LEGAL UPDATE

RECENT FEDERAL CIRCUIT DECISION CONCERNING ERYTHROPOETIN (EPO): *AMGEN V. TKT*

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I. INTRODUCTION

In January of this year, the Federal Circuit decided a patent infringement dispute concerning the recombinant human glycoprotein, erythropoietin ("EPO").[1] Recombinant EPO, sold under the brand-names Epogen® by Amgen and Procrit® by Ortho Pharmaceuticals, a subsidiary of Johnson & Johnson, is the highest grossing recombinant protein therapeutic, reaping gross annual sales of nearly $7 billion in a $20 billion protein therapeutics market.[2] The success of EPO has allowed Amgen to become the largest biotech company in the world but it also has been the source of much litigation as competitors seek to capture a piece of the lucrative EPO market.[3]

In the most recent litigation, Amgen sued Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. ("TKT") for infringement of five Amgen patents covering various aspects of the recombinant EPO process and product.[4] All five of Amgen's patents share inventor, disclosure, ancestry and priority to a

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[1] Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003).

[2] Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69, 77 (D. Mass. 2001) (citing Vicki Brower, *Amgen Comes Out on Top in Blood Drug Patent Tussle*, BIOTECHNOLOGY NEWSWATCH, Jan. 4, 1999); Bill Alpert, *High Stakes Game: Amgen wants to retake sales of its top-selling drug from J&J; For the benefit of patients, of course*, BARRONS 20, Sept. 2, 2002; Transkaryotic Therapies Inc. Web Site, *Gene Activation Technology*, *available at* http://www.tktx.com/devplatform/activation.htm (last visited, Mar. 13, 2003).

[3] *See*, *e.g.* Amgen, Inc. v. Genetics Institute, 98 F.3d 1328 (Fed. Cir. 1997); Amgen, Inc. v. Elanex, 160 F.R.D. 134 (W.D. Wash. 1994); Amgen v. Chugai, 927 F.2d 1200 (Fed. Cir. 1991); Amgen, Inc. v. Chugai Pharmaceutical Co., 808 F. Supp. 894 (D. Mass. 1992).

[4] *Hoechst*, 314 F.3d at 1322-23. In April 1997, when Amgen initially filed against TKT for a declaratory judgment of infringement, three patents were at issue; however in October 1999, Amgen amended their complaint to include infringement of two additional patents that were issued after the initial complaint. *Id.*

long-abandoned December 1983 application. [5] At trial, TKT's position was that its EPO product ("GA-EPO"), produced from proprietary technology that allows for the alteration of human cells via homologous recombination, did not infringe on the Amgen patents, or in the alternative, that the Amgen patents were invalid.[6]

Judge Young, presiding over the district court case, ruled that TKT (1) either did not infringe Amgen's '933 patent disclosing non-naturally occurring EPO or the patent was invalid under §112; (2) did not infringe Amgen's '698 patent disclosing a process for recombinant EPO production; (3) infringed, under the doctrine of equivalents, Amgen's '080 patent disclosing isolated or non-natural EPO with a specific amino acid sequence; (4) literally infringed the product claims of Amgen's '349 patent disclosing recombinant vertebrate cells that produce EPO but did not infringe the process claim of that patent disclosing a process for producing EPO using those cells; and (5) literally infringed Amgen's '422 patent disclosing a therapeutically effective pharmaceutical composition containing EPO purified from mammalian cells grown in culture.

Both parties appealed to the Federal Circuit. On appeal, TKT argued that the district court erred in claim construction, or alternatively, that it erred in finding that four of the Amgen patents were valid under §102(a) (novelty), §103 (obviousness) or §112 (enablement).[7] Amgen argued on appeal that the district court erred in finding that its '933 patent was invalid under §112 and in its finding of non-infringement of Amgen's process claims (all claims of the '698 patent and Claim 7 of the '349 patent).[8]

The Federal Circuit affirmed-in-part, vacated-in-part and remanded for further consideration.[9] Among the many issues reviewed, only three are discussed in this Update. First, the Federal Circuit affirmed the district court's claim construction and the resulting alternative finding that Amgen's '933 patent was invalid for indefiniteness.[10] Second, the Federal Circuit found error in the district court's infringement analysis of patent process claims and reversed the district court's finding that the TKT did not infringe those claims.[11] Third, in regard to the district court's §102(a) anticipation analysis, the Federal Circuit found that the district court erred in constructing a claim term according to expert opinion during its §102(a) analysis, and erred in placing the burden on TKT to show by clear and convincing evidence that a

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[5] *Id.*

[6] *Hoechst*, 126 F. Supp. 2d 69, 81, 99. *See also*, Transkaryotic Therapies, Inc. Web Site, *supra* note 2.

