 15, 1991). The *Noelle* opinion reviewed an interference proceeding and rejected every claim that challenged the patent at issue; thus, the *Noelle* court avoided adjudicating the patent's validity. *See Noelle*, 355 F.3d at 1349–50.

[48] *Noelle*, 355 F.3d at 1349; *Johns Hopkins*, 152 F.3d at 1359–61.

[49] *See, e.g.*, Ex parte Gately, No. 11-003784, 2011 WL 3843855, at *1–3 (B.P.A.I. Aug. 26, 2011).

genus, the resultant opinions invalidated each patent.[50] First, in 2000, Chiron sued Genentech claiming the therapeutic antibody Herceptin infringed a patent that claimed all antibodies to the same target.[51] Herceptin's primary market consists of breast cancer patients, and its 1999 sales surpassed $188 million while Chiron marketed no competing product.[52] In this case, the jury invalidated Chiron's patent and the Federal Circuit upheld the verdict.[53] Second, in 2007, Centocor sued Abbott claiming the fully-human therapeutic antibody Humira infringed a patent that claimed both fully-human and chimeric antibodies.[54] Centocor began marketing its chimeric antibody Remicade in 1998 while Abbott introduced Humira in 2003; both drugs are administered to treat rheumatoid arthritis, among other conditions.[55] In this case, the jury found Centocor's patent valid and infringed, and it awarded Centocor $1.67 billion.[56] The Federal Circuit, however, invalidated Centocor's patent as a matter of law and vacated the jury award.[57]

---

[50] Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341 (Fed. Cir. 2011); Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1247 (Fed. Cir. 2004).

[51] *Chiron*, 363 F.3d at 1252.

[52] *Id*. at 1260–61 (the district court admitted evidence of Herceptin's commercial success and "the absence of a commercial embodiment by Chiron"); Genentech Inc., Annual Report (Form 10-K405) (Feb. 8, 2000) (describing Herceptin's market).

[53] *Chiron*, 363 F.3d at 1261. Herceptin's annual sales currently exceed $5 billion. *See* Roche, 2011 Annual Report 66 (2012), *available at* http://www.roche.com/gb11e.pdf (*1 CHF = $1.1 USD*).

[54] *Centocor*, 636 F.3d at 1346–47.

[55] Letter from Jay P. Siegel, FDA, to Jeanne Fox, Abbott Laboratories (Dec. 31, 2002), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/adalabb123102L.htm; Letter from Karen Weiss, FDA, to Martin Page, Centocor (Nov. 10, 1999), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1999/inflcen111099L.htm (approving Remicade for treating rheumatoid arthritis); Letter from Jay P. Siegel, FDA, to Martin Page, Centocor (Aug. 24, 1998), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/inflcen082498L.htm (approving Remicade for treating Crohn's disease, Remicade's first approved indication). In the years preceding the lawsuit, Humira slowly eroded Remicade's market share, and the year before Centocor filed its complaint, Humira sales totaled $2 billion. *See* Abbott Labs., Annual Report (Form 10-K) 27 (Feb. 23, 2007); *see also* Francine Knowles, *Abbott Sees Humira Benefiting from Rivals' Marketing*, CHICAGO SUN-TIMES, March 17, 2003, at 50 (quoting Tim Walbert of Abbott, and stating that Centocor's advertising for Remicade would increase Abbott's sales of Humira). In comparison, Centocor's sales of Remicade exceeded $3 billion. Johnson & Johnson, Annual Report (Form 10-K) 40 (Feb. 21, 2007) (Centocor is a subsidiary of Johnson & Johnson); *see also* Schering-Plough Corp., Annual Report (Form 10-K) 9 (Feb. 28, 2008) (Schering-Plough licensed Remicade from Centocor, and its 2007 sales totaled $1.6 billion).

[56] *Centocor*, 636 F.3d at 1343–44.

[57] *Id*. at 1353. Humira sales now surpass Centocor's Remicade sales, with 2011 sales totaling $7.8 and $5.5 billon, respectively. *See* Abbott Labs., Annual Report (Form 10-K)

In both the Humira and the Herceptin lawsuits, the asserted patents not only contained broad genus claims, but they also claimed their competitors' products. In the Humira litigation, Centocor's patent claimed "[an] antibody . . . wherein the antibody . . . comprises a human constant region and a human variable region."[58] This claim expressly encompasses Humira, which is comprised of human constant and variable regions.[59] Notably, this dependent claim fell within the scope of a broader genus claim.[60] Thus, rather than relying on a broad genus claim to exclude Humira, Centocor chose to expressly claim Humira. Centocor never created or disclosed such an antibody, and the patent was invalidated for failing to enable this claim.[61] Similarly, Chiron attempted to claim Herceptin, albeit a bit more subtly. Chiron's patent claimed "[a] monoclonal antibody that binds to human c-erbB-2 antigen."[62] This broad genus claim encompasses Herceptin, a humanized antibody, but the patent did not expressly claim humanized antibodies. Instead, the patent defined the genus claim to include Herceptin, stating "[t]he term 'antibody' encompasses . . . humanized antibodies."[63] Chiron's patent, however, did not enable humanized antibodies.[64] Thus, both Centocor and Chiron's patents defined their scope to encompass antibodies the inventors neither created nor disclosed, which provided a basis to cancel the offending claims.

