United States Court of Appeals for the Federal Circuit

01-1191, -1218

AMGEN INC.,

Plaintiff-Cross Appellant,

v.

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

Defendants-Appellants.

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

Chief Judge William G. Young

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Plaintiff-Cross Appellant,

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Defendants-Appellants.

DECIDED: January 6, 2003

Before MICHEL, CLEVENGER, and SCHALL, Circuit Judges.

Opinion for the court filed by Circuit Judge MICHEL. Dissenting opinion filed by Circuit Judge CLEVENGER.

MICHEL, Circuit Judge.

Plaintiff-Cross Appellant Amgen Inc. ("Amgen") is the owner of numerous patents directed to the production of erythropoietin ("EPO"), a naturally occurring hormone that controls the formation of red blood cells in bone marrow. Amgen markets and sells EPOGEN®, a highly successful commercial embodiment of the patented erythropoietin. Seeking to impede defendants-appellants Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. (collectively "TKT") from commercializing a competitive EPO product, Amgen filed a declaratory judgment action in the United States District Court for the District of Massachusetts in April 1997, alleging that TKT's Investigational New Drug Application ("INDA") infringed United States Patent Nos. 5,547,933 ("the '933 patent"); 5,618,698 ("the '698 patent"); and 5,621,080 ("the

'080 patent"). The complaint was amended in October 1999 to include United States Patent Nos. 5,756,349 ("the '349 patent") and 5,955,422 ("the '422 patent"), which issued after suit was filed.

After a three-day Markman hearing, the case was tried to the court for 23 days over the course of four months. In January 2001, the district court issued an exhaustive 244-page opinion in which it: (i) construed the disputed claims; (ii) held each of the patents enforceable; (iii) held the '080, '349 (product claims), and '422 patents valid and infringed; (iv) held the '698 patent not infringed; and (v) held the '933 patent not infringed or, in the alternative, invalid for failure to satisfy 35 U.S.C. § 112. Amgen, Inc. v. Hoescht Marion Roussel, Inc., 126 F. Supp. 2d 69, 57 USPQ2d 1449 (D. Mass. 2001). On appeal, TKT urges reversal on the grounds that the patents in suit are all unenforceable, that the district court's claim construction was erroneous, and alternatively, if that claim construction was correct, that the court's validity determinations were erroneous. Amgen asserts, in its cross appeal, that the district court committed error: (i) by comparing the accused process to the examples in the specification rather than the limitations of the method claims of the '349 and '698 patents; and (ii) by holding the '933 patent invalid for failure to comply with § 112. We heard oral argument on May 7, 2002.

We commend the district court for its thorough, careful, and precise work on what is indubitably a legally difficult and technologically complex case. There is no doubt that the court marshaled tremendous time and resources in its effort to reach correct results. Nevertheless, because we must conclude that the court committed certain errors of law in certain of its validity and infringement determinations, we cannot affirm the judgment in its entirety.

We affirm in toto the district court's claim construction. We also affirm: (i) its determination that none of the patents in suit is unenforceable for inequitable conduct; (ii) its contingent determination that the '933 patent is invalid under § 112 ¶ 1; (iii) its grant of summary

judgment of infringement of '422 patent claim 1; (iv) its determination that the '080, '933, '349, and '698 patents are not anticipated by the Sugimoto reference; and (v) its determination that '349 patent claims 1, 3-4, and 6 are infringed. Because the district court misapplied the law, however, we vacate: (i) its determination that the '933 patent is not infringed; (ii) its determination that the '080 patent is infringed under the doctrine of equivalents; (iii) its determination that the '080, '349, and '422 patents are not invalid; and (iv) its determination that the asserted method claims of the '698 patent and '349 patent claim 7 are not infringed. Accordingly, we remand for the district court to reconsider: (i) whether the '080, '349, and '422 patents are obvious in light of the Sugimoto prior art or anticipated or obvious in light of the Goldwasser prior art; (ii) whether the '422 patent is anticipated by Sugimoto reference (and whether Amgen can prove its nonenablement); (iii) whether the asserted claims of the '698 patent and '349 patent claim 7 are infringed by the accused method; and (iii) whether the '080 patent is infringed under the doctrine of equivalents. In sum, as further explained in detail below, we affirm in part, vacate in part, and remand for further proceedings consistent herewith.

BACKGROUND

As the district court set out in painstaking detail the basics of the underlying technology, we will provide only a brief summary here. The reader's familiarity with the fundamentals of molecular biology, genetics, and recombinant DNA technology necessary to this appeal is presumed.[1]

EPO is a naturally occurring protein that initiates and controls erythropoiesis, the production of red blood cells in bone marrow. Red blood cells are critical because they contain

[1] For further reading on these subjects, see generally Robert A. Meyers, ed., Molecular Biology and Biotechnology: A Comprehensive Desk Reference, VCH Publishers (1995); Benjamin Lewin, Genes VII, Oxford Univ. Press (2000); James D. Watson et al., Recombinant DNA (2d ed. 1992).

hemoglobin, a protein responsible for transporting oxygen from the lungs to peripheral tissues. Because EPO is produced in the kidney, patients with chronic kidney (renal) failure lack normal levels of EPO and, as a result, have a sub-optimal number of red blood cells -- a condition called anemia. The therapeutic goal for treating anemic patients is to increase the "hematocrit level," which represents the ratio of red blood cells to total blood volume, to normal or near-normal levels. This is accomplished through the introduction of additional EPO into the patient's system.

The implementation of this seemingly simple solution, introduction of exogenous EPO, proved to be difficult. Because human EPO is produced in very small amounts (even from the healthy human kidney), it is difficult to obtain by conventional methods. Early attempts to recover EPO from plasma or from human urine ("urinary EPO" or "uEPO") were unsuccessful because such recovery employed techniques that were complicated, yet still resulted in a low-yield, high-impurity, or unstable EPO end product. '933 patent, col. 6, line 60 — col. 7, line 42. Similar attempts using antibody techniques failed because of difficulty in providing for the large-scale isolation of quantities of EPO from mammalian sources sufficient for further analysis, clinical testing, or therapeutic use. Id., col. 9, lines 2-8. The first successful method of production of a therapeutically effective amount of erythropoietin used recombinant EPO ("rEPO") techniques; Amgen is recognized as the pioneer. See, e.g., Molecular Biology and Biotechnology at 108.

Amgen scientist Dr. Fu-Kuen Lin is the named inventor on all five patents in suit. Instead of attempting to purify EPO from natural sources, Lin isolated and characterized monkey and human EPO genes, then used conventional recombinant DNA technology to produce large amounts of rEPO. '933 patent, col. 13, lines 50-53. Lin was able to determine the entire DNA sequence of human EPO and from that, its predicted amino acid sequence. Id., Fig. 6; col. 10,

lines 65 — col. 11, line 2. Using the isolated human EPO gene, Lin described several methods for producing therapeutically effective amounts of human EPO using an expression vector.[2] Id., col. 21, line 42 — col. 25, line 27.

EPOGEN®, the commercial embodiment of Amgen's patented EPO product, is produced by the method disclosed in patent specification Example 10. That example describes the production of human EPO through transfection (introduction) of exogenous DNA into host Chinese hamster ovary ("CHO") cells. The CHO host cell, using its own transcription machinery, then expresses human rEPO in abundance, which then accumulates in the host cell cytoplasm or in the culture media. Id., col. 37, lines 43-49. The rEPO so recovered has the same or similar amino acid sequences and biological properties as naturally occurring human EPO, but differs in its "glycosylation," i.e., in the patterns of branched carbohydrate chains that attach to the protein. '933 patent, col. 10, lines 34-41.

The patents in suit, which all claim priority to a December 1983 application long since abandoned, are continuations of a common ancestor -- United States Patent No. 4,703,008 -- which was at issue in this court's landmark decision in Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).[3] The '933 patent issued on August 20, 1996, containing 14 claims drawn primarily to a non-naturally occurring EPO product with certain characteristics. At issue in this lawsuit are claims 1, 2, and 9 (with the disputed claim terms here and below underscored):

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[2] An "expression vector" is a circular piece of DNA (or "plasmid") that is inserted into a host cell to produce (or "express") a protein. The expression vector carries the gene encoding for the protein of interest (in this case human EPO), a marker that assures that the vector is properly introduced into the host cell, and a promoter site that the host will recognize to transcribe the vector's DNA. See generally Thomas E. Crieghton, ed., Encyclopedia of Molecular Biology, vol. 2, John Wiley & Sons, Inc. (1999) at 883-86.

[3] Because the patents in suit share an identical disclosure, all citations will be to the '933 specification unless otherwise noted.

1. 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.

2. The non-naturally occurring EPO glycoprotein product according to claim 1 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE.

9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

The '698 patent issued on April 8, 1997, containing nine claims drawn to a process for producing a glycosylated erythropoietin polypeptide. At issue are claims 4-9:

4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps:

a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells

5. The process of claim 4 wherein said promoter DNA is viral promoter DNA.

6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

7. The process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA.

8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.

9. The process according to claims 2, 4 and 6 wherein said cells are mammalian cells.

The ’080 patent, which issued with seven claims on April 15, 1997, claims both an isolated erythropoietin glycoprotein and a method for therapeutically administering a pharmaceutical composition thereof. Only product claims 2-4 are at issue:

> 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.

The ’349 patent, which issued on May 26, 1998, contains one method claim and six product claims that are drawn generally to types of vertebrate cells grown in culture. At issue are claims 1, 3-4, and 6-7:

> 1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin.
>
> 3. Vertebrate cells according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 4. Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay
>
> 6. Vertebrate cells according to claim 4 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6.

Last,

the ’422 patent, containing two claims directed to therapeutically effective pharmaceutical compositions of EPO, was granted on September 21, 1999. Only claim 1 is in dispute:

> 1. 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.

The district court conducted the Markman hearing in late March and early April 2000 in advance of Amgen’s motion for summary judgment of infringement. The court entertained oral argument, aided by demonstrative exhibits, but heard no witness testimony and received no evidence. Amgen, 126 F. Supp. 2d at 81, 57 USPQ2d at 1455. At the close of the hearing, the court announced its claim constructions from the bench; these oral rulings were included and expounded upon in the written opinion ruling on the merits following trial. Id. at 84-94, 57 USPQ2d at 1457-64.

Immediately following the Markman hearing, the court turned to Amgen’s pending motion for summary judgment of infringement of ’422 patent claim 1 and ’349 patent claims 1, 3-4, and 6. As to the ’422 patent, the district court found: (1) that it was uncontradicted that the accused product, HMR4396, was a pharmaceutical composition; (2) that it necessarily contained a therapeutically effective amount of human erythropoietin (otherwise, the filing of an INDA would be pointless); and (3) that the record evidence demonstrated that HMR4396 contained a pharmaceutically acceptable diluent, adjuvant, or carrier as claimed in claim 1. Id. at 94-95, 57 USPQ2d at 1455-56. The sole remaining question was whether the accused erythropoietin product had been “purified from mammalian cells grown in culture.” The court found, in light of its claim construction that the term “mammalian” comprises human cells, that the last limitation had

been met. Id. at 95-96, 57 USPQ2d at 1466. The court therefore granted summary judgment of infringement of '422 patent claim 1.

Trial commenced on May 15, 2000. When Amgen rested at the close of its infringement case, the court granted TKT's motions for judgment of non-infringement of the '698 patent and literal non-infringement of the '080 patent. Id. at 99-104, 57 USPQ2d at 1469-73. At the close of TKT's rebuttal case, the court granted Amgen's motion for judgment of validity, finding that TKT had not carried its burden of clearly and convincingly proving anticipation or obviousness. Id. at 104-17, 57 USPQ2d at 1473-82. The remaining issues were taken under advisement. The court's opinion issued on January 19, 2001, and these timely cross-appeals followed. Vested with jurisdiction under 28 U.S.C. § 1295(a)(1), we address below the myriad issues before us.

DISCUSSION

I

The rules are by now well known. Because claim language defines claim scope, the first step in an infringement analysis is to construe the claims, i.e., to determine the scope and meaning of that which is allegedly infringed. Markman v. Westview Instr., Inc., 52 F.3d 967, 976, 34 USPQ2d 1321, 1326 (Fed. Cir. 1995), aff'd, 517 U.S. 370, 38 USPQ2d 1461 (1996). To properly construe the claims, a court must examine the claims, the rest of the specification, and, if in evidence, the prosecution history. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1576-77 (Fed. Cir. 1996). Thereafter, the properly construed claims are compared to the accused product or process to determine whether each of the claim limitations is met, either literally or equivalently. CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1365, 62 USPQ2d 1658, 1662 (Fed. Cir. 2002).

There are two general areas of dispute TKT raises regarding the district court's claim construction. First, TKT urges that the court erred by failing to limit the asserted claims to

exogenous DNA, despite the fact that none of the claims in suit contain an "exogenous DNA" limitation. Second, TKT asserts that the court erred by refusing to limit the terms "vertebrate," "mammalian," and "non-naturally occurring" -- each of which appear in varying degrees within the asserted claims -- such that they exclude host human cells which, of course, are used by the accused infringers. We consider the trial court's claim construction -- a matter of law -- afresh on appellate review. See Cybor Corp. v. FAS Tech., Inc., 138 F.3d 1448, 1455, 46 USPQ2d 1169, 1173 (Fed. Cir. 1998) (en banc).

A

We turn first to address a threshold definitional dispute that carries with it important consequences for the infringement issues decided by the district court and facing us on appeal, to wit, what is the distinction between exogenous, as opposed to endogenous, DNA in recombinant DNA parlance? According to TKT, it practices an innovative process using homologous recombination: it takes the ordinarily unexpressed endogenous (or "native") EPO gene in human cells and transfects "a viral promoter and certain other DNA" that does not encode EPO. That "other" DNA is inserted into the chromosome at a pre-determined, targeted location upstream from the endogenous EPO gene to produce what TKT has termed "Gene-Activated EPO," or "GA-EPO." TKT contrasts this method with that of Amgen, which TKT asserts undeniably uses exogenous DNA.

None of the asserted claims contain either an "exogenous DNA" or "endogenous DNA" limitation.[4] Based upon representations allegedly made by Amgen during the prosecution of the patents in suit, however, TKT argues that many of the claims the district court construed should

[4] That is not to say that there are no claims that have such a limitation. Unasserted claim 3 of the '933 patent, for example, does contain such a limitation: "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin . . . ." col. 38, lines 26-29.

have been defined narrowly to include only exogenous DNA. The district court rejected this argument, as do we.

