United States Court of Appeals for the Federal Circuit

05-1157

AMGEN INC.,

Plaintiff-Appellee,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals Inc.)
and TRANSKARYOTIC THERAPIES, INC.,

Defendants-Appellants.

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Appealed from: United States District Court for the District of Massachusetts

Judge William G. Young

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DECIDED: August 3, 2006

Before MICHEL, Chief Judge, CLEVENGER, Senior Circuit Judge, and SCHALL, Circuit Judge.

Opinion for the court filed by Circuit Judge SCHALL. Dissenting-in-part opinion filed by Chief Judge MICHEL.

SCHALL, Circuit Judge.

This is a patent case. Amgen, Inc. ("Amgen") is the owner of U.S. Patent Nos. 5,547,933 ("the '933 patent"), 5,618,698 ("the '698 patent"), 5,621,080 ("the '080 patent"), 5,756,349 ("the '349 patent"), and 5,955,422 ("the '422 patent"). The patents are directed to recombinant deoxyribonucleic acid ("DNA") technology relating to the production of the hormone erythropoietin ("EPO"). All five patents share a common

specification and descend from Application No. 06/561,024 ("the '024 application"), filed on December 13, 1983.

In April of 1997, Amgen brought a declaratory judgment action against Hoechst Marion Roussel, Inc. (now known as Aventis Pharmaceuticals Inc.) ("HMR") and Transkaryotic Therapies, Inc. ("TKT") (collectively, "HMR/TKT") in the United States District Court for the District of Massachusetts, alleging that HMR/TKT's Investigational New Drug Application ("INDA") for an EPO product infringed the five patents. In January of 2001, following a Markman hearing, summary judgment proceedings, and a bench trial, the district court issued an opinion in which it: (i) construed the disputed claims; (ii) held the patents not unenforceable; (iii) held the asserted claims of the '080, '349, and '422 patents not invalid and infringed with the exception of claim 7 of the '349 patent, which it found not infringed; (iv) held the asserted claims of the '698 patent not infringed; and (v) held the asserted claims of the '933 patent not infringed or, in the alternative, invalid for failure to satisfy 35 U.S.C. § 112. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69, 165–66 (D. Mass. 2001) ("Amgen I").

In Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003) ("Amgen II"), we affirmed in toto the district court's claim construction. We also affirmed (i) the court's determination that none of the patents at issue is unenforceable by reason of inequitable conduct; (ii) its contingent determination that the asserted claims of the '933 patent are invalid under section 112; (iii) its grant of summary judgment that claim 1 of the '422 patent is infringed; (iv) its determination that the '933, '698, '080, and '349 patents are not anticipated by U.S. Patent No. 4,377,513 ("the Sugimoto patent"); and

(iv) its determination that claims 1, 3, 4, and 6 of the ’349 patent are infringed. Id. at 1320.

However, we vacated (i) the district court’s determination that the asserted claims of the ’933 patent are not infringed; (ii) its determination that Dr. Eugene Goldwasser’s clinical study, described in Dr. Goldwasser’s grant application entitled “Erythropoietin: Purification, Properties, Biogenesis” (“the Goldwasser reference”), and the Sugimoto patent do not anticipate claim 1 of the ’422 patent; (iii) its determination that the Sugimoto patent does not render claim 1 of the ’422 patent obvious; (iv) its determination that claims 2-4 of the ’080 patent are not invalid and are infringed under the doctrine of equivalents; (v) its determination that the asserted method claims of the ’698 patent are not rendered obvious by the Sugimoto patent and are not infringed; and (vi) its determination that the Sugimoto patent does not render claims 1, 3, 4, 6, and 7 of the ’349 patent invalid and that claim 7 of the ’349 patent is not infringed. Id.

We remanded the case to the district court to do the following: (i) construe the term “therapeutically effective amount” in claim 1 of the ’422 patent and then determine whether either the Goldwasser reference or the Sugimoto patent anticipates claim 1 or whether the Sugimoto patent renders claim 1 obvious, id. at 1354, 1356, 1358; (ii) determine whether the Sugimoto patent renders claims 2-4 of the ’080 patent obvious and whether, as far as claims 2-4 are concerned, Amgen can rebut the presumption of the surrender of equivalents and thus assert infringement of those claims under the doctrine of equivalents, id. at 1345, 1358; (iii) determine whether the Sugimoto patent renders claims 4-9 of the ’698 patent obvious and whether claims 4-9 are infringed, id. at 1357, 1358; and (iv) determine whether the Sugimoto patent renders claims 1, 3, 4,

6, and 7 of the ’349 patent obvious and whether claim 7 of the ’349 patent is infringed, id. at 1357, 1358.

The case is now back before us following proceedings on remand in which the district court construed the term “therapeutically effective amount” in claim 1 of the ’422 patent and conducted a further bench trial. See Amgen, Inc. v. Hoechst Marion Roussel, Inc., 339 F. Supp. 2d 202 (D. Mass. 2004) (“Amgen III Validity & Literal Infringement Judgment”); Amgen, Inc. v. Hoechst Marion Roussel, Inc., 287 F. Supp. 2d 126 (D. Mass. 2003) (“Amgen III Doctrine of Equivalents Judgment”). Based upon various findings and rulings, the court entered judgment in favor of Amgen as follows: (i) claim 1 of the ’422 patent is not invalid, Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 334, 336; (ii) claims 2-4 of the ’080 patent are not invalid, id. at 336, and Amgen is not estopped from asserting infringement of claims 2-4 under the doctrine of equivalents because it rebutted the presumption of surrender of equivalents, Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 160; (iii) claims 4-9 of the ’698 patent are not invalid and are literally infringed, Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 336; (iv) claims 1, 3, 4, 6, and 7 of the ’349 patent are not rendered obvious by the Sugimoto patent, id. at 325, 336, and claim 7 of the ’349 patent is literally infringed, Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 336.

On appeal, HMR/TKT challenges all of the above rulings. Our disposition of the appeal is as follows:

(i) Because we hold that the district court erred in its construction of the term “therapeutically effective amount” in claim 1 of the ’422 patent, we vacate the judgment

of the district court that claim 1 is not invalid. We remand the case to the district court for a determination as to whether the Goldwasser reference anticipates claim 1 under a revised claim construction. (ii) We reverse the judgment of the district court that HMR/TKT's accused product infringes claims 2-4 of the '080 patent under the doctrine of equivalents. We do so because we hold that the district court erred in ruling that Amgen rebutted the presumption that, during prosecution, it surrendered coverage to EPO with a 165-amino acid sequence, which is the sequence of HMR/TKT's product. Because claims 2-4 of the '080 patent are not infringed, it is unnecessary for us to address HMR/TKT's alternative argument by way of an affirmative defense that claims 2-4 are anticipated by the Goldwasser reference. (iii) We affirm the judgment of the district court that claims 4-9 of the '698 patent are not invalid and are literally infringed. (iv) We affirm the judgment of the district court that claim 7 of the '349 patent is not invalid and is literally infringed. Thus, we affirm-in-part, reverse-in-part, vacate-in-part, and remand.[1]

BACKGROUND

I.

As noted, the patents at issue relate to recombinant DNA technology for the production of EPO. EPO, which is a naturally occurring hormone, stimulates the production of red blood cells in the bone marrow through a process called erythropoiesis. Thus, the production of EPO is useful in treating blood disorders

[1] Even though we do not agree with all of the district court's rulings in this case, we note the court's careful and thorough opinions in both Amgen III Validity & Literal Infringement Judgment and Amgen III Doctrine of Equivalents Judgment.

characterized by low hematocrit, which is a low ratio of red blood cells to total blood cells. The production of EPO in usable amounts was made possible by Amgen's team led by Dr. Fu-Kuen Lin, who first successfully identified the EPO DNA sequence. See '422 patent, col. 20, ll. 28-33. Amgen markets and sells its EPO product under the brand name "Epogen."

DNA is the genetic material of all living things.[2] Id. col. 1, ll. 28-29. DNA is composed of a series of subunits, called nucleotides, that are linked together to form a linear polymeric form—a strand. Id. col. 1, ll. 33-35. Each nucleotide contains one of four nitrogen-containing ring compounds, called bases. The bases fall into two categories: pyrimidines, which include cytosine ("C") and thymine ("T"), and purines, which include adenine ("A") and guanine ("G"). Id. col. 1, ll. 35-46; James D. Watson et al., Molecular Biology of the Gene 98 (5th ed. 2004); Bruce Alberts et al., Molecular Biology of the Cell 63, 120 (4th ed. 2002). The sequence of A, T, G, and Cs on a strand of DNA forms what is known as a "DNA sequence." DNA is double-stranded, such that two complimentary strands are linked together. '422 patent, col. 1, ll. 35-42.

Genetic information is expressed through the production of proteins, which are molecules containing long chains of amino acids. Alberts, supra, at 129. Ribonucleic acid ("RNA") determines the composition of proteins. Watson, supra, at 31; see also Alberts, supra, at 301. During a process called transcription, DNA is used to make messenger RNA ("mRNA") with the sequence corresponding to the DNA sequence of A,

[2] The basics of recombinant DNA technology are set forth in Amgen I and, to a lesser extent, in Amgen II. We repeat here only the points necessary for an understanding of the issues presented in this appeal.