[7] *Hoechst*, 314 F.3d at 1320, 1330, 1352.

[8] *Id.* at 1320.

[9] *Id.* at 1313.

[10] *Hoechst*, 314 F.3d at 1324-30 (affirming claim construction), 1342 (affirming the district court's §112 ¶ 2 finding of indefiniteness for the '933 patent and suggesting that a finding of indefiniteness obfuscates infringement analysis).

[11] *Id.* at 1346, 1351.

prior art U.S. patent was enabled.[12] As a result, the Federal Circuit instructed the district court to conduct a formal, Markman construction of the claim term, "therapeutically effective," to place the burden of showing that a prior art U.S. patent is not enabled onto Amgen, and to reconsider the resulting §102(a) and §103 validity aspects of Amgen's '080, '349 and '422 patents.[13]

II. THE DISTRICT COURT'S CLAIM CONSTRUCTION

At the outset of the district court's decision on claim construction, it made an explicit appeal to the Federal Circuit to clarify the proper procedure for conducting the Markman hearing relative to the summary judgment hearing.[14] Some judges prefer to perform both functions in the same hearing.[15] Others, such as Judge Young, are careful to conduct the Markman hearing before and independent of the summary judgment hearing to insure that factual aspects of infringement considered during a summary judgment hearing will not creep into the claim construction of the Markman hearing and thereby "risk that issues of fact and law will be conflated."[16]

On appeal, the Federal Circuit did not explicitly indicate whether or not it is proper to hold the Markman and Summary Judgment hearings together. However, it did fully agree with the district court's findings with regard to claim construction.[17] Further, the Federal Circuit indicated that the "first step . . . is to construe the claims" and "[t]hereafter" conduct infringement analysis.[18]

At the Markman hearing, the district court interpreted ten specific terms in the eighteen disputed claims of Amgen's five patents.[19] As might be expected, Amgen tended to argue for broad claim interpretations according to the "ordinary meaning" of the terms while TKT tended to argue for narrow interpretations, based on the specification prosecution history.[20] For example, TKT argued that the term "vertebrate cells," controlling all six disputed claims in the '698 patent and all five disputed claims in the '349 patent, should exclude human cells (used by TKT) because Amgen's specification limited discussion to placing human genes into non-human cells.[21] Amgen argued that the claim term was clear and that they were not required in their specification to discuss every last embodiment that their claims referred to.[22]

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[12] *Id.* at 1352-57.

[13] *Id.* at 1358.

[14] *Hoechst*, 126 F. Supp. 2d at 80.

[15] *Id.* at 80.

[16] *Id.* at 80-81.

[17] *Hoechst*, 314 F.3d at 1320.

[18] *Id.* at 1324.

[19] *Hoechst*, 126 F. Supp. 2d at 80-93.

[20] *Id.* at 81.

[21] *Id.* at 84-85.

[22] *Id.* at 84.

The district court agreed with Amgen on a broad interpretation for eight of the ten disputed claims, citing ample precedent that claim terms are to be interpreted, as Amgen argued, "pursuant to the plain and ordinary meaning ascribed to them by one skilled in the art."[23] In response to TKT's position Judge Young wrote, "[t]he Federal Circuit has warned . . . that the canon that claims ought be interpreted to sustain their validity is not without limits. . . . The Court is not permitted to construe a term that has a plain and ordinary meaning in a manner contrary to that meaning."[24]

