**UNITED STATES DISTRICT COURT**
**DISTRICT OF MASSACHUSETTS**

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| AMGEN INC., | ) | |
| Plaintiff, | ) | |
| v. | ) | CIVIL ACTION |
| | ) | NO. 97-10814-WGY |
| HOECHST MARION ROUSSEL, INC. and TRANSKARYOTIC THERAPIES, INC., | ) | |
| Defendants. | ) | |

MEMORANDUM AND ORDER

YOUNG, D.J. October 2, 2008

Amgen brought this action seeking a declaratory judgment of infringement of several patents related to recombinant erythropoietin ("EPO"), which mimics a naturally occurring hormone that stimulates production of red blood cells. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 339 F. Supp. 2d 202, 213 (D. Mass 2004) [hereinafter "Amgen III"]. Over the past decade, the Court has taken evidence in two bench trials, and this Court's opinions have twice been appealed to the Federal Circuit. See Amgen, Inc. v. Hoechst Marion Roussel, Inc., 457 F.3d 1293, 1296-97 (Fed. Cir. 2006) [hereinafter "Amgen IV"].[1] In its most

[1] The course of this litigation has been set forth in no fewer than four lengthy opinions. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69 (D. Mass. 2001) ("Amgen I"); Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003) ("Amgen II"); Amgen Inc. v. Hoechst Marion Roussel Inc., 339 F. Supp. 2d 202 (D. Mass. 2004) ("Amgen III"); Amgen Inc. v. Hoechst Marion Roussel Inc., 457 F.3d 1293 (Fed. Cir. 2006) ("Amgen IV"). The Court will not belabor the details here.

recent opinion, the Federal Circuit vacated this Court's construction of the term "therapeutically effective" in claim 1 of U.S. Patent No. 5,955,422. Id. at 1303. On remand, the Court must answer one question: Did EPO purified from the urine of Japanese aplastic anemia patients and administered to three patients by Dr. Eugene Goldwasser anticipate claim 1 of the '422 patent? Simply put, no.

Claim 1 of the '422 patent teaches:

> [1] A pharmaceutical composition comprising [2] a therapeutically effective amount of human erythropoietin [3] and a pharmaceutically acceptable diluent, adjuvant[,] or carrier, [4] wherein said erythropoietin is purified from mammalian cells grown in culture.

'422 pat. col. 38 ll. 36-41.

The Court must reject TKT/HMR's anticipation challenge because TKT/HMR has failed to demonstrate with clear and convincing evidence that the Goldwasser reference embodied two of these limitations. See In re Omeprazole Patent Litg., 483 F.3d 1364, 1371 (Fed. Cir. 2007) (noting that a defendant seeking to invalidate a claim via anticipation must prove that each element was disclosed in a single prior art reference). TKT/HMR has demonstrated with clear and convincing evidence that Dr. Goldwasser's urinary preparation was "a pharmaceutical composition" and "a pharmaceutically acceptable diluent, adjuvant[,] or carrier." The Court cannot conclude, however, that the urinary EPO administered in the Goldwasser study was "therapeutically effective" because TKT/HMR has failed to prove with clear and convincing evidence that the urinary EPO actually

caused an increase in reticulocyte count or an increase in ferrokinetic effects. Although Dr. Goldwasser stated that he observed a slight increase in reticulocyte count in three patients and an increase in plasma iron clearance in two patients, these observations lack a firm statistical foundation. The three-patient study did not rely on adequate baseline data, did not employ controls, and was ultimately discontinued before Dr. Goldwasser could collect sufficient data to draw conclusions about a causal link between urinary EPO and the purportedly observed effects. In light of this incomplete data, the fact that the Goldwasser preparation did not increase the hematocrit of any patient and the fact that Dr. Goldwasser and his collaborator Dr. Joseph Baron did not publish their results for peer review cast further doubt on TKT/HMR's assertions. Finally, the Federal Circuit has upheld this Court's conclusion that "purified from mammalian cells grown in culture" limits the source of the product taught in claim 1. Amgen II, 314 F.3d at 1329. It is undisputed that the EPO in the Goldwasser study was purified from the urine of aplastic anemia patients.