Although *Chiron* and *Centocor* illustrate the perils of genus claims, they neglect to identify whether the asserted patents failed for making genus claims or for defining their scope. The *Chiron* opinion hints that Chiron's patent might have remained valid had it not defined "antibody" to include humanized antibodies, stating that "the law does not expect an applicant to disclose knowledge invented or developed after the filing date."[65] The opinion provides no guidance, however, as to whether the *Chiron* court would have vacated the jury's finding of invalidity under these facts, and if so, whether Herceptin would have infringed a valid genus claim. In an interesting twist to the *Centocor* case, Bayer owned a composition patent claiming all human antibodies that target the same molecule as Humira, and Bayer engaged Abbott

28 (Feb. 21, 2012) (Humira, $7.9 billion); Johnson & Johnson, Annual Report (Form 10-K) 28 (Feb. 23, 2012) (Remicade, $5.5); *see also* Merck & Co., Inc., Annual Report (Form 10-K) 4 (Feb. 28, 2012) (Remicade, $2.7 billion).

[58] U.S. Patent No. 7,070,775 col.107 l.43–46 (filed July 18, 2002).

[59] *Centocor*, 636 F.3d at 1347.

[60] U.S. Patent No. 7,070,775 col.107 l.34–42.

[61] *Centocor*, 636 F.3d at 1349 ("[V]ery little in the '775 patent supports that Centocor possessed [the fully-human antibody it claimed].").

[62] U.S. Patent No. 6,054,561 col.80 l.42–43 (filed June 7, 1995).

[63] *Id*. col.8 l.36–39.

[64] Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1253–57 (Fed. Cir. 2004).

[65] *Id*. at 1254 (citing *In re* Hogan, 559 F.2d 595, 605–06 (C.C.P.A. 1977)).

in infringement litigation.[66] Bayer stipulated to a judgment to appeal an adverse trial court order, but the appeal was subsequently dismissed.[67] Consequently, the Federal Circuit missed a prime opportunity to distinguish or extend its *Centocor* holding.

In response to *Chiron*, most therapeutic antibody patents now claim individual antibodies rather than genera.[68] As a precaution, many of these patents describe genera of antibodies without claiming them to render subsequent, competing antibodies unpatentable.[69] These disclosures may serve the additional purpose of aiding infringement claims pursuant to the doctrine of equivalents, to which this Update now turns.

IV. COMPOSITION PATENTS II: COMPOSITION PATENTS INCREASINGLY CLAIM SPECIES OF ANTIBODIES AND DECLARE RIGHTS PURSUANT TO THE DOCTRINE OF EQUIVALENTS.

Patent holders increasingly rely on the doctrine of equivalents to exclude competition rather than claims to genera of antibodies.[70] Although the USPTO

[66] U.S. Patent No. 5,654,407 col.23 l.6–8 (filed May, 5, 1995). Following the termination of Bayer's attempts to enforce this patent, the USPTO canceled the patent's genus claims. *See* '407 Patent, at Ex parte Reexamination Certificate col.2 l.4–5. *See also* Abbott Labs. v. Bayer Healthcare LLC, No. 09-40002, 2010 WL 4340565 (D. Mass. Oct. 25, 2010). Bayer also sued Centocor in an attempt to enforce the patent against Centocor's fully-human therapeutic antibody Simponi. *See* Bayer Healthcare, LLC v. Centocor Ortho Biotech Inc., No. 09-11362 (D. Mass. filed Aug. 14, 2009).

[67] *Abbott Labs*., 2010 WL 4340565; Abbott Labs. v. Bayer Healthcare LLC, 458 F. App'x 895, 895 (Fed. Cir. 2011).

[68] Each party involved in aforementioned litigation now claims individual antibodies in its patents instead of antibody genera. *See, e.g*., U.S. Patent No. 8,030,026 col.87–88 (filed Feb. 24, 2009) (Abbott); U.S. Patent No. 8,012,482 col.129–32 (filed Apr. 14, 2009) (Genentech); U.S. Patent No. 7,993,878 col.19–22 (filed Sept. 26, 2008) (Novartis, Chiron's parent company); U.S. Patent No. 7,718,778 col.33–34 (filed Oct. 27, 2006) (Centocor); U.S. Patent No. 7,285,640 col.93–94 (filed Dec. 16, 2002) (Bayer). Other biotech and pharmaceutical companies have followed suit. Interestingly, Genentech includes genus claims in its patent applications prior to allowance, possibly in anticipation of a change to the case law. *See, e.g*., U.S. Patent Application No. 13/087247 (filed Apr. 14, 2011) (claim 15); U.S. Patent Application No. 13/069582 (filed Mar. 23, 2011) (claim 1); U.S. Patent Application No. 13/034551 (filed Feb. 24, 2011) (claim 1).

[69] *See, e.g*., U.S. Patent No. 8,029,783 (filed Jan. 30, 2006) (claiming individual antibodies, but disclosing methods of making chimeric, humanized, and fully-human antibodies).