However, the district court did agree with TKT's interpretation of one claim term, "human urinary [EPO]."[25] Interestingly for this claim term, TKT argued for a broad interpretation and Amgen argued for a narrow interpretation.[26] TKT argued that the term referred to any and all EPO purified by any method from human urine while Amgen argued that the term should be limited to EPO from pooled urine of aplastic anemia patients purified by prior art procedures referred to in the specification.[27] This term, employed by Amgen to avoid prior art that discussed purification and clinical experimentation of EPO purified from urine, limited Amgen's three '933 disputed product claims to cover only EPO that is empirically distinct (in glycosylation and/or molecular weight) from human urinary EPO.[28]

Amgen argued for a narrow claim interpretation because evidence showed that EPO purified from human urine by means other than those suggested in Amgen's specification had various glycosylation patterns and one skilled in the art would be unable to identify that variable human urinary EPO from any other human EPO. Consistent with it's deference to the plain and ordinary meaning of the claim language, the district court decided to construe "human urinary [EPO]" broadly (purified from any human urine by any means), in favor of TKT. As a result, the district court later found and the circuit court affirmed that the '933 patent claims were invalid for §112 ¶ 2 indefiniteness because one skilled in the art would be unable to empirically distinguish human urinary EPO from any other human EPO.[29]

The district court abstained at the Markman hearing from interpreting a final claim term, "mature [EPO] amino acid sequence of Fig. 6" that controlled all

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[23] *Id.* at 82, 84-91. In addition to the "vertebrate cell" claim, Judge Young interpreted broadly and in Amgen's favor the following: "mammalian cells," "purified from mammalian cells grown in culture," "non-human DNA sequences that control transcription," "not originating in the human genome," "DNA encoding human [EPO]," "non-naturally occurring," "glycosylation which differs" and "operatively linked." *Id.*

[24] *Hoechst*, 126 F. Supp. 2d at 83.

[25] *Id.* at 92.

[26] *Id*.

[27] *Id.*

[28] *Id.* at 92 (discussing claim construction), 122-32 (discussing prior art of 'human urinary [EPO]' limitation).

[29] *Hoechst*, 314 F.3d at 1341-42.

disputed claims in the '698 and '080 patents.[30] The sequence in the referenced figure described a 166 amino acid polypeptide but, as was subsequently discovered, mature EPO contains 165 amino acids.[31] At trial, the district court became convinced the labels and description of Fig. 6 defined mature EPO with 166 amino acids rather than, as Amgen asserted at trial, some precursor of mature EPO from which the mature EPO was claimed.[32] As a result, the court found that TKT's 165 amino acid EPO did not literally infringe the three '080 product claims and the six '698 method claims limited by the Fig. 6 reference.[33] In dicta, Judge Young suggested that Amgen's argument for infringement might have been more convincing if they had limited their patent claims to mature EPO, without reference to Fig. 6.[34] While the reference to mature EPO as having 166 amino acids instead of 165 precluded a finding of literal infringement of the '698 and '080 claims, the district court did find infringement of the '080 claims under the doctrine of equivalents.[35] For reasons not discussed in this Update (concerning the Supreme Court's decision in *Festo* subsequent to this district court decision), the Federal Circuit vacated and remanded the infringement under the doctrine of equivalents findings.

III. THE DISTRICT COURT'S INFRINGEMENT ANALYSIS OF PROCESS CLAIMS

The district court pointed to an alternative reason why TKT did not infringe the '698 method patent either literally or under the doctrine of equivalents. The Court indicated that process patents are different from product patents in that the entire process, rather than the resulting product, is the protected invention.[36] As such, the court looked beyond the '698 claims and eschewed an element-by-element infringement analysis for an analysis of the details of TKT's process as compared to the process described in '698 specification.[37] Thus, the process claims of the '698 patent were found not infringed by TKT's process even though the disputed claim terms were interpreted broadly to arguably cover TKT's process.[38] As the basis for non-infringement, the court

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[30] *Hoechst*, 126 F. Supp. 2d at 86-87.

[31] *Id.* at 86-87.

[32] *Id.* at 100.

[33] *Id.*

[34] *Id.*

[35] *Id.* at 101 n.22.

[36] *Id*. at 101-02.

[37] *Id.* at 102-04.