T, G, and Cs coding for a particular gene.[3] '422 patent, col. 1, ll. 42-43, 49-51. Transcription of the gene is prompted by a promoter, a sequence of DNA that initiates transcription. Id. col. 2, ll. 4-6. The promoter is typically located upstream of the gene to be transcribed.[4] Id. After transcription is completed, the mRNA non-coding sequences, called introns, are spliced out and the mRNA coding sequences, called exons, are spliced together. The mRNA sequence is then translated by ribosomes to form a protein composed of amino acids. Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 145.

The common specification of Amgen's patents describes how Dr. Lin combined his discovery of the DNA sequence for EPO with recombinant DNA technology to make EPO-producing cells. In order to create these EPO-producing cells, Dr. Lin made an expression vector carrying the EPO DNA sequence he had discovered. '422 patent, col. 11, ll. 1-10. An expression vector is a circular piece of DNA on which a desired gene may be coded. See id. Figs. 2-4, col. 2, ll. 36-54. In addition to the desired gene, an expression vector may also contain a marker and a promoter site. See id. col. 3, ll. 35-37, col. 25, ll. 33-36. The expression vector incorporates itself into a host cell's genetic code. The promoter then triggers the host cell to transcribe mRNA

[3] As the name "messenger" implies, mRNA transcripts are intermediates in the process of protein synthesis. Transcription of mRNA from DNA is completed in the nucleus of the cell. After it undergoes additional processing in the cell's nucleus, the complete mRNA is exported to the cell's cytoplasm, where it guides the synthesis of proteins. See Alberts, supra at 304-05, 327-28.

[4] "Upstream" refers to the location of a particular segment of the genetic sequence on a strand of DNA in relation to a particular gene. For example, if a segment is "upstream" of a particular gene and transcription proceeds in a completely linear order along the DNA sequence, then the segment will be transcribed before the gene.

corresponding to the genetic code encoded on the vector. See id. col. 2, ll. 30-35. This mRNA is then translated into a protein by the host cell. Id. The marker in the expression vector enables scientists to identify the cells that successfully incorporated the desired gene. Id. col. 25, ll. 64-66. The DNA inserted into the genetic code of the host cell through the expression vector is characterized as exogenous DNA because it is not "native" to the host cell. Genetic recombination using exogenous DNA is referred to as heterologous recombination. Id. col. 1, l. 53–col. 2, l. 3.

The expression vector described in Example 10 of the common specification of Amgen's patents contains Dr. Lin's EPO DNA sequence, a selectable dihydrofolate ("DHFR") marker, and a promoter 44 base pairs upstream of the EPO DNA sequence. Id. col. 24, l. 17, col. 25, 36-40. When exposed to Chinese hamster ovary ("CHO") cells, Dr. Lin's expression vectors integrate themselves into the DNA of the host CHO cells. Id. col. 25, ll. 58-66. The general disclosures in the background section of the '422 patent describe how promoters, like the one used in Example 10, prompt host cells to transcribe mRNA corresponding to exogenous genes such as the EPO and DHFR genes in Example 10. See id. col. 1, ll. 53-56, col. 25, ll. 64-66. In the invention of the five patents, prior to production of a protein from the mRNA with the sequence coding for EPO, the mRNA sequence is spliced to remove introns and to connect exons. After splicing, the mRNA is translated into the 166-amino acid protein shown in Figure 6 of the common specification of the patents.

Prior to secretion from the cell, the 166-amino acid EPO protein undergoes cleaving. In this process, the final amino acid in the sequence shown in Figure 6 of the

’422 patent, arginine, is cleaved off, leaving a 165-amino acid protein. This 165-amino acid protein is then secreted as mature human EPO by the cell.

II.

HMR and TKT collaborated to develop a drug known as HMR4396. HMR4396 consists of human EPO produced from TKT’s R223 cell line grown in culture. Amgen I, 126 F. Supp. 2d at 98. The R223 cell line produces human EPO through the use of a viral promoter that prompts transcription of the human EPO gene. In order to create the R223 cell line, HMR/TKT transfected human tumor cells with the viral promoter. This viral promoter is located far upstream of the EPO gene in the R223 cells. Because the viral promoter is not “native” to the human tumor cells, the R223 promoter is considered exogenous DNA. However, the R223 cells are described as using homologous or endogenous recombination because the human EPO gene that the viral promoter controls is “native” to the cells.

III.

Amgen filed suit for a declaratory judgment that HMR/TKT’s HMR4396 infringed the ’933 patent, the ’698 patent, the ’080 patent, the ’349 patent, and the ’422 patent. Amgen alleged infringement of claims 1, 2, and 9 of the ’933 patent, claims 4-9 of the ’698 patent, claims 2-4 of the ’080 patent, claims 1, 3, 4, 6, and 7 of the ’349 patent, and claim 1 of the ’422 patent. See Amgen I, 126 F. Supp. 2d at 96–98. The case proceeded as outlined above and is again before us on appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

On this appeal, we are presented with issues relating to the '422, '080, '698, and '349 patents.[5] We begin with the '422 patent.

I.

The '422 Patent

Claim 1 is the only claim of the '422 patent at issue in the present case. Claim 1 provides:

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

'422 patent, col. 38, ll. 36-41.

HMR4396 already has been found to infringe claim 1 of the '422 patent. See Amgen II, 314 F.3d at 1320. In our remand instructions in Amgen II, we instructed the district court to construe the limitation "therapeutically effective amount" in claim 1 and then determine whether the Goldwasser reference or the Sugimoto patent anticipated claim 1 or whether the Sugimoto patent rendered claim 1 obvious.

A.

Claim Construction

On remand, the district court construed "therapeutically effective amount" in claim 1 of the '422 patent to require that the claimed EPO increase hematocrit and also be

[5] As noted above, in Amgen II, we affirmed the ruling of the district court in Amgen I that claims 1, 2, and 9 of the '933 patent are invalid. Amgen II, 314 F.3d at 1342.

useful in healing or curing the class of patients listed at column 33, lines 22-28 of the specification of the '422 patent:

> A therapeutically effective amount is a quantity that produces a result that in and of itself helps to heal or cure. A therapeutically effective amount is one that elicits in vivo biological activity of natural EPO such as those listed in the specification, column 33, lines 24 through 28: 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 (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals.
>
> Therapeutically effective is to be interpreted as being therapeutically effective with respect to the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.

Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 245-46. In arriving at this construction, the district court focused on the portion of the specification of the '422 patent found at column 33, lines 11-28.[6] Id. at 232–36. The court also pointed to statements in the prosecution history asserting that the claimed invention of recombinant human EPO could be used to treat anemia and other similar disorders. Id. at 238–42.

[6] The district court's claim construction references passages of the '933 patent found at column 33, lines 24-28 and column 33, lines 31-36. Id. at 214, 236, 245. The '422 patent contains identical passages at column 33, lines 16-20 and column 33, lines 23-28 respectively. These passages are part of a larger portion of the specification that runs from column 33, lines 11-28.

On appeal, HMR/TKT contends that the district court erred in construing the term "therapeutically effective" in claim 1 of the '422 patent by requiring that EPO increase hematocrit. HMR/TKT argues that the court incorrectly read the specification as limiting the scope of claim 1 to products that increase hematocrit. HMR/TKT urges that "therapeutically effective amount" means "an amount that elicits any of the biological effects listed in the specification." Under this construction, HMR/TKT asserts, claim 1 is anticipated by the Goldwasser reference.

Amgen responds that the district court correctly interpreted the specification to mean that "when a 'therapeutically effective amount' of EPO is used . . . it produces an increase in hematocrit—along with any or all of the biological affects [sic] previously attributed to natural EPO." Appellee's Br. 21 (quoting Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 234). Amgen points out that although the passage at column 33, lines 11-22 does not actually use the term "therapeutically effective," other passages do, in fact, use the term. For example, at column 33, lines 43-50, Amgen notes, the patent actually uses the words "therapeutically effective" before explaining the required dosages for patients. According to Amgen, this indicates that "therapeutically effective" amounts are those related to healing or curing disease. Amgen also directs our attention to the portion of the specification found at column 33, lines 22-28. This passage states, "Included within the class of humans treatable with products of the invention are patients generally requiring blood transfusions . . . and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like." According to Amgen, only amounts of EPO producing effects—particularly increased hematocrit—that counteract

these anemia-like diseases are "therapeutically effective." Amgen buttresses this argument with citations to the prosecution history where the patentee recounts the benefits of the claimed invention over prior art in treating disease.

The district court's claim construction is a matter of law, which we review de novo. Cybor Corp. v. FAS Techs.,138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). In Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005) (en banc), we stated that claim construction must begin with the words of the claims themselves. Id. at 1312. A claim term has "the meaning that the term would have to a person of ordinary skill in the art. . . ." Id. at 1313. This meaning is ascertained "in the context of the entire patent, including the specification." Id. In particular, we stated in Phillips that "we must look at the ordinary meaning in the context of the written description and the prosecution history." Id. (quoting Medrad, Inc. v. MRI Devices Corp., 401 F.3d 1313, 1319 (Fed. Cir. 2005)). When dealing with technical terms, we noted, a court should look to "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." Id. (quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1116 (Fed. Cir. 2004)).