[70] *See, e.g*., U.S. Patent No. 8,034,904 col.10 l.36–56 (filed Dec. 8, 2003) ("The invention also includes functional equivalents of the antibodies described in this specification."); U.S. Patent No. 7,482,434 col.60 l.39–46 (filed Dec. 19, 2006) ("[T]he invention should be construed in accordance with the appended claims and any equivalents thereof."); U.S. Patent No. 6,764,679 col.42 l.31–47 (filed June 28, 2001) ("[A]ny

still allows claims to genera of antibodies,[71] such patents risk invalidation in light of *Chiron* and *Centocor*.[72] The *Chiron* and *Centocor* plaintiffs alleged the literal infringement of genera claims. If the patents claimed individual antibodies instead of antibody genera, the plaintiffs could have maintained a cause of action pursuant to the doctrine of equivalents, and their patents might have survived. By arguing the doctrine of equivalents, patentees need not assert that a patent claim encompasses a competitor's product, but instead they may assert simply that a competing product "steals the benefit" of the patented invention.[73]

The doctrine of equivalents provides that if two products "work in substantially the same way, and accomplish substantially the same result, they are the same," and the Federal Circuit's *Goldenberg* opinion preserved the right to enforce an antibody patent pursuant to the doctrine.[74] The doctrine prevents competitors from circumventing a patent by making trivial changes to the invention to avoid literal infringement.[75] Thus, the doctrine allows inventors to tailor a patent's disclosure to an invention while nevertheless excluding competition from similar products that do not literally infringe a patent claim.[76] For example, none of the patents claiming the therapeutic antibody ReoPro claim a genus of antibodies, but patent holder Centocor (or licensee Eli Lilly) could potentially assert its patents against the maker of any therapeutic antibody that treats the same medical conditions by targeting the

constructs that are functionally equivalent are within the scope of this invention."). For an extreme example, see U.S. Patent No. 8,048,420 (filed June 12, 2008), which repeats the phrase "including any functionally equivalent antibody or functional parts thereof" eighty-four times in the patent's text.

[71] U.S. PATENT & TRADEMARK OFFICE, WRITTEN DESCRIPTION TRAINING MATERIALS 45–46 (Mar. 25, 2008), *available at* http://www.uspto.gov/web/menu/written.pdf; *see, e.g.*, Ex parte Gately, No. 11-003784, 2011 WL 3843855, at *1–3 (B.P.A.I. Aug. 26, 2011).

[72] Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1353 (Fed. Cir. 2011); Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1261 (Fed. Cir. 2004).

[73] Royal Typewriter Co. v. Remington Rand, Inc., 168 F.2d 691, 692 (2d Cir. 1948) (Hand, J.) (stating that the doctrine of equivalents "prevent[s] an infringer from stealing the benefit of the invention"); *accord* Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608 (1950) (quoting *Royal Typewriter*, 168 F.2d at 692); *see also* Goldenberg v. Cytogen, Inc., 373 F.3d 1158, 1168–69 (Fed. Cir. 2004) (stating that plaintiffs may attempt to enforce methods patents pursuant to the doctrine of equivalents when a competing antibody performs the same function as the patented antibody).

[74] *Graver Tank*, 339 U.S. at 608 (quoting Union Paper-Bag Mach. Co. v. Murphy, 97 U.S. 120, 125 (1877)); *accord* Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 35 (1997); *Goldenberg*, 373 F.3d at 1169.

[75] Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 733 (2002).

[76] *See* Johnson & Johnston Assocs. v. R.E. Serv. Co., 285 F.3d 1046, 1052–54 (Fed. Cir. 2002).

same molecule.[77] Finally, the doctrine of equivalents is tempered by claim limitations that were necessary to obtain a patent, and infringement claims made pursuant to the doctrine of equivalents present a question of fact to be submitted to the jury.[78]

Centocor attempted to discourage competition against ReoPro by invoking the doctrine of equivalents, expressly stating in its patent:

> Equivalents: Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.[79]

Interestingly, this language successfully thwarted competition. While Centocor developed the chimeric therapeutic antibody ReoPro, Genentech humanized a competing antibody.[80] Shortly after Centocor patented ReoPro, however, Genentech ceased developing its competing product—despite the

[77] Seven patents claim ReoPro's composition and methods of use. *See* U.S. Patent No. 5,976,532 (filed May 17, 1995) (claiming a method of treatment using ReoPro); U.S. Patent No. 5,877,006 (filed May 17, 1995) (claiming methods for making ReoPro); U.S. Patent No. 5,770,198 (filed Jan. 17, 1995) (claiming the composition of ReoPro); U.S. Patent No. 5,440,020 (filed Oct. 8, 1993) (claiming the composition of a second generation antibody); U.S. Patent No. 5,387,413 (filed Sept. 27, 1991) (claiming a method of treatment using the second generation antibody); U.S. Patent No. 5,336,618 (filed Nov. 22, 1988) (claiming the composition of a first generation antibody); U.S. Patent No. 5,275,812 (filed Feb. 25, 1993) (claiming a method of treatment using the first generation antibody).

[78] *Warner-Jenkinson*, 520 U.S. at 30 (holding the doctrine of equivalents is inapplicable when it would serve to "vitiate the central functions of the patent claims"); *Festo Corp*., 535 U.S. at 733–34 (holding the doctrine of equivalents inapplicable when an inventor surrenders the equivalent during patent prosecution). The question of fact creates a hurdle for patent holders because alleged infringers preserve the right to trial on the issue. *See Warner-Jenkinson*, 520 U.S. at 38–39 (reviewing case law ruling on whether issues arising under the doctrine of equivalents should be submitted to a jury). This hurdle might prove difficult for patent holders when their patents lack a corresponding commercial product. *See supra* Part III.C (jury verdicts may hinge on whether an asserted patent protects a competing, commercial drug).