"It is the claims that measure the invention." SRI Int'l v. Matsushita Elec. Corp., 775 F.2d 1107, 1121, 227 USPQ 577, 585 (Fed. Cir. 1985) (en banc). Because the claims are best understood in light of the specification of which they are a part, however, courts must take extreme care when ascertaining the proper scope of the claims, lest they simultaneously import into the claims limitations that were unintended by the patentee. See, e.g., Hoganas AB v. Dresser Indus., Inc., 9 F.3d 948, 950, 28 USPQ2d 1936, 1938 (Fed. Cir. 1993) ("It is improper for a court to add extraneous limitations to a claim, that is limitations added wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim." (citation omitted)). The danger of improperly importing a limitation is even greater when the purported limitation is based upon a term not appearing in the claim. "If we once begin to include elements not mentioned in the claim in order to limit such claim . . ., we should never know where to stop." Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 990, 50 USPQ2d 1607, 1610 (Fed. Cir. 1999) (quoting McCarty v. Lehigh Val. R.R., 160 U.S. 110, 116 (1895)).

Amgen's inventive EPO product, according to the disclosure in the '933 patent, is "uniquely characterized by being the product of prokaryotic or eucaryotic host expression (e.g., by bacteria, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis." '933 patent, col. 10, lines 15-20. In discussing United States Patent No. 4,237,224 (issued to Cohen), the '933 patent defines "exogenous DNA" by reference as DNA that is foreign to the host organism. See id. col. 2, lines 41-47 ("[T]he Cohen et al. patent first involve[s] manufacture of a transformation vector by enzymatically cleaving viral or circular plasmid DNA to form linear DNA strands. Selected foreign ('exogenous' or 'heterologous') DNA strands usually including sequences coding for desired

product are prepared in linear form through use of similar enzymes."). During the prosecution of Serial No. 08/468,369, which became the '349 patent, the examiner commented that the application "teaches and enables only cells that have been transformed with exogenous DNA that encodes erythropoietin (EPO) that have the high EPO production required by the claims." TKT asserts, as a result, that its GA-EPO product and process fall outside the scope of the asserted claims because Amgen repeatedly has characterized its claimed products and processes as requiring the use of exogenous EPO DNA, and hence the claims should be limited thereto.

Guided by our principles of claim construction, we agree with the district court that TKT improperly seeks to import the "exogenous" limitation into the claims. The plain meaning of the claims controls here, and they plainly are not so limited. The statement that the invention is "uniquely characterized" by the expression of exogenous DNA sequences does not impel us to accept TKT's position when the asserted claims do not contain such an express limitation. In fact, TKT's position is undermined by the doctrine of claim differentiation, as reference to other claims clearly indicates that Amgen did not intend to limit the invention to the use of exogenous DNA. Unasserted claim 3 of the '933 patent, for example, is virtually identical to claim 1, save for the express limitation regarding the use of "exogenous DNA" (underlined portioned indicating differences).

Claim 1	Claim 3
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.	A non-naturally occurring glycoprotein product of the expression in a mammalian host cells of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing 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.

Our court has made clear that when a patent claim "does not contain a certain limitation and another claim does, that limitation cannot be read into the former claim in determining either validity or infringement." SRI Int'l, 775 F.2d at 1122, 227 USPQ at 586; see also O.I. Corp. v. Tekmar Co., Inc., 115 F.3d 1576, 1582, 42 USPQ2d 1777, 1781 (Fed. Cir. 1997) (expressing the notion that there are practical limits to the doctrine of claim differentiation: "the doctrine cannot alter a definition that is otherwise clear from the claim language, description, and prosecution history."). There is a rebuttable presumption that different claims are of different scope. See Kraft Foods, Inc. v. Int'l Trading Co., 203 F.3d 1362, 1366-67, 53 USPQ2d 1814, 1817 (Fed. Cir. 2000); Multiform Dessicants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1479-80, 45 USPQ2d 1429, 1434 (Fed. Cir. 1998).

The examiner's statement in the prosecution history gives us no pause, as the basis for his rejection was not because transformation with exogenous DNA was not taught, but because "the high EPO production required by the claims" was not. See J.A. at 1302 ("The instant application does not guide one of ordinary skill in the art in the discovery of non-transformed vertebrate cells that are capable of the high EPO production recited in the instant claims, [as demonstrated in the reference,] each of which discloses levels of EPO production by vertebrate cells in culture that are far below those levels required in the instant claims."). TKT's position is further undermined because the asserted claims issued. We must presume the examiner did his job, and if he truly thought that the specification taught or enabled only the use of exogenous DNA, the asserted claims would not have issued.

In the end, TKT has not directed our attention to anything in the intrinsic record that rebuts the presumption that the plain meaning of the terms controls. Accordingly, we conclude that the scope of the asserted claims should not be limited to the expression of exogenous DNA.

B

TKT asserts, in addition to the exogenous/endogenous distinction discussed above, that the district court misconstrued the terms "non-naturally occurring," "vertebrate cells," and "mammalian cells" -- which appear in many of the asserted claims -- to include human cells. Reviving the same argument the district court rejected below, TKT contends Amgen expressly disavowed the use of human cells to make human EPO.

The district court found that the definition of the term "non-naturally occurring" can be discerned through the doctrine of claim differentiation. Specifically, the court concluded that TKT's proffered construction must fail in light of '933 patent claim 3, discussed previously, which claims a "non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence encoding human erythropoietin . . . ." By its terms, then, this claim would cover the expression of human DNA in a cat host cell, for example, because a cat is a mammal. The court thus concluded that the phrase "non-naturally occurring" would be redundant in claim 3 if the phrase had the meaning TKT sought to ascribe to it. Further, because the patent specification compares the biological activity of synthetic products to "EPO isolates from natural sources" or "natural EPO isolates," the court concluded that non-naturally occurring simply means "not occurring in nature." Amgen, 126 F. Supp. 2d at 90-91, 57 USPQ2d at 1462-63.

Similarly, finding that the term vertebrate is widely known and understood to cover anything with "a segmented bony or cartilaginous spinal cord [which obviously includes humans]," id. at 85, 57 USPQ2d at 1457-58, the court adopted Amgen's proposed construction. The court

also adopted Amgen's proposed construction of the term "mammalian cells" appearing in '422 patent claim 1 and '698 patent claim 9 under a similar rationale. Id. at 84-86, 57 USPQ2d at 1458.

We indulge a heavy presumption that a claim term carries its ordinary and customary meaning. CCS Fitness, 288 F.3d at 1366, 62 USPQ2d at 1662; see also Gart v. Logitech, Inc., 254 F.3d 1334, 1341, 59 USPQ2d 1290, 1295 (Fed. Cir. 2001). Although TKT is correct that the prosecution history is always relevant to claim construction, it is also true that the prosecution history may not be used to infer the intentional narrowing of a claim absent the applicant's clear disavowal of claim coverage, such as an amendment to overcome a rejection. See York Prods., Inc. v. Central Tractor & Farm Fam. Ctr., 99 F.3d 1568, 1575, 40 USPQ2d 1619, 1624 (Fed. Cir. 1996). No such clear disavowal occurred here.

We agree with Amgen that the specification expressly describes humans as a subset of mammals, and mammals, in turn, as a subset of vertebrates. See '933 patent, col. 4, lines 47-48; col. 10, line 21. Moreover, the specification can fairly be read to, if not expressly, disclose the use of human DNA in human host cells in culture:

> Conspicuously comprehended are expression systems involving vectors of homogeneous origins applied to a variety of bacterial, yeast, and mammalian cells in culture as well as to expression systems not involving vectors . . . . In this regard, it will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and human host cells in culture, actually constitute instances of 'exogenous' DNA expression inasmuch as the EPO DNA whose high level expression is sought would not have its origins in the genome of the host.

'933 patent, col. 37, lines 33-43 (emphasis added). The astute reader will observe what appears to be a breakdown in the parallelism of the sentence emphasized in the block quote above. Specifically, the reference to the expression of "monkey origin DNA in monkey host cells in culture and human host cells in culture" seems a bit nonsensical because the expression of monkey origin DNA in human host cells is perforce the expression of exogenous DNA. The

original 1983 application from which all the patents in suit claim priority, by contrast, contained language that upholds the parallelism of the sentence and logically makes sense. It read, in pertinent part: "[I]t will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and human DNA in human host cells in culture constitute instances of 'exogenous' DNA expression." J.A. at 2862 (emphasis added).

TKT boldly asserts that the variance between the original application and the patents in suit bespeaks some volitional act by Amgen to narrow the scope of the asserted claims in light of certain experimental data. In particular, TKT advances a theory whereby Amgen intentionally removed the language from subsequent applications (allegedly) because test results using human cells were not good, and later admitted (during an opposition proceeding against the European counterpart patent) that the omission was not inadvertent. But the record contains a more benign explanation as to what happened. According to the testimony of Dr. Lin, he was unaware of, and therefore did not authorize, the change. Further, the prosecuting attorney testified in his deposition that to the best of his knowledge the error was a typographical error.

But even assuming that the error was intentional, the district court's claim construction would not be foreclosed: our precedent is clear that claims are not perforce limited to the embodiments disclosed in the specification. E.g., Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1344, 60 USPQ2d 1851, 1856 (Fed. Cir. 2001) ("[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention."). Here, the patent plainly discloses the use of human host cells in culture, and our review of the record indicates no "clear disavowal" sufficient to undercut the express disclosure in the specification.

As a result, we are satisfied that the terms "non-naturally occurring," "vertebrate," and "mammalian" should be construed as they were by the district court, in a manner consistent with

their plain meaning. Accordingly, we reject TKT's attempt to limit the scope of the asserted claims under an unduly constricted reading of the specification.

C

The final claim construction issue TKT raises is aimed at the district court's alleged failure to discern "source and process" limitations in claims of the '080, '349, and '422 patents. According to TKT, the trial court erred by concluding that the asserted claims are product claims, i.e., that they are directed to a structural entity that is not defined or limited by how it is made. TKT summarily states that this holding must be erroneous because, it asserts, the patentability of the claims depended on the process since "Amgen tried, but failed, to distinguish rEPO from prior art EPOs based on physical differences." We do not agree.

It is telling that neither in the briefing nor at oral argument did TKT direct us to any specific statement in the prosecution history to support the contention that the patentability of the product claims in suit depended upon the process by which those products are obtained. In fact, the original claims of at least one of the patents (the '080 patent) were drafted as product-by-process claims, which claims were cancelled and replaced with "pure" product claims. This is strong evidence that both the patentee and the examiner viewed the claims that ultimately issued as lacking a process component. See Vanguard Prods., Inc. v. Parker Hannifin Corp., 234 F.3d 1370, 1372, 57 USPQ2d 1087, 1089 (Fed. Cir. 2000) ("Parker Hannifin argues that the prosecution history shows that the Vanguard inventors viewed co-extrusion as 'fundamental' to manufacture of the claimed gasket, thereby imposing this process of manufacture upon the product claims . . . . However, review of the prosecution history shows that during examination the examiner as well as the applicant treated the product claims as directed to the product itself, and examined the application accordingly.").

In any event, we are not convinced that the source limitations in the asserted claims convert the claims into anything other than product claims. As to the '080 patent, the "non-naturally occurring" limitation in claims 3 and 4 merely prevents Amgen from claiming the human EPO produced in the natural course. By limiting its claims in this way Amgen simply avoids claiming specific subject matter that would be unpatentable under § 101. This court has endorsed this approach, recognizing that patentees can use negative limitations such as "non-human" and "non-natural" to avoid rejection under § 101. See Animal Legal Def. Fund v. Quigg, 932 F.2d 920, 923, 18 USPQ2d 1677, 1680 (Fed. Cir. 1991). The district court arrived at a similar conclusion, Amgen, 126 F. Supp. 2d at 89, 57 USPQ2d at 1462-63, and TKT has not demonstrated any error in that conclusion. Similarly, the "not isolated from human urine" limitation in claims 2 and 4 of the '080 patent simply requires that the claimed EPO, however made, be obtained from a source other than human urine. Each of these limitations only excludes human EPO from specific sources and does not restrict the claimed EPO to that produced from any particular source or by any particular method. In sum, claims 2, 3, and 4 of the '080 patent remain broadly drawn to the described "erythropoietin glycoprotein" or "pharmaceutical composition" produced by any method, or obtained from any source, other than those specifically excluded.

As to the '422 patent, the limitation "purified from mammalian cells grown in culture" in claim 1 clearly limits the source of the EPO used in the claimed "pharmaceutical composition." The limitation only speaks to the source of the EPO and does not limit the process by which the EPO is expressed. Rather, the claim is broadly drawn to a "pharmaceutical composition" having

certain elements, one of those being EPO "purified from mammalian cells in culture." This reading is in line with the district court's construction and, again, TKT directs us to no error.[5]

II

It is axiomatic that claims are construed the same way for both invalidity and infringement. W.L. Gore & Assoc., Inc. v. Garlock, Inc., 842 F.2d 1275, 1279, 6 USPQ2d 1277, 1280 (Fed. Cir. 1988). But because the features of the accused product or process are often undisputed, this axiom invites a common approach in the appellate arguments by accused infringers: the principal argument challenges the correctness of a trial court's broad claim construction; the contingent argument, assuming the trial court's claim construction is affirmed, challenges validity under 35 U.S.C. § 112 ¶ 1 of the asserted patents in light of that broad construction. See, e.g., Adv. Cardiovascular Sys. v. Medtronic, Inc., 265 F.3d 1294, 60 USPQ2d 1161 (Fed. Cir. 2001); PPG Indus. v. Guardian Indus. Corp., 75 F.3d 1558, 37 USPQ2d 1618 (Fed. Cir. 1996); Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983). TKT employs that approach here. We therefore think it appropriate to address the relevant § 112 issues before turning to the issue of infringement.

Section 112 of the patent statute describes what must be contained in the patent specification. Among other things, it must contain "a written description of the invention, and of the manner and process of making and using it . . . [such] as to enable any person of ordinary skill in the art to which it pertains . . . to make and use the same . . . ." 35 U.S.C. § 112 ¶ 1. Thus, this statutory language mandates satisfaction of two separate and independent requirements: an applicant must both describe the claimed invention adequately and enable its reproduction and use. See Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111,

[5] We do not hold that these limitations lack meaning, only that they mean just what they say. Accordingly, they limit only the source from which the EPO is obtained, not the method by which it is produced.

