AQUALUNG INFERRED:
INEQUITBLE CONDUCT IN REGENERON PHARMACEUTICALS INC. V MERUS N.V.[1]

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Biography

Gerard Reinhardt is an Intellectual Property attorney, and a principal in the Reinhardt IP law firm (see ReinhardtIP.com). Mr. Reinhardt is licensed to practice law in New York, Texas and the District of Columbia, and is registered to practice before the U.S. Patent & Trademark Office. In addition to a J.D. from the University of Houston, he holds B.S. and M.S. degrees in Chemical Engineering from UVa and Georgia Tech, respectively. He has litigated complex patent cases with the New York law firm of Morgan & Finnegan, and functioned for almost ten years as Senior Counsel to Schering-Plough Corp. and Merck & Co., acquiring an in-depth knowledge of practice in chemical and life science patents. He can be contacted at Gerard@ReinhardtIP.com.

Introduction

Jethro Tull's 1971 album *Aqualung* starts with the title track, which opens with a rather menacing six-note guitar sequence, rendered twice by Martin Barre. Then, these verses are starkly delivered by Ian Anderson:

Sitting on a park bench
Eying little girls with bad intent[2]

It seems that our hero Aqualung is a homeless tramp with a bit too much time on his hands. We are flatly informed that his "eyeing of little girls" is done with "bad intent." No trial here.

This paper reviews the patent case of Regeneron v Merus,[3] in which "bad intent" that accompanied the withholding of certain references during patent prosecution before the U.S. Patent & Trademark Office was inferred from litigation misconduct that occurred years after

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[2] Copyright 1970, Ian Anderson and Jennie Anderson.

[3] 864 F.3d 1343 *; 2017 U.S. App. LEXIS 13578 **; 123 U.S.P.Q.2D (BNA) 1469 ***; 2017 WL 3184400.

prosecution had closed, resulting in a finding that the patent was unenforceable for inequitable conduct.

Background

In March 2014, Regeneron filed suit in the Southern District of New York accusing Merus B.V. ("Merus") of infringing the '018 patent. The district court heard argument and expert testimony on claim construction and issued an opinion construing various terms.[4] The court also declared one term indefinite.[5]

Merus asserted a counterclaim of unenforceability due to inequitable conduct. It argued that Regeneron's patent prosecutors withheld four references (the "Withheld References") from the U.S. Patent and Trademark Office ("PTO") during prosecution of the '018 patent. According to Merus, these references were cited in a third-party submission in related U.S. patent prosecution and in European opposition briefs, were but-for material, and were withheld by Regeneron with the specific intent to deceive the PTO. There was no dispute that Regeneron knew of the Withheld References during prosecution of the '018 patent. Regeneron argues, however, that the references were not but-for material, that they were cumulative of references the PTO actually relied on during prosecution, and that Regeneron did not have any specific intent to deceive the PTO.

The district court scheduled a bench trial on Regeneron's inequitable conduct, but bifurcated the trials based on the two elements of inequitable conduct: a first bench trial on the materiality of the Withheld References, and a second bench trial regarding the specific intent to deceive the PTO[6].

Following the first trial, the district court issued a lengthy opinion detailing the materiality of the Withheld References.[7] The district court, however, never held the scheduled second trial on Regeneron's specific intent to deceive the PTO. Instead, in its opinion following the first bench trial, the court exhaustively detailed Regeneron's discovery misconduct throughout litigation and sanctioned Regeneron by drawing an adverse inference of specific intent to deceive the PTO. In particular, the district court discussed Regeneron's repeated violations of the district court's discovery orders and improper secreting of relevant and non-privileged documents. Based on this misconduct, the district court drew an adverse inference that

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[4] *See* *Regeneron Pharms., Inc. v. Merus B.V.*, No. 14-cv-1650, 2014 U.S. Dist. LEXIS 163350, 2014 WL 6611510 (S.D.N.Y. Nov. 21, 2014).