## I. BACKGROUND

EPO is a naturally occurring hormone produced in the kidneys and liver that travels through the bloodstream and into bone marrow to stimulate the production of red blood cells. See Amgen III, 339 F. Supp. 2d at 214. EPO produces red blood cells by bonding with EPO receptors in the bone marrow to generate

reticulocytes, which are "newly formed red cells." Def's App. [Doc. No. 864, Exh. 1], Goldwasser Dep. Tr. at 184. Most of these reticulocytes blossom into red blood cells, which are critical because they contain hemoglobin, the vehicle for transporting oxygen to the body. Amgen III, 339 F. Supp. 2d at 214. Erythropoiesis, the process of producing red blood cells, occurs continuously throughout a person's life in order to offset the natural destruction of red blood cells. Id. People whose kidneys do not function properly, however, do not produce enough EPO to keep up with the rate of cell destruction. Id.

A primary indicator of the effectiveness of an anemia treatment is its effect on a patient's hematocrit. See id. Hematocrit measures the ratio of red blood cells relative to the total volume of blood and is indicative of the blood's ability to supply oxygen to the body. Id. "Under normal conditions, a person has a hematocrit of about forty-five to fifty, which means forty-five to fifty percent of the blood is made up of red blood cells." Id. Patients suffering from kidney failure have a low hematocrit due to their kidneys' failure to produce sufficient EPO. See id. Introducing exogenous EPO into the bloodstream of persons suffering from kidney failure can allow a patient suffering from anemia to overcome the red blood cell deficit. See id.

**A. RACE FOR THE PRIZE**

Scientists first identified the hormone regulating red blood cell production in 1906. Def.'s App. Exh. 18A [Doc. No. 864],

Testimony of Dr. E. Goldwasser Before the International Trade Commission in Investigation No. 337-TA-281 as it was Submitted to the U.S. Patent & Trademark Office with Notice III by Lin Under 37 CFR 1.682(a), at 7-8 [hereinafter "Goldwasser ITC Tr."]. By the early 1950's, Finnish scientists had dubbed the hormone erythropoietin, 'erythro' meaning red, to signify the specificity of its action." Id. at 9. Through the 1950s, researchers sought to isolate EPO, learn more about its properties and reduce it to a therapeutic agent. See id. at 9-12. Although it was apparent that introduction of exogenous EPO into the bloodstream could increase the hematocrit of an anemia patient, obtaining EPO from natural sources proved extraordinarily difficult because EPO is produced in small quantities, even in the healthy body. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1321 (Fed. Cir. 2003) [hereinafter "Amgen II"]. "Early attempts to recover EPO from plasma or from human urine . . . were unsuccessful because such recovery employed techniques that were complicated, yet still resulted in a low-yield, high-impurity, or unstable EPO end product." Id.

Dr. Eugene Goldwasser, a professor at the University of Chicago, began working to isolate EPO in 1954. Dr. Goldwasser's initial attempts to purify EPO from urine failed. Def's App. Exh. 1, Goldwasser Dep. Tr. at 13-14; 16. In 1975, however, working with Dr. Takaji Miyake, Dr. Goldwasser was able to purify a significant quantity of EPO from urine collected from aplastic anemia patients in Japan. Goldwasser ITC Dep. at 12. Dr.

Goldwasser tested this urinary EPO preparation in two studies. First, collaborating with Dr. Joseph Baron, Dr. Goldwasser conducted a study using eight hamsters, with four receiving "18 times the intended human dose" and four serving as controls. Def.'s App. Exh. 34, Review and Evaluation of Pharmacology and Toxicology Data IND 16,234 (May 24, 1979) [Doc. No. 865 Exh. 34B] at HMR 935344. The hamsters receiving urinary EPO exhibited an increase in hematocrit and "[n]o evidence of adverse effect." Id.

Following the hamster study, Drs. Goldwasser and Baron obtained approval for a limited study with three human patients. See Amgen I, 126 F. Supp. 2d at 112. During the course of that study, they administered a total of 10,000 units of EPO to the three patients. Id. The first two patients received a dose of urinary EPO intravenously every 12 hours, and the third patient received a considerably larger dose every two to three days. See Def.'s App. Exh. 34 [Doc. No. 865], Letter from Dr. Joseph Baron to the National Center for Drugs and Biologics (February 6, 1984) at HMR 935322 [hereinafter "Baron Ltr."].