Using Phillips as a guide, we turn first to the language of the claims. Neither the language of claim 1, nor the language of claim 2, of the '422 patent offer any guidance as to the meaning of "therapeutically effective."[7] However, several passages of the

[7] Claim 2 is an independent claim, which provides: "A pharmaceutically-acceptable preparation containing a therapeutically effective amount of erythropoietin wherein human serum albumin is mixed with said erythropoietin." '422 patent, col. 38, ll. 42-44.

specification shed light on the meaning of the term. In particular, the text found at column 33, lines 11-22 states:

> [T]o the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., 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 (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals.

'422 patent, col. 33, ll. 11-22 (emphases added). This language indicates that the claimed invention is used in "therapy" to produce "any or all" of the following "effects": stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, stimulation of hemoglobin, and increasing hematocrit levels. Thus, increasing hematocrit is only one of the biological effects produced by the claimed invention. Accordingly, we agree with HMR/TKT that the district court misinterpreted this passage when it read it as limiting the claimed invention to products with "any or all" of the first four listed effects ascribed in vivo to EPO and also an increase in hematocrit.

Further, in the August 2, 1993 office action response, the patentee cited the above language of the specification and then stated, "It is believed that these sentences from the specification and others provide a clear and definite description of the uses for which the claimed erythropoietin compositions would be therapeutically effective." (emphasis added). Thus, the patentee interpreted the passage at column 33, lines 11-22 of the specification as listing the therapeutic effects of the invention disclosed in the '422 patent. We think the district court made an artificial distinction between the first

four effects listed in column 33, lines 11-22, stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, and stimulation of hemoglobin, and the fifth effect, an increase in hematocrit. The specification lists all five effects after stating that "any or all" of them may be an effect of therapy with the claimed invention. Thus, this section of the specification supports the construction that the '422 patent encompasses a pharmaceutical composition which produces "any or all" of the five listed effects.

As seen, the district court also determined that the specification indicates that the invention is limited to products that are "therapeutically effective" with respect to patients with anemia-like disorders, such as those listed at column 33, lines 22-28 of the '422 patent. Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 235–36, 245–46. For this determination, the court relied on a passage that recites several diseases that may be treated by the claimed invention. The passage begins, "Included within the class of humans treatable with products of the invention . . . ." '422 patent, col. 33, ll. 22-28. However, this passage does not state that the claims encompass only products that treat such patients. Rather, by using the non-limiting word "included," it suggests some persons, but not all persons, who may benefit from the invention.

Moreover, an additional section of the specification states, "It is noteworthy that the absence of in vivo activity for any one or more of the 'EPO products' of the invention is not wholly preclusive of therapeutic utility (see Weiland, et al., supra). . . ." Id. col. 36, ll. 9-12. We think the message of this passage is that "therapeutic utility" is not limited to products with "in vivo" effects. Thus, "therapeutic utility" is not dependent on the product having an effect in a living being, such as curing disease. Although this

passage relates to a different EPO product than the one disclosed in claim 1 of the '422 patent, we think it illustrates the broad meaning of "therapeutic utility" used throughout the '422 patent. It shows that the patentee did not use the word "therapy" in order to limit the scope of the '422 patent to only EPO that cured disease. Thus, products that are not necessarily effective in actually curing disease in humans are encompassed by claim 1 of the '422 patent. Based on a reading of the claims in light of the specification, it appears that the patentee used the words "therapeutically effective" in order to broadly claim a pharmaceutical composition with a wide range of effects. Those effects do not necessarily include curing disease in humans.

During the prosecution of the '422 patent, in an office action response filed October 23, 1997, the patentee noted that recombinant EPO, like that found in the claimed invention, "is the first therapeutic product which can be used to effectively treat hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts." In our view, this statement merely lists some of the uses of the invention, without restricting the scope of the invention.

In sum, we disagree with the district court's claim construction to the extent that it limits the scope of claim 1 of the '422 patent to EPO products that have one of the in vivo effects listed at column 33, lines 16-20 and that also increase hematocrit. We also disagree with the district court's conclusion that claim 1 of the '422 patent is limited to EPO products that may be used to treat patients with the disorders listed at column 33, lines 22-28 of the '422 patent's specification. On remand, the district court should utilize the following revised construction of "therapeutically effective:"

> 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 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.

B.

Anticipation—The Goldwasser Reference

Based on its claim construction, the district court found in Amgen III Validity & Literal Infringement Judgment that the Goldwasser reference did not anticipate claim 1 of the '422 patent because Dr. Goldwasser's study was not effective in healing or curing. 339 F. Supp. 2d at 327. The parties dispute whether the Goldwasser reference anticipates claim 1 of the '422 patent under a revised claim construction. The purpose of the Goldwasser study was to examine EPO and its effects on erythropoiesis. Dr. Goldwasser acknowledged that mass production of EPO from recombinant DNA was not yet possible. Therefore, Dr. Goldwasser utilized EPO isolated from urine in an attempt to discover the chemistry and mode of action of EPO. In one portion of his study, Dr. Goldwasser performed a "very small clinical trial" using pure urinary EPO ("uEPO"). The uEPO was administered to three anemic patients. Two patients received injections of 520 units twice daily for ten days. The third patient received a 1000 unit injection every 2-3 days for three weeks. In his 1984 grant application, Dr. Goldwasser described the results of the clinical study as follows:

> 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.

In Amgen I, the district court noted that Dr. Goldwasser testified that this "abortive, three-patient trial was a failure." 126 F. Supp. 2d at 112.

The district court found that the Goldwasser reference did not anticipate claim 1 of the '422 patent because none of the effects listed in Dr. Goldwasser's study included healing or curing within the court's construction of "therapeutically effective." Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 327–34. HMR/TKT argues that under a revised construction of "therapeutically effective" that broadens the scope of claim 1 to encompass EPO that "elicits any of the biological effects listed in the specification [at column 33, lines 16-22]," Dr. Goldwasser's study anticipates. Amgen counters that even under a broader construction of "therapeutically effective," Dr. Goldwasser's study does not anticipate claim 1 of the '422 patent because its recombinant EPO ("rEPO") product differs in structure and function from the uEPO utilized in Dr. Goldwasser's study. Amgen argues that a remand is not necessary because HMR/TKT admitted in its petition for a panel rehearing and rehearing en banc following Amgen II that the rEPO disclosed in claim 1 of the '422 patent differs in structure from naturally occurring uEPO.

Anticipation under 35 U.S.C. § 102 is a question of fact, which we review for clear error after a bench trial. Merck & Co., Inc. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1369 (Fed. Cir. 2003); Alza Corp. v. Mylan Labs., Inc., 391 F.3d 1365, 1369 (Fed.

Cir. 2004). The district court's factual findings on anticipation are clearly erroneous when "'although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.'" Merck & Co, 347 F.3d at 1369 (quoting United States v. U.S. Gypsum Co., 333 U.S. 364, 395 (1948)). A prior art reference anticipates a patent if it discloses all the limitations of the claimed invention. Oney v. Ratliff, 182 F.3d 893, 895 (Fed. Cir. 1999).

The district court's findings of fact on anticipation centered on whether the effects produced on patients in Dr. Goldwasser's study resulted in healing or curing. Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 327. Under our construction of "therapeutically effective," however, the district court's findings of fact as to "healing or curing," while relevant, do not end the anticipation inquiry. Additional findings of fact are necessary to determine whether the Goldwasser study anticipates under our new construction of "therapeutically effective." When findings of fact are necessary under a revised claim construction, it is appropriate for us to remand to the district court. See Seachange Int'l, Inc. v. C-Cor Inc., 413 F.3d 1361, 1381 (Fed. Cir. 2005) (remanding for the district court to consider anticipation after revising the claim construction). On remand, the district court should make findings of fact as to whether the Goldwasser reference meets the "therapeutically effective" limitation under our construction.[8]

[8] If, on remand, the district court finds that the Goldwasser reference contains the "therapeutically effective" limitation, it must then determine whether the uEPO meets the other limitations of claim 1 of the '422 patent.

C.

Anticipation—The Sugimoto Patent

The Sugimoto patent, filed August 10, 1981, discloses a method for creating EPO-producing cells by creating hybrid cells from lymphoblastoids[9] and kidney tumor cells. The Sugimoto patent suggests using recombinant techniques to introduce the EPO genes from a human kidney tumor cell into human lymphoblastoids. Sugimoto patent, col. 1, l. 55–col. 2, l. 11. The patent involves in vivo production of EPO in which human lymphoblastoid cells capable of producing EPO are transferred to an animal body. The Sugimoto patent explains that the EPO produced by the animal according to this technique is then "collected easily by purification and separation techniques using conventional procedures . . . ." Id. col. 3, ll. 51-53.