[79] U.S. Patent No. 5,976,532 col.31 l.24–30 (filed May 17, 1995); *see also* U.S. Patent No. 5,877,006 col.30 l.30–36 (filed May 17, 1995); U.S. Patent No. 5,770,198 col.29 l.18–23 (filed Jan. 17, 1995); U.S. Patent No. 5,440,020 col.8 l.25–28 (filed Oct. 8, 1993); U.S. Patent No. 5,387,413 col.8 l.26–29 (filed Sept. 27, 1991).

[80] Conversation with Joel S. Bennett, Professor of Medicine, University of Pennsylvania Sch. of Med., in Phila., Pa. (2008) (Bennett discovered the prior art antibody and licensed it to Genentech); *see also* Joel S. Bennett et al., *Inhibition of Fibrinogen Binding to Stimulated Human Platelets by a Monoclonal Antibody*, 80 PROC. NAT'L ACAD. SCI. USA 2417 (1983) (describing the antibody that Genetech sought to humanize).

tantalizing market potential that earned Pfizer's Lipitor $130 billion.[81]

As ReoPro's patent portfolio claims only three antibodies, and the ReoPro antibody could be altered any of millions of different ways to create equally efficacious therapeutic antibodies, only two appreciable obstacles hamper competition: regulatory barriers and the threat of infringement litigation pursuant to the doctrine of equivalents.[82] Many different companies enjoy sufficient technical expertise to overcome regulatory barriers.[83] Thus, presuming a biotech or pharmaceutical company would pursue a share in ReoPro's $960-million-a-year market,[84] Centocor's patent warnings have teeth: ReoPro owes its market dominance to the doctrine of equivalents.

In the future, patents declaring rights to equivalent antibodies may become increasingly common and patents claiming genera correspondingly uncommon, in part because the lawsuits attempting to enforce genus claims

[81] Conversation with Joel S. Bennett, *supra* 80. ReoPro is administered prophylactically to prevent heart attacks, similar to Lipitor; however, ReoPro is too powerful for healthy individuals, and doctors only administer it to hospitalized heart patients at risk of subsequent ischemic events. *See, e.g.*, Letter from Karen D. Weiss, FDA, to John H. Parker, Centocor (Nov. 5, 1997), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1997/abcicen110597-ltr.pdf. For Lipitor's lifetime sales, see Randsdell Pierson & Bill Berkot, *Lipitor, Legendary Cash Cow, Prepares for Fadeout*, REUTERS, Nov. 6, 2011, *available at* http://www.reuters.com/article/2011/11/06/us-lipitor-idUSTRE7A51R520111106.

[82] *See supra* note 79 (describing the patent portfolio protecting ReoPro). The patents claim a first-generation antibody, a second-generation antibody fragment, called a Fab, and the third generation Fab ReoPro.

[83] *See, e.g.*, *supra* Part I (each of the world's twelve largest pharmaceutical companies either sell a therapeutic antibody or have therapeutic antibodies in late stage clinical trials). Additionally, a South Korean company markets a generic version of ReoPro. *See* Ben Shankland, *First Antibody Therapy in South Korea Receives Approval*, GLOBAL INSIGHT, Apr. 12, 2007.

[84] ReoPro's global market approached $960 million in 2010, but generic, small molecule drugs will likely erode its market share over the next decade. *See The Uptake of Oral Agents with Novel Modes of Action Such as Brilinta/Brilique Will Drive Sales in the 12-Month Post-Hospital Acute Coronary Syndrome Drug Market to Reach Approximately $2.8 Billion in 2020*, DECISION RESOURCES, Oct. 17, 2011, *available at* http://decisionresources.com/News-and-Events/Press-Releases/Acute-Coronary-Syndrome-101711 (ReoPro's market constitutes "the therapy market for ACS [acute coronary syndrome] in the acute, hospital setting."); *Investor Fact Sheet*, MEDICURE, http://www.medicure.com/factsheet.pdf (last visited Oct. 21, 2012) (estimating the domestic market at $450 million). ReoPro shares its market with two small molecule drugs, Integrilin and Aggrastat, which preform essentially the same function. *See* Eric J. Topol, Tatiana V. Byzova & Edward F. Plow, *Platelet GPIIb-IIIa Blockers*, 353 LANCET 227, 229 (1999). Additionally, multiple clinical trials are underway that could expand ReoPro's market. *See* CLINICALTRIALS.GOV, http://clinicaltrials.gov/ct2/search/advanced (search "Open Studies" for "ReoPro").

failed.[85] Thus, the doctrine of equivalents may become an increasingly important tactic to insulate therapeutic antibodies from competition.

V. METHOD-OF-USE PATENTS: GENERA CLAIMS IN METHOD-OF-USE PATENTS MAY SUCCEED IN LITIGATION WHERE SIMILAR CLAIMS IN COMPOSITION PATENTS FAILED.

The *Chiron* and *Centocor* opinions limited the applicability of genus claims but declined to define precise criteria distinguishing valid and invalid claims.[86] These two opinions invalidated composition patents. In comparison, the *In re Wands* opinion upheld claims to genera of antibodies in a method-of-use patent.[87] Courts could extend *In re Wands* to methods of using therapeutic antibodies and distinguish method patents from the composition patents disputed in *Chiron* and *Centocor*.

