Amgen preserves erythropoietin monopoly for now

Amgen (Thousand Oaks, CA) has won its US district court patent battle against Transkaryotic Therapies (TKT; Cambridge, MA) and Aventis Pharmaceuticals (Bridgewater, NJ) over its multi-billion dollar red blood cell-stimulating drug, erythropoietin (EPO). On January 19, Judge Young of the Federal District Court of Massachusetts ruled that TKT's gene-activated EPO (GA-EPO) infringed claims in three of Amgen's US patents [5,621,080, 5,756,349, and 5,955,422]. The news prompted a 13% gain in Amgen stock to $67.625, while TKT's stock sank 32% to $23.125. However, Amgen has yet to emerge victorious from the Federal Court of Appeals for the Federal Circuit. And with a case pending before the High Court of Justice in London, where TKT has a better chance of prevailing, a split decision is also possible.

Amgen's EPO brought in nearly four billion dollars in sales last year, under the trade names Epogen, and Procrit (sold by Johnson & Johnson). TKT's GA-EPO (Dynepo) differs from Epogen in the way that it is made and possibly in carbohydrate structure. GA-EPO is made by introducing, through homologous recombination, regulatory sequences that activate the otherwise quiescent endogenous EPO gene of a human cell line. Epogen, on the other hand, is made by introducing an exogenous human EPO cDNA linked to regulatory sequences into Chinese hamster ovary cells.

There is an old rule in patent law that "natural products" cannot be patented in the form they exist in nature. Because GA-EPO is made by activating a cell's endogenous EPO gene, TKT believed that Amgen's claims could not encompass it. "Simply because Amgen discovered the purified gene does not give them the right to the gene in its natural environment," says Mark Hofer, an attorney at Brown, Rudnick, Freed & Gesmer (Boston MA). However, TKT's argument, based on this antiquated rule, was not persuasive. Because TKT's human cells would not make EPO without human intervention, Young found that GA-EPO was non-natural and within the scope of the '080 patent claims.

Young correctly recognizes that genes are inherently heterogeneous and ruled that the heterogeneity will be taken into account when determining the validity and infringement of patent claims: To avoid the natural products rule, Amgen consistently argued to the US Patent Office that Epogen differed from natural EPO isolated from human urine. It follows that if GA-EPO has the same carbohydrate structure as natural urinary EPO it would avoid infringement. However, Young concluded that Amgen had failed to prove the difference: Based on expert testimony that the carbohydrate structure of "human urinary" EPO varies depending on how and from whom it was isolated, Young ruled that the term is a moving target and a "standardless standard."

Another key aspect of the case was whether Amgen's claims to products could be avoided by TKT on the grounds that GA-EPO was made by a different process. TKT pleaded that because in 1983 (when the patents were filed) other methods for making GA-EPO were not known, they could not be covered by Amgen's product claims. However, this argument is misplaced: As Judge Young correctly ruled, in patent law inventors are required to teach one method only for making the claimed product.

But legal questions are rarely disposed of that easily. At the heart of the dispute is whether Amgen's claims are, in fact, product claims or process claims. "Amgen's so-called product claims contain several process limitations," says Jon Alsenas, managing director, Equity Research at ING Ferman Selz Asset Management (New York). "Judge Young totally failed to take that into consideration," he adds. Indeed, several of Amgen's claims contain language that the EPO product can not be "isolated from human urine" or that the vertebrate cells produce "in excess of 100 U of erythropoietin per 10^6 cells." The Federal Circuit has invalidated product claims that were described in terms of function rather than structure on the grounds that they are not enabled, including some of Amgen's claims in earlier litigation with Chugai over EPO. If the Federal Circuit takes a hard line on Amgen's functional language, claims that Young already thought were barely enabled could be invalidated during the appeal.

Meanwhile, there was a significant ruling for genomic companies hoping to ward off would-be competitors using variants that offer no advantage: the court ruled that minor amino acid changes unaccompanied by improved biological activity will be held to infringe the '080. TKT's inability to demonstrate a difference in biological activity led Young to rule that GA-EPO infringed. Unknown to Amgen at the time it filed its patent, the arginine residue at position 166 is cleaved prior to secretion, resulting in GA-EPO containing 165 amino acids—one less than the sequence described in Amgen's patent. While Young found that the single amino acid change was sufficient to avoid literal infringement, he nevertheless ruled that the GA-EPO infringed under the so-called doctrine of equivalence.

Another notable ruling—this time for pioneering biotechnology companies bringing biologics to market—was the court's view that companies that prove the commercial viability of products should not be penalized by small and inconclusive clinical trials. TKT argued that EPO and its therapeutic properties were in the public domain and unpatentable based on a clinical trial using "highly purified" EPO conducted at the University of Chicago in 1979–1980 by Eugene Goldwasser three years before Amgen filed its first patent. While Goldwasser reported a change in certain hematological parameters following EPO administration, he failed, according to Young, to achieve the "true mark of therapeutic effectiveness"—increased red blood cell count. Importantly, the judge took into consideration the size of the study and the inability of Goldwasser to purify EPO in sufficient quantities to complete the trial.

Meanwhile, with ex-US sales of about two billion dollars for EPO, the US is but part of the battle. TKT has filed a marketing authorization application for GA-EPO with the European Medicines Evaluation Agency and expects approval in September. Amgen has filed a lawsuit hoping to stop TKT from commercializing GA-EPO in Europe, and the trial, being heard by the High Court of Justice in London, is expected to conclude in late February with a decision following a few months later. Different legal standards make it difficult to predict the outcome of the litigation. Unlike the US, however, Amgen has only one European patent (EP 0148605 B2) covering both EPO and processes for making EPO. Thomas Dietz, managing director at Pacific Growth Equities (San Francisco, CA) says "Protein claims held infringed in the US were submitted and rejected by the EU patent office." Indeed, most of the claims contain limitations that the host cell be "transformed or transfected" or that the EPO DNA be "exogenous." These limitations are not found in the US counterpart and should significantly favor TKT's plea of non-infringement. Another important difference is that the patent expires in December of 2003 clearing the way for TKT and other would-be competitors much sooner than in the US, where Amgen's US patents expire in 2013.

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