1117 (Fed. Cir. 1991). Third, though not in issue here, he must disclose what he considers the best mode of practicing his invention.

A

The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Id. at 1561, 19 USPQ2d at 1115 (citation omitted). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. Lockwood v. Am. Airlines, Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (citation omitted). Because of its fact intensive nature, we review a district court's decision on the adequacy of written description for clear error. Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (citations omitted).

In addressing TKT's written description arguments, the district court carefully examined whether Amgen's specification adequately described the full breadth of the claims. In the end, the district court rejected TKT's written description challenge, finding that TKT had proven its case only by a preponderance of the evidence -- not the clear and convincing standard required as a matter of law. Acknowledging the presence of "a genuine dispute between the expert witnesses," the court weighed the testimony and found that the evidence showed that the descriptions adequately described to those of ordinary skill in the art in 1984 the use of the broad class of available mammalian and vertebrate cells to produce the claimed high levels of

human EPO in culture. Amgen, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507. In so doing, the court credited in particular the testimony of Amgen's expert, Dr. Harvey Lodish, who testified, among other things, that there might be "minor differences" in applying the method of the disclosed examples (utilizing CHO and COS-1 (monkey) cells) to any vertebrate or mammalian cells, but that those of ordinary skill could "easily" figure out those differences in methodology. Id., 57 USPQ2d at 1507.

Much of TKT's argument on appeal challenging this finding dovetails with its claim construction arguments we have already found lacking. For example, TKT asserts that the Amgen patents do not satisfy the written description requirement because: (1) Amgen failed to sufficiently describe the use of all vertebrate and mammalian cells; (2) Amgen deleted use of exogenous human EPO DNA in human cells from its applications;[6] (3) Amgen expressly excluded the use of endogenous EPO DNA; (4) Amgen emphasized that the advantage of its invention was "freedom from association with human proteins"; and (5) in using the "uniquely characterized" language to describe the polypeptides of the invention, Amgen identified exogenous EPO DNA as an essential element of the invention. As a result of these shortcomings, argues TKT, it has clearly and convincingly proven invalidity under Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998), and Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). We are not persuaded that these precedents mandate reversal of the trial court's factual findings as clearly erroneous regarding the written descriptions.

First, in addressing the adequacy of the written description of the '422 patent and with

[6] We addressed this point in our claim construction analysis on pages 17-18 ante, finding that the written description did not exclude human cells from the scope of the claims. That analysis suffices here as well.

respect to TKT's exogenous DNA arguments, the district court noted:

> When the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in the way in which the claimed composition is made that may arise after the patent application is filed. See United States Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1251 [9 USPQ2d 1461, 1465] (Fed. Cir. 1989); In re Koller, 613 F.2d 819, 824-25 [204 USPQ 702, 707] (Fed. Cir. 1980); see also In re Hogan, 559 F.2d 595, 606 [194 USPQ 527, 538] (C.C.P.A. 1977). Instead, section 112 only requires the Court to determine whether the specification conveys to one of ordinary skill in the art as of 1984 that Dr. Lin invented the subject matter claimed in the patents-in-suit. Reiffin, 214 F.3d at 1346 [Reiffin v. Microsoft Corp., 214 F.3d 1342, 1346, 54 USPQ2d 1915, 1917 (Fed. Cir. 2000)]. The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claim -- not comparison between how the product was made as disclosed in the patent and future developments of this process that might alter or even improve how the same product is made.

Amgen, 126 F. Supp. 2d at 150, 57 USPQ2d at 1508; see also id. at 152, 57 USPQ2d at 1509 (discussing the '080 patent), 154 n.51, 57 USPQ2d at 1510 (discussing the '349 patent). The district court therefore considered TKT's exogenous DNA arguments and, for the reasons stated above, rejected them. On appeal TKT has not argued that its legal analysis was erroneous. Because we have not been directed to any case law to the contrary, we conclude the district court's legal conclusion based on Phillips Petroleum was not erroneous and that it properly handled the exogenous DNA issue.

We move now to TKT's argument that Amgen failed to sufficiently describe all vertebrate and mammalian cells as engineered in the claimed invention. We held in Eli Lilly that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself -- not merely a recitation of its function or a reference to a potential method for isolating it. 119 F.3d at 1566-67, 43 USPQ2d at 1406 (holding the disclosure of the cDNA sequence of the insulin gene of a rat did not adequately describe the cDNA sequence of the insulin gene of every vertebrate). More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written

description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613. Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend.[7] Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell -- not the human DNA itself. This difference alone sufficiently distinguishes Eli Lilly, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words "vertebrate" and "mammalian" readily "convey[] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." Eli Lilly, 119 F.3d at 1567, 1568, 43 USPQ2d at 1406.[8] Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders Eli Lilly listless in this case. Amgen, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507.

TKT's remaining arguments rely on Gentry Gallery. However, we see Gentry Gallery as similarly inapt. TKT would have us view Gentry as a watershed case, in reliance on an isolated statement -- probably only dicta -- that one of ordinary skill in the art would clearly understand that

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[7] Indeed, Amgen's patents appear to satisfy the sequence requirement in Eli Lilly insofar as Figure 6 of the patents expressly discloses the complete (albeit slightly incorrect) sequence of human genomic EPO DNA and the encoded DNA.

[8] There is no issue here as to in haec verba description because, as stated in the body of the opinion, in contrast to "cDNA" -- that clearly does not describe the actual sequence of the cDNA -- the words "mammalian cells" and "vertebrate cells" convey exactly what they are. Thus, this aspect of the holding in Eli Lilly is also inapplicable here.

the location of the reclining controls on the claimed sectional sofa "was not only important, but essential to [the] invention." 134 F.3d at 1480, 45 USPQ2d at 1503. But as we recently indicated in Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc., 291 F.3d 1317, 1323, 62 USPQ2d 1846, 1850-51 (Fed. Cir. 2002), "we did not announce [in Gentry] a new 'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements." See also Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1114; cf. Aro Mfg. Co. v. Convertible Top Replacement Co., 365 U.S. 336, 345 (1961) ("[T]here is no legally recognizable or protected 'essential element,' 'gist' or 'heart' of the invention in a combination patent."). Understood in this light, one sees the holding in Gentry for what it really was: an application of the settled principle that a broadly drafted claim must be fully supported by the written description and drawings. See Cooper Cameron, 291 F.3d at 1323, 62 USPQ2d at 1850-51. After considering extensive testimony from both parties, the district court held this principle met and TKT failed to demonstrate that this analysis was clearly erroneous factually or based on an error of law. Amgen, 126 F. Supp. 2d at 149-50, 57 USPQ2d at 1507-08.

To the extent the particular facts of Gentry are relevant, we also find it distinguishable. First, there is a fundamental difference between Amgen's patented invention and the invention in Gentry. In Gentry the invention was the placement of reclining controls on a central console on a unit of a sectional sofa so as to allow the sofa to have two independent reclining seats face in the same direction (solving a problem present in the prior art). 134 F.3d at 1475, 45 USPQ2d at 1499. The undisclosed element leading to the Gentry court's holding of invalidity for lack of an adequate description was a location for the controls other than on the console -- leading to a different and undescribed product. See id. at 1479, 45 USPQ2d at 1502-03. Amgen's invention is not the location of the control sequences and EPO DNA in relation to the cell, but

rather the production of human EPO using those sequences. Thus, the undisclosed element TKT urges invalidates Amgen's product claims is a different method (endogenous activation) of making the claimed compositions. But, as the district court noted, under our precedent the patentee need only describe the invention as claimed, and need not describe an unclaimed method of making the claimed product. Amgen, 126 F. Supp. 2d at 150, 57 USPQ2d at 1507 (citing Phillips Petroleum, 865 F.2d at 1251, 9 USPQ2d at 1465; In re Koller, 613 F.2d at 824-25, 204 USPQ at 707); see also Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117. This factual difference alone is sufficient to distinguish this case from Gentry.

Second, the statements by the patentee in the written description in this case fall short of what Gentry prohibits. The court in Gentry concluded that the inventor had clearly expressed in the written description that he considered his invention to be limited to the specific location of the controls on the console on the sofa ("the only possible location") and that any variation was "outside the stated purpose of the invention." Gentry Gallery, 134 F.3d at 1479, 45 USPQ2d at 1503. Indeed, in Gentry the inventor testified that he only considered locating the controls outside of the console -- and only broadened his application claims accordingly -- after seeing Gentry's competitors introduce products with controls located off the console. Id. Here, to be sure, Amgen made statements that its invention is "uniquely characterized" by exogenous expression of DNA. '933 patent col. 10, lines 15-20. When considered in context, however, these statements do not lead to the same conclusion as in Gentry. Amgen's statements simply do not clearly indicate that exogenous expression is the only possible mode of the invention or that other methods were outside the stated purpose of the invention. Instead, Amgen begins the background section of its written description by stating "[t]he present invention relates generally to the manipulation of genetic materials and, more particularly, to recombinant procedures making possible the production of polypeptides possessing part or all of the primary structural

conformation and/or one or more of the biological properties of naturally occurring erythropoietin." '933 Patent, col. 1, lines 18-23. Because of this lack of clear statements by the patentee limiting the claimed invention (and in light of the case law discussed, ante), we cannot invalidate a patent for failure to describe a method of producing the claimed compositions that is not itself claimed. Nor could the patentee have described the other method, as it was not developed until 10 years later. We see Gentry Gallery as inapplicable in this regard. In light of the evidentiary record and TKT's inability to persuade us that precedent requires a contrary result, we hold that the district court's finding that Amgen satisfied the written description requirement is not clearly erroneous.

B

The enablement requirement is often more indulgent than the written description requirement. The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Before the district court, TKT bore the burden of clearly and convincingly proving facts showing that the claims were not enabled. E.g., Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1375, 52 USPQ2d 1129, 1141 (Fed. Cir. 1999). Enablement is a question of law; we therefore review the trial court's determination de novo, deferring to its assessment of subsidiary facts underlying the legal question unless clearly erroneous. Bruning v. Hirose, 161 F.3d 681, 686, 48 USPQ2d 1934, 1939 (Fed. Cir. 1998).

TKT contends that the asserted claims are invalid for lack of enablement. Taking a position that virtually mirrors the written description (and claim construction) arguments

previously rejected, TKT posits that the specifications do not enable an ordinarily skilled artisan to practice the full scope of the asserted claims without undue experimentation because they fail to describe the production of EPO using human cells or endogenous human EPO DNA. At bottom, TKT complains that the court erred by failing to follow its findings to their logical conclusion.[9]

But the district court made thorough and complete factual findings supporting its holding that the claims were not proven not enabled, expressly incorporating many of its factual determinations made with respect to written description. As to TKT's endogenous/exogenous arguments, the court concluded the arguments were inapplicable as a matter of law for two reasons. First, "where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed." Amgen, 126 F. Supp. 2d at 160, 57 USPQ2d at 1515 (citing Phillips Petroleum, 865 F.2d at 1251, 9 USPQ2d at 1465; In re Koller, 613 F.2d at 824-25, 204 USPQ at 707 ; In re Hogan, 559 F.2d at 606, 194 USPQ at 538); see also id. at 161, 57 USPQ2d at 1516 (discussing the '080 patent), 163-64, 57 USPQ2d at 1518 (discussing the '349 patent). Thus, the specification's failure to disclose the later-developed endogenous activation technology cannot invalidate the patent. Id. at 160, 57 USPQ2d at 1516. Second, "the law makes clear that the specification need teach only one mode of making and using a claimed composition." Id. at 160, 57 USPQ2d at 1515 (citing Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342, 1361, 47 USPQ2d 1705,

[9] TKT refers here to the district court's statement that "it appears that Dr. Lin claimed far more than he delivered." Amgen, 126 F. Supp. 2d at 158, 57 USPQ2d at 1514. Although this statement does seem out of kilter with the court's ultimate holding, we understand it in light of how close the court viewed the issue: "After much reflection, the court finds that Amgen survives [the enablement challenge], albeit barely." Id. at 157, 57 USPQ2d at 1513.

1719 (Fed. Cir. 1998); Engel Indus. Inc. v. Lockformer Co., 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991)); see also Durel Corp. v. Osram Sylvania Inc., 256 F.3d 1298, 1308, 59 USPQ2d 1238, 1244 (Fed. Cir. 2001). This conclusion again makes the specification's failure to disclose TKT's endogenous activation technology legally irrelevant. Amgen, 126 F. Supp. 2d at 160, 57 USPQ2d at 1515. We reach the same conclusion on appeal, as TKT has not persuaded us that the district court's conclusions in this regard were erroneous.

Focusing specifically on the '422 patent, the enablement inquiry is whether Amgen has enabled all pharmaceutical compositions comprising "a therapeutically effective amount of human erythropoietin," "a pharmaceutically acceptable diluent, adjuvant or carrier," and human erythropoietin "purified from mammalian cells grown in culture." The court found that the specification described and enabled various possible diluents and carriers and provided specific information on effective dosages and therapeutic effect in mice. Id. at 148, 57 USPQ2d at 1506. Amgen also described and enabled at least one way of obtaining EPO purified from mammalian cells in culture: the genetic manipulation of CHO and COS-1 cells, followed by both described and other well known purification techniques. Finally, the court accepted testimony indicating that an ordinarily skilled artisan would infer from the COS-1 (monkey) and CHO cell examples that similar outcomes could be expected from other mammalian cells since all mammalian cells produce and secrete hormones like EPO by means of the same fundamental processes. Id. at 159, 57 USPQ2d at 1514-15. These are all findings of fact and they have not been shown to be clearly erroneous.

As to the '080 patent, the inquiry is whether Amgen has enabled the production of all EPO glycoproteins having "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells," "the mature erythropoietin amino acid sequence

of FIG. 6," and "[are] not isolated from human urine" or "non-naturally occurring." The court noted that Amgen disclosed the in vivo biological effect of EPO upon hematocrit levels in mice and adequately disclosed the sequence of the amino acid residues in figure 6. Id. at 151, 57 USPQ2d at 1508-09. Amgen also described and enabled at least one method of producing EPO that was both "non-naturally occurring" and "not isolated from human urine": the genetic manipulation of CHO and COS-1 cells. The court noted with particularity that even TKT's witness, Dr. Kingston, agreed that if one of ordinary skill in the art followed the teachings of Example 10, then such a person could successfully practice the claimed invention. Id. at 161, 57 USPQ2d at 1516.