Inventors can patent new drugs using "composition of matter" claims, "method-of-use" claims, or both.[88] Composition claims exclude competitors from marketing a drug for any purpose regardless of whether the patent discloses the use. In contrast, method claims exclude only claimed treatments, but this limitation has advantages. For example, method claims allowed Pfizer to patent Viagra for treating impotence even though the drug's composition was already well known.[89] In fact, the USPTO initially awarded Pfizer a claim for every chemical entity that treats impotence by binding the same molecule as Viagra—which would theoretically include antibody genera.[90] The Board of Patent Appeals and Interferences later cancelled this vast genus claim because it encompassed previously known remedies for impotence, but the USPTO never addressed whether the claim's scope exceeded permissible

[85] *See supra* Part III.C.

[86] *See supra* Part III.C.

[87] *In re Wands*, 858 F.2d 731, 735–40 (Fed. Cir. 1988) (upholding Wands' patent because the claims to genera of antibodies do not require undue experimentation to practice the invention).

[88] Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1385–86 (Fed. Cir. 2003) (citing *In re* Byck, 48 F.2d 665, 666 (1931)). Inventors generally cannot obtain separate patents for composition and method claims. *See id.*

[89] U.S. Patent No. 6,469,012 col. 1 l.46–66, col.6 l.43–36 (filed Mar. 4, 1996).

[90] *Id.* col.9 l.36–41. Early therapeutic antibodies would be incapable of binding the same molecule as Viagra because they do not penetrate cells, and thus, they cannot reach the same intracellular molecule that Viagra targets. Next-generation therapeutic antibodies can deliver payloads within cells, which could theoretically encroach on Viagra's original patent claim. *See, e.g.*, Patricia M. LoRusso et al., *Trastuzumab Emtansine: A Unique Antibody-Drug Conjugate in Development for Human Epidermal Growth Factor Receptor 2–Positive Cancer*, 17 CLINICAL CANCER RES. 6437, 6440 (2011) (figure 1) (describing a next-generation therapeutic antibody that utilizes the Herceptin antibody to deliver a small molecule drug across cell membranes).

bounds.[91] Thus, the USPTO's analysis of the Viagra patent raises an unresolved legal question of tremendous consequence: can a method patent claim a broader class of pharmaceuticals than a composition patent?

A. Oklahoma Medical Research Foundation's sale of a method-of-use patent to Alexion for $10 million likely reflects the nonprofit Foundation's mission and undervalues the patent.

Patents protecting methods of using therapeutic antibodies remain virtually untested in the courts. Two closed cases in which the plaintiffs asserted method-of-use patents provide negligible precedent: one concluded with a confidential settlement, and the settlement ending the other might not adequately reflect the lawsuit's value.[92]

Regarding that second case, the Oklahoma Medical Research Foundation ("OMRF") filed a lawsuit in 2007 alleging that Alexion's therapeutic antibody, Soliris, infringed its method-of-use patent.[93] OMRF performed the initial research underpinning Soliris,[94] obtained a patent claiming methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering antibodies,[95] and licensed its patent to Alexion.[96] Alexion subsequently obtained FDA approval to treat PNH by administering Soliris, but Alexion refused to pay royalties.[97]

OMRF's case seemed compelling. Following the allowance of OMRF's patent, Alexion's CEO stated that the patent covered Soliris.[98] Additionally,

---

[91] Ex parte Pfizer, Inc., No. 2009-004106, 2010 WL 532133, at *22–24 (B.P.A.I. Feb. 12, 2010).

[92] Okla. Med. Research Found. v. Alexion Pharm., Inc., No. 07-00163 (N.D. Okla. Dismissed Feb. 15, 2008); Rockefeller Univ. v. Centocor, Inc., No. 04-000168, 2006 WL 5925020 (E.D. Tex. Sep. 26, 2006). Oklahoma Medical Research Foundation may have settled for less than the lawsuit's value. *See infra* Part IV.A.

[93] Plaintiff's First Amended Complaint at ¶ 12, Okla. Med. Research Found. v. Alexion Pharm., Inc., No. 07-00163, 2007 WL 3359950 (N.D. Okla. Oct. 12, 2007).

[94] *See, e.g.*, Karen K. Hamilton et al., *Regulatory Control of the Terminal Complement Proteins at the Surface of Human Endothelial Cells: Neutralization of a C5b-9 Inhibitor by Antibody to CD59*, 76 BLOOD 2572 (1990).

[95] U.S. Patent No. 5,635,178 col.16 l.4–39 (filed Mar. 8, 1994).

[96] Plaintiff's First Amended Complaint at ¶ 1, *Okla. Med. Research Found.*, 2007 WL 3359950; *see also* Thomas C. Thomas et al., *Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single-Chain Fv*, 33 MOLECULAR IMMUNOLOGY 1389, 1390–91 (1996) (describing Alexion's humanization of the therapeutic antibody Soliris).

[97] Plaintiff's First Amended Complaint at ¶ 11, *Okla. Med. Research Found.*, 2007 WL 3359950; Letter from Richard Pazdur, FDA, to Nancy Motola, Alexion Pharmaceuticals (Mar. 16, 2007), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/125166s0000_LTR.pdf.

[98] *Alexion Receives Issued Patent for Class of C5 Complement Inhibitors*, PR NEWSWIRE (June 11, 1997), *available at* http://www.thefreelibrary.com/Alexion+Receives+Issued+

Alexion reiterated that it would owe OMRF royalties based on sales of Soliris in multiple SEC filings.[99] Nevertheless, Alexion won a resounding victory.