[5] 2014 U.S. Dist. LEXIS 163350, [WL] at *23-24.

[6] *See* *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1287 (Fed. Cir. 2011) (en banc).

[7] *Regeneron Pharms., Inc. v. Merus B.V.*, 144 F. Supp. 3d 530 (S.D.N.Y. 2015) ("*Regeneron I*").

Regeneron's agents failed to disclose the Withheld References to the PTO with the specific intent to deceive the PTO. Having determined the but-for materiality of the Withheld References and drawn an adverse inference of Regeneron's specific intent to deceive the PTO, the district court concluded that Regeneron had committed inequitable conduct and held the '018 patent unenforceable.

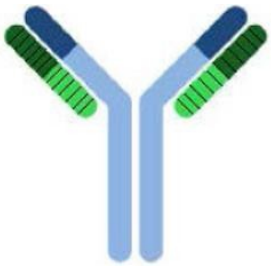
Regeneron timely appealed the district court's claim construction order and final judgment of inequitable conduct.

The '018 Patent

In December 2000, Regeneron filed a patent application entitled "Methods of Modifying Eukaryotic Cells." Thereafter, Regeneron filed a sequence of continuations, continuations-in-part and divisional applications claiming priority to that original case. A continuation application issued as the '018 patent on August 6, 2013, to inventors Drs. Andrew J. Murphy and George D. Yancopoulos, who assigned it to Regeneron.

In general, the '018 patent relates to using large DNA vectors to target and modify endogenous genes and chromosomal loci in eukaryotic cells.[8] One practical use of this technology is that users may target and modify specific genes in mice so that the mice develop antibodies that can be used by humans.

Antibodies are proteins that the body uses to counteract specific pathogens such as bacteria, viruses, and other foreign substances in the blood. Antibodies are typically represented by a "Y" shape consisting of four chains of amino acids: two longer "heavy" chains, and two shorter "light" chains. Each of the chains, in turn, consists of two regions: a "variable" region toward the top of the "Y," and a "constant" region toward the bottom. One such antibody is illustrated below:



In this antibody, the light chains are striped and the heavy chains are solid. Further, the constant regions are represented in lighter shades, and the variable regions in darker shades.

Mouse DNA coding for antibodies can be modified using human DNA in various different ways. For example, mouse DNA can be manipulated to create chimeric antibodies that have mouse

[8] '018 patent col. 1 ll. 17-33.

variable region DNA and human constant region DNA. Similarly, mice can be used to create humanized antibodies that have some mouse variable region DNA, some human variable region DNA, and human constant region DNA. Further, genetically modified mice can be used to create antibodies that have fully human DNA. Finally, mice can also be modified to create reverse chimeric antibodies that have mouse constant region DNA and human variable region DNA. This spectrum of modified antibodies is illustrated below.

Claim 1 of the '018 patent, the only claim at issue here, recites, in its entirety, "[a] genetically modified mouse, comprising in its germline human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus.[9] As discussed in greater detail below, Regeneron contends that under the broadest reasonable construction, this claim is limited to mice that produce reverse chimeric antibodies. Merus, on the other hand, argues that under the broadest reasonable construction, claim 1 includes mice that can produce humanized, fully human, or reverse chimeric antibodies.

Prosecution of the Patent Application

In a January 2013 Reply to a Final Office Action, Regeneron amended claim 1 to include the additional limitation that the human unrearranged variable region gene segments would be inserted at "an endogenous" mouse immunoglobulin locus. Regeneron also sent a presentation to the PTO with the Reply. In that presentation, Regeneron asserted that it had developed a commercial embodiment of the claimed mouse with surprising results. It is undisputed that that assertion was false. Regeneron had not developed any such mouse at the time.

Following receipt of Dr. Smeland's Reply and presentation, the PTO issued an Advisory Action maintaining the rejection of claims 1-19 as anticipated by Lonberg, and claim 20 remained rejected in view of Lonberg and other references. Shortly thereafter, in February 2013, Regeneron retained Brendan Jones, Ph.D., to assist with prosecution. Drs. Jones and Smeland together planned an in-person meeting with the Examiner during which they relied on the misleading presentation asserting that Regeneron had developed a commercial embodiment of the claimed mouse. That meeting occurred in March 2013.