In Amgen I, the district court found that the Sugimoto patent did not anticipate claim 1 of the '422 patent because it was not enabled. 126 F. Supp. 2d at 109. The court considered the testimony of Amgen's expert, Dr. Allan Erslev, who stated that the Sugimoto procedure was "very complex." Id. at 108. Dr. Erslev stated that no one had used the Sugimoto process prior to 1984, even though it would have been highly profitable if successful. Id. After recounting Dr. Erslev's testimony, the court discounted HMR/TKT's arguments. Id. HMR/TKT had put Dr. Michael Heartlein on the stand. By attempting to replicate the Sugimoto process, Dr. Heartlein produced cells that generated six times as much EPO as their parent cells. Id. at 108–09. The court found that Dr. Heartlein's experiments were not sufficient to show enablement, however,

[9] Lymphoblastoids are cells that are typically isolated from patients with leukemia, which is a cancer of the blood. Amgen I, 126 F. Supp. 2d at 106.

because Dr. Heartlein followed a different procedure than the one disclosed in the Sugimoto patent. First, Dr. Heartlein used an in vitro technique rather than an in vivo technique like that disclosed in the Sugimoto patent. Id. at 109. Second, the district court found that Dr. Heartlein used different starting materials than the Sugimoto patent because he could not obtain kidney tumor cells like those disclosed in the Sugimoto patent. Id. Based on the foregoing, the district court found that HMR/TKT had failed to demonstrate that the Sugimoto patent was enabled by clear and convincing evidence. Id. at 108–09.

On appeal, we ruled in Amgen II that the district court had erred in placing the burden of proving enablement on HMR/TKT. Id. at 1357. We indicated that the Sugimoto patent should have been presumed enabled and that Amgen should have had the burden of proving otherwise. Id. at 1355.

On remand, the district court affirmed its previous holding of non-enablement, finding that "Amgen has shown by a preponderance of the evidence that Sugimoto is not enabled . . . ." Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 307. The court based its conclusion that the Sugimoto patent was not enabled on three findings. First, the court noted that the Sugimoto patent did not disclose the starting materials necessary to repeat the process it describes. Id. at 307–09. The Sugimoto patent required the use of kidney tumor cells, but the inventor neither deposited these cells publicly nor did he disclose them so that a person of ordinary skill in the art could procure them. Id. at 307. Second, the court found that the Sugimoto patent was not enabled because it did not teach a person of ordinary skill in the art how to select EPO-producing hybrid cells. The court based its finding largely on the

testimony of Dr. Howard Green, a cell biologist with over forty years of experience, who stated that although methods for selecting hybrids were available at the time the Sugimoto patent was filed, they were inconsistently successful and required undue experimentation to produce results. Id. at 309. Third, the court found that the Sugimoto patent did not enable a method for purifying EPO even though the Sugimoto patent claimed to teach how to produce purified EPO. Id. at 311–12. The court found support for this finding in the testimony of Dr. Green, id. at 311, as well as in evidence that the Sugimoto patent's disclosure still had not been put into practice years after it issued in March of 1983, id. at 312. In addition, in connection with all three findings, the court noted that Dr. Heartlein had failed to duplicate the Sugimoto starting materials, selection methods, or purification techniques when using the disclosure of the Sugimoto patent. Id. at 307–08, 311–12.

HMR/TKT makes several arguments for reversing the district court's finding of non-enablement. With regard to the district court's finding that the cells necessary for the Sugimoto procedure were not adequately disclosed or deposited, HMR/TKT urges that the description of the starting materials in the Sugimoto patent was sufficient despite the fact that the cells were not deposited. HMR/TKT notes that the Patent and Trademark Office found that there was an adequate written description and that a person of ordinary skill in the art would have understood the disclosure. HMR/TKT asserts that the district court's use of Dr. Heartlein's experiments as proof of non-enablement was flawed because the district court previously found in Amgen I that Dr. Heartlein did not follow the Sugimoto patent's disclosure.

Amgen defends the district court's decision on remand by arguing that the district court correctly identified deficiencies in the Sugimoto patent's disclosure. First, Amgen argues that the lack of starting materials is illustrated by both Amgen's and Dr. Heartlein's inability to obtain the kidney tumor cells described in the Sugimoto patent. Amgen also notes that EPO-producing cells prior to Dr. Lin's invention were "poor producers." In addition, Amgen argues that the district court correctly found that the Sugimoto patent was not enabled based on the lack of disclosure of a method for hybrid cell selection or purification.

In order to anticipate, a prior art reference must not only disclose all of the limitations of the claimed invention, but also be enabled. Elan Pharms., Inc. v. Mayo Found., 346 F.3d 1051, 1054 (Fed. Cir. 2003). A reference is enabled when its disclosures are sufficient to allow one of skill in the art to make and use the claimed invention. Id. (quoting Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1374 (Fed. Cir. 2001)). Like a patent, a prior art reference is enabled even if some "routine experimentation is required in order to practice a claimed invention, but . . . such experimentation must not be 'undue.'" Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371 (Fed. Cir. 1999). When considering whether or not a prior art reference requires "undue experimentation" we look at the reference from the perspective of a person of ordinary skill in the art. In re Wands, 858 F.2d 731, 735 (Fed. Cir. 1988).

We established in Amgen II that when a piece of prior art is a patent, like the Sugimoto patent, there is a presumption of enablement. 314 F.3d at 1355. The patentee, Amgen, must present persuasive evidence of non-enablement to overcome

this presumption. Id. As seen, in Amgen II, we vacated and remanded the finding of non-enablement with regard to claim 1 of the '422 patent. On remand, the district court found that Amgen had met its burden of proving by a preponderance of the evidence that the Sugimoto patent was not enabled. 339 F. Supp. 2d at 306. We review the district court's ultimate determination of enablement de novo while the underlying factual inquiries made by the district court are reviewed for clear error. Enzo Biochem, 188 F.3d at 1369.

The district court's factual finding that the Sugimoto patent did not adequately disclose the starting materials was not clearly erroneous. The court based its conclusion on the testimony of several scientists with experience in the field of erythropoeisis, including Dr. Green, Dr. Lin, and Dr. Harvey Lodish, a research biologist at the Whitehead Institute and the Massachusetts Institute of Technology. Dr. Green testified that Dr. Heartlein, who attempted to duplicate the Sugimoto disclosure, searched "for a long time and in many different ways" to find a suitable cell line and finally settled on a liver tumor cell line—not a kidney tumor cell line like Sugimoto's. Dr. Lin testified that he had searched extensively for an EPO-producing cell line during his research, but never acquired a EPO-producing kidney tumor cell line. Dr. Lodish stated that the Sugimoto patent failed to demonstrate that the kidney tumor cells disclosed in the patent actually produced EPO. In addition, Amgen presented evidence that it failed to locate any kidney tumor cells, like those described in the Sugimoto patent, despite repeated efforts to do so. At the same time, we do not see clear error in the court's finding that Dr. Heartlein's non-conforming experiments show that a person of ordinary skill in the art would not be able to obtain the required kidney tumor cells based on the

Sugimoto patent's disclosures. The failure of Dr. Heartlein to obtain the cells disclosed by the Sugimoto patent and the expert testimony of Drs. Green, Lin, and Lodish support this finding. Further, Sugimoto did not deposit the EPO-producing kidney tumor cells described in the Sugimoto patent. In sum, the Sugimoto patent was not enabled due to the patentee's failure to adequately describe how to derive the starting materials or deposit the cells. See In re Wands, 858 F.2d at 735 ("Where an invention depends on the use of living materials such as microorganisms or cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure."). Because we discern no clear error in the district court's finding that the Sugimoto patent's failure to disclose or deposit the starting materials necessary to produce EPO rendered the patent not enabled, it is unnecessary for us to address Amgen's arguments that the Sugimoto patent also did not teach how to select hybrid cells and that the Sugimoto patent did not disclose a means for purifying EPO.

D.

Obviousness—The Sugimoto Patent

The district court held in Amgen I that the Sugimoto patent did not render claim 1 of the '422 patent obvious because the Sugimoto patent was not enabled. 126 F. Supp. 2d at 114 & n.29. In Amgen II we vacated this finding and remanded because non-enablement does not preclude a finding of obviousness. 314 F.3d at 1357. On remand, in Amgen III Validity & Literal Infringement Judgment, the district court again concluded that the Sugimoto patent did not render claim 1 of the '422 patent obvious. In reaching this conclusion, the court considered the scope and content of the prior art, differences

between the claimed invention and the prior art, the level of ordinary skill in the art, and reasonable expectation of success. Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 316–19. The court also placed emphasis on the "objective indicia of non-obviousness," or "secondary considerations." Id. at 314, 319. Specifically, the court found that there had been a long-felt, but unmet need for EPO-producing cells prior to Dr. Lin's discovery. Id. at 319. Thus, the district court concluded that HMR/TKT "failed to persuade the Court by clear and convincing evidence that the asserted claims of [Amgen's patents] were obvious in light of Sugimoto." Id. at 325. HMR/TKT appeals the district court's ruling.

We have considered the various arguments made by HMR/TKT on the obviousness issue. Having done so, we see no reason to disturb the ruling of the district court that HMR/TKT failed to establish that claim 1 of the '422 patent was obvious in view of the Sugimoto patent.

II.