Less than a year after OMRF filed its complaint, OMRF and Alexion reached a settlement.[100] Consequently, the *Alexion* docket lacks filings that shed light on the merits of the case. Nevertheless, some insight may be gleamed from the settlement agreement, in which OMRF assigned its patent to Alexion in exchange for $10 million.[101] First, Alexion stood to spend at least $6 million in attorney's fees and costs by proceeding to trial.[102] Second, Alexion would have paid OMRF royalties in excess of $239 million under the licensing agreement.[103] Thus, Alexion paid slightly more than nuisance value to settle the case—roughly a $4 million premium to dispose of potential liability in excess of $239 million—a clear victory for Alexion.[104]

OMRF likely settled because it did not possess adequate capital to fund the litigation or to risk exposure to counterclaims.[105] In 2009, for example,

---

Patent+for+Class+of+C5+Complement+Inhibitors-a019486806 (quoting Leonard Bell, CEO, Alexion) ("[T]he patent provides protection for a variety of products, including 5G1.1-SC [Soliris] . . . .").

[99] *See, e.g.*, Alexion Pharm., Inc., Annual Report (FORM 10-K) 37 (Oct. 29, 1996) ("[T]he Company [Alexion] entered into certain patent licensing agreements with Oklahoma Medical Research Foundation . . . . The agreements provide that the Company agreed to pay such institutions [OMRF] royalties based on sales of products incorporating technology licensed thereunder . . . .").

[100] *Id*. at 4.

[101] *Id*.

[102] AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION, REPORT OF THE ECONOMIC SURVEY 29–30 (2009). For example, in a contemporaneous pharmaceuticals patent case, Brigham Young University spent $1.6 million over the course of a year litigating a discovery dispute against Pfizer. Brigham Young Univ. v. Pfizer, Inc., 262 F.R.D. 637, 648 (D. Utah 2009).

[103] Alexion agreed to pay OMRF a 6% royalty. *See* Plaintiff's First Amended Complaint at ¶ 12, Okla. Med. Research Found. v. Alexion Pharm., Inc., No. 07 -00163, 2007 WL 3359950 (N.D. Okla. Oct. 12, 2007). Soliris sales totaled $66 million in 2007, $259 million in 2008, $387 million in 2009, $541 million in 2010, and $783 in 2011. *See* Alexion Pharm., Inc., Annual Report (Form 10-K) 39 (Feb. 17, 2012). Thus, the royalty would have totaled $122 million through the end of 2011 (*6% × ($66 + $259 + $387 + $541 + $783) = $122*). Conservatively estimating future sales of $783 million per year through June, 2014, the expiration of the patent, future royalty payments would total $117 million (*6% × $783 × 2.5 years = $117*). Thus, Alexion's cumulative royalty payment would be $239 million (*$122 + $117 = $239*). Further, Soliris's actual sales reflect analyst forecasts. *See, e.g.*, *Alexion Pharmaceuticals Predicts 2008 Sales in the Range of Wall Street's Forecast*, ASSOCIATED PRESS, Feb. 14, 2008 (predicting 2008 sales in excess of $200 million); *Alexion shares set 6-year high as Analysts Expect Greater Sales of blood drug Soliris*, ASSOCIATED PRESS, Oct. 26, 2007 (predicting peak annual sales between $500 million and $1 billion).

[104] *$10 million − $6 million = $4 million*

[105] The lawsuit exposed OMRF to counterclaims in excess of $55 million. *See* Marie

OMRF's total operating revenue was just shy of $60 million, mostly dedicated to research.[106] OMRF may have felt that expending capital on litigation might not have adequately advanced its nonprofit mission: "that more may live longer, healthier lives."[107] Accordingly, the $10 million settlement might be indicative of a risk-adverse nonprofit rather than a prudent business decision, and OMRF probably undervalued its intellectual property. In the two pending cases addressed below, parties appraise method-of-use patents at significantly higher values.

B. Method-of-use claims allowed the University of Pennsylvania to patent a genus of antibodies that includes Genentech's Herceptin.

On May 11, 2011, Genentech filed a complaint seeking declaratory judgment against the University of Pennsylvania ("Penn"), requesting the invalidation of one of Penn's patents.[108] Interestingly, Genentech licensed the technology underpinning Penn's patent from 2000 through 2004, before the patent issued.[109]

The patent claims methods of using a genus of antibodies that includes Herceptin,[110] the same antibody disputed in *Chiron v. Genentech*.[111] Genentech might have requested the license to mount a collateral attack against Chiron's patent; it did not approach Penn for a license until 2000, just after the USPTO allowed Chiron's patent.[112] Then, following the patent's issue and ensuing lawsuit, Genentech launched a counterattack against Chiron. Brandishing an exclusive license to Penn's pending patent application, Genentech initiated interference proceedings asserting that Penn's application

---

Price, *Drug Company Files Countersuit Against Oklahoma Medical Research Foundation*, J. REC. (Okla. City, Okla.), May 14, 2007, *available at* https://secure.omrf.org/omrf/news_releases/archives/features/2007/20070514.asp.

[106] Okla. Med. Research Found., OMRF 2009 Annual Report 22 (2009), http://omrf.org/pdfs/2009AnnualReport.pdf.