We address the product claims of the '349 patent in more detail, as they differ slightly from the patents we discussed above. The '349 patent claims genetically manipulated "vertebrate cells" -- a composition -- having certain characteristics and properties, including an ability to produce the claimed levels of human EPO.[10] The enablement question thus posed is this: having disclosed one way to make the claimed EPO-producing cell, is Amgen entitled to claim all such cells that "can be propagated in vitro," comprise "non-human DNA sequences that control transcription," transcribe "DNA encoding human erythropoietin," and produce the claimed amount of EPO? While our precedent does hold that disclosure of one or two species may not enable a broad genus, e.g., In re Vaeck, 947 F.2d at 495-96, 20 USPQ2d at 1444-45, the district court made several fact-findings indicating that any gaps between the disclosures and the claim breadth could be easily bridged. See, e.g., Amgen, 126 F. Supp. 2d at 149, 57 USPQ2d at 1514 (crediting Amgen's expert Dr. Lodish's statement that "one of ordinary skill in

[10] Following the dissent's "machine" analogy, the "machine" is a genetically altered vertebrate cell containing transcription control sequences used to transcribe a human EPO gene to express the claimed levels of human EPO. Simply altering the way the human EPO gene is inserted or activated -- whether it be through transformation with exogenous DNA or through

the art, me, my students, would have understood this not to be limited to the specific types of cells that were used in this example, that other vertebrate cells, mammalian cells, could have been used"); cf. Enzo Biochem, 188 F.3d at 1367-68, 1372, 52 USPQ2d at 1133, 1136-37 (affirming nonenablement of claims to anti-sense DNA technology applied to all eukaryotic and prokaryotic organisms because anti-sense was a "highly unpredictable technology" and a "high quantity of experimentation" would be needed to practice the invention outside of the disclosed example); Vaeck, 947 F.2d at 495-96, 20 USPQ2d at 1444-45 (holding the examiner did not err in rejecting as nonenabled claims drawn to all genetically-engineered cyanobacteria expressing a given protein because the claimed 150 genera of cyanobacteria represent a vast, diverse, and poorly understood group; heterologous gene expression in cyanobacteria was "unpredictable"; and the patent's disclosure referred to only a genus). The district court found that a skilled artisan could readily have used various cultured vertebrate and mammalian cells to produce human EPO, and this fact was buttressed by numerous post-filing publications that demonstrated the extent of the enabling disclosure. Amgen, 126 F. Supp. 2d at 162, 57 USPQ2d at 1517 (citing Gould v. Quigg, 822 F.2d 1074, 3 USPQ 1302 (Fed. Cir. 1987) for the proposition that an expert may rely on post-filing publications to show enablement). The court also found that for those skilled in the art it was a relatively simple matter to determine whether a certain promoter would work within a specific vertebrate cell, whether a particular vertebrate cell would produce human EPO in culture, and whether a particular promoter could be operatively linked to control the transcription of the human EPO DNA. Id. In summary, the court once again chose to credit Amgen's witnesses, Drs. Lodish and Wall, on the issue of enablement:

> Throughout the testimony of these witnesses, a theme becomes apparent: any challenge which one of ordinary skill in 1984 might have encountered in attempting to make and use the claimed invention using other cultured mammalian cells could

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activation of an endogenous gene -- does not make this a different "machine" once built; rather, it only changes the way it was "constructed."

be resolved by experimentation falling short of undue.

Id. at 159, 57 USPQ2d at 1515.

With these factual findings before us, TKT cannot prevail simply by reasserting in a conclusory manner that Amgen's disclosure does not enable the transformation of all mammalian or vertebrate cells or the production of human EPO. The district court carefully considered these issues, finding in the end that TKT had not met its clear and convincing burden of proof. Finding no clear error in these factual determinations, and having been directed to no legal error committed by the trial court, we will not disturb its holding that the asserted patents are not invalid for failure to meet the enablement requirement of § 112 ¶ 1.

C

Certain concerns are raised by the dissent. My brother in dissent sees the district court as having "abstained from fully inquiring" about compliance with the written description and enablement requirements of § 112, ¶ 1. In light of this strong statement, we write here to highlight what the district court did and did not do in deciding the case below. The district court should be seen as deciding the challenges to validity under each requirement as presented to it by the accused infringer. In doing so, the court fully found the facts that under-girded its conclusions on validity and relied on our case law interpreting and applying § 112. We are largely limited on review to deciding whether those findings based on that testimony are clearly erroneous and we cannot so conclude. We may, of course, review de novo the court's interpretation of our precedent.

The dissent, however, does not directly challenge the court's factual findings, nor does it mention the decisions relied on by the district court. Instead, it finds fault in the absence of discussion of other precedents, namely Eli Lilly, Gentry Gallery, In re Mayhew, and In re Vaeck, and makes broader arguments seemingly based upon policy considerations.

The dissent would vacate and remand the written description issue because the district court did not cite our precedents Eli Lilly and Gentry Gallery. According to the dissent, the district court "did not focus on the correct law to be applied" and, for that reason, its "factual findings merit no deference." It is difficult to see how the district court's analysis must be rejected because it did not include discussions of these two decisions or, per the dissent, "the principles they espouse." First, it is far from clear that the defendant based its written description challenge below primarily on these two cases. Second, as we hold above, these cases are simply inapplicable here. Given these considerations, we decline to hold that the failure of the district court to cite these precedents constitutes reversible error.

In addressing the enablement inquiry the dissent looks to two other cases not discussed by the district court. It cites In re Mayhew, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (C.C.P.A. 1976), for the proposition that "claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure." There, however, the method claims omitted a step without which the invention as claimed was wholly inoperative (meaning it simply would not work and could not produce the claimed product). Id. Here, the lack of a limitation directed to the exogenous expression vector in the product claims is not a failure to describe the structure of the cell or a necessary element of the claimed EPO. Once inside the cell, the transcription control sequence and the human EPO DNA integrate randomly into the host cell chromosomes. The only required description, then, is of the EPO DNA and the transcription control sequences because it is the presence of these sequences in the cell that causes the cell to produce the EPO as claimed. Thus, the lack of a description of (or a limitation directed to) the expression vector itself (as separate from the EPO DNA and transcription control sequences) does not render the invention inoperable and therefore does not run afoul of In re Mayhew, 527 F.2d at 1233, 188 USPQ at 358 (affirming examiner's rejection of claims not limited to having a cooling zone at the exit of a

steel strip from a zinc bath because the specification indicated that without that cooling bath the invented process would not work).

The dissent's reliance on In re Vaeck is also misplaced. Vaeck is cited for the proposition that the disclosure of one or two species (here monkey and hamster cells) "may not enable a broad genus under the circumstances." 947 F.2d at 496, 20 USPQ2d at 1444-45. But then again, it may; the inquiry is fact-specific. Here the district court held the disclosure did enable the genus because the differences between using the two described mammalian (and vertebrate) cells and other such cells were small and easily accommodated by the artisan. Thus, in assessing the evidence, the court found that the defendant's evidence fell short of clear and convincing.

But more fundamentally, we think the dissent unfairly characterizes the district court's careful and reasoned handling of the § 112 issues. The dissent repeatedly suggests that the district court "simply refused" to consider whether, having disclosed only one means to make EPO produced by vertebrate or mammalian cells, Amgen was entitled to claims for all such cells and EPO. Specifically, the dissent asserts that the district court "abstained" from considering whether the absence of a claim limitation on the means of expression raises § 112 issues.[11] We find this hard to understand. The district court explicitly analyzed these requirements in addressing defendant's specific challenges to validity. It decided they were not proven sufficiently and its decision is supported both by citations to our precedent and its own factual findings. Thus, rather than refusing to answer the § 112 questions, it seems the district court did answer them affirmatively.

[11] In this same vein, the dissent suggests that our court here has somehow "waived" the requirements of § 112 for product claims.

In addressing this specific issue, the district court relied principally on two of our precedents: Phillips Petroleum and Cellpro. The court construed the former as not requiring the written description to include later-developed methods for making a claimed product. Amgen, 126 F. Supp. 2d at 150, 160, 57 USPQ2d at 1508, 1515. The court construed the latter as holding that a product claim is supported by adequate written description and enabling disclosure even if it describes only one method of making the claimed product. Id. at 160, 57 USPQ2d at 1515. These cases have not been shown to be incorrectly applied by the district court. And we, like the district court, are obligated to follow them both, as they explicitly support the court's rulings. Phillips Petroleum, 865 F.2d at 1251, 9 USPQ2d at 1465 (holding that the patentee was entitled to a prior filing date because the earlier disclosure of polypropylene as known at that time described and enabled a later claim to "[n]ormally solid polypropylene" even though a new, higher molecular weight form of polypropylene had been subsequently discovered), and Cellpro, 152 F.3d at 1361, 47 USPQ2d at 1719 (affirming summary judgment of enablement of a product claim over a challenge that two alternative embodiments disclosed in the patent were not enabled because "the enablement requirement is met if the description enables any mode of making and using the invention").

Rather than addressing these precedents, the dissent makes broad arguments that are not specifically grounded in our precedent. The dissent asks whether Amgen's disclosure "entitles it to claim all EPO produced by mammalian cells in culture, or all cultured vertebrate cells that produce EPO." (emphasis in original). While this broad entitlement question may be important as a policy matter, where, as here, we have applicable precedents, we are bound by the specific inquiries they mandate. Here, we, as did the district court, look to the requirements of § 112 as interpreted by our precedent. In short, the district court cannot have committed legal error by faithfully following controlling precedent of this court.

Lastly, the dissent emphasizes that omissions in the claim limitations and in the disclosures of the specifications "raised enablement issues." If the claims were still in prosecution before the PTO, perhaps the examiner could make an issue of such omissions. The dissent talks of what is "essential for the patentability of the claims." (emphasis added). But the question here is not patentability of application claims, but validity of issued claims that are presumed valid by statute. Now a heavy burden falls on the challenger. The district court found that the challenger had not carried that burden. It admitted that the questions were close -- indeed, it found invalidity proven, but only by a preponderance. Hence, rather than refusing to decide questions of validity under § 112, it did decide them under the proper standard of proof. We see no reversible error.

III

Having addressed the claim interpretation and § 112 issues, we move to the second step of the infringement analysis: comparison of the properly construed claims to the accused product or process. See, e.g., CCS Fitness, 288 F.3d at 1365, 62 USPQ2d at 1662. Our review of this step differs depending upon whether the issue of infringement was resolved on summary judgment or after a full trial. See Cole v. Kimberly-Clark Corp., 102 F.3d 524, 528, 41 USPQ2d 1001, 1004 (Fed. Cir. 1996). In the case of summary judgment, as with claim 1 of the '422 patent, we review de novo the trial court's finding that there was no genuine issue as to any material fact regarding infringement. Id., 41 USPQ2d at 1004; Fed. R. Civ. P. 56(c). After a full bench trial, infringement is a question of fact that we review, of course, for clear error. Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co., 204 F.3d 1360, 1363, 53 USPQ2d 1892, 1895 (Fed. Cir. 2000). When JMOL is entered under Fed. R. Civ. P. 52(c), as with the '698 and '080 patents, we review the district court's determination for clear error, as if it had been entered at the close of all the evidence. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343,

56 USPQ2d 1641, 1643 (Fed. Cir. 2000). Anchored in the proper scope of review for each claim in dispute, we now address the trial court's infringement analysis.

A. The '933 Patent

Amgen asserted the following three claims of the '933 patent against TKT:

> 1. 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.
>
> 2. The non-naturally occurring EPO glycoprotein product according to claim 1 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE.
>
> 9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Critical for our purposes is the final limitation of claim 1, which states that the claimed glycoprotein has "glycosylation which differs from that of human urinary erythropoietin." Glycosylation is the addition of carbohydrate side chains to amino acid residues in protein sequences to form glycoproteins. Encyclopedia of Molecular Biology at 1047. At the Markman hearing, Amgen asserted that the phrase meant "the attached carbohydrate groups differ when analyzed by standard prior art techniques known as of 1983-84." TKT argued, by contrast, that it meant "the carbohydrate groups attached to side chains of the erythropoietin polypeptide backbone differ by Western blot analysis and SDS/PAGE and carbohydrate composition analysis from those of human urinary erythropoietin to at least the degree described in the patents-in-suit."

Thus, the primary difference concerned which, if any, techniques were acceptable to determine whether the glycosylation was different. The district court found that the examples in the specification teach three measurement methods, but that they failed to limit "glycosylation

which differs" to those methods. The court ruled, therefore, that the phrase means: "Glycosylation as to which there is a detectable difference based upon what was known in 1983-1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." Amgen, 126 F. Supp. 2d at 91-92, 57 USPQ2d at 1463.

It is undisputed that in 1983, there were at least two analytical techniques available for detecting differences in glycosylation between two glycoproteins. SDS-PAGE is a type of gel electrophoresis in which the glycoprotein of interest is bound to a charged compound that denatures the glycoprotein, which in turn is subjected to an electric field; glycoproteins of different molecular weight (reflecting their different glycosylations) will migrate through the electric field at different speeds. Id. at 124, 57 USPQ2d at 1488. Isoelectric focusing ("IEF"), a second technique known to artisans in 1983, is similar to SDS-PAGE except that it determines the pH at which a protein is electrically neutral because the charge is placed in the gel in the form of a pH gradient, rather than on the glycoprotein itself. Id. at 125, 57 USPQ2d at 1488. The data obtained by both these methods can be visualized by Western blot, allowing an approximation of the molecular weight.

There was little dispute that any of these tests could be used to determine the glycosylation of a glycoprotein. Indeed, the district court noted that the testimony of an Amgen witness, Dr. Cummings, "would discharge Amgen's duty of showing by a preponderance of the evidence that HMR4396 has glycosylation which differs from that of human urinary EPO." Id. at 127, 57 USPQ2d at 1490. However, the court also credited evidence that indicated two uEPO preparations produced from the same batch of starting materials could nevertheless have different glycosylation patterns. Id. at 129, 57 USPQ2d at 1492 ("[A] skilled artisan in 1984 would have understood that urinary erythropoietin samples obtained using different purification

methods could have different glycosylation. As a result, the glycosylation of human urinary erythropoietin was in 1984, and continues to be, a moving target."). Consequently, because the district court concluded that the patent failed to identify a single standard by which the "difference" could be measured, it held that TKT did not infringe and the '933 patent was invalid for failure to satisfy 35 U.S.C. § 112:

> The claim language of the '933 patent, however, presupposes that the glycosylation of urinary erythropoietin is a fixed, identifiable marker against which the glycosylation of recombinant EPOs can be measured. Yet, how can one prove that a recombinant EPO has glycosylation which differs from that of urinary EPO when the glycosylation of urinary EPO itself varies? The Court need not answer this conundrum. All that need be said is that Amgen's showing that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs is insufficient to carry its burden of proving infringement by a preponderance of the evidence that TKT infringes the claim limitation.