Following that meeting, in April 2013, the PTO issued a Notice of Allowance for the '176

[9] 018 patent col. 29 ll. 24-26.

application. In the statement of reasons for allowance, the Examiner stated that "[t]he prior art does not teach or suggest a genetically modified mouse comprising, in its germline cells, human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus."

Days before the PTO issued its notice of allowance for the '176 application, which would become the '018 patent, a third-party filed a submission in the parent application of the '018 patent, describing three references:

1. Marianne Brüggemann & Michael S. Neu-berger, "Strategies for Expressing Human Antibody Repertoires in Transgenic Mice," 17(8) Review Immunology Today 391 (1996) ("Brüggemann");

2. Shinsuke Taki et al., "Targeted Insertion of a Variable Region Gene into the Immunoglobu-lin Heavy Chain Locus," 262 Science 1268 (1993) ("Taki"); and

3. Yong—Rui Zou et al, "Cre-loxP-mediated Gene Replacement: A Mouse Strain Producing Humanized Antibodies," 4(12) Current Biology 1099 (1994) ("Zou").

Dr. Rajewsky co-authored both the Taki and Zou references. Further, Dr. Alt, another inventor, co-invented WIPO Patent Publication No. WO 91/00906 entitled "Chimeric and Transgenic Animals Capable of Producing Human Antibodies," credited to Clive Wood et al. ("Wood"). Collectively, the Brüggemann, Taki, Zou, and Wood references are the "Withheld References."

Given their prior work, Regeneron recruited Drs. Alt and Rajewsky to its scientific advisory board to work on the claimed mouse before Regeneron filed the '018 patent. During prosecution, these individuals corresponded with Dr. Murphy, an '018 patent inventor, expressing concerns about his characterizations of the prior art in related publications.

Dr. Smeland knew of the third party submission as well as all four Withheld References during prosecution, yet withheld them from the '018 patent's examiner. Although Regeneron did not disclose the Withheld References during prosecution of the '018 patent, once the '018 patent had been allowed, Regeneron disclosed the Withheld References to the PTO in every related application having the same specification and similar claims. Merus contended that Regeneron's failure to disclose the Withheld References constituted inequitable conduct. Regeneron responded that Dr. Smeland was under no obligation to disclose these references because they were not but-for material.

The trial court construed claim 1 to cover mice that can produce humanized, fully human or reverse chimeric antibodies. With this holding Regeneron withdrew it’s infringement claim, and now faced Merus’ counterclaim of inequitable conduct.

The Law of Inequitable Conduct

"Inequitable conduct is an equitable defense to patent infringement that, if proved, bars enforcement of a patent."[10] Unlike validity defenses, which are claim specific, inequitable conduct regarding a single claim renders the entire patent unenforceable.[11] Inequitable conduct has two separate requirements: materiality and intent.[12]

"[A]s a general matter, the materiality required to establish inequitable conduct is but-for materiality."[13] A prior art reference is "but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art."[14] In determining the materiality of a reference, the court applies the preponderance of the evidence standard and gives claims their broadest reasonable construction.[15]

A reference is not but-for material, however, if it is merely cumulative.[16] A reference is cumulative when it "teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO."[17].

In addition to proving the materiality of withheld references, "the accused infringer must prove that the patentee acted with the specific intent to deceive the PTO."[18] Direct evidence of intent is not, however, required. A court may infer intent from circumstantial evidence. "[A] court must weigh the evidence of intent to deceive independent of its analysis of materiality. Proving that the applicant knew of a reference, should have known of its materiality, and decided not

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[10] *Therasense*, 649 F.3d at 1285.

[11] *Id. at 1288*.

[12] *Id. at 1290*.