Drs. Goldwasser and Baron acknowledged that the study was not a success. Dr. Baron reported that the urinary EPO cleared more rapidly from the body than they had expected and seemed to break down in the body. Id. at HMR 935322-323. There is no indication that any patient was harmed, but none of the patients experienced a significant increase in hematocrit. Id. "[H]owever each patient . . . showed a mild to modest increase in

reticulocyte number, with peaks noted at days 9, 10 and 11 . . . ." "The first two patients had increased erythroid cells in the marrow and an increased plasma iron clearance rate." Def.'s App. Exh. 23A [Doc. No. 864], Application for Continuation Grant re "Erythropoietin: Purification, Properties, Biogenesis" at A 8036 [hereinafter "Application for Continuation Grant"]. In addition, "[o]ne of the first two patients showed an increase in red cell mass." Id. The study discontinued without further testing because it was "too difficult getting enough erythropoietin" from human urine. Goldwasser Dep. Tr. at 186.

Dr. Goldwasser subsequently characterized the study as a failure. See Amgen I, 126 F. Supp. 2d 69, 112. He downplayed the significance of the results in subsequent proceedings, emphasizing that the study was "a very limited" and "abortive trial" on three patients. Goldwasser ITC Tr. at 23. In a grant application filed in 1984, he suggested that the results "show that epo can have a physiological effect in this type of anemia." Nevertheless, he cautioned that the data was "fragmentary" and "need[ed] to be reinforced with more extensive and extended studies." Grant App. at 19. "If [EPO's] potential therapeutic effect were ever to be found out, it needed to have large enough amounts to use relatively large doses in the patient, and to use enough patients to get statistically significant results." Goldwasser ITC Tr. at 23.

**1. The source of Amgen's EPO helped distinguish it from the prior art**

The key to the success of Amgen's recombinant EPO was the source. Previous researchers had attempted to purify EPO from naturally occurring sources such as plasma or urine. Amgen II, 314 F.3d at 1321. As Dr. Goldwasser's aborted experiment illustrated, this strategy had its limitations because scientists could never obtain a sufficient quantity for statistically significant human testing, much less administration to the swath of patients suffering from red blood cell deficiencies. See Goldwasser ITC Tr. at 23. Dr. Fu-Kuen Lin, Amgen's lead researcher, was able to decipher EPO's genetic code and construct a strand of DNA that, when injected into a cell, would produce a protein with an amino acid sequence identical to naturally occurring EPO. See Amgen III, 339 F. Supp. 2d at 214-15. Harnessing the natural processes of transcription and translation in Chinese hamster ovary cells ("CHO cells"), Dr. Lin was able to produce EPO with "one or more [of] the biological properties of naturally occurring EPO but differ[ing] from natural EPO in its 'glycosylation,' that is, it has a different average carbohydrate composition." Id. at 215. Perhaps most importantly, recombinant EPO, unlike natural EPO, can be produced in enormous quantities to satisfy global demand for anemia drugs. See Amgen I, 126 F. Supp. 2d at 77 (noting EPO's success in meeting the market's demand). In short, by looking to a different type of source, recombinant DNA technology, Dr. Lin was able to produce a virtually limitless supply of a superior product.

The Court has construed the source to limit claim 1, see

Amgen I, 126 F. Supp. 2d at 88-89, and the Federal Circuit has upheld that construction. See Amgen II, 314 F.3d at 1329 (noting that "'purified from mammalian cells grown in culture' in claim 1 clearly limits the source of the EPO used in the claimed 'pharmaceutical composition'"). "[A]s has long been recognized by the Federal Circuit, source or process limitations can and do serve to define the structure of a claimed product where such limitations are the best means to distinguish a claimed product from the prior art." Amgen, Inc. v. F. Hoffmann-La Roche Ltd., 494 F. Supp. 2d 54, 65 (D. Mass. 2007) (citing In re Luck, 476 F.2d 650, 653 (C.C.P.A. 1973)). As Dr. Lin testified, "'the only way [to] characterize [his claimed] product is by the way they were making . . . [it.]'" Id.

Evidence suggests that the source accounts for structural characteristics that help to distinguish recombinant EPO from urinary EPO. A critical difference between recombinant and urinary EPO is that a urinary EPO preparation is comprised of EPO that the body has selected for excretion and that has been subjected to the degrading effects of enzymes and bodily processes that may degrade EPO and affect urinary EPO's molecular weight and glycosylation.