The '080 Patent

As seen, in Amgen III Doctrine of Equivalents Judgment, the district court ruled that claims 2-4 of the '080 patent were not invalid and that Amgen was not estopped from asserting infringement under the doctrine of equivalents. 287 F. Supp. 2d at 160. Accordingly, the court reinstated its vacated finding in Amgen I that claims 2-4 of the '080 patent were infringed under the doctrine of equivalents by HMR/TKT's HMR4396 product. Id. The only issue before us on appeal is infringement under the doctrine of equivalents. Claims 2-4 provide:

> 2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.
>
> 3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.
>
> 4. A pharmaceutical composition comprising a therapeutically effective amount [of] an erythropoietin glycoprotein product according to claim 1, 2 or 3.

'080 patent, col. 38, ll. 39-53. Claims 2-4 of the '080 patent each contain the limitation that the "erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6." The sequence shown in Figure 6 of the '080 patent has a DNA sequence coding for 166 amino acids. However, as noted above, mature human EPO actually contains 165 amino acids, because the 166th amino acid, arginine, is cleaved off prior to the EPO's secretion from the cell. The question before us is whether prosecution history estoppel bars Amgen from claiming that claims 2-4 of the '080 patent encompass EPO with 165 amino acids under the doctrine of equivalents. This is critical because HMR/TKT's EPO product, HMR4396, has only 165 amino acids. Id. at 129.

A.

The application that resulted in the '080 patent was filed on June 6, 1995 as Application No. 08/468,556 ("the '556 application"). The '556 application, which contained 60 claims, was a continuation-in-part of the '024 application. In the first

preliminary amendment of the ’556 application, the patentee cancelled claims 1-60 and added claims 61-67. Of the seven new claims added by amendment, claims 61-64 comprised the only independent product claims. Proposed claims 61-64 provided as follows:

> 61. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having glycosylation which differs from that of human urinary erythropoietin.
>
> 62. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having a higher molecular weight than human urinary erythropoietin as measured by SDS-PAGE.
>
> 63. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources and free of other human proteins.
>
> 64. The in vivo biologically active erythropoietin product of the process comprising the steps of:
> (a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6, (2) the protein coding sequences set out in FIGS 5 and 6, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2) or their complimentary strands; and
> (b) isolating said erythropoietin product therefrom.

The patentee made a second preliminary amendment to the ’556 application on December 20, 1995. In the second preliminary amendment, claims 61-63 were cancelled, claim 64 was amended, and a new claim, claim 68, was added. The amended version of claim 64 provided as follows:

> 64. The non-naturally occurring in vivo biologically active erythropoietin product of the process comprising the steps of:

> (a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6, (2) the protein coding sequences set out in FIGS 5 and 6, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2) or their complimentary strands; and
> (b) isolating said erythropoietin product therefrom.

Claim 68, which was added in the second preliminary amendment, provided as follows:

> 68. A non-naturally occurring erythropoietin product of the process comprising the steps of:
> a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof; and
> b) isolating an erythropoietin product therefrom.

In the third and final amendment made to the ’556 application for the ’080 patent, the patentee cancelled claims 64 through 68 and added claims 69-75. Claims 70-72, which issued as claims 2-4 of the ’080 patent, provided as follows:

> 70. An isolated erythropoietin glycoprotein having the <u>in vivo</u> biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6 and is not isolated from human urine.
>
> 71. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6.
>
> 72. A pharmaceutical composition comprising a therapeutically effective amount [of] an erythropoietin glycoprotein product according to claim 69, 70 or 71.

As seen, after the first preliminary amendment, the claims of the '556 application broadly encompassed an isolated human EPO product. The application claimed an EPO product made using the human EPO DNA sequence set out in Figure 6 or the monkey EPO DNA sequence set out in Figure 5. With the second preliminary amendment, the patentee added claim 68, which claimed an EPO product made using the amino acid sequence for EPO set out in Figure 6 "or a fragment thereof." With the third preliminary amendment, the patentee removed all references to non-human monkey EPO and also deleted claims for an EPO product made using "a fragment" of the amino acid sequence of Figure 6. Instead, as of the third preliminary amendment, the '556 application claimed only a human EPO product having the complete amino acid sequence of Figure 6.

B.

In Amgen I, the district court found that the amendments to the '556 application were made to preempt a double-patenting rejection based on claim 1 of the '933 patent.[10] 126 F. Supp. 2d at 135. The district court held that an amendment made to avoid a double-patenting rejection is not an amendment related to patentability. Id. at 136. Therefore, the court held that Amgen was not estopped from claiming that EPO

[10] Claim 1 of the '933 patent provides:

> A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

'933 patent, col. 38, ll. 18-22.

with a 165-amino acid sequence infringed the asserted claims of the '080 patent under the doctrine of equivalents. Id.

In Amgen II, citing Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 740–41 (2002) ("Festo II"), we vacated the district court's finding and held instead that Amgen's double-patenting amendment was an amendment related to patentability that gave rise to prosecution history estoppel. 314 F.3d at 1345. We vacated the district court's finding of infringement of the '080 patent under the doctrine of equivalents and remanded for "an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel." Id. These "narrow ways" were first set forth in Festo II. They are (i) showing that an equivalent was unforeseeable; (ii) demonstrating that the purpose for an amendment was merely tangential to the alleged equivalent; or (iii) establishing "some other reason" that the patentee could not have reasonably been expected to have described the alleged equivalent. 535 U.S. at 740–41.

On remand, in Amgen III Doctrine of Equivalents Judgment, the district court evaluated whether any one of the three grounds for rebutting the Festo presumption of estoppel had been demonstrated by Amgen. 287 F. Supp. 2d at 147–59. The court determined that Amgen had failed to show that a 165-amino acid EPO was unforeseeable at the time of the third preliminary amendment. Id. at 149. However, the court determined that Amgen had succeeded in showing that the third preliminary amendment, which restricted the literal scope of the '080 patent to EPO having the complete amino acid sequence shown in Figure 6, was added only to limit the '080 patent to human EPO products. Id. at 152. The court found that the third preliminary

amendment was therefore no more than tangentially related to the 165-amino acid equivalent. Id. at 154. The court based this finding on the prosecution history, noting that "the chronology and language of the amendments support Amgen's position that it added the amendment in question (the third amendment) to distinguish the '080 patent from the '933 patent on the basis that the '080 was limited to human EPO." Id. at 152 (emphasis in original). The human EPO limitation thus was merely tangential, the district court found, to the 165-amino acid equivalent. The court buttressed its finding of tangentiality with a "reasonable inference" that the amendment was not made with the intention of surrendering equivalents because, as of December of 1996, when the third preliminary amendment was made, the Patent and Trademark Office and Amgen both were aware that mature EPO had 165 amino acids. Id. at 153.

Although the district court found that the Festo presumption was rebutted because the amendment limiting the claims of the '080 patent to EPO with the amino acid sequence of Figure 6 was tangential to EPO having a 165-amino acid sequence, it set forth an alternate rationale based on the "some other reason" language in Festo II. The court looked to both extrinsic and intrinsic evidence suggesting that the drafter of the amendment, as well as those of ordinary skill in the art, would have considered the amendment to cover all human EPO, regardless of whether or not the EPO had 165 or 166 amino acids. Id. at 157. In essence, the court construed the claims based on the extrinsic record (with support from the intrinsic record). Id. The court reasoned that this evidence reflected a "shortcoming[ ] of language" or "linguistic" limitation, which were mentioned in Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 344 F.3d 1359, 1372 (Fed. Cir. 2003) (en banc) ("Festo III"), as possible reasons for rebuttal of the

Festo presumption. Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 159. The court then found that those equivalents encompassed by this construction were not surrendered, relying on the "some other reason" exception to the Festo presumption of surrender of equivalents. Id.

HMR/TKT argues on appeal that the district court erred in finding that Amgen's third preliminary amendment was merely tangential to the equivalent EPO having a 165-amino acid sequence. It contends that if the patentee had intended solely to limit the scope of claims 2-4 of the '080 patent to human EPO, the patentee would have used the word "human" to describe the EPO. Instead, according to HMR/TKT, the third preliminary amendment uses the word "mature," while both of the previous amendments used the word "human" to describe the EPO claimed. HMR/TKT urges that the district court also erred by finding that Amgen rebutted the Festo presumption based on "some other reason." HMR/TKT argues that Amgen amended the claims of the '080 patent to include only a 166-amino acid EPO out of fear of a new matter rejection, which does not fall under Festo's "some other reason" criterion.

Amgen counters that the district court was correct in its conclusion because the purpose of the third preliminary amendment was to distinguish the '080 patent, which encompasses only human EPO, from claim 1 of the '933 patent, which encompasses both human and animal EPO. In support of its argument, Amgen recites its remarks during prosecution "that claims 69, 70, and 71 [currently claims 2-4 of the '080 patent] all differ in scope from glycoprotein claim 1 of U.S. 5,547,933 in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6. Claim 69 [currently claim 1 of the '080 patent] (like ['933] glycoprotein claim 1) recites

carbohydrate differences in comparison to human urinary [EPO] and claim 70 [currently claim 2 of the '080 patent] recites a negative limitation with respect to isolation from human urine." (footnote omitted). Based on the foregoing statement in the patentee's remarks accompanying the third preliminary amendment, Amgen contends that the amendment was meant to distinguish Amgen's EPO from naturally-occurring EPO through differences in glycosylation, or "carbohydrate differences." Thus, Amgen argues that the mention of the EPO sequence of Figure 6 was merely tangential. Further, Amgen defends the district court's conclusion that Amgen successfully rebutted the Festo presumption under the "some other reason" rationale. Amgen argues that because a person of ordinary skill in the art would have understood the claims to encompass a 165-amino acid equivalent, the Festo presumption was rebutted. Finally, Amgen argues that the district court erred in finding that a 165-amino acid equivalent was foreseeable because the patentee expected the claims to encompass this equivalent.