[13] *Id. at 1291*.

[14] *Id.*

[15] *Id. at 1291-92*.

[16] *See Dig. Control Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1319 (Fed. Cir. 2006) ("However, a withheld otherwise material prior art reference is *not* material for the purposes of inequitable conduct if it is merely cumulative to that information considered by the examiner.").

[17] *Regents of the Univ. of Calif. v. Eli Lilly & Co.*, 119 F.3d 1559, 1575 (Fed. Cir. 1997).

[18] *Therasense*, 649 F.3d at 1290. *Id.* (citing *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008)).

to submit it to the PTO does not prove specific intent to deceive."[19]

An inference of intent to deceive is appropriate where the applicant engages in "a pattern of lack of candor," including where the applicant repeatedly makes factual representations "contrary to the true information he had in his possession."[20] "In a case involving nondisclosure of information, clear and convincing evidence must show that the applicant *made a deliberate decision* to withhold a *known* material reference."[21]

At trial, it was held that all four of the Withheld References were "but-for" references, and thus the materiality prong of the inequitable conduct test was satisfied. The second prong, intent to deceive, was thus key to the question of inequitable conduct.

Regeneron's Litigation Misconduct and the Adverse Inference of Intent to Deceive

At trial, Regeneron's counsel adopted a highly aggressive strategy. Specifically, Regeneron's counsel refused to disclose its infringement contentions by provide an element-by-element claim chart, as required by the local court rules. Adhering to this gamesmanship, Regeneron refused to provide an element-by-element claim construction, also in violation of the local court rules.

However, it was Regeneron's discovery abuses that appeared to most greatly incur the wrath of the trial judge. In all, the district court concluded that there were three categories of documents that presented serious concerns of discovery misconduct:

> 1. Non-privileged documents that were not produced and instead resided throughout litigation on the privilege log (e.g., numerous Excel spreadsheets with scientific test results, third party filings to the PTO, and fact statements by non-lawyers not seeking legal advice).
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> 2. Previously privileged documents as to which Regeneron affirmatively waived the privilege by disclosure of a related document and that the district court ordered be produced pursuant to its Order.
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> 3. Documents on the privilege log relating to precisely those topics waived by Regeneron when Regeneron filed trial declarations of those involved in the prosecution of the '018 patent application.

The district court determined that Regeneron's failure to make full and adequate production of

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[19] *Id.*

[20] *Apotex Inc. v. UCB, Inc.*, 763 F.3d 1354, 1362 (Fed. Cir. 2014).

[21] *Therasense*, 649 F.3d at 1290. (quoting *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1181 (Fed. Cir. 1995)) (internal quotation marks omitted).

documents in the first two categories during the period of fact discovery independently of the trial misconduct warranted serious sanction. But the third category was the most egregious. According to the district court, the production failure was undoubtedly larger than the few exemplars revealed by the court's *in camera* review. Given the thousands of documents on Regeneron's privilege log, the district court concluded that it could not possibly learn the full extent of the problem.

The district court ultimately concluded that it would be unfair to Merus to reopen discovery on the eve of trial and inject further delay in the case entirely due to Regeneron's behavior. The court also concluded that doing so would impose an unfair burden on the court and require expending substantial additional judicial resources. Further, because Regeneron's behavior suggested "a pattern" of misconduct, simply reopening discovery, striking the problematic affidavits, and/or shifting costs would not ensure fairness.[22]. Accordingly, the district court sought an alternative remedy and concluded that it was appropriate to draw an adverse inference against Regeneron from the undisclosed documents. In particular, the district court cancelled the scheduled trial on the question of intent and drew an adverse inference that Regeneron failed to disclose the Withheld References to the PTO during prosecution of the '018 patent with the specific intent to deceive the PTO. Hence, this conclusion was made without the benefit of a trial proceeding in which witnesses would be cross-examination.