Id. at 129, 57 USPQ2d at 1492.

Amgen argues on appeal that an ordinarily skilled artisan in 1984 would have understood, based upon the patent disclosure, that there were two principal processes for purifying uEPO, with the technique taught by Miyake (SDS-PAGE) recognized as the standard. It asserts that it carried its burden of proving infringement because its empirical evidence "unequivocally demonstrated the glycosylation difference between Miyake-purified uEPO and the accused product." But it seems to us that Amgen has failed to address the trenchant question on this issue, i.e., whether uEPO is necessarily glycosylated in the same way. Amgen deals rather cavalierly with the question in both its principal and reply brief, stating summarily that the district court erred and suggesting that the question is unimportant.

By definition, one must know what the glycosylation of uEPO is with certainty before one can determine whether the claimed glycoprotein has a glycosylation different from that of uEPO. In its discussion characterizing recombinant glycoprotein products, the specification of the '933 patent does not direct those of ordinary skill in the art to a standard by which the appropriate

comparison can be made. See '933 patent, col. 28, line 33 - col. 29, line 7. The district court considered evidence that experiments conducted by Amgen in 1984 showed that different urinary EPO preparations had different glycosylation. For example, EPO purified from the urine of a single patient ("Lot 82") using a modified Miyake procedure was shown to have a different glycosylation from other human uEPO (taken from Goldwasser). Amgen, 126 F. Supp. 2d at 129, 57 USPQ2d at 1491-92. And so, even assuming that Amgen is correct that one of ordinary skill in the art would have understood the benchmark test for glycosylation to be Miyake, its contention still fails. As the district court noted, the Miyake article provides a method of purification, but hardly suggests uniformity of glycosylation of the human uEPO studied:

> The 1977 Miyake et al. publication, for example, describes the purification from the same starting material of two homogeneous urinary EPO preparations (Fraction II and Fraction IIIA) that had about the same potency in terms of biological activity. Fractions II and IIIA . . . had different carbohydrate compositions and, therefore, differed from each other in glycosylation. Thus, these two uEPO preparations, though produced by the same procedure (*Miyake) and derived from the same batch of starting material, nonetheless had different glycosylation.

Id. at 129, 57 USPQ2d at 1491; see also Miyake, Purification of Human Erythropoietin, J. Bio. Chem. 5558, 5562 (1977) ("In spite of our finding of similar potency and molecular size, these two preparations [Fractions II and IIIA] must be considered different. The chemical basis for this difference is now being studied."). Amgen fails to controvert or otherwise address this evidence in its cross-appeal.

Under 35 U.S.C. § 112 ¶ 2, a patent applicant is required, at the close of his specification, to "particularly point[] out and distinctly claim[] the subject matter the applicant regards as his invention." The requirement of claim definiteness set out in § 112 ¶ 2 assures that claims in a patent are "sufficiently precise to permit a potential competitor to determine whether or not he is infringing." Morton Int'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993). The standard of indefiniteness is somewhat high; a

claim is not indefinite merely because its scope is not ascertainable from the face of the claims. Cf., e.g., LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc., 275 F.3d 1347, 1359-60, 61 USPQ2d 1193, 1202 (Fed. Cir. 2001) (affirming district court finding that patent was not indefinite, despite testimony from a co-inventor that he did not understand what the claim limitation "substantially completely wetted" meant). Rather, a claim is indefinite under § 112 ¶ 2 if it is "insolubly ambiguous, and no narrowing construction can properly be adopted." Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1375, 60 USPQ2d 1272, 1276 (Fed. Cir. 2001); Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1349, 63 USPQ2d 1769, 1776 (Fed. Cir. 2002) ("It is not our function to rewrite [indefinite] claims to preserve their validity."). Applying these legal maxims to the facts of this case, we agree with the district court that the claims requiring "glycosylation which differs" are invalid for indefiniteness.

We find erroneous, however, its conclusion that invalidity for indefiniteness should be found only in the alternative. A claim is indefinite if, when read in light of the specification, it does not reasonably apprise those skilled in the art of the scope of the invention. See Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1378, 55 UPQ2d 1279, 1282 (Fed. Cir. 2000) (citing Personalized Media Comm., LLC v. ITC, 161 F.3d 696, 705, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998)). So it is here. Recognizing that it was faced with a "conundrum" regarding claim construction, the court held that the patent was not infringed because Amgen could not meet its burden simply by showing "that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs." Amgen, 126 F. Supp. 2d at 129, 57 USPQ2d at 1492. That the court recognized that one of ordinary skill in the art would have been faced with this "conundrum" should have ended the inquiry, for such ambiguity in claim scope is at the heart of the definiteness requirement of 35 U.S.C. § 112 ¶ 2. One cannot logically determine whether an accused product comes within the bounds of a claim of unascertainable scope. Accordingly, the

finding that TKT does not infringe the '933 patent is vacated and the finding that the '933 patent is invalid under § 112 is affirmed.

B. The '080 Patent

Claims 2-4 of the '080 patent are at issue:

> 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.

The critical limitation of the asserted claims in the '080 patent is the requirement that the erythropoietin glycoprotein "comprise[] the mature erythropoietin amino acid sequence of Fig. 6." The court construed the claim term "mature erythropoietin amino acid sequence of Figure 6" that appears in claims 4 and 6 of the '698 patent and claims 2 and 4 of the '080 patent. The dispute here arises out of a mistake in the specification. At the time the patent was drafted, it was believed that the sequence included 166 amino acids, and this belief is depicted in Figure 6. In fact, later research demonstrated that the full sequence was actually 165 amino acids; the last (arginine) is actually cleaved off prior to the protein's secretion from the cell. Amgen argued that the reference to Figure 6 was irrelevant, even if the figure had too many amino acids, because it still showed the "mature [i.e., 165] erythropoietin amino acid sequence." TKT argued that the reference to Figure 6 required the term to be construed as depicted in Figure 6, and thus with 166 amino acids. Following trial,[12] the court adopted TKT's proposal, relying on what it

[12] The court declined to rule on this issue at the Markman hearing, instead choosing to take the matter under advisement. See 126 F. Supp. 2d at 87, 57 USPQ2d at 1459.

considered key language in the specification supporting that construction: "Fig. 6 thus serves to identify the primary structural conformation (amino acid) sequence of mature human EPO as including 166 specified amino acid residues . . . ." '080 patent, col. 12, lines 3-5. Amgen, 126 F. Supp. 2d at 86-87, 57 USPQ2d at 1459.

In total, Figure 6 consists of five separate figures denominated Figs. 6A through 6E, which collectively disclose the sequence of human genomic EPO DNA and the encoded EPO. The detailed description in the '080 patent indicates that the specificity of Figure 6 is not to be lightly disregarded:

> Fig. 6 thus serves to identify the primary structural conformation (amino acid sequences) of mature human EPO as including 166 specified amino acid residues (estimate M.W.=18,399). Also revealed in the Figure is the DNA sequence coding for a 27 residue leader sequence along with 5' and 3' DNA sequences which may be significant to promoter/operator functions of the human gene operon. Sites for potential glycosylation of the mature human EPO polypeptide are designated in the Figure by asterisks. It is worthy of note that the specific amino acid sequence of Fig. 6 likely constitutes that of a naturally occurring allelic form of human erythropoietin. Support for this position is found in the results of continued efforts at sequencing of urinary isolates of human erythropoietin which provided the finding that a significant number of erythropoietin molecules therein have a methionine at residue 126 as opposed to a serine as shown in the Figure.

'080 patent, col. 21, lines 29-40.

When the district court revisited the "Figure 6" issue, it concluded that the language of the claims, read in conjunction with the portion of the specification excerpted above, clearly identified the mature erythropoietin amino acid sequence as exactly depicted in Figure 6. In so doing, the court expressly rejected Amgen's contention that the claim should be read as covering the mature amino acid sequence, of erythropoietin, whatever its number of amino acids. Amgen, 126 F. Supp. 2d at 100, 57 USPQ2d at 1470 ("Had Amgen claimed only 'the mature erythropoietin amino acid sequence' without associating or linking that amino acid sequence to Figure 6 its argument that its claims cover whatever sequence (whether it contained 165 or 166

amino acids) is ultimately secreted by the cell might have more momentum."). The district court therefore found at the close of Amgen's case that HMR4396 does not literally infringe the asserted claims of the '080 patent.

The issue of infringement under the doctrine of equivalents was much closer, and likewise centered on the "Figure 6" limitation.[13] The district court concluded that Amgen had proven by a preponderance of the evidence that the 165 amino acid sequence satisfied the function-way-result test, crediting in particular the testimony of Dr. Lodish that TKT's missing arginine residue (the 166th amino acid appearing in Figure 6) does not affect the in vivo biological activity of its EPO product. Id. at 133, 57 USPQ2d at 1495. In reaching its conclusion, the court rejected TKT's argument that Amgen was not entitled to any range of equivalents under Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki, 234 F.3d 558, 566, 56 USPQ2d 1865, 1870 (Fed. Cir. 2000), because during prosecution it had narrowed the scope of the claim for reasons related to patentability. The parties have cross-appealed on this patent, with Amgen asserting that the district court erred by finding no literal infringement and TKT continuing to press its estoppel theory as a basis for denying any range of equivalents.

Naturally, Amgen continues to focus on the "mature" portion of the relevant claim limitations to support its argument that the trial court erred by finding no literal infringement. According to Amgen, the practical result of the trial court's conclusion is to read out from the claims the preferred embodiment of the invention because the specification makes clear that "mature" human EPO is that form which circulates in the blood, i.e., the 165 amino acid form that

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[13] The district court held that every other limitation of the asserted claims in the '698 patent were met literally by the accused product/process. Amgen, 126 F. Supp. 2d at 132-33, 57 USPQ2d at 1493. Thus, whether equivalent infringement occurred turned on whether the "Figure 6" limitation was equivalently met.

has already been secreted. This argument strains reason to its breaking point; our reading of the patent, like the district court's, will support no such interpretation.

Amgen's argument is based upon a misconstruction of the term "including" that evinces a misunderstanding of the plain meaning of that term, as well as the term "comprise," which appears in the '080 patent claims.[14] "Comprising is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1633 (Fed. Cir. 1997). The word "include" means the same thing. See Hewlett-Packard Co. v. Repeat-O-Type Stencil Mfg. Corp., Inc., 123 F.3d 1445, 1451, 43 USPQ2d 1650, 1655 (Fed. Cir. 1997) ("The claim term 'including' is synonymous with 'comprising,' thereby permitting the inclusion of unnamed components."); see also Webster's II New Riverside University Dictionary 619 (1984) ("include: 1. To have or take in as a part or member: CONTAIN; 2. To put into a group class, or total."). Thus, a claim reciting "a widget comprising A and B," for example, would be infringed by any widget containing A and B, no matter that C, D, or E might be present.

If, then, as the specification states, "the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues," it is simply illogical for Amgen to argue that that means anything other than, at minimum, the 166 amino acids shown in Figure 6. This is verified by the fact that '080 claims 2 and 3 claim an erythropoietin glycoprotein "compris[ing] the mature erythropoietin amino acid sequence of Fig.

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[14] Amgen argues: "The specification describes the mature amino acid sequence of human EPO as 'including' -- not 'limited to' -- the 1-166 sequence. Properly construed, Lin's claimed sequence -- the mature sequence -- includes the fully processed form of any glycoprotein having the Figure 6 sequence. That includes both the 1-165 and the 1-166 amino acid sequences of Figure 6. Only this construction affords 'mature' its proper meaning, and includes Lin's preferred embodiment."

6 . . . ." Again, read properly in light of the term "comprising," this means that the claimed glycoprotein must have -- at minimum -- all 166 amino acids shown in Figure 6.

Turning to the finding of infringement under the doctrine of equivalents, TKT asserts that Amgen should be estopped from obtaining such coverage under Festo. Specifically, TKT alleges that the "mature amino acid sequence of Figure 6" limitation that appears in the '080 patent was added to overcome a double-patenting rejection, and therefore constitutes an amendment related to patentability. We agree.

The district court correctly found that the amendment, although voluntary, was made to avoid a "same invention" double patenting rejection, Amgen, 126 F. Supp. 2d at 135, 57 USPQ2d at 1496, and although the Supreme Court reversed our decision in Festo and rejected the notion of an absolute bar to the doctrine of equivalents, it agreed with our holding "that a narrowing amendment to satisfy any requirement of the Patent Act may give rise to an estoppel." Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki, 535 U.S. 722, 122 S. Ct. 1831, 1839 (2002). Contrary to the district court's conclusion, "'[s]ame invention' double patenting is based upon 35 U.S.C. § 101, which states that an inventor may obtain 'a patent' for an invention." In re Lonardo, 119 F.3d 960, 965, 43 USPQ2d 1262, 1266 (Fed. Cir. 1997) (emphasis added). Therefore, the district court's finding of equivalent infringement of the '080 patent is vacated and remanded for an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel. Festo, 122 S. Ct. at 1839.

C. The '698 Patent

The '698 patent is directed generally to a process for producing a glycosylated erythropoietin polypeptide. Claims 4-9 are at issue. Independent claims 4 and 6 read as follows:

> 4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells
>
> 6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

Infringement of dependent claims 5 and 7-9 rises or falls with the analysis that applies to independent claims 4 and 6.[15] The phrase “operatively linked” appears in claim 4 of the '698 patent, and is related by dependency to claims 5 and 9. According to the district court, the phrase relates to the relationship between promoter DNA and the DNA that is transcribed downstream from the promoter DNA. Amgen contended that the phrase means "positioned such that it provides for initiation of transcription of a gene." TKT argued that the term means positioned adjacent “to the DNA encoding EPO in a way that maintains the capability to initiate transcription of EPO DNA." In other words, Amgen argued that the words "operatively linked" imposed no spatial restriction, whereas TKT contended that because the patent allegedly taught placing the promoter DNA immediately adjacent to the DNA encoding EPO, the term

[15] Claim 5 claims “[t]he process of claim 4 wherein said promoter DNA is viral promoter DNA.” Claim 7 claims “[th]e process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA.” Claim 8 claims “[t]he process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.” And claim 9 claims “[t]he process according to claims 2, 4 and 6 wherein said cells are mammalian cells.”