[107] Len Cason, *Mission Remains Strong: Celebrating 65 Years at Thriving OMRF*, OKLAHOMAN, Aug. 28, 2011, at 27A; *see also* OKLA. MED. RESEARCH FOUND., BYLAWS 1 (2008), http://omrf.org/wp-content/uploads/2010/03/OMRFBylaws.pdf ("The general purpose of this Foundation is to promote the improvement of human health and well-being by encouraging and engaging directly in the continuous active conduct of medical research . . . .").

[108] Complaint for Declaratory Judgment at ¶ 3, Genentech, Inc. v. Trs. of Univ. of Pa., No. 10-02037, 2010 WL 2320034 (N.D. Cal. May 11, 2010).

[109] Complaint for Declaratory Judgment at ¶¶ 9–10, *Genentech*, 2010 WL 2320034.

[110] U.S. Patent No. 6,733,752 col.8 l.49–67 (filed Nov. 20, 1995).

[111] Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1252 (Fed. Cir. 2004); *see supra* Part II.C.

[112] U.S. Patent No. 6,733,752 col.8 l.49–67 (filed Nov. 20, 1995).

invalidated Chiron's patent.[113] After Genentech prevailed in the infringement suit, however, it declined to renew the license.[114] Accordingly, Penn engaged Genentech in a second lawsuit.

Penn's patent mirrors the patent invalidated in *Centocor* because it claims broad antibody genera as well as smaller subgenera tailored to Herceptin.[115] The trial court narrowed the scope of the subgenera claims precluding a finding of their infringement, but Penn maintains its infringement action pursuant to the broader genus claims.[116] Penn's aggressive pursuit of litigation in the wake of Centocor's appellate loss suggests it believes its patent is distinguishable from Centocor's patent.[117] Specifically, Penn argues that its patent describes a previously unknown medical application for which Herceptin is now administered.[118] This method-of-use claim clearly differs from claims to an antibody's composition, and the *In re Wands* opinion may provide precedent that allows Penn's method claims to prevail where Centocor's composition claims failed.[119]

---

[113] Greene v. Ring, No. 105,022 (B.P.A.I. filed Aug. 12, 2002); Denise Gellene, *Genentech Wins Suit Over Rights to Cancer Drug*, L.A. TIMES, Sept. 7, 2002, http://articles.latimes.com/2002/sep/07/business/fi-patent7 (citing Sean Johnston, Genentech) (In the interference proceedings "Genentech claims that two scientists at the University of Pennsylvania are the actual inventors of human breast cancer antibodies."). Genentech acted on Penn's behalf during the interference proceedings. *See, e.g.*, Ex parte Greene, No. 105,022 (B.P.A.I. Oct. 24, 2002) ("While the assignee of Greene '899 is the Trustees of the University of Pennsylvania, Genentech is an exclusive licensee of Greene '899 and is said to be the real party in interest.").

[114] Genentech declined further licensing agreements following a meeting with Penn in January, 2005, the same month the Supreme Court denied certiorari in the *Chiron* case. *See* Chiron Corp. v. Genentech, Inc., 543 U.S. 1050, 1050 (2005); Complaint for Declaratory Judgment at ¶¶ 9–10, Genentech Inc. v. Trs. of Univ. of Pa., No. 10-02037 (N.D. Cal. May 11, 2010), 2010 WL 2320034.

[115] U.S. Patent No. 6,733,752 col. 8–10 (filed Nov. 20, 1995).

[116] Genentech, Inc. v. Trs. of Univ. of Pa., No. 10-02037, 2011 WL 2259114, at *17–19 (N.D. Cal. May 9, 2011).

[117] For example, Penn's Docket contains 707 entries—587 of which were filed after *Centocor*—whereas the *Centocor* docket contains only 362 entries. *Compare* Genentech, Inc. v. Trs. of Univ. of Pa., No. 10-02037 (N.D. Cal. filed May 9, 2010), *with* Centocor Ortho Biotech, Inc. v. Abbott Labs., No. 07-00139 (E.D. Tex. filed Apr. 16, 2007).

[118] Penn claims its patent covers auxiliary treatments to suppress secondary tumor formation. *See* Brief for Trs. of Univ. of Pa's Opening Claim Construction at Part II.D, Genentech, Inc. v. Trs. of Univ. of Pa., No. 10-02037, 2011 WL 1038855 (N.D. Cal. Feb. 11, 2011); *see also* Letter from Patricia Keegan, FDA, to Todd W. Rich, Genentech, Inc. (Nov. 16, 2006), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/103792%205150ltr.pdf (approving Herceptin for adjuvant treatment, which Penn claims).

[119] *In re Wands*, 858 F.2d 731, 735–40 (Fed. Cir. 1988).

C. Litigation disputing whether GlaxoSmithKline's Arzerra infringes a patent protecting Biogen's Rituxan could distinguish genera claims in method-of-use patents from similar claims in composition patents.