On appeal to the Court of Appeals of the Federal Circuit. two of the three empaneled judges (Prost and Wallach) upheld the district court's rulings. A third (Newman) dissented. Judge Newman disagreed with the district court's findings of materiality of the Withheld References. Judge Newman went on to question her colleagues' willingness to find inequitable conduct based on litigation misbehavior.[23]

> Instead of requiring proof of intent to deceive the examiner during patent prosecution, the panel majority upholds the district court's "adverse inference" in light of "widespread litigation misconduct." Maj. Op. at 38. Misconduct during litigation—as the district court viewed counsel's actions concerning discovery and the privilege log—cannot substitute for evidence of intent to deceive by withholding but-for material prior art during patent prosecution.
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> Precedent is long-standing, unambiguous, and binding. In *Keystone Driller Co. v. General Excavator Co., 290 U.S. 240, 54 S. Ct. 146, 78 L. Ed. 293, 1934 Dec. Comm'r Pat. 639 (1933)*, the Court established that litigation misconduct can support the dismissal of the suit, whereas patent invalidity or unenforceability must be established on the law of validity or enforceability. Applying *Keystone Driller*, in *Aptix Corp. v. Quickturn Design Systems, Inc., 269 F.3d 1369 (Fed. Cir. 2001)*, this court held that:
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> > [T]he remedies for litigation misconduct bar the malfeasant who committed the misconduct. The property right itself remains independent of the conduct of a litigant.

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[22] *Regeneron 1*, at 595-596.

[23] *Regeneron Pharms. v Merus N.V.*, 864 F.3d 1342, 1365-1366.

Id. at 1375. This court elaborated:

> Leaving the patent right intact, the Supreme Court repeatedly stressed that litigation misconduct bars the litigant. Again in *Hazel—Atlas Glass Co. v. Hartford—Empire Co., 322 U.S. 238, 64 S. Ct. 997, 88 L. Ed. 1250, 1944 Dec. Comm'r Pat. 675 (1944)*, *overruled on other grounds by Standard Oil Co. v. United States, 429 U.S. 17, 18, 97 S. Ct. 31, 50 L. Ed. 2d 21 (1976)*, another instance of extreme litigation misconduct, the Supreme Court "require[d] that Hartford be denied relief," but left the patent right intact. *Id. at 251*.

We continued to explain that in order to invalidate the patent, the inequitable conduct must have occurred in patent prosecution:

> Litigation misconduct, while serving as a basis to dismiss the wrongful litigant, does not infect, or even affect, the original grant of the property right.

We concluded:

> No case law from the Supreme Court or this court provides a basis for nullifying property rights granted by the United States when such property rights did not themselves accrue through inequitable conduct.

Judge Newman is famous for her insightful dissents, and this one is no outlier from that history.

After the Federal Circuit issued its opinion upholding the district court decision, Regeneron filed a petition for a writ of *certiorari* with the U.S. Supreme Court in May 2018. Five *amicus curiae* briefs were filed with the court by various legal associations, all arguing that the adverse inference based on litigation misconduct was contrary to Federal Circuit and Supreme Court precedent. However, the Justices apparently disagreed, and the petition was denied without comment by the Court in October 2018.[24] Subsequently, it was determined that this case was "exceptional"[25] and accordingly, the district court granted *Merus*' motion for attorney fees, expert fees, and costs, which were found to be $10,514,944 in aggregate.[26]

Conclusion

It is now the law of the land that litigation misconduct can be the basis for an adverse inference that material references were withheld during prosecution with intent to deceive the examiner, and thus can be the basis to hold the patent unenforceable for inequitable conduct.

Thus, it would seem that our friend Aqualung would not get a trial on "bad intent."

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[24] *Regeneron Pharms. v. Merus N.V.*, 2018 U.S. LEXIS 5109 (U.S., Oct. 1, 2018).

[25] See *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 572 U.S. 545, 134 S. Ct. 1749, 1756, 188 L. Ed. 2d 816 (2014).

[26] *Regeneron Pharms. v Merus N.V.*, 2018 U.S.Dist. LEXUS 115661.