C.

The burden of rebutting the Festo presumption lies with the patentee. Festo III, 344 F.3d at 1368. Whether a patent-holder has successfully rebutted the Festo presumption of the surrender of equivalents is a question of law, which we review de novo. Chimie v. PPG Indus., Inc., 402 F.3d 1371, 1376 (Fed. Cir. 2005); see also Festo III, 344 F.3d at 1368; Biagro W. Sales, Inc. v. Grow More, Inc., 423 F.3d 1296, 1302 (Fed. Cir. 2005); Glaxo Wellcome, Inc. v. Impax Labs., Inc., 356 F.3d 1348, 1351 (Fed. Cir. 2004). For the reasons which follow, we uphold the district court's finding that Amgen failed to show that EPO with a 165-amino acid sequence was not foreseeable at

the time of the amendment. However, we hold that the district court erred when it held that Amgen had met its burden of rebutting the Festo presumption under both the tangentiality and "some other reason" rationales.

The presumption that equivalents are surrendered may be rebutted if a patentee shows that "one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." Festo III, 344 F.3d 1365 (quoting Festo II, 535 U.S. at 741). As noted, in Festo II, the Supreme Court listed three ways in which a patentee may make this showing. First, the patentee may demonstrate that "the equivalent [would] have been unforeseeable at the time of the [amendment]." 535 U.S. at 740–41. Second, the patentee may show that "the rationale underlying the amendment [bears] no more than a tangential relation to the equivalent in question." Id. Third, a patentee may demonstrate that "there [is] some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." Id.

In Festo III, we offered some guidance as to what must be shown by a patentee in order to succeed in rebutting the Festo presumption under each of the three showings enumerated by the Supreme Court. In order to demonstrate that an invention is not foreseeable, a patentee may utilize extrinsic evidence. 344 F.3d at 1369. We suggested that after-arising technology is more likely to be unforeseeable than old technology, but did not set forth any hard or fast rule on foreseeability. Id. We stated that "if the alleged equivalent were known in the prior art in the field of the invention, it certainly should have been foreseeable at the time of the amendment." Id. With regard to the tangentiality of an amendment to an equivalent, we did not set forth any concrete

definition, but we did note that an amendment "made to avoid prior art that contains the equivalent in question is not tangential; it is central to allowance of the claim." Id. Thus, an amendment is tangential when the "reason for [it] was peripheral, or not directly relevant, to the alleged equivalent." Id. The determination of whether or not an amendment is merely tangential to the equivalent is based on the "patentee's objectively apparent reason for the narrowing amendment." Id. Thus, the inquiry must be based on the intrinsic record alone and, if necessary, expert testimony to aid in interpretation of that record. Id. Finally, we noted that the third way to rebut the Festo presumption, the "some other reason" route, is a narrow one. Id. at 1370. We stated that "the third criterion may be satisfied when there was some reason, such as the shortcomings of language, why the patentee was prevented from describing the alleged equivalent when it narrowed the claim." Id.

1.

With regard to the first Festo rebuttal argument, foreseeability, we see no error in the district court's holding that, at the time the third preliminary amendment was made, EPO with 165 amino acids was a foreseeable equivalent. Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 147–49. We reject Amgen's assertion that the relevant inquiry is whether it was "objectively foreseeable that the amended claim language would not read on the accused equivalent." Appellee's Br. at 74. The question of how a person of ordinary skill in the art would understand claims 2-4 of the '080 patent is one of claim construction, which was settled in Amgen II. 314 F.3d at 1344–45 (affirming the district court's construction of claims 2-4 as being limited to EPO with 166 amino acids). EPO with a 165-amino acid sequence was a foreseeable

equivalent because the patentee admittedly knew about the 165-amino acid equivalent at the time of the third preliminary amendment. Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 157 (finding that during prosecution Amgen informed the examiner that human EPO has 165 amino acids); see Festo III, 344 F.3d at 1369 (noting that if an equivalent is known in the field, then it is foreseeable); Glaxo Wellcome, Inc., 356 F.3d at 1355–56 (finding that a patentee did not rebut the presumption of surrender when a person of ordinary skill in the art at the time of the amendment would have considered the equivalent).

2.

We next examine whether Amgen has met its burden of showing that the reason for the addition of the reference to the "amino acid sequence of FIG. 6" was merely tangential to the alleged equivalent.

In Insituform Technologies, Inc. v. CAT Contracting, Inc., 385 F.3d 1360 (Fed. Cir. 2004), we were asked to review whether a patentee had successfully rebutted the surrender of equivalents. Id. at 1370–71. The patented method in Insituform involved using a vacuum to impregnate a flexible tube with resin. Id. at 1362–63. During prosecution, the patentee limited the number of suction cups that could be placed on the tube to create the vacuum to just one cup. Id. at 1366. The amendment that limited the number of vacuum cups was made to overcome prior art which had a single vacuum source located at the end of the tube a distance from the resin source. Id. at 1370. The reason for the amendment was to clarify the location of the vacuum source relative to the resin—not to limit the number of vacuum cups. Id. Thus, we ruled that the reason for the amendment was merely tangential to the alleged equivalent using multiple cups.

Id. Accordingly, we held that the patentee in Insituform successfully rebutted the Festo presumption of surrender of the equivalent in question.

Amgen was required to show that the reason for adding the requirement in the third preliminary amendment that EPO have 166 amino acids was peripheral to the 165-amino acid equivalent. See Festo III, 344 F.3d at 1369. As seen, the third preliminary amendment was made to avoid a double patenting rejection in light of the '933 patent. Amgen I, 126 F. Supp. 2d at 135. Thus, the 165-amino acid equivalent is only tangential if the patentee's reason for limiting the '080 patent to EPO with 166 amino acids was unrelated to distinguishing the scope of the '080 patent from the scope of the '933 patent.

We must reject Amgen's argument that the sole reason for the amendment requiring EPO with 166 amino acids was to limit the '080 patent to human EPO and that therefore the amendment was merely tangential to a 165-amino acid equivalent. As seen, in claim 1 the '933 patent claimed:

> A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

'933 patent, col. 38, ll. 18-22. Thus, claim 1 contains no limitation pertaining to human or non-human EPO. Claim 1 of the '933 patent, which covers both human and non-human EPO, also lacks any limitation concerning the amino acid sequence of the claimed EPO product. Accordingly, claim 1 of the '933 patent broadly encompasses EPO with any amino acid sequence, which would include amino acid sequences differing from that set forth in Figure 6.

We think Amgen's third preliminary amendment did more than limit the scope of the asserted claims of the '080 patent to human EPO. The third preliminary amendment limited the '556 application, and consequently the '080 patent, to EPO having 166 amino acids. Claim 68, which was added with the second preliminary amendment to the '556 application, encompassed cells "encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof." Thus, after the second preliminary amendment, the '556 application and the '933 patent overlapped in claim scope. That is because the '556 application encompassed EPO having the incomplete amino acid sequence set forth in Figure 6. Likewise, claim 1 of the '933 patent encompassed EPO having any amino acid sequence, which would include an incomplete amino acid sequence of Figure 6. In other words, an incomplete amino acid sequence of Figure 6 (a "fragment") was encompassed by both the '556 application and the '933 patent. The deletion of "or fragment thereof" with the third preliminary amendment limited the '556 application to the complete 166-amino acid sequence shown in Figure 6. This limitation reduced the overlap between the scope of the '556 application, which encompassed only EPO with the complete amino acid sequence of Figure 6, from the scope of claim 1 of the '933 patent, which encompassed EPO with any amino acid sequence. Indeed, as the inventor himself stated in the remarks accompanying the third preliminary amendment, the amended claims "all differ in scope from glycoprotein claim 1 of [the '933 patent] in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6." Third Preliminary Amendment at 164 (Dec. 20, 1996), quoted in Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 152 n.36 (emphasis added) (footnote omitted). Accordingly, the limitation added in the third

preliminary amendment may have been central to overcoming a double patenting rejection in light of claim 1 of the '933 patent. Under these circumstances we cannot say that the reason for the addition of the limitation pertaining to the complete amino acid sequence of Figure 6 was merely tangential to the alleged 165-amino acid equivalent. Thus, unlike Insituform, where it was clear that the amendment in question was not made to limit the number of cups and overcome the prior art, the requirement that EPO have exactly 166 amino acids may have been central to the allowance of claims 2-4 over a double patenting rejection.

Finally, we think that if the patentee had wished only to limit the claims to human EPO, the patentee could have done so by continuing to use the adjective "human" when referring to EPO in the third preliminary amendment; instead the patentee chose to further narrow the claims in the third preliminary amendment by making reference to the specific sequence in Figure 6 rather than human EPO. We thus hold that Amgen has not met its burden of showing that the addition of the "the mature amino acid sequence of FIG. 6" amendment was tangential to a 165-amino acid equivalent.

