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Federal Circuit Patent Bulletin: *Regeneron Pharm., Inc. v. Merus B.V.*

July 28, 2017

[Where] litigation misconduct [obfuscated] prosecution misconduct . . . the district court did not abuse its discretion by drawing an adverse inference of specific intent to deceive the PTO."

On July 27, 2017, in *Regeneron Pharm., Inc. v. Merus B.V.*, the U.S. Court of Appeals for the Federal Circuit (Prost,* Newman, Wallach) affirmed the district court's judgment that U.S. Patent No. 8,502,018, which related to using large DNA vectors to modify endogenous genes and chromosomal loci in eukaryotic cells to facilitate the manufacture of human antibodies by mice, was unenforceable due to inequitable conduct. The Federal Circuit stated:

"Inequitable conduct is an equitable defense to patent infringement that, if proved, bars enforcement of a patent." Unlike validity defenses, which are claim specific, inequitable conduct regarding a single claim renders the entire patent unenforceable. Inequitable conduct has two separate requirements: materiality and intent. "[A]s a general matter, the materiality required to establish inequitable conduct is but-for materiality." 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." In determining the materiality of a reference, the court applies the preponderance of the evidence standard and gives claims their broadest reasonable construction. A reference is not but-for material, however, if it is merely cumulative. 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."

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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." "[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 to submit it to the PTO does not prove specific intent to deceive." "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." Direct evidence of intent is not, however, required. A court may infer intent from circumstantial evidence. 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."

On appeal, Merus asserts that Drs. Smeland and Murphy violated their duty of candor and engaged in inequitable conduct. Regeneron does not contest that both of these individuals had a duty of candor to the PTO. Regeneron, however, argues that the duty was not violated because none of the Withheld References were but-for material and because the district court improperly concluded that the applicants possessed the necessary specific intent to deceive the PTO. "[W]e review the district court's findings of materiality and intent for clear error." A finding of inequitable conduct based on those facts is reviewed for an abuse of discretion. . . .

Both Regeneron and Merus agree that the claimed mouse has, as recited in claim 1, "human unrearranged variable region gene segments." But Regeneron argues that under the broadest reasonable construction of claim 1, the non-variable (constant) region of the claimed mouse's modified gene segments exclusively contains mouse genes. In other words, Regeneron argues that claim 1 is limited to a reverse chimeric mouse. Merus, on the other hand, argues that the constant region of the gene segments in the claimed mouse may contain mouse genes or human genes, and may, therefore, be reverse chimeric, humanized, or fully human.

Regeneron first relies on the claim language to support its position. [C]laim 1 recites "[a]genetically modified mouse, comprising in its germline human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus." According to Regeneron, because claim 1 only recites modifying the mouse by inserting "human unrearranged variable region gene segments," it implies leaving the remainder of the mouse's DNA unmodified. This, however, is inaccurate. Because "comprise" is inclusive or open-ended, the use of the term does not exclude unrecited elements. A germline that "comprises" human variable region gene segments may very well also include human constant gene segments. Thus, the "customary and ordinary" meaning of the language in claim 1 is not limited to a reverse chimeric mouse. . . . Under this broadest reasonable construction, the court next determines if the district court clearly erred in finding the Withheld References but-for material and not cumulative of prior art that the PTO considered during prosecution. . . .

During prosecution, Drs. Smeland and Murphy knew of the Withheld References and did not disclose them to the PTO. [T]he four Withheld References were Brüggemann, Wood, Taki, and Zou.

First, Regeneron argues that the district court improperly found Brüggemann to be but-for material. Brüggemann is a review paper that teaches the use of transgenic mice to express human antibodies. In particular, Brüggemann teaches that "[a]n attractive alternative [to the random integration of human genes into mouse genes] would be to replace the mouse Ig loci with the human Ig loci." Brüggemann further expands that in doing so, "much of the DNA of the mouse Ig loci" might be replaced with human Regeneron only contests Brüggemann's materiality because Brüggemann purportedly does not disclose a reverse-chimeric mouse. [H]owever, claim 1 is not limited to reverse-chimeric mice. Claim 1 encompasses humanized, fully human, and reverse chimeric mice as well. We therefore are not persuaded by the distinction drawn by Regeneron and conclude that the district court did not clearly err in finding Brüggemann but-for material.

Second, Regeneron argues that the district court improperly found Wood to be but-for material. According to Regeneron, Wood does not teach inserting a human variable gene into a mouse by targeting the mouse Ig locus. Instead, Regeneron contends that Wood teaches "randomly integrating human transgenes" into a mouse genome with no such targeting. . . . Wood teaches that "[t]he present invention relates generally to immunoglobulin rearrangement in chimeric and transgenic animals, and more specifically to a mouse containing in its germline . . . the ability to generate immunoglobulins . . . ." Wood further teaches that when human DNA is combined with mouse DNA, the "constant region," i.e., the constant region of the DNA in the Ig locus, "is of exogenous or endogenous species origin" and that this constant region may be "from the animal itself." Skilled artisans are therefore taught to specifically target the endogenous Ig locus when inserting human DNA into the mouse. The district court did not err in finding Wood but-for material. . . .

Third, Regeneron argues that the district court improperly found Taki to be but-for material. According to Regeneron, Taki only teaches inserting rearranged variable region DNA from one mouse into the genome of another mouse. Claim 1, on the other hand, recites inserting unrearranged human variable region DNA into a mouse genome. . . . Taki teaches targeting at the specific locus—the Ig locus—with operable linkage . . . taking advantage of the mouse regulatory and constant regions. Taki, in short, provides the motivation to target human variable region DNA into the mouse Ig locus. The district court did not err by finding Taki's disclosure of targeting insertion of exogenous variable region DNA to be but-for material.

Fourth, Regeneron argues that the district court improperly found Zou to be but-for material. Regeneron contends that Zou only teaches modifying a mouse's constant region whereas the '018 patent teaches modifying a mouse's variable region. . . . The district court properly found that Zou's teaching of inserting portions of human constant, rather than variable, DNA did not detract from its motivation to insert human variable regions in the mouse Ig locus. . . . Thus, the district court properly concluded that Zou was also but-for material.

[T]he district court never held a second trial to determine if Regeneron acted with the specific intent to deceive the PTO during prosecution. Instead, the court sanctioned Regeneron for its litigation misconduct by drawing an adverse inference of specific intent. Contrary to Regeneron's arguments, we determine that the district court did not abuse its discretion by sanctioning Regeneron in this manner. Regeneron's behavior in district court was beset with troubling misconduct. . . .

Regeneron is accused not only of post-prosecution misconduct but also of engaging in inequitable conduct during prosecution. Regeneron's litigation misconduct, however, obfuscated its prosecution misconduct. In particular, Regeneron failed to disclose documents directly related to its prosecuting attorneys' mental impressions of the Withheld References during prosecution of the '018 patent. The district court drew an adverse inference to sanction this litigation misconduct. The district court did not punish Regeneron's litigation misconduct by holding the patent unenforceable. Only after Merus proved the remaining elements of inequitable conduct did the district court hold the patent unenforceable. In light of Appellant's widespread litigation misconduct, including Appellant's use of sword and shield tactics to protect Drs. Smeland and Murphy's thoughts regarding disclosure of the Withheld References to the PTO during prosecution of the '018 patent, we conclude that the district court did not abuse its discretion by drawing an adverse inference of specific intent to deceive the PTO.