When a strand of DNA directs the formation of a protein, it not only directs a specific amino acid sequence, but also certain enzymes that will transfer sugars onto the protein and give the protein its three-dimensional shape. Amgen I, 126 F. Supp. 2d at 124. Glycosylation is the process by which the genetically

selected enzymes transfer sugars to proteins. Id. As the Court noted in Amgen I:

> As disclosed in Column 28 of the patent . . . according to Western blot and SDS-PAGE analyses, "the CHO-produced EPO material had a somewhat higher molecular weight than the COS-1 expression product which, in turn, was slightly larger than the pooled source human urinary extract." [U.S. Patent No. 5,955,422] at [col.] 28 [ll.] 38-41. Amgen scientists then treated the proteins with neuraminidase, which removes the sialic acids from the protein. Id. at [col.] 28 [ll.] 42-43. Following neuraminidase treatment, the COS-1 and CHO recombinant products had approximately equal apparent molecular weights, but were both nonetheless larger than the resulting asialo human urinary extract. See id. at [col.] 28 [ll.] 42-46. Amgen then treated the CHO and human urinary products with endoglycosidase F, which removes not only sialic acids, but also any other carbohydrate chains attached to the protein. Id. at [col.] 28 [ll.] 46-48. Amgen scientists discovered that the CHO and urinary products were "substantially homogenous products having essentially identical molecular weight characteristics." Id. at [col.] 28 [ll.] 49-50. The conclusion to be drawn from this series of tests is that the difference in the apparent molecular weights of recombinant and urinary EPO products on SDS-PAGE and Western blot is explained by differences in glycosylation between the two types of EPO glycoproteins. In light of this data reported in Column 28, one skilled in the art in 1983 would understand that the recombinant proteins are glycosylated differently than the naturally-occurring protein, and that these differences can be revealed by running an SDS-PAGE and doing a western blot . . .

Id. at 125 (some internal citations omitted).

Differences in molecular weight and glycosylation may be indicative of bodily degradation or some other deficiency that helps to explain urinary EPO's ineffectiveness in increasing hematocrit. By contrast, "[t]he results of the first clinical trials with recombinant human EPO were 'dramatic beyond anyone's dreams.'" Id. at 116. Again, as the Court explained in Amgen I:

> Failure to increase hematocrit levels may have been caused by the fact that the potency of Goldwasser's urinary EPO was less than half that of recombinant EPO. See Trial Ex. 137 at 699; Trial Tr. at 1742:3-23. Likewise, the failure to stimulate the production of mature red blood cells may have been caused by the fact that, compared to recombinant EPO, Goldwasser's uEPO cleared from circulation rapidly.

Id. at 112 n.27.

**II. ANALYSIS**

Once the Patent and Trademark Office has issued a patent, the patent holder enjoys a presumption of validity. See Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1349 (Fed. Cir. 2007) (noting that "deference to the decisions of the USPTO takes the form of the presumption of validity under 35 U.S.C. § 282"). A defendant seeking to overcome that presumption via an anticipation defense must demonstrate with clear and convincing evidence that a single prior art reference disclosed every limitation of the claim. See id.; In re Omeprozole, 483 F.3d at 1371. Thus, TKT/HMR must leave the Court with a firm and abiding conviction that Dr. Goldwasser's urinary EPO satisfied every limitation of claim 1 of the '422 patent. It cannot carry this burden.

As a threshold matter, Amgen continues to assert that the Goldwasser study does not constitute prior art under 35 U.S.C. § 102. The Court has already rejected this argument, and "the Court rebuffs this attack as well." Amgen I, 126 F. Supp. 2d at 111. In addition, the Court should note that Amgen does not contest that the Goldwasser preparation consisted of "a

pharmaceutically acceptable diluent, adjuvant[,] or carrier," and the Court is satisfied that TKT/HMR has met its burden with respect to that limitation. The parties dispute whether the Goldwasser reference was "a pharmaceutical composition," "therapeutically effective," or "purified from mammalian cells grown in culture."

First, the Court concludes that TKT/HMR has demonstrated that the urinary EPO preparation was a "pharmaceutical composition" because it was suitable for administration to humans. Second, Dr. Goldwasser indicated that the patients in his study experienced an increase in reticulocyte count and the plasma iron turnover rate. Nevertheless, the failure to collect proper baseline data, the absence of controls, and the fact that the study was limited to three patients and ultimately discontinued -- along with other circumstantial evidence -- prevent TKT/HMR from proving that the urinary EPO actually caused the claimed biologic effects. Finally, the Federal Circuit has upheld this Court's decision that the source "purified from mammalian cells grown in culture" limits claim 1. Amgen II, 314 F.3d at 1329. Since it is undisputed that Dr. Goldwasser's EPO was purified from urine, TKT/HMR cannot demonstrate that the reference satisfied that limitation.