[38] *Id.* at 101-04. The '698 patent contains two independent claims (4 and 6). Claim 4 reads:

> A process for the production of glycosylated [EPO] polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
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> (a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human [EPO] promoter DNA, operatively linked to DNA encoding the mature [EPO] amino acid sequence of Fig. 6; and

first recognized that the '698 specification instructed exogenous heterologous recombination whereas the TKT process employs homologous recombination.[39] Interestingly, this distinction was the basis of TKT's losing argument to narrow the '698 patent term, "vertebrate cells" in the Markman hearing.[40] Secondly, the district court recognized that the promoter insertion in the '698 specification was distinct from TKT's promoter insertion.[41] Interestingly, this distinction was the basis of TKT's losing argument to narrow the '698 patent term "operatively linked" in the Markman hearing.[42] Using this same analysis of process details rather than claim elements, the district court ruled that TKT did not infringe the only other process claim in dispute, Claim 7 of the '349 patent.[43]

On appeal, Amgen argued that the district court committed error by failing to conduct an element-by-element comparison of Amgen's process claims and TKT's process.[44] The Federal Circuit agreed with Amgen and vacated and remanded the district court's infringement findings on all disputed process claims.[45] In review, the Federal Circuit noted that the difference between process and products claims is the subject matter of the element-by-element analysis, not the analysis itself.[46]

IV. THE DISTRICT COURT'S ANALYSIS OF ANTICIPATION

When TKT rested, Amgen moved for a court decision of infringement.[47] In regard to TKT's showing of proof to invalidate Amgen's patents for §102(a) anticipation, the district court found that TKT failed to prove to a clear and convincing standard that any of the eighteen disputed patent claims in Amgen's five patents was anticipated, and thereby invalidated, by any one of TKT's cited prior art references.[48] As the district court pointed out, patent invalidation under §102(a) requires that any single prior art (a) precede the date of invention, (b) be accessible before the date of invention, (c) be enabling, and (d) contain every element of the claim ("the four-corners

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(b) isolating said glycosylated [EPO] polypeptide expressed by said cells.

Claim 6 reads identical to Claim 4, except for the (a) clause, which reads:

(a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature [EPO] amino acid sequence in Fig. 6; and . . . .

U.S. Patent No. 5,618,698 (issued Apr. 8, 1997).

[39] *Hoechst*, 126 F. Supp. 2d at 102.

[40] *Id.* at 85.

[41] *Id.* at 103.

[42] *Id*. at 90.

[43] *Id.* at 122.

[44] *Hoechst*, 314 F.3d at 1346, 1351.

[45] *Id.*

[46] *Id.* at 1347.

[47] *Hoechst*, 126 F. Supp. 2d at 104.

[48] *Id.* at 105-13.

rule").[49] The district court found that all of the references failed §102(a) anticipation because they were either non-enabling or failed the four-corners rule, or both.[50]

The Federal Circuit remanded for further consideration of anticipation by two references, the Goldwasser reference and Sugitomo reference.[51] The Goldwasser reference discloses clinical studies conducted at the University of Chicago in which EPO, purified from human urine, was administered to three patients.[52] The patients in Goldwasser's study showed several biological responses to the urinary EPO, including increases in reticulocytes and red blood cell mass.[53] However, Dr. Goldwasser considered the experiment a failure because the patients did not show increases in their hemocrit levels, which is the accepted standard of therapeutic efficacy for anemia.[54] The district court found that because the Goldwasser reference was not "therapeutically effective," it did not meet the four corners of the disputed claims that contained that term.[55] Moreover, the district court explained with a quote from a Federal Circuit decision, "another's experiment, imperfect and never perfected, will not serve either as an anticipation or as part of the prior art, for it has not served to enrich it."[56]

On appeal, the Federal Circuit agreed with TKT that the district court did not properly proceed in construing the term, "therapeutically effective," and remanded for a Markman hearing to properly construe the term.[57] As the Federal Circuit pointed out, before looking to those skilled in the art for a proper construction of a term, the court should look first to the claims, the specification, and the prosecution history for any express definitions.[58] Specifically, the Federal Circuit took issue with the fact that the district court defined "therapeutically effective" out of hand as the accepted standard agreed to by experts on anemia. Though remanded, the Federal Circuit suggested in dicta that the Amgen specification does, in fact, define "therapeutically effective" to encompass the patient responses observed in the Goldwasser study. If, on remand, the district court agrees, the Goldwasser study could anticipate some of Amgen's patent claims, "even if [Goldwasser] did not

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[49] *Id.* at 105-07.