In 2010, Biogen filed a lawsuit against GlaxoSmithKline alleging that the recently approved therapeutic antibody Arzerra infringes its patent protecting Rituxan, which had sales of $6.7 billion in 2011.[120] The patent claims "[a] method of treating chronic lymphocytic leukemia . . . [by] administering an anti-CD20 antibody," and different claims are directed at chimeric, humanized, and fully-human antibodies.[121] These genus claims encompass fully-human Arzerra, an anti-CD20 antibody approved to treat chronic lymphocytic leukemia.[122] The trial court narrowed the claim scope, however, precluding a finding of literal infringement.[123] Consequently, Biogen stipulated to judgment to appeal the order.[124]

The trial court limited genus claims to antibodies that target the same portion of CD20 as Rituxan, called an epitope.[125] Biogen wields a powerful argument to reverse the order on appeal as the *Johns Hopkins* opinion affirmed a different construction upon de novo review of similar claims.[126]

---

[120] Biogen Idec, Inc. v. GlaxoSmithKline LLC, No. 10-00608 (S.D. Cal. filed Mar. 23, 2010); Biogen Idec Inc., Annual Report (Form 10-K) 35 (Feb. 3, 2012) (Biogen's sales totaled $118 million in 2011); *Roche Business Report 2011*, ROCHE HOLDING LTD, at 66 (2012), http://www.roche.com/gb11e.pdf (Genentech co-markets Rituxan and it is fully owned by Roche; Genentech's sales of Rituxan totaled $6.6 billion in 2011; 1 CHF = $1.1 USD). IDEC Pharmaceuticals originally developed the chimeric antibody Rituxan, partnered with Genentech to market Rituxan, then merged with Biogen. *See* Biogen Idec Inc., Annual Report (Form 10-K) 6 (Mar. 10, 2004); IDEC Pharm. Corp., Annual Report (Form 10-K405) 16 (Mar. 31, 1997).

[121] U.S. Patent No. 7,682,612 col. 7–9 (filed Nov. 9, 1999).

[122] Letter from Richard Pazdur, Director of Office of Oncology Drug Products, FDA, to Philip Witman, Associate Director, GlaxoSmithKline (Oct. 26, 2009), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/125326s000ltr.pdf.

[123] Claim Construction Order, *Biogen Idec*, No. 10-00608, 2011 WL 4949042, at *7–9.

[124] Order Granting Joint Motion and Stipulation for Final Judgment of Non-Infringement, *Biogen Idec*, No. 10-00608 (S.D. Cal. Mar. 24, 2010) (order granting joint motion and stipulation for final judgment of non-infringement); Notice of Appeal, *Biogen Idec*, No. 10-00608 (S.D. Cal. Dec. 5, 2010).

[125] Claim Construction Order, *Biogen Idec*, No. 10-00608, 2011 WL 4949042, at *7–9.

[126] Johns Hopkins's patents claimed all anti-CD34 antibodies but disclosed antibodies targeting only a single epitope of CD34. CellPro marketed an antibody targeting a different epitope. A jury found no literal infringement. The district court, however, found literal infringement and granted judgment as a matter of law. The Federal Circuit conducted *de novo* review and affirmed. Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1357–59 (Fed. Cir. 1998). Interestingly, the *Biogen Idec* Markman order did not cite *Johns Hopkins*, and the parties did not brief the case. *See* Claim Construction Order, *Biogen Idec*, No. 10-00608, 2011 WL 4949042.

Presuming the Federal Circuit vacates the trial court order and litigation proceeds, the case will provide an opportunity for the Federal Circuit to revisit the *Centocor* opinion in light of a method-of-use patent. As discussed in Part III.C, the *Centocor* opinion held that a composition patent could not claim fully-human antibodies by disclosing only chimeric antibodies.[127] Similarly, Biogen seeks to enforce a patent claiming fully-human antibodies that discloses only chimeric antibodies.[128] Thus, Biogen calculates its method-of-use patent will succeed where composition patents failed.[129]

VI. CONCLUSION

Federal Circuit opinions lag behind technical advances in the realm of antibodies, a technology underpinning many multibillion-dollar pharmaceuticals. This interval fosters a void in the case law, which led the USPTO to allow patent claims that the Federal Circuit later cancelled.[130] Despite this precedent, two pending lawsuits dispute the validity of similarly-styled claims in method-of-use patents.[131] Thus, parties asserting method claims calculate that method-of-use patents will succeed in litigation where composition patents failed.

---

[127] Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1349–53 (Fed. Cir. 2011).

[128] U.S. Patent No. 7,682,612 (filed Nov. 9, 1999); Mitchell E. Reff et al., *Depletion of B Cells In Vivo by a Chimeric Mouse Human Monoclonal Antibody to CD20*, 83 BLOOD 435, 435–36 (1994) (describing Rituxan).

[129] The *Centocor* opinion also noted that the creation of fully-human antibodies was not routine enough in 1994 to afford Centocor constructive possession at its claimed 1994 priority date. *See Centocor*, 636 F.3d at 1352–53. In contrast, the prior art predicating Biogen's 1999 patent application might afford constructive possession of fully-human antibodies. *See, e.g.*, Tristan J. Vaughan et al., *Human Antibodies with Sub-Nanomolar Affinities Isolated from a Large Non-Immunized Phage Display Library*, 14 NATURE BIOTECHNOLOGY 309, 309–10 (1996).

[130] *Centocor*, 636 F.3d 1341; Chiron Corp. v. Genentech, Inc., 363 F.3d 1247 (Fed. Cir. 2004).

[131] Complaint for Declaratory Judgment, Genentech, Inc. v. Trs. of Univ. of Pa., No. 10-02037, 2010 WL 2320034 (N.D. Cal. filed May 11, 2010); Declaratory Relief Complaint for Patent Infringement, Biogen Idec, Inc. v. GlaxoSmithKline LLC, No. 10-00608 (S.D. Cal. filed Mar. 24, 2010).