### A. Dr. Goldwasser's Urinary EPO Preparation Was a "Pharmaceutical Composition"

The Court has yet to construe the term "pharmaceutical composition" in the instant litigation. In the related Roche

litigation, however, the Court construed the term as a "composition suitable for administration to humans." Amgen, Inc. v. F. Hoffmann-La Roche Ltd., 494 F. Supp. 2d at 66. Because claim construction is matter of law, Markman v. Westview Instruments, Inc., 517 U.S. 370, 384 (1996), and because the Court is satisfied with the construction in the Roche matter, the Court will apply it in the instant case. In light of this construction, the Court finds that TKT/HMR has demonstrated that the Goldwasser reference was "suitable for administration to humans." Dr. Goldwasser received approval for human testing from the FDA as well as from the University of Chicago Investigation Committee. EPO was administered to patients without any evidence of pyrogens or any significant deleterious consequence. See Baron Ltr. at 1. In addition, the record reveals no ground from which to draw an inference that the hamsters suffered adverse effects. See Def.'s App. Exh. 34, Letter from Dr. Joseph Baron to Dr. Robert Temple of the FDA [Doc. No. Exh. 34B] at HMR 935357.

Nevertheless, Amgen emphasizes the Court's observation that Dr. Goldwasser's EPO was "unsuitable for increased dosages." Pl.'s Mem. On Anticipation of '422 claim 1 [Doc. No. 835] at 35 (quoting Amgen III, 339 F. Supp. 2d at 333). It also points to an increase of white blood cells in the hamster studies. Id. As Amgen acknowledges, however, the dosage the hamsters received was 18 times that administered to human patients. Id. at 35 n.139. That the urinary EPO might have been unsuitable for

humans at doses 18 times greater than they were intended to receive does not render the Goldwasser preparation unsuitable as it was administered in the study.

### B. TKT/HMR has Failed to Prove with Clear and Convincing Evidence that the Increase in Reticulocyte Count or any Ferrokinetic Effects Were Attributable to the Urinary EPO Preparation

The Court previously concluded that the Goldwasser reference did not anticipate because the urinary EPO was not "therapeutically effective." This finding, however, was based on the Court's erroneous claim construction. The Court had "interpreted the term to mean an increase in hematocrit." Amgen III, 339 F. Supp. 2d at 223. The Federal Circuit has since construed the term as follows:

> A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the ['422] specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals.

Amgen IV, 457 F.3d at 1303.

TKT/HMR contends that the urinary EPO preparation in the Goldwasser study elicited an increase in reticulocytes as an increase in the plasma iron clearance rate, a ferrokinetic effect. TKT/HMR relies heavily on four sentences Dr. Goldwasser used to describe the study in a grant application to conduct further EPO related research:

> There was no significant change in hematocrit in any patient; each patient, however[,] showed an increase in

> reticulocyte count, with peaks at 9, 10 and 11 days. The first two patients had increased erythroid cells in the marrow and an increased plasma iron clearance rate. One of the first two patients showed an increase in red cell mass. These fragmentary data[] need to be reinforced with more extensive and extended studies but they show that epo can have a physiological effect in this type of anemia.

Application for Continuation Grant at 19. In addition, Dr. Baron observed a "mild to modest increase in reticulocyte number with peaks noted at days 9, 10, and 11 respectively." Amgen III, 339 F. Supp. 2d at 332-33.

These assertions cannot serve as the basis of a finding of anticipation because Dr. Goldwasser lacked a firm statistical foundation. Even at the time he filed the grant application, he recognized that the data was "fragmentary" and "need[ed] to be reinforced with more extensive and extended studies." Application for Continuation Grant at 19. The studies that Dr. Goldwasser believed were necessary never occurred because he could not procure sufficient urine from Japanese aplastic anemia patients. See Goldwasser Dep. Tr. at 186. The existing data is simply insufficient.