3.

In the alternative, the district court relied on the "some other reason" language in the Supreme Court's Festo II decision in ruling that Amgen had rebutted the Festo presumption of surrender of equivalents. In Festo II, the Court held that the presumption of the surrender of equivalents could be rebutted by showing that "there [is] some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." 535 U.S. at 740–41.

As previously noted, the district court based its conclusion that Amgen had rebutted the Festo presumption under the "some other reason" rationale on its finding that, before the patentee made the third preliminary amendment, the patentee disclosed information to the Patent and Trademark Office concerning the fact that human EPO has 165 amino acids. Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 157. The district court also relied on extrinsic evidence that a person of ordinary skill in the art would understand that Amgen meant to claim human EPO having either 165 or 166 amino acids at the time the third preliminary amendment was made. Id. The court reasoned that Amgen had rebutted the Festo presumption under the "some other reason" criterion because the patentee could not have reasonably been expected to have described the 165-amino acid equivalent because those of skill in the art would have interpreted the amendment to cover the 165-amino acid equivalent. Id. at 158.

However, the district court's analysis does not correctly apply the Supreme Court's explanation of the "some other reason" rebuttal argument: the other reason must be such that the patentee could "not reasonably be expected" to write a claim to encompass the equivalent, see Festo II, 535 U.S. at 741, such as a shortcoming of language, Festo III, 344 F.3d at 1370. The patentee knew of the 165-amino acid sequence at the time of the amendment, Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 157, but chose to limit the claims to the 166-amino acid sequence depicted in Figure 6. Contrary to Amgen's argument, whether the patentee, the examiner, or a person of skill in the art may have thought the claims encompassed EPO with 165 amino acids does not excuse the patentee's failure to claim the equivalent. See Biagro, 423 F.3d at 1307 (rejecting the patentee's argument that the "some other

reason" rebuttal argument applied when the patentee allegedly understood the claim language to refer to the equivalent in question). Further, there were no shortcomings of language that might have prevented the patentee from claiming EPO having 165 amino acids. The patentee could have simply claimed mature human EPO without reference to Figure 6. Alternatively, the patentee could have claimed, as it did prior to the third preliminary amendment, EPO having the amino acid sequence disclosed in Figure 6 or a "fragment thereof." In short, there was no linguistic barrier to claiming EPO comprised of 165 amino acids. Amgen has not argued on appeal, nor do we find, that any other reason exists that might rebut the Festo presumption. Therefore, we find that the patentee could have reasonably been expected to accurately point out and particularly claim the 165-amino acid sequence.

The facts in this case are analogous to those in Festo III, where we ruled that the Festo presumption was not rebutted by "some other reason." In Festo III, we rejected Festo's argument that it was not estopped from asserting the doctrine of equivalents because the patentee "could not reasonably have been expected to have drafted a claim to cover what was thought to be an inferior and unacceptable design." 344 F.3d at 1372–73. Like the patentee in Festo, who knew about the "inferior" equivalent, the patentee of the '080 patent knew about the 165-amino acid sequence at the time of the amendment, but still chose to claim the incorrect 166-amino acid sequence in Figure 6. We conclude that Amgen has not rebutted the Festo presumption based on "some other reason."

In sum, we uphold the district court's finding that the 165-amino acid EPO equivalent was foreseeable at the time of the third preliminary amendment. The district

court erred, however, in finding that Amgen successfully rebutted the Festo presumption of surrender of equivalents under both the tangentially related rebuttal argument and the "some other reason" rebuttal argument. This means that HMR/TKT cannot be found to have infringed the claims 2-4 of the '080 patent under the doctrine of equivalents. Accordingly, the judgment of infringement of claims 2-4 is reversed. It is unnecessary for us to reach HMR/TKT's alternative argument by way of affirmative defense that claims 2-4 of the '080 patent are invalid as anticipated by the Goldwasser reference.

III.

The '698 and '349 patents

The '698 patent is directed to a process for producing EPO in host cells using recombinant DNA techniques. On remand, in Amgen III Validity & Literal Infringement Judgment, the district court rejected HMR/TKT's argument that the asserted claims of the '698 patent (claims 4-9) are invalid because they lack an adequate written description. The court also rejected HMR/TKT's argument that the asserted claims were not enabled. Having rejected HMR/TKT's validity challenges, the court found claims 4-9 of the '698 patent literally infringed.

The '349 patent is directed to vertebrate cells capable of producing EPO and a process for making EPO using the claimed cells. On remand, the district court rejected HMR/TKT's argument that the asserted claims of the '349 patent (claims 1, 3, 4, 6, and 7) were invalid by reason of obviousness. Since the district court already had ruled in Amgen I that claims 1, 3, 4, and 6 of the '349 patent were infringed, in Amgen III Validity & Literal Infringement Judgment it only was necessary for the court to address Amgen's

claim that HMR/TKT's HMR4396 literally infringed claim 7 of the '349 patent. Doing so, the court found literal infringement. 339 F. Supp. 2d at 258, 336.

On appeal, HMR/TKT argues that the district court made various claim construction errors and also erred in its validity and infringement rulings in the case of both the '698 and '349 patents. We have carefully considered all of HMR/TKT's arguments relating to the '698 and '349 patents. Having done so, we see no error in the district court's legal conclusions; nor do we see clear error in its findings of fact. Accordingly, we affirm in all respects the court's rulings with respect to the '698 and '349 patents.

CONCLUSION

For the foregoing reasons, we vacate the district court's judgment that claim 1 of the '422 patent is not invalid under 35 U.S.C. § 102(a) and remand to the district court for a determination of whether, in view of our construction of the limitation "therapeutically effective," claim 1 is anticipated by the Goldwasser reference and for such further proceedings as may be necessary.[11] We reverse the court's judgment that HMR/TKT infringes claims 2-4 of the '080 patent under the doctrine of equivalents. We affirm the court's judgment that HMR/TKT infringes claims 4-9 of the '698 patent and claims 1, 3, 4, 6, and 7 of the '349 patent.

[11] See footnote 10, supra.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART, and REMANDED

United States Court of Appeals for the Federal Circuit

05-1157

AMGEN INC.,

Plaintiff-Appellee,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals Inc.)
and TRANSKARYOTIC THERAPIES, INC.,

Defendants-Appellants.

MICHEL, Chief Judge, dissenting-in-part.

I write separately to voice my strong disagreement with the majority's holdings that (1) contrary to the district court's construction, "therapeutically effective" in claim 1 of the '422 patent means simply eliciting in vivo biological effects even if not tending to cure certain diseases and (2) claim 1 of the '422 patent could therefore be invalid in light of the Goldwasser reference, which describes a prior art compound eliciting biological activity without curing. Because the majority concludes that the district court erred in construing "therapeutically effective" to mean having a disease-curing effect, it remands the case for a re-adjudication of whether the Goldwasser reference anticipates claim 1 of this particular patent, only one of several asserted.

At the outset, I compliment the district court for the meticulous attention it has given to this extraordinarily complicated, highly-technical, and very difficult case. The district court's two opinions on remand, the subject of our present review, were well-reasoned, well-grounded in the evidence, and well-written. The trial court clearly

exerted tremendous effort to carefully consider all the issues raised by the parties as well as our remand instructions in Amgen II.

After discovery, the district court conducted a three-day Markman hearing and a bench trial spanning twenty-three days in 2000 and then, following our remand, a second Markman hearing and second bench trial spanning nine days in 2003. The district court also took the creative steps of employing Professor Chris Kaiser of the Massachusetts Institute of Technology as a technical advisor on the underlying technology and Michele D. Beardslee as a special master to aid in researching the law, analyzing the issues, and drafting the remand opinion. Assisted by them, the district court spent more than ten months rendering its revised claim constructions and making extensive findings of fact and conclusions of law; it subsequently issued two opinions, together totaling over 360 pages.[*] Plainly, these decisions were not reached in a haphazard or hurried manner by a court intimidated by either the science or the law. On the contrary, the district court's management and resolution of this case is, I think, a model for all trial courts confronted with such patent suits.

I.

The district court construed "therapeutically effective amount" to mean "a quantity that produces a result that in and of itself helps to heal or cure." Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 245. It further elaborated that a therapeutically effective amount would elicit certain in vivo biological effects, such as those described in the specification, col. 33, ll. 17-22, (i.e., stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, stimulation of

[*] The district court's original opinion in this case contained 244 pages.

hemoglobin C synthesis, and increasing hematocrit levels), which reflect a "healing" or "curing" effect in "patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiological anemias, and the like." '422 patent, col. 33, ll. 23-28. I believe the court correctly recognized that merely eliciting a biological effect is not the same as being therapeutically effective.