[50] *Id.* at 108-13.

[51] *Hoechst*, 314 F.3d at 1353, 1356.

[52] *Hoechst*, 126 F. Supp. 2d at 111.

[53] *Id.* at 111-12.

[54] *Id*. at 112.

[55] *Id*. at 112. Note that Amgen's '422 and '080 patents have claim language that includes the term "therapeutically effective."

[56] *Id*. at 112 (citing Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549,1558 (Fed.Cir. 1985)).

[57] *Hoechst* 314 F.3d at 1354.

[58] *Id.* at 1324 (citing Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir. 1996)).

achieve his intended result."[59] In a footnote, the Federal Circuit also instructed the district court to be "cognizant" of the rule that a product claim cannot survive anticipation or obviousness invalidation by the addition of a source limitation (possibly referring to claim language such as in Amgen's '080 Claim, "and is not isolated from human urine").[60]

The Federal Circuit also remanded the Sugimoto reference for further consideration of anticipation.[61] The Sugimoto reference is a U.S. patent that discloses a means for fusing lymphoblastoid cells with kidney cells and culturing them to produce EPO.[62] At trial, the district court found that TKT failed to carry its burden of showing with clear and convincing evidence that the Sugimoto reference met the enablement and four-corners requirements necessary to invalidate by anticipation any of Amgen's patent claims.[63] The Federal Circuit agreed with TKT's assertion, on appeal, that the district court erred in placing on TKT the burden of proving enablement of an issued patent. However, rather than grounding its decision in 35 U.S.C. § 282 (which TKT relied on) the Federal Circuit relied on its own precedent to hold that "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled."[64] Therefore, the burden should have rested with Amgen to show that the Sugimoto patent was not enabled.[65]

Because the district court also found that the Sugitomo reference failed to meet the four-corners requirements against all of Amgen's patent claims, the Federal Circuit found the erroneous placement of burden to be a distinction without a difference for the '080, '349 and '698 patents.[66] However, the Federal Circuit remanded for consideration of whether or not the Sugitomo reference met the four-corners of the disputed '422 patent claim.[67] In reference to one element of the '422 claim, "a therapeutically effective amount of human [EPO]," the Federal Circuit instructed that it should be interpreted with the "new" definition of "therapeutically effective."[68] In reference to another element of the '422 claim, "wherein said [EPO] is purified from mammalian cells grown in culture," the Federal Circuit repeated its warning for the district court to be cognizant of the rule that anticipated product claims cannot escape invalidity by adding source limitations.[69]

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[59] *Id.* at 1354.

[60] *Id.* at 1354 n.20 (citing General Electric Co. v. Wabash Corp., 304 U.S. 364, 367 (1938); Cochrane v. Badische Anilin & Soda Fabrik, 111 U.S. 293, 311 (1884)).

[61] *Id.* at 1356.

[62] *Id.* at 1354. The Sugitomo patent is U.S. Patent No. 4,377,513 (issued Mar. 1983).

[63] *Hoechst*, 126 F. Supp. 2d at 109.

[64] *Hoechst*, 314 F.3d at 1355.

[65] *Id*. at 1355.

[66] *Id.* at 1356-57.

[67] *Id.* at 1357.

[68] *Id.* at 1357.

[69] *Id.* at 1357.

V. CONCLUSION

EPO is the most successful biotechnology product to date. As such, it has, is and will be the subject of much litigation. Fresh contenders in the EPO ring have not had much success to this point. The current interim Federal Circuit decision in the dispute between Amgen and TKT leaves the final outcome of this most recent battle a mystery. As ground-breaking technologies in protein therapeutics continue to evolve, arguably as TKT's has evolved, it will be interesting to observe what factual observations will finally sway the courts to anoint a new champion in the EPO market.