The Court's confidence in the Goldwasser study is undermined by the fact that Drs. Goldwasser and Baron abandoned their protocol. The first two patients were given the same amount of urinary EPO every 12 hours for ten days. Tr. Of Proceedings on Remand vol. 6 at 781 ("Remand Tr."). For the third patient, however, they administered "four times as much urinary [EPO] to the patient, but . . . only every two to three days . . . ." Id.

at 782. Thus, as the Court observed, the patients received different doses at different intervals. Amgen III, 339 F. Supp. 2d at 325. This failure to follow protocol does not enhance the Court's confidence in the study's purported results. Moreover, the fact that Drs. Goldwasser and Baron abandoned their protocol and increased dosage suggests that they recognized the first two administrations had not had the intended effect. Were it true that the urinary EPO actually caused the uptick in reticulocyte count in the first two patients, then it would be reasonable to suspect that the significant increase in dosage would lead to a significant increase in reticulocytes, if not an increase in hematocrit. But despite the nearly doubled dosage, neither reticulocytes nor hematocrit exhibited a significant increase. Remand Tr. vol. 6 at 782.

Even taking at face value Dr. Goldwasser's claims about the increase in reticulocytes in this limited sample, the Court cannot conclude with any certainty that this increase was actually attributable to urinary EPO. Primarily, Dr. Goldwasser failed to gather sufficient baseline data on the patients before the study began. Id. at 676. Moreover, as TKT/HMR's expert conceded, the experiment had "no controls." Remand Tr. vol. 7 at 845. This is significant because as another of TKT/HMR's experts admitted, "a failure to use controls can lead to erroneous or misleading results[,] and . . . a competent technician controls for the variables that could cause certain results." Amgen III, 339 F. Supp. 2d at 294. Without controls or adequate baseline

data, it is no wonder that Dr. Goldwasser conceded that the study data was "fragmentary" and insufficient to serve as the basis for an opinion about the effectiveness of urinary EPO. Application for Continuation Grant at 19.

The absence of adequate baseline data or controls makes it difficult to draw any definitive conclusions about whether Goldwasser's urinary EPO actually caused an increase in reticulocytes or ferrokinetic effects. Without a control, it is impossible to measure the reported increase in reticulocyte count against ordinary variability. Dr. Eshbach, Amgen's expert, testified that the Goldwasser data "did not show a meaningful increase" in reticulocytes. Def.'s App. Exh. 11 [Doc. No. 864], Eshbach Dep. Tr. at 683. In his opinion, "the normal variation in reticulocyte values was not exceeded in the reticulocyte, so-called reticulocyte response observed; and two, there's no comparison between what would be expected, what was seen with recombinant human erythropoietin and the urinary erythropoietin preparation." Id. TKT/HMR faults Amgen's arguments about ordinary variability, arguing that Amgen has failed to illuminate the patient's ordinary range of variability. See Def.'s Rep. Mem. on Anticipation of '422 Claim 1 [Doc. No. 866] at 10. Yet TKT/HMR tacitly acknowledges the fact of ordinary reticulocyte variability and recognizes that the study did not control for it. See id.

With respect to ferrokinetic effects, Dr. Eshbach testified that there were three accepted measurements of ferrokinetic

activity in 1984: plasma iron turnover (PIT), red cell utilization, and marrow transit time. See Remand Tr. vol. 6 at 690. Dr. Goldwasser did not attempt to measure PIT or marrow transit time. See Remand Tr. vol. 6 at 694-95; Remand Tr. vol. 7 at 841-42; Pl.'s Mem. on Anticipation '422 Claim 1 at 33 (noting that TKT/HMR does not contest that Dr. Goldwasser failed to measure marrow transit time). He could not calculate PIT because he failed to collect data on plasma iron concentration values. Remand Tr. vol. 6 at 694-95; Remand Tr. vol. 7 at 841-42. Moreover, the study only reported results on red cell utilization, an indicator of ferrokinetic effects, for patient number two. Remand Tr. vol. 6 at 694. The red cell utilization in patient number two actually declined, "suggesting that there was no evidence of marrow stimulation from the urinary [EPO], in fact, there was a decrease." Id.

The only data Goldwasser recorded was iron clearance. Iron clearance measures the time iron stays in the bloodstream. Id. at 693. A shorter clearance time is significant because it may suggest that the iron is being taken from the plasma to be incorporated into red blood cells. Id. The problem with measuring plasma iron clearance in absence of plasma iron concentration or a calculation of marrow transit time is that plasma iron clearance may suggest that the iron is leaving the plasma, but it does not provide a definitive answer about where it is going. Id. at 693-94. Moreover, again, there was no control. See Remand Tr. vol. 7 at 845. Hence, the study did not

take into account the possibility of variability in iron clearance that might be attributable to some factor other than urinary EPO. Furthermore, while the study measured patients' iron clearance at different points over the course of the study, the baseline consisted of a single data point for each patient. Given the objective of measuring plasma iron clearance over time, it strikes the Court as unusual that the baseline would not also consist of measurements at different intervals. Finally, it is important to note that only the first two patients showed an increased plasma iron clearance rate. Application for Continuation Grant at 19. The patient who received the most urinary EPO, patient number three, did not show an improved plasma iron clearance rate. Id. This suggests that the urinary EPO may not have been the cause of any increase in plasma iron clearance.