"operatively linked" ought be limited by location. The district court held that the term "operatively linked" means "the promoter DNA is linked to the EPO DNA is such a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." Amgen, 126 F. Supp. 2d at 90, 57 USPQ2d at 1462.

The district court granted TKT summary judgment of non-infringement of independent claims 4 and 6 (and hence dependent claims 5 and 7-9) of the '698 patent because it found that Amgen had failed to carry its Rule 52(c) burden. Id. at 102, 57 USPQ2d at 1471. Amgen assails this conclusion as not in accordance with law, inasmuch as the differences considered dispositive by the district court are not claimed and thus have no bearing on a proper infringement analysis. In fact, according to Amgen, the district court neglected to identify any limitation of the '698 patent that the accused process fails to literally meet, and also failed to explain why, in the absence of literal infringement, those limitations were not otherwise equivalently met. We agree with Amgen, and therefore conclude vacatur is appropriate.

The district court properly recognized that the infringement analysis of process claims is necessarily different from that for product claims. See id. at 102, 57 USPQ2d at 1471 ("The process patent gives notice to competitors that the steps described therein are not to be repeated to achieve the same result. Thus, whereas in the product patent context, differences in process are meaningless, here, in the process patent context, these differences mean everything."). But after a correct discussion of the differences in the infringement analysis, the court eschewed the cardinal principle that the accused device must be compared to the claims rather than to a preferred or commercial embodiment. Id. ("Based on . . . the many differences between Amgen's and TKT's processes . . . Amgen's proof of infringement on the '698 patent [is] insufficient . . . .") (emphasis added).

For example, the court concluded that a fundamental distinction between the respective processes was that TKT employs homologous rather than heterologous recombination, whereas "[i]n order to make EPOGEN®, Amgen transfects [CHO] cells with a vector that contains both viral promoter DNA and the human EPO gene." Id. This clear reference to the preferred embodiment of Example 10, which the district court considered "the process most heavily relied upon by Amgen in its patent," id. at 103, 57 USPQ2d at 1472, misses the point that none of the claims at issue contain such a limitation. And apart from the limitations of the asserted claims, the differences in the two processes are wholly irrelevant to the infringement analysis.

The district court likewise found material the fact that TKT places its promoter and enhancer farther upstream than does Amgen. In light of the court's claim construction, however, it would seem TKT satisfies the "operatively linked" limitation, as there is no question that TKT's promoter causes its intended functional effect. In any event, the trial court once again compared the accused process by reference to an example rather than the claimed process:

> As explained in Example 7 and illustrated in Figure 4, Amgen created the vector by cleaving, with BstEII restriction endonucelases . . . 'at a position which is 44 base pairs 5' to the initiating ATG coding for the pre-peptide and approximately 680 base pairs 3' to the HindIII restriction site' . . . . TKT's process has within the DNA sequence upstream of the codons that express the EPO polypeptide several ATG sites . . . . The court finds that such a process is sufficiently different from that encompassed by Amgen's invention that judgment of non-infringement should follow.

Id.

Again, this was legal error insofar as the infringement analysis is not tied to the asserted claims. We therefore vacate and remand so that the court may conduct a proper infringement inquiry in the first instance, comparing the accused device to the properly construed claims without limiting their scope to the examples in the specification or other limitations that are not properly a part of claims 4-9.

D. The '422 Patent

Claim 1 of the ’422 patent, the only one in dispute, claims “[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.” In the Markman hearing, Amgen contended the phrase “purified from mammalian cells grown in culture” meant "purified from the in vitro culture in which the mammalian cells have been grown,” whereas TKT argued that it meant "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media." Concluding that TKT's construction would exclude the patent's preferred embodiment (Example 10), the court read the phrase "mammalian cells grown in culture" as a whole to encompass purification techniques from the cells or the cell culture medium. Id. at 88-89, 57 USPQ2d at 1460-61. As indicated earlier, the district court immediately turned to and granted Amgen’s motion for summary judgment of infringement of the ’422 patent at the close of the Markman hearing.

According to the district court, it was clear from the beginning that the accused product met most limitations of claim 1. That HMR4396 was a pharmaceutical composition that contained a therapeutically effective amount of human erythropoietin was plain, in view of the Investigational New Drug Application (“INDA”) that TKT filed with the Food and Drug Administration. Id. at 94-95, 57 USPQ2d at 1465. The district court further concluded that HRM4396 contained “a pharmaceutically acceptable diluent, adjuvant or carrier” in view of the testimony of TKT’s Rule 30(b)(6) designee, who testified that the HRM4396 recovered in bulk from the culturing of human cells was diluted with a phosphate buffer to control the pH and provide a product of desired strength. See id. at 95, 57 USPQ2d at 1466. The sole remaining issue, then, was whether the accused product was “purified from mammalian cells grown in

culture." Rather than taking the utterly untenable position that humans are not mammals, TKT conceded infringement under the court's claim construction. Id. at 95, 57 USPQ2d at 1466.

TKT tries three different tactics on appeal to escape this concession of infringement. First, TKT argues that "mammalian cells," as the phrase is used in the '422 patent, do not include its cells because Amgen excluded the use of human cells to produce human EPO from its invention. Second, TKT asserts that the finding of infringement was in error because the patent specification defines pharmaceutical compositions "as comprising 'polypeptides of the invention'," and HRM4396 is not a "polypeptide of the invention" inasmuch as the invention is "uniquely characterized" by (and hence limited to) exogenous EPO DNA. Finally, TKT challenges the finding of infringement because, it asserts, the intrinsic evidence limits the phrase "purified from mammalian cells grown in culture" to purification that takes place inside the cells, and not -- like TKT -- from the culture media.[16] As infringement of the '422 patent was granted on summary judgment, we review the district court's conclusion de novo, applying the same standard applied by the trial court. Schering Corp. v. Amgen, Inc., 222 F.3d 1347, 1351, 55 USPQ2d 1650, 1653 (Fed. Cir. 2000). Under this standard, we agree with the trial court that a grant of summary judgment of infringement of the '422 patent was warranted.

We cannot accept, for the reasons already stated, TKT's proposed reading of the claim term "mammalian" and its attempt to import the term exogenous into the claims; we therefore reject out of hand the contention that Amgen expressly excluded the use of human cells to express EPO and the use of endogenous DNA from the scope of its invention. Thus, the issue resolves to a narrow one: the accused product, HRM4396, infringes '422 patent claim 1 unless

[16] The basis for this argument is that claim 2 of the '698 patent recites recombinant EPO "isolated from the host cell or the medium of its growth." Therefore, asserts TKT, "Amgen also knew how to claim what it now seeks, but failed to do so."

TKT is correct that the claim limitation "purified from mammalian cells grown in culture" means that the EPO product must be recovered directly from the cell, and not from the culture medium.

At the Markman hearing, Amgen contended the phrase means "purified from the in vitro culture in which the mammalian cells have been grown"; TKT argued that it means "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media. The trial court read the phrase to encompass purification techniques from the cells or the cell culture medium because to do otherwise, it found, would exclude the patent's preferred embodiment as disclosed in Example 10. Amgen, 126 F. Supp. 2d at 88-89, 57 USPQ2d at 1461.

Example 10 "describes expression systems employing Chinese hamster ovary (CHO) $DHFR^-$ cells and the selectable marker, DHFR." '422 patent, col. 25, lines 38-40. As a part of the description, the example discloses that gene amplification in cell culture media is possible to increase productivity of the targeted recombinant EPO product. After describing an example of such a gene amplification system, the specification goes on to state: "The productivity of the EPO producing CHO cell lines described above can be improved by appropriate cell culture techniques. The propagation of mammalian cells in culture generally requires the presence of serum in the growth media. A method for production of erythropoietin from CHO cells in media that does not contain serum greatly facilitates the purification of erythropoietin from the culture media." Id., col. 27, lines 8-14 (emphasis added). We agree with the district court that this disclosure -- the undisputed preferred embodiment of the invention -- contemplates purification of erythropoietin from the culture media. See also '933 patent, col. 28, lines 28-32 ("Mammalian cell expression products may be readily recovered in substantially purified form from culture media using HPLC (C4) employing an ethanol gradient, preferably at pH7." (emphasis added)).

TKT does not challenge the district court's conclusion regarding the disclosure of Example 10. Accordingly, TKT's challenge ultimately must fail unless we read the preferred embodiment out of the daims, but rare is the case where we should or will do so. A claim interpretation that reads out a preferred embodiment "is rarely, if ever, correct and would require highly persuasive evidentiary support." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1578 (Fed. Cir. 1996). We have done so only one time -- in an instance where the patent applicant limited the full scope of the claim language to omit the preferred (and only disclosed) embodiment in order to overcome an examiner's rejection. See Elektra Instr. S.A. v. O.U.R. Scientific Int'l, Inc., 214 F.3d 1302, 1308, 54 USPQ2d 1910, 1914 (Fed. Cir. 2000). The present case lacks the "persuasive evidentiary support" necessary for us to read the claims so as to exclude the preferred embodiment disclosed in Example 10; we therefore decline to do so.

E. The '349 Patent

The '349 patent contains one method claim and six product claims that are drawn generally to types of vertebrate cells grown in culture. At issue are claims 1, 3-4, and 6-7:

> 1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences that control transcription of DNA encoding human erythropoietin.
>
> 3. Vertebrate cells according to claim 1 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.
>
> 4. Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.
>
> 6. Vertebrate cells according to claim 4 capable of producing in excess of 1000 U erythropoietin per 10^6 cells in 48 hours.

7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6.

Each of the claims contain the limitation "non-human DNA sequences that control transcription" that appears in claim 1 of the '349 patent or the limitation "transcriptional control DNA sequences, other than human erythropoietin transcription control sequences" that appears in claim 4 of the '349 patent. Transcription is the process whereby RNA polymerase copies genetic information contained in a DNA nucleotide sequence into an RNA sequence. It is a critical step in the expression of proteins like erythropoietin and is itself controlled by specific DNA sequences. According to the patent, "transcription control sequences" is the collective term for DNA sequences that not only "provide a site for initiation of transcription into mRNA," but also are capable of binding proteins that determine "the frequency (or rate) of transcriptional initiation." '349 patent, col. 2, lines 3-12.

Amgen contended that this phrase means "non-human DNA sequences that are able to initiate or regulate RNA synthesis from EPO DNA." TKT argued that the phrase means "DNA sequences which did not originate in the human genome, which initiate and regulate RNA synthesis of adjacent DNA, and which replace the human EPO transcription control sequences." By including the term "adjacent DNA" in its construction, TKT sought to require the DNA sequences that control transcription to be located in a position adjacent to the gene segment intended to be expressed. Furthermore, TKT contended that in order to "control" transcription, the DNA sequences must both initiate and regulate the transcription of a gene. Amgen objected to the use of "and," preferring a construction that required DNA sequences either to initiate or regulate transcription. Finally, the parties disagreed as to the meaning of "non-human." Amgen

argued that "non-human" means "not part of the human genome," whereas TKT contended it meant "not originating in the human genome."[17]

First, the court rejected TKT's position and concluded that "non-human" DNA sequences are DNA sequences that are "not part of the human genome." The court similarly rejected TKT's "adjacent" language because "no claim term could reasonably be construed to be limiting the transcription control DNA sequences by their location." Finally, the court held that DNA sequences that control transcription are DNA sequences that initiate and regulate the processes of transcription. Amgen, 126 F. Supp. 2d at 88, 57 USPQ2d at 1459-60.

The district court entered judgment of noninfringement for TKT on method claim 7 of the '349 patent under an identical rationale to that used to grant judgment of noninfringement for the method claims of the '698 patent. Id. at 122, 57 USPQ2d at 1486. As we have found the court's analysis with respect to the '698 patent to be legally unsupportable, see supra at 41-42, we likewise vacate the district court's judgment with respect to claim 7 of the '349 patent and remand for further consideration. As to the product claims of the '349 patent, the court held that each of claims 1, 3, 4, and 6 were literally infringed, and further held (alternatively) that claims 3 and 6 were equivalently infringed.[18]

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[17] The importance of this distinction is that, because it is scientifically arguable that viral DNA originates in the human genome, the viral promoter DNA that TKT employs thus might not fall within the meaning of the claim.

[18] We note also that the trial court granted summary judgment of infringement of the product claims of the '349 patent. It modified its summary judgment finding (but reached the same result) with respect to the "controlling transcription" limitation in light of extensive trial testimony. Amgen, 126 F. Supp. 2d at 118, 57 USPQ2d at 1485. Accordingly, unlike the other limitations in the '349 patent, we review the court's conclusion with respect to "controlling transcription" for clear error, even though it comes to us from a grant of summary judgment of infringement. Because TKT has not demonstrated clear error in the trial court's conclusion, we affirm the finding of infringement.

Aside from the challenge, already rejected, to the trial court's construction of the term "vertebrate cells," TKT mounts a weak challenge to these findings of infringement apparently under the reverse doctrine of equivalents.[19]

Under the reverse doctrine of equivalents, an accused product or process that falls within the literal words of a claim nevertheless may not infringe if the product or process "is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way." Graver Tank & Mfg. Co. v. Linde Air Prod. Co., 339 U.S. 605, 608-09, 85 USPQ 328, 330 (1950); see generally Donald S. Chisum, 5A CHISUM ON PATENTS § 18.04 (1999). This doctrine is equitably applied based upon underlying questions of fact, see Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1581, 18 USPQ2d 1001, 1013 (Fed. Cir. 1991), when the accused infringer proves that, despite the asserted claims literally reading on the accused device, "it has been so changed that it is no longer the same invention." Del Mar Avionics, Inc. v. Quinton Instr. Co., 836 F.2d 1320, 1325, 5 USPQ2d 1255, 1259 (Fed. Cir. 1987) (citing Graver Tank, 339 U.S. at 608-09).

We are not persuaded by TKT that this is a case where equity commands a determination of non-infringement despite its product literally falling within the scope of the asserted claims. TKT relies on findings of the district court regarding differences in the way the accused device controls transcription in the '698 patent. It is true, as Amgen candidly admits, that the method by which TKT controls transcription is not identical. Whereas the patent describes placing the promoter DNA in close proximity, or even adjacent, to the EPO leader

[19] The sum total of TKT's challenge to the infringement finding, aside from the "vertebrate" issue, is as follows: "[TKT] also do[es] not use the 'transcription control sequences' of the '349 patent. As the court found, [TKT]'s transcription control sequences are not only structurally different from Amgen's sequences but also function in a different way. Because of those differences in structure and function, [TKT] do[es] not infringe the 'transcription control sequences' limitation in the '349 claims."

peptide, TKT places its promoter further upstream. But again, it is error to conduct infringement analyses in a vacuum, without reference to the claims at issue.