Indeed, prior art compounds could trigger the very in vivo biological effects enumerated in the specification but were utterly incapable of "healing" or "curing" the class of patients described in the '422 patent. Notably, an article published in the Renal Extrarenal Sources of Erythropoietin Journal in 1971 revealed that a patient suffering from renal anemia was treated with an urinary EPO preparation but, despite experiencing an increase in reticulocytes, died five days later. The district court was particularly aware of this article and even mentioned it when addressing the issue of obviousness after the first bench trial. See Amgen I, 126 F. Supp. 2d at 116. Had this uEPO or any other prior art EPO product been shown to "heal" or "cure" anemia or similar blood disorders, there would have been little need for the claimed invention.

When a compound is truly "therapeutically effective," that is, when it "heals" or "cures" such a blood disorder, it necessarily increases hematocrit as well as causes one or more of the other listed in vivo biological effects. Reading lines 17-22 of column 33 in context, the patentee clearly recognized this.

> As previously indicated, recombinant-produced and synthetic products of the invention share, to varying degrees, the in vitro biological activity of EPO isolates from natural sources and consequently are projected to have utility as substitutes for EPO isolates in culture media employed for growth

> of erythropoietin cells in culture. Similarly, to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., . . . and, as indicated in Example 10, increasing hematocrit levels in mammals.

'422 patent, col. 33, ll. 6-22 (emphasis added). This disclosure clarifies three aspects of the claimed invention. First, the claimed EPO shares the in vitro biological activity of natural EPO. Second, the claimed EPO elicits the very same in vivo activity as natural EPO and, therefore, is suitable for use in EPO therapy procedures. Third, the claimed EPO increases hematocrit in mammals, as exemplified in Example 10 of the '422 patent. By reciting "therapeutically effective amount of human erythropoietin," the patentee thus demonstrated an intention to claim EPO that (1) causes the same in vivo biological effects as the natural EPO; and also (2) increases hematocrit.

The subsequent disclosure strengthens my view that the district court correctly construed the "therapeutically effective" limitation.

> A preferred method for administration of polypeptide products of the invention is by parenteral (e.g., IV, IM, SC, or IP) routes and the compositions administered would ordinarily include therapeutically effective amounts of product in combination with acceptable diluents, carriers and/or adjuvants. . . . Effective dosages are expected to vary substantially depending upon the condition treated but therapeutic doses are presently expected to be in the range of 0.1 (~70) to 100 (~7000 U) µg/kg body weight of the active material.

'422 patent, col. 33, ll. 41-52 (emphasis added). In the only part of the specification where the term "therapeutically effective" actually appears, the patentee uses the term in the ordinary sense of the phrase to mean promoting "healing" or "curing." That is, the patentee teaches the preferred amount of EPO product and a preferred method of administration for a patient suffering from a disorder characterized by a low red blood

cell count. Inherently, the ultimate goal is to "heal" or "cure" the disorder. That healing is characterized by an increased red blood cell count, i.e., a higher hematocrit level.

Significantly, I note that the words "therapeutically effective" are conventionally employed in the pharmaceutical arts to indicate that the claimed pharmaceutical product has utility in the treatment of a human disease where such treatment tends to cause the "healing" or "curing" of the disease. The patentee, I think, intended to invoke that very convention. While the majority might be correct that the '422 patent is not necessarily limited to the exact class of patients described in the specification (as opposed to other blood disorders associated with low hematocrit levels), the district court correctly recognized that it would be "foolish to construe a term such as 'therapeutically effective,' without reference to a class of patients for which the product is intended to be 'therapeutically effective.'" Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 237.

The specification further discloses various analogs of EPO at columns 35-36:

> In addition to naturally-occurring allelic forms of mature EPO, the present invention also embraces other "EPO products" such as polypeptide analogs of EPO and fragments of "mature" EPO. . . . Especially significant in this regard are those potential fragments of EPO which are elucidated upon consideration of the human genomic DNA sequence of FIG. 6, i.e., "fragment" of the total continuous EPO sequence which are delineated by intron sequences and which may constitute distinct "domains" of biological activity. It is noteworthy that the absence of in vivo activity for any one or more of the "EPO products" of the invention is not wholly preclusive of therapeutic utility (see, Weiland, et. al., supra) or of utility in other contexts, such as in EPO assays or EPO antagonism.

'422 patent, col. 35, ll. 34-37; col. 36, ll. 4-14. The majority mistakenly relies on this disclosure to support its view that the "therapeutically effective" means merely capable of triggering any in vivo biological activity, regardless of degree. Correctly read, the

emphasized passage plainly concerns only analogs of EPO, not the EPO of claim 1. That is, the full disclosure teaches that analogs of EPO may offer therapeutic utility even though they may not have in vivo activity. The emphasized sentence says nothing about the claimed EPO and hence cannot be relied upon to construe the "therapeutically effective" limitation.

The prosecution history further confirms that "therapeutically effective" connotes more than simply eliciting any cited in vivo biological effect. The district court emphasized that during prosecution of the '422 patent, the patentee differentiated its invention from natural EPO, which also elicits the aforementioned biological activity, on the basis that the latter was not available in large enough quantities to treat patients, i.e., help cure their diseases. Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 239. Likewise, during the prosecution of the Application No. 07/113,178, a parent application of the '422 patent which itself issued as United States Patent No. 5,441,868, the patentee distinguished the claimed EPO from the prior art, emphasizing that the claimed EPO could be used as a therapeutic product to treat humans with blood disorders characterized by a low red blood cell count whereas the prior art EPO could not. In particular, the patentee stated:

> [N]aturally occurring human erythropoietin is not a viable human therapeutic product; human recombinant erythropoietin, on the other hand, has been proved to be clinically effective, and is the first therapeutic product which can be used to effectively treat the hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts.

In so differentiating the claimed EPO from the prior art, the patentee said that the claimed EPO is capable of doing more, i.e., the claimed EPO "heals" or "cures" anemia and other such disorders by raising a patient's red blood cell count.

Thereafter, during the prosecution of the Application No. 08/100,197, a continuation of Application No. 07/113,178 discussed above, the examiner objected that "Claim 62 is vague and indefinite because it is unclear what the claimed composition is required to be 'effective' for." In response, after quoting column 33, lines 11-28, which includes a description of the in vivo biological effects, the "increasing hematocrit" language, and various diseases treatable with the claimed invention, the patentee again explained that the claimed EPO could be used to treat, (i.e., "heal" or "cure"), various blood disorders:

> It is believed that these sentences from the specification and others provide a clear and definite description of the uses for which the claimed erythropoietin compositions would be therapeutically effective. A person of skill in the art would understand that the amount of erythropoietin necessary to achieve these defined therapeutic results would vary for each use. However, clinicians can readily determine the "therapeutically effective" amounts for each condition, and indeed for each patient. Application submits that the claim language "therapeutically effective amount" is commonly used in this type of case where the product is usable to treat various conditions.

(emphasis added). Accordingly, I must conclude that the district court's construction of the "therapeutically effective" limitation comports with the patentee's own repeated descriptions of the claimed invention. It is exactly the way a skilled artisan would interpret the patent, as the district court held.

II.

Regarding possible anticipation of the invention of the '422 patent by the Goldwasser reference, the district court set forth very specific reasons why none of the in vivo biological effects mentioned in the Goldwasser reference (i.e., an increase reticulocytes, an increase in plasma iron clearance, and red cell mass changes) demonstrated therapeutic effectiveness. HMR does not contend that the district court

clearly erred. Rather, it merely asserts that all of these biological results fall under its proposed claim construction for the term "therapeutically effective amount," which is any amount of EPO that elicits any in vivo biological effect, even if not accompanied by an increased hematocrit. Because I think that the district court correctly rejected HMR's proposed construction and properly construed "therapeutically effective" to mean "healing" or "curing," HMR's validity challenge necessarily fails. While all of the results described in the Goldwasser reference represent in vivo biological responses, none demonstrate that the subject anemic patients were even partially "healed" or "cured." In fact, Dr. Goldwasser himself considered his study a failure because the patients' hematocrit levels did not increase. I therefore conclude that the district court correctly found that the Goldwasser reference does not anticipate claim 1 of the '422 patent. Clear error has not been shown. We should therefore affirm the judgment as to validity.

III.

This litigation has already dragged on for almost ten years, yet the end is nowhere in sight. The majority again remands this case to the district court, this time for a re-adjudication of whether the Goldwasser reference anticipates claim 1 of the '422 patent in light of its revised construction of "therapeutically effective." The district court, as a result, will conduct further proceedings and render a third opinion. Inevitably, at least one party will appeal that judgment, prompting a third review by this Court. We, in turn, will issue another opinion, perhaps even remanding the case a third time. The district court, however, has yet to decide whether to grant an injunction, the specific relief sought by the patentee. Presumably, after our decision in that potential third appeal, the district court would conduct a trial or hearing on that issue and reach

another decision, which will likely be appealed by one or both of the parties. We consequently would hear a fourth appeal and issue a fourth decision, which could involve yet another remand. When will it end? Ironically, the patents in dispute may expire before this litigation concludes.

Moreover, since the majority holds that other asserted patents are not invalid and are literally infringed by HMR 4396, (and here I agree), the district court likely will enter an injunction precluding appellants from marketing HMR 4396 until the expiration of at least the '698 and '349 patents. Prolonging this litigation seems futile when, in the end, an injunction will likely issue regardless of how "therapeutically effective" is construed or whether claim 1 of the '422 patent is invalid.