TKT/HMR states that one patient experienced a decrease in iron half-life from 225 to 157 minutes, and another experienced a decrease from 192 to 171 minutes. Def.'s Rep. Mem. on Anticipation of '422 Claim 1 [Doc. No. 866] at 10-11. TKT/HMR cites nothing in the way of expert testimony to illuminate the statistical significance of these numbers. Nor does it explain why one patient's clearance rate changed by 68 minutes while the other's decreased by only 21 minutes when both patients received the same dosage. Given the problems noted above, these numbers are of dubious value. For all of the reasons above, to the extent that the first two patients actually exhibited an

increased plasma iron clearance rate, the Court cannot infer that such an effect was directly attributable the urinary EPO.

TKT/HMR's claims are further undermined by the fact that Dr. Goldwasser did not publish the results of his study in a peer review journal. TKT/HMR asks the Court to disregard Dr. Goldwasser's deposition testimony by reminding the Court that he was a consultant for Amgen at the time he testified. But if Dr. Goldwasser's version of events bends to the almighty dollar, then the Court must also discount the cursory conclusions he provided in the grant application. TKT/HMR's motive argument is undermined by the fact that Drs. Goldwasser and Baron had every incentive to trumpet the results of the study. It is perhaps only a slight exaggeration to say that at the time that Goldwasser reported his findings, EPO had taken the role of an El Dorado for a bevy of extraordinarily talented researchers. Two decades and tens of billions of dollars later, EPO has lived up to expectations by becoming one of the biggest blockbuster drugs in industry history. See Amgen I, 126 F. Supp. 2d at 77. If Dr. Goldwasser was even reasonably certain of the physiological effects he purportedly observed, then surely he would have unveiled the results of his study in some form other than a half paragraph buried on page 19 of a 36-page grant application. Even Jed Clamped knew what to do when he struck oil.

The fact that Drs. Goldwasser and Baron never published the results or continued the study suggests that they were not as confident in the results as TKT/HMR would have the Court believe.

In short, Dr. Goldwasser's failure to publish the results gives more weight to Dr. Goldwasser's subsequent characterization of the study as "very limited" and "abortive." Because the "fragmentary data" was never supported by further study and because the observations were not subjected to formal peer review, the Court cannot give Dr. Goldwasser's observations the weight TKT/HMR would have them bear.

A closer examination of the study's results reveals that Dr. Goldwasser had reason to be reticent about publication and peer review. With respect to the effects the urinary EPO preparation allegedly elicited, the data exhibits internal inconsistencies. While one patient showed an increase in red cell mass, two did not. While two of the patients showed an increased plasma iron turnover, one did not. Moreover, while the reticulocyte count of each patient supposedly exhibited a "mild to modest increase," no patient showed a significant increase in hematocrit.

The fact that the hematocrit did not increase lends legitimacy to Amgen's contention that the Court should not infer a causal link between any increase in reticulocyte count and ferrokinetic effects and the efficacy of urinary EPO. Ordinarily, "reticulocytes mature into red blood cells . . . ." Remand Tr. vol. 7 at 806. As one of TKT/HMR's witnesses testified, "an increase in reticulocytes is an indicator or marker that an increase in hematocrit will follow." Amgen III, 339 F. Supp. 2d at 329. Moreover, when "iron clears from the plasma, [it] goes into the bone marrow, and then is incorporated

into the red blood cells. The use of EPO would enhance this incorporation . . . since the number of red cells are going to increase." Remand Tr. vol. 7 at 805-06. In short, an increase in reticulocyte count and increased iron clearance should normally be followed by an increase in hematocrit. If it is true that reticulocytes and iron clearance did increase, why did the Goldwasser study exhibit "no significant change in hematocrit in any patient"? Application for Continuation Grant at 19. TKT/HMR has provided no explanation.