The vertebrate cells of the '349 patent, as claimed, are comprised of non-human DNA sequences that control transcription of DNA encoding human erythropoietin. And "control[ling] transcription of DNA encoding human erythropoietin" simply means initiating and regulating the process of transcription. Amgen, 126 F. Supp. 2d at 88, 57 USPQ2d at 1460. This limitation is met literally because the cytomegalovirus in TKT's R223 cells performs this function, id. at 118, 57 USPQ2d at 1484, notwithstanding TKT's reliance on the court's erroneous analysis of the '698 patent method claims.

IV

Our affirmance of the district court's findings that certain of the asserted claims are infringed is not yet the coup de grâce for TKT; non-frivolous validity issues remain. One of the statutory requirements for patentability is that the invention for which a patent is sought was not known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention by the applicant. See 35 U.S.C. § 102(a). Similarly, one is not entitled to a patent if the subject matter of the invention as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the invention is directed. See id. § 103. TKT relies particularly on two items of prior art that allegedly render certain of the asserted claims anticipated under § 102(a) or obvious under § 103. We discuss each in turn.

A

TKT contends the asserted claims are anticipated by the work of Dr. Eugene Goldwasser ("Goldwasser"). Beginning in 1979-80, Goldwasser conducted a clinical study at the University of Chicago at Illinois in which he obtained a preparation of highly purified erythropoietin derived

from human urine and administered approximately 10,000 units of human urinary EPO to three anemic patients. Amgen, 126 F. Supp. 2d at 111, 57 USPQ2d at 1478. Although this study showed an increase in reticulocyte count in all three patients, and an increase in erythroid cells, plasma iron clearance rate, and red cell mass in at least one patient, Goldwasser admitted that "[t]here was no significant change in hematocrit in any patient." Id. at 111-12, 57 USPQ2d at 1478. And because there was no increase in hematocrit, Goldwasser testified in his deposition that he considered the study a failure. The district court concluded, as a result, that the study could not be invalidating anticipatory prior art: "[A]nother's experiment, imperfect and never perfected will not serve either as an anticipation or as part of the prior art, for it has not served to enrich it." Id. at 112, 57 USPQ2d at 1479 (quoting Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1558, 225 USPQ 26, 33 (Fed. Cir. 1985)).

The district court similarly concluded that Goldwasser did not render the patents obvious. Of paramount importance to the court was the fact that the prior art references, including Goldwasser, lacked Amgen's disclosure of the genetic sequence of EPO and failed to describe any transcription control sequences. Id. at 115, 57 USPQ2d at 1481. The court also considered the secondary factors -- particularly long-felt need and commercial success -- to be of high importance. Id. at 116, 57 USPQ2d at 1482 ("Before the advent of Amgen's product, whether EPO could actually produce a sustainable increase in a patient's hematocrit was not known. Furthermore, Amgen's EPO product, which was the first EPO-containing pharmaceutical composition to obtain FDA approval, has greatly improved the quality of life of chronic renal failure patients throughout the world. As a result, Dr. Lin received widespread public acclaim for his work.").

TKT assigns error to the district court's alleged blind acceptance of Goldwasser's assertion that the test was a failure without considering the contemporaneous testimony of

Goldwasser's collaborator, Dr. Baron, who reported to the Food and Drug Administration in 1984 that evidence of erythroid marrow stimulation was detected. In particular, according to TKT, the court erred by failing to "look[] at the definition of therapeutic effect in the specification." We agree that "therapeutically effective" must be defined in accordance with Markman v. Westview Instruments before this issue can be properly resolved, and we therefore vacate and remand for further proceedings with respect to Goldwasser.

For the Markman hearing in this case, ten terms were "pre-selected" based upon their relationship to Amgen's then-pending motion for summary judgment of infringement. Id. at 81, 57 USPQ2d at 1455. Whether those "pre-selected" terms were chosen by the court or the parties is unclear from the record, but what is clear is that "therapeutically effective" was not among them. And so the district court, assumedly viewing "therapeutically effective" as not in dispute, construed it in its discussion of the Goldwasser reference:

> Such evidence [of, e.g., increased erythroid marrow stimulation] should be outweighed by the fact that the actual production of mature red blood cells was not achieved and, as a result, hematocrit levels were unchanged. Because an increase in hematocrit and hemoglobin levels is the true mark of therapeutic effectiveness, Dr. Goldwasser's study, which revealed only inchoate indicators of red blood cell production, falls far short of anticipating claims requiring a therapeutic amount of human EPO.

Id. at 112, 57 USPQ2d at 1479 (second emphasis ours). Had "therapeutically effective" not been in dispute, no error would arise. A district court may -- indeed, often must -- interpret or define a term in the claims that is not in dispute in order to provide a proper context for the discussion of the terms that are in dispute. See, e.g., DeMarini Sports v. Worth, Inc., 239 F.3d 1314, 1323, 57 USPQ2d 1889, 1893-94 (Fed. Cir. 2001). But here, the term "therapeutically effective" is in dispute because it is central to whether Goldwasser is properly considered prior art. See In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (holding that a non-enabled disclosure will not suffice as § 102 prior art).

Although the endgame in the treatment of chronically anemic patients is to increase the hematocrit, as recognized by the district court, the claim term "therapeutically effective" must be understood in light of the specification of which it is a part. And that specification appears to teach that results in addition to simply an increase in hematocrit can provide effective therapy. See '933 patent, col. 33, lines 19-31 ("[The claimed polypeptide products] are conspicuously suitable for use in erythropoietin therapy procedures . . . to develop any or all of the effects heretofore attributed in vivo to EPO, e.g., stimulation of reticulocyte response . . ., erythrocyte mass changes . . ., and, as indicated in Example 10, increasing hematocrit levels in mammals." (emphasis added)).

Amgen asserts that the district court's construction of "therapeutically effective" is supported by admissions of TKT's experts that the term means "increasing and maintaining the patient's hematocrit to normal or near normal levels." But the relevant question is not whether one of ordinary skill would so understand the term, but whether that term should be limited based upon the express disclosure in the specification. CCS Fitness, 288 F.3d at 1367, 62 USPQ2d at 1662-63 ("[A] claim term will not carry its ordinary meaning if the intrinsic evidence shows that the patentee distinguished that term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the invention."). If the claim term "therapeutically effective" encompasses the patient responses described in the specification, as it appears to us it does, then the Goldwasser study may constitute invalidating prior art under § 102(a) or § 103 even if he did not achieve his intended result. We therefore vacate the trial court's determination that Goldwasser cannot constitute prior art because the study was a failure. Resolution of the issue turns on the construction of the meaning of "therapeutically effective," which the trial court should have an opportunity to construe in the first instance under Markman principles. See Bayer AG v. Biovail Corp., 279 F.3d 1340,

1349, 61 USPQ2d 1675, 1682 (Fed. Cir. 2002). Accordingly, on remand, the court should construe this term and, in light of that construction, should determine whether Goldwasser invalidates any of the asserted patents under 35 U.S.C. §§ 102(a) or 103.[20]

B

A second item of prior art germane to this appeal is United States Patent No. 4,377,513 ("Sugimoto"), issued in March 1983. Sugimoto discloses a process for producing human erythropoietin "characterized by multiplying human lymphoblastoid cells capable of producing human erythropoietin by transplanting said cells into a non-human warm-blooded animal body, or alternatively multiplying said cells by allowing said cells to multiply with a device by which the nutrient body fluid of a non-human warm-blooded animal is supplied to said cells, and allowing the cells multiplied by either of the above multiplication procedures to release human erythropoietin." Sugimoto, col. 1, lines 30-38. Given the similarity of Sugimoto's disclosure to the patents asserted by Amgen, TKT naturally raised Sugimoto as potentially invalidating prior art, even though Sugimoto had been before the examiner.

The district court concluded that Sugimoto was not prior art under 35 U.S.C. § 102(a) because it was not proven to be enabled. Amgen, 126 F. Supp. 2d at 108, 57 USPQ2d at 1476 ("In light of the intense competition that grew out of the race to make human EPO suitable for treatment of chronic anemia, one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race."). On appeal, TKT argues that the trial court erred in placing on it the burden of proving enablement of Sugimoto, because United States patents --

[20] We note also that on remand when considering obviousness and anticipation issues relating to the '080 and '422 patents the district court should be cognizant of the rule that a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations. General Electric Co. v. Wabash Co., 304 U.S. 364, 373 (1938); Cochrane v. Badische Anilin & Soda Fabrik, 111 U.S. 293, 311 (1884).

even those only asserted as prior art in an invalidity defense -- are presumed enabled under 35 U.S.C. § 282. We agree that prior art patents are presumed enabled, but under authority going beyond § 282.

A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. Long ago our predecessor court recognized that a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to "enable one of skill in the art to reduce the disclosed invention to practice." In re Borst, 345 F.2d 851, 855, 145 USPQ 554, 557 (C.C.P.A. 1962); accord In re Donohue, 766 F.2d at 533, 226 USPQ at 621. Thus, the critical issue here is not whether Sugimoto must be enabled, but rather whether it is the plaintiff or the defendant who bears the burden of proof with respect to that question.

On appeal, Amgen argues that there should be no presumption of enablement in this case because under § 282 courts only presume the claimed subject matter in a patent is enabled. Thus, Amgen argues, because only the unclaimed disclosures of Sugimoto are at issue here, no presumption of enablement should apply. This argument is not relevant, however, because, as reasoned below, we do not only rely on § 282 as the source for a presumption. Instead, relying on our precedent, we hold a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled.

In patent prosecution the examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled or whether or not it is the claimed material (as opposed to the unclaimed disclosures) in that patent that are at issue.[21] In re Sasse, 629 F.2d 675, 681, 207 USPQ 107, 111 (C.C.P.A. 1980)

[21] Additionally, we think it unwise as a matter of policy to force district courts to conduct a mini-trial on the proper claim construction of a prior art patent every time an allegedly anticipating patent is challenged for lack of enablement. As we frequently revisit district courts'

("[W]hen the PTO cited a disclosure which expressly anticipated the present invention . . . the burden was shifted to the applicant. He had to rebut the presumption of the operability of [the prior art patent] by a preponderance of the evidence." (citation omitted)). The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled. Id. We hold that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff. Thus, a court cannot ignore an asserted prior art patent in evaluating a defense of invalidity for anticipation, just because the accused infringer has not proven it enabled. Like the applicant in ex parte prosecution, however, the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and therefore are not pertinent prior art. If a patentee presents evidence of nonenablement that a trial court finds persuasive, the trial court must then exclude that particular prior art patent in any anticipation inquiry, for then the presumption has been overcome.[22] Therefore, it was Amgen who bore the burden of proving the nonenablement of Sugimoto before the district court. TKT did not bear a bear burden of proving enablement.

Turning now to the district court's opinion, we think a fair reading is that the court, at least implicitly, put a burden of proving enablement of Sugimoto on TKT. The court began its analysis of Sugimoto by discussing evidence from Amgen and concluding "one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race [to make human EPO suitable for treating anemia]." Amgen, 126 F. Supp. 2d at 108, 57 USPQ2d at

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determinations in matters of claim construction and validity, we are certainly aware that such a task can occupy a great deal of a court's resources. In any event, because the presumption outlined here does not rely on § 282, we see no reason to impose these burdens on litigants and the district courts.

[22] We note that by logical extension, our reasoning here might also apply to prior art printed publications as well, but as Sugimoto is a patent we need not and do not so decide today.

1476. Proceeding from that standpoint, the court analyzed whether TKT's evidence was sufficient "to counter" this apparent conclusion that Sugimoto was not enabled. Id. at 108-09, 57 USPQ2d at 1476. Next, the court concluded its discussion of the enablement of Sugimoto by stating "TKT provided no evidence adequate to overcome the presumption that the Patent Office correctly rejected the contention that Sugimoto was an anticipating reference." Id. at 109, 57 USPQ2d at 1477. Importantly, only after apparently concluding that Sugimoto was not enabled did the district court discuss whether Sugimoto contained each and every limitation of any of Amgen's claims. The logical implication being that the court concluded that because TKT had not proven the enablement of Sugimoto, it could not anticipate any of Amgen's claims. In sum, we determine that ultimately, the district court placed the burden of proving the enablement of Sugimoto on TKT.

In addition, looking at the evidence Amgen did present, we cannot conclude the district court properly found Amgen had met any burden that the court did place on it. At trial Amgen's expert, Dr. Erslev, testified that "no one reported using Sugimoto's process to make a pharmaceutical composition of human EPO, nor has any patient ever been treated by any EPO produced by the Sugimoto procedure." Id. at 108, 57 USPQ2d at 1476. The mere fact that no one has so used the Sugimoto process is only minimally probative of non-enablement: a conclusion that no one could have used Sugimoto. Amgen also pointed out that Sugimoto was before the patent examiner during the prosecution of Amgen's patents. Id. While this was true, Sugimoto's non-enablement was only one of several arguments Amgen presented to overcome a rejection during prosecution and the examiner did not state his agreement with this position when he allowed the patent. Because we cannot assume the acceptance of every argument presented during prosecution, the mere fact this argument was made is also only minimally

probative of the enablement of Sugimoto. In sum, the evidence presented by Amgen was insufficient to meet the burden Amgen apparently was assigned.

We must therefore conclude that to the extent it placed a burden on TKT the district court committed error. However, we hold this error to be, for the most part, harmless. After analyzing enablement and apparently finding the relevant unclaimed disclosures of Sugimoto nonenabled, the court nevertheless conducted a full anticipation analysis. Indeed, the district court performed a detailed analysis of each piece of anticipating prior art -- including Sugimoto -- asserted against each of Amgen's claims. Id. at 109-10, 57 USPQ2d at 1477. From this analysis the court found that "none of the cited references disclose [sic] each and every limitation of any of Amgen's individual claims." Id. at 109, 57 USPQ2d at 1477. It does not appear that TKT has argued this alternative finding was clear error. However, we do not rest on waiver, but affirm the district court's finding that Sugimoto does not anticipate any asserted claims of the '080, '349, or '698 patents because from our review of the evidence and the subsidiary finding of the court, it was not clear error to find in each claim one or more limitations not disclosed in Sugimoto. But given our earlier holdings, we must vacate and remand the finding that Sugimoto does not anticipate claim 1 of the '422 patent. On remand, the district court should consider whether claim 1 of the '422 patent is novel over Sugimoto in light of the court's new definition of "therapeutically effective" and while mindful of the principle that source limitations cannot impart novelty to old compositions.

Our review is not yet finished, however, because it is apparent from the district court's opinion that TKT relied upon Sugimoto to assert invalidity of the patents in suit under both § 102 and § 103. In its obviousness inquiry, the district court disregarded Sugimoto because it concluded it was not enabled. It recognized, however, the important and potentially dispositive role that Sugimoto would have otherwise played in the obviousness analysis:

> Had the court concluded otherwise [i.e., that Sugimoto was enabled], the Sugimoto patent would go a long way toward proving TKT's obviousness defense. As explained above, Sugimoto disclosed EPO-producing fused cells and advised that (1) conventional techniques can be utilized to achieve purification and (2) the human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Thus, the patent itself suggested combining its invention with prior art sources relating to both purification and therapeutic delivery. Provided that one of ordinary skill in the art could actually make the EPO-producing cells described in the Sugimoto patent, a point on which TKT failed to persuade this court, such a combination of prior art materials might render invalid the pharmaceutical composition claims of the '933, '080, and '422 patents.

Id. at 114 n.29, 57 USPQ2d at 1480 n.29. Under § 103, however, a reference need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein. See Symbol Tech., Inc. v. Opticon, Inc., 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991); Reading & Bates Constr. Co. v. Baker Energy, 748 F.2d 645, 652, 223 USPQ 1168, 1173 (Fed. Cir. 1984). Therefore, the district court's obviousness holdings with respect to Sugimoto are vacated and remanded. On remand, the district court should reconsider obviousness with respect to Sugimoto, but should do so without reference to whether Sugimoto is enabled, as enablement of the prior art is not a requirement to prove invalidity under § 103.

V

The last issue on appeal is inequitable conduct. TKT raised before the district court essentially three instances of allegedly inequitable activities by the patentee: withholding crucial details regarding the Goldwasser study; withholding certain results of its own experiments that undermined the validity of the '933 patent; and failing to disclose to the Patent and Trademark Office the existence of this litigation. The district court found that TKT had not proven inequitable conduct by clear and convincing evidence, and we have not been persuaded on appeal that a contrary result is compelled. In reaching this conclusion, we need look no further than the district court's determination that TKT's case was doomed because it was bereft of evidence of intentional deception:

> TKT has failed to produce any persuasive evidence that causes the Court to doubt the integrity of the individuals who bore the duty of shepherding the Amgen patent applications through the Patent and Trademark Office, [so] its charge of inequitable conduct utterly fails . . . . TKT has failed to prove by clear and convincing evidence that this [experimental] data was material or that it was withheld with intent to deceive . . . . [And] TKT has not even begun to demonstrate that Amgen representatives possessed an intent to deceive the [PTO] in failing to provide specific notification regarding this litigation . . . . In summary, TKT's proof of inequitable conduct with respect to each of these charges falls short of the mark. Although the directness of Amgen's disclosures varies depending on the particular piece of disputed information, one truth remains the same throughout: Amgen's representatives never intended to deceive the Patent Office. Consequently, a finding of inequitable conduct would be error and the Court does not so find on the complete record.

Id. at 141, 145, 147, 57 USPQ2d at 1500, 1504, 1505.

A patent applicant commits inequitable conduct when, during prosecution of the application, he makes an affirmative representation of a material fact, fails to disclose material information, or submits false material information, and does so with the intent to deceive. Refac Int'l, Ltd. v. Lotus Dev. Corp., 81 F.3d 1576, 1581, 38 USPQ2d 1665, 1669 (Fed. Cir. 1996). As a general principle, materiality and intent are balanced -- a lesser quantum of evidence of intent is necessary when the omission or misrepresentation is highly material, and vice versa. See, e.g., GFI, Inc. v. Franklin Corp., 265 F.3d 1268, 1273, 60 USPQ2d 1141, 1143 (Fed. Cir. 2001). At the same time, however, there must be some threshold showing of intent to be balanced; we will not find inequitable conduct on an evidentiary record that is completely devoid of evidence of the patentee's intent to deceive the PTO. See Allen Eng'g Corp. v. Bartell Indus., Inc., No. 01-1238, 2002 U.S. App. LEXIS 15418, at *33 (Fed. Cir. Aug. 1, 2002) ("Materiality does not presume intent, which is a separate and essential component of inequitable conduct." (quoting Allen Organ Co. v. Kimball Int'l, Inc., 839 F.2d 1556, 1567, 5 USPQ2d 1769, 1778 (Fed. Cir. 1988))).

Here, the district court determined that there was no evidence of intent to deceive, and TKT has directed us to none on appeal. Thus, to conclude the Amgen patents are unenforceable

-- as TKT requests -- we must conclude (1) that the district court clearly erred by failing to find the minimal requisite intent to deceive, and (2) that it abused its discretion in weighing the degree of materiality against the degree of deceptive intent and by not then rendering the patents unenforceable. On the record before us, we decline to do so.

CONCLUSION

We summarize our decision as follows. Affirmed are: the district court's claim construction; its finding that all of the patents in suit are enforceable; its finding that the '933 patent is invalid; and its finding that the '349 (product claims only) and the '422 patents are infringed. We vacate: its finding that the '933 patent was not infringed; several of its validity findings with respect to the '080, the '349, the '422, and the '698 patents; and its infringement findings with respect to the '698 patent and '349 patent claim 7. On remand, the district court should: construe the claim term "therapeutically effective" and then reconsider validity under §§ 102 and 103 in view of Goldwasser; reconsider validity of all asserted claims under § 103 and claim 1 of the '422 patent under § 102 in view of Sugimoto, with Amgen bearing the burden of proof on its non-enablement (for § 102 purposes only); reassess infringement of the accused method by comparing it solely to the limitations of each of the asserted method claims; and reevaluate its finding of infringement under the doctrine of equivalents of the '080 patent, focusing on the application of prosecution history estoppel.

AFFIRMED IN PART, VACATED IN PART, REMANDED.

No costs.

United States Court of Appeals for the Federal Circuit

01-1191, -1218

AMGEN INC.,

Plaintiff-Cross Appellant,

v.

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

Defendants-Appellants.

CLEVENGER, Circuit Judge, dissenting in part.

I join my colleagues' thorough opinion in all respects save one, albeit significant, exception. Because the claims lack meaningful limitations on the structure of the erythropoietin-producing cells, I cannot agree that the district court should have abstained from inquiring fully whether the claims were suspect under the enablement and written description provisions of 35 U.S.C. § 112, ¶ 1.

As described by the specifications of the patents in suit, Amgen in 1984 cloned and sequenced the DNA encoding human erythropoietin (EPO). Amgen then showed that by introducing the cloned EPO DNA (linked to a promoter sequence) into mammalian cells, those cells could be engineered to express high levels of functional human EPO protein. The parties refer to this as "exogenous DNA" expression of EPO. Amgen obtained several patents that cover the use and manipulation of cloned EPO DNA, and these patents, battle-tested through litigation, have been the foundation of Amgen's successful business of manufacturing and selling recombinant EPO. But these patents are not in suit here, and TKT's method for producing EPO

does not rely upon manipulation of cloned EPO DNA or "exogenous DNA" expression technology.

The claims in suit here contain no significant limitations as to how the recombinant EPO is expressed, or as to the structure of the EPO-producing cells, so long as the EPO is "non-naturally occurring" or produced in "vertebrate cells." The central question in this case is therefore whether Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultured vertebrate cells that produce EPO. I think this is a question of some importance. Yet it is a question that the district court simply refused to consider. Although the district court admitted that Amgen's disclosure was limited to exogenous DNA expression, the district court quite clearly and explicitly refused to decide whether the absence of any exogenous DNA limitations rendered the asserted claims vulnerable to the enablement challenge mounted by TKT under section 112. According to the district court, because the asserted claims were to "compositions" rather than "processes," "the specification need teach only one mode of making and using a claimed composition." Amgen Inc. v Hoescht Marion Roussel, Inc., 126 F. Supp. 2d 69, 160, 57 USPQ2d 1449, 1515 (D. Mass. 2001). See also id. at 160, 164 n.57, 57 USPQ2d at 1516, 1518 n.57. Likewise, the district court refused to inquire whether the absence of limitations on the means of EPO expression raised questions of compliance with the written description requirement, holding that such an inquiry was irrelevant to composition claims. Id. at 150-51, 57 USPQ2d at 1508.

With respect to the '080 and '422 patents, which claim "non-naturally occurring" EPO and EPO "purified from mammalian cells grown in culture," the majority, like the district court, essentially passes over the question of whether these limitations—which are essential for patentability of the claims—raise issues of compliance with the enablement and written

description requirements of section 112. The majority holds that patentees are free to decorate their composition claims with source and process limitations without any concern for whether the full scope of those limitations is enabled or described, and that these requirements of section 112 are waived so long as the patentee succeeds in characterizing its daims as "product" claims. Competent patent attorneys should be quick to take advantage of the majority's broad exemption from the disclosure requirements by the appropriate phraseology. Rather than endorse the district court's elevation of form over substance, I would vacate its decision on these issues regarding the '080 and '422 patents, and remand for further consideration in light of the vast scope of the claims in suit for which there appears to be insufficient enabling disclosure or written description.

With particular reference to the '349 patent, which claims not EPO polypeptides but the cells that produce them, I think the district court's abstention from scrutiny under section 112 is even more patent error. The majority focuses on the district court's findings that the invention could readily be practiced in mammalian or vertebrate cells other than the hamster and monkey cells taught by the specification. I agree that TKT has not shown error in these findings. But, as it did for the EPO claims, the district court simply refused to consider whether the absence of any exogenous DNA limitations raised enablement issues, "[b]ecause Amgen is only required to enable skilled artisans to make its claimed product by only one method . . . ." Id. at 164 n.57, 57 USPQ2d at 1518 n.57. For the EPO-secreting cells, the absence of an exogenous DNA limitation is not a failure to limit how the product is made, but a failure to limit the structure of the claimed product itself. A cell, as employed in the patents in suit, is nothing more than a biological machine for making EPO. Even in more predictable arts, one who is first to make a machine is not entitled as a matter of law to claim any or all machines so long as they perform the same function. I would think it uncontroversial that even one who is first to make polymer X or

alloy Y cannot obtain a claim as broad as "A machine that makes polymer X," or "A process that yields alloy Y," without reciting additional limitations that define the structure of the claimed machine or the steps necessary to carry out the claimed process.

Yet that is exactly what the district court and the majority allow the '349 patent to achieve. It claims any or all cultured vertebrate cells that can secrete a defined amount of EPO, with only a single limitation on their structure: that they "compris[e] non-human DNA sequences which control transcription of DNA encoding human erythropoietin," or that they "comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin." This is little more precise than a recitation of "A machine that makes polymer X, wherein the machine comprises means for controlling how much polymer X is made." The specification teaches only a single means by which the use of a transcription control sequence can coax a vertebrate cell to secrete EPO: by transforming that cell with an exogenous expression vector on which the transcription control sequence is linked to cloned EPO DNA. Yet the claims leave this essential aspect of the invention undefined. It is black-letter law that claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure, In re Mayhew, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (CCPA 1976), and that disclosure of one or two species may not enable a broad genus under these circumstances. In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1444-45 (Fed. Cir. 1991). At the very least, the absence of structural limitations in the '349 patent raises questions of its enablement, and I cannot agree that the district court chose correctly by ignoring those questions altogether. We should vacate the district court's judgment that the '349 patent passes enablement muster, and require the court to apply the correct law to the plain facts.

I must also disagree with the majority that the district court's approach was faithful to this court's articulation of the written description requirement of section 112, as expressed in

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998). Eli Lilly articulated two principles of the written description requirement: that in haec verba description of broadly described generic subject matter may not suffice to describe the subject matter of that particular claim, 119 F.3d at 1567, 43 USPQ2d at 1404-05, and that disclosure of a species may not suffice to describe a genus, id. at 1568-69, 43 USPQ2d at 1405-06. The district court followed neither of these principles here, and the majority, dismissing Eli Lilly on the grounds that no undisclosed DNA molecule appears in this case, verges on confining Eli Lilly to its facts.

Nor am I convinced that the district court's approach was faithful to Gentry Gallery. In Gentry, only those claims that included limitations such as "wherein the control means are located on the console" satisfied the written description requirement. Because the specification failed to disclose any location for the controls other than on the console, those claims that lacked such limitations were invalid under § 112, ¶ 1. 134 F.3d at 1479-80, 45 USPQ2d at 1503-04. The question here is similar: whether the claims fail the written description requirement for lack of "exogenous DNA" limitations, because the specification discloses only the exogenous DNA technology that was state of the art in 1984.

Even if we ignore the patents' statement that the claimed EPO molecules are "uniquely characterized by being the product of . . . expression . . . of exogenous DNA sequences" (which of course we cannot), I think the parallels between this case and Gentry Gallery are inescapable. The invalid claims in Gentry recited elements that could readily be found in the text of the specification (a couch, controls, a console), but those claims nonetheless failed the written description requirement because they included no limitations on how those elements were arranged. Likewise, the '349 claims—for which I think it must be conceded that structure of the

EPO-secreting cell is a relevant question—recite particular elements found in the specification (cells, non-human control sequences, EPO-coding DNA), but do not include limitations on the arrangement of those elements, e.g. that the non-human control sequences and coding DNA are present on an exogenous expression vector in the cell. I agree that as a matter of claim interpretation there is no justification for importing an "exogenous DNA" limitation into the claims. But the absence of such limitations must weigh heavily in the section 112 inquiry, else we hold that claims become more resistant to written description challenges the more broadly drafted they are.

While I share my colleagues' admiration for the considerable efforts of the district court in this complicated case, I cannot share their faith that the district court properly and conscientiously applied Eli Lilly and Gentry Gallery, when the district court's opinion is completely devoid of reference either to those cases or to the principles they espouse. If the district court did not focus on the correct law to be applied, then its factual findings merit no deference, and the correct remedy for this omission is to vacate the district court's judgment on this point and remand for further consideration. Our precedent has little value if the district courts may overlook its certain pertinence, if not its plain applicability.