To be clear, the Court is in no way suggesting that an increase in hematocrit is required to satisfy the "therapeutically effective" limitation. Such a conclusion would be contrary to the Federal Circuit's mandates. But the Court cannot turn a blind eye to the undisputed fact that properly functioning EPO will not merely stimulate an increase in reticulocytes and ferrokinetic effects, but also cause an increase in hematocrit. Here, however, there is evidence to suggest that this EPO was not working properly. Dr. Baron's representations to the FDA suggest that the urinary EPO cleared quickly from the body and broke down in fragments. Baron Ltr. at HMR 935322-323.

TKT/HMR argues that Dr. Goldwasser's tests on hamsters, which unlike the tests on human patients included controls, resulted in an increase in hematocrit for all four hamsters that received urinary EPO. Def.'s Rep. Mem. on Anticipation of '422 Claim 1 at 11. The first problem with the hamster data is that

the proffered increase in hematocrit is contradicted by the undisputed results of the three-patient study, where no significant increase in hematocrit occurred. But assuming the administration of urinary EPO did increase the hamsters' hematocrit, those tests involved doses 18 times the strength that would be appropriate for humans. To the extent the hamster study succeeded in raising the hamster's hematocrit, the results only underscore the oddity of the inference TKT/HMR has asked the Court to draw here. TKT/HMR has failed to present a compelling explanation why this Court ought infer a cause in absence of the ordinary effect. While the lack of explanation is not dispositive, it adds to the cumulative total of reasons TKT/HMR has failed to cross the clear and convincing threshold.

The Goldwasser study included only three patients, did not employ controls, did not collect adequate baseline data, did not follow the protocol, and did not significantly increase the hematocrit in any patient, despite nearly doubling the dosage for the third patient. Moreover, the doctors in charge did not publish the results for peer review. Given the "fragmentary data," the Court must take Dr. Goldwasser at his word that "his abortive, three-patient trial was a failure." Amgen III, 339 F. Supp. 2d at 325. In short, the Court cannot conclude that TKT/HMR has shown with clear and convincing evidence that Goldwasser's urinary EPO elicited any of the effects described in column 33 of the '422 patent's specification.

**C. "PURIFIED FROM MAMMALIAN CELLS GROWN IN CULTURE" LIMITS CLAIM 1**

**AND PRECLUDES A FINDING OF ANTICIPATION SINCE IT IS UNDISPUTED THAT THE GOLDWASSER PREPARATION WAS PURIFIED FROM URINE**

As noted in the background section, the Court has construed "purified from mammalian cells grown in culture" to limit the claim. It is undisputed that Dr. Goldwasser's EPO was purified from urine. Therefore, his urinary preparation cannot anticipate claim 1 of the '422 patent because it does not contain every limitation. See In re Omeprazole, 483 F.3d at 1371. TKT/HMR raises a number of objections, but the Court has addressed essentially the same arguments raised by TKT/HMR in an opinion issued in a related case, Amgen v. Roche, No. 05-cv-12237 (D. Mass. Oct. 2, 2008). Its reasoning applies here as well.

**III. CONCLUSION**

The Court has concluded that TKT/HMR has failed to demonstrate anticipation of claim 1 of the '422 patent. Although TKT/HMR demonstrated that the Goldwasser preparation was a "pharmaceutical composition," it could not meet its burden with respect to "therapeutically effective" and "purified from mammalian cells grown in culture."

As noted above, this litigation began in 1997. For a session of the Court that takes pride in expeditious resolution of the cases on its docket, it may be fairly said that this matter has become something of a white whale. In crafting this most recent exposition, which the Court hopes will fare better than the Pequod, the Court is mindful of Ishmael's admonition: "Unless you own the whale, you are but a provincial and

sentimentalist in Truth." HERMAN MELVILLE, MOBY DICK 370 (Penguin 150th Ann. Ed.).

For the reasons stated above, the Court again enters declaratory judgment that TKT/HMR are hereby enjoined for the life of these patents from such infringement.

SO ORDERED.

/s/ William G. Young

WILLIAM G. YOUNG
DISTRICT JUDGE

**Publisher Information**

**Note* This page is not part of the opinion as entered by the court. The docket information provided on this page is for the benefit of publishers of these opinions.**

1:97-cv-10814-WGY Amgen, Inc. v. Hoechst Marion, et al
William G. Young, presiding
Date filed: 04/15/1997
Date terminated: 10/02/2008
Date of last filing: 10/02/2008

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