UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LAROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN LAROCHE INC., a New Jersey Corporation, Defendants.	Civil Action No.: 05-12237 WGY

AMGEN INC.'S CLAIMS CONSTRUCTION BRIEF

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I. INTRODUCTION

In response to Defendants' interrogatories, Amgen provided its construction for each claim term in the asserted claims of the patents-in-suit.[1] Many of these claim terms have been thoroughly examined and construed in prior litigations and, as such, their constructions are beyond serious challenge.[2] While Defendants have indicated that they intend to challenge some of Amgen's proposed constructions, for the most part Defendants have declined to identify the terms they intend to challenge or provide their proposed claim constructions.[3]

Based on Amgen's limited understanding of Defendants' positions, Defendants appear to contend that Dr. Lin's claims should be construed to exclude their accused pegylated EPO ("peg-EPO") product. Because Defendants' regulatory submissions to FDA confirm that their accused peg-EPO product contains recombinant human EPO,[4] Defendants apparently contend that Dr. Lin's asserted product and composition claims should be construed to exclude EPO products to

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[1] Amgen timely provided to Defendants its detailed claim construction and infringement chart on January 9, 2007 in response to Defendants' first set of interrogatories. *See generally* Docket No. 252, Exh. C (at Exhibit A therein) (Exhibit A to Amgen's Response to Roche First Set of Interrogatories Nos.1-12, as well as Amgen's Interrogatory Responses were publicly filed with the Court by Defendants as Exhibit C to their January 29, 2007 Motion to Amend Their Answer and Counterclaims).

[2] *See generally Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 69 (D. Mass. 2001), *aff'd in part, rev'd in part, vacated in part*, 314 F.3d 1313 (Fed. Cir. 2003), *on remand*, 339 F. Supp. 2d 202 (D. Mass. 2004), *aff'd in part, rev'd in part, vacated in part*, 457 F.3d 1293 (Fed. Cir. 2006).

[3] Amgen propounded interrogatories in December 2006 seeking Defendants' proposed claim constructions. In response, Defendants provided their construction for only seven terms, asserted that at least 22 categories of terms (comprising 42 separate terms) would require construction, but offered no construction for these terms, stating instead that "Roche's proposed construction of these terms will be forthcoming in Roche's *Markman* brief." *See* Exhibit 13 (non-confidential excerpt from Defendants' February 9, 2007 Suppl. Responses and Objections to Amgen's First Set of Interrogatories (Nos. 1-15)). On February 27, in response to Amgen's repeated request to narrow the issues at *Markman,* Defendants provided additional, but incomplete, constructions of terms previously construed by the Court in the *Amgen v. HMR* litigation. Exhibit 10 (2/27/07 letter from Thomas Fleming to Deborah Fishman). Notably, however, Defendants did not offer any construction for the majority of terms on which they rely to assert that their peg-EPO product does not infringe Amgen's asserted claims.

which any additional molecule has been attached to the sequence of amino acid residues that comprise the protein backbone of EPO. Similarly, even though Defendants use Dr. Lin's claimed processes to produce the recombinant human EPO contained in their peg-EPO product,[5] they apparently contend that Dr. Lin's asserted process claims should be construed to exclude processes that add steps beyond those recited in Dr. Lin's claimed processes, such as Defendants' attachment of a peg molecule to EPO.

But Defendants' arguments find no support in the language of the asserted claims or anywhere else in the intrinsic record. Rather, the intrinsic record demonstrates that Dr. Lin claimed these inventions by reference to the essential structural characteristics recited in the claims, not by reference to the exclusion of other possible structures or characteristics that are not recited in the claims. Defendants' arguments also fly in the face of the fundamental principle that claims are to be construed by reference to the express limitations recited in the claim, not by reference to unstated negative limitations read into the claims.[6] Neither the intrinsic record nor the law support a restrictive reading of Dr. Lin's claims, and Defendants' attempt to construe Dr. Lin's claims to exclude such unrecited structures or steps should be rejected.

Accordingly, Amgen believes that Defendants will raise two central issues for the Court's determination. The first issue is whether the asserted product and composition claims in Dr. Lin's patents should be construed by reference to the essential structural characteristics expressly recited in the claims themselves or, alternatively, by reference to unrecited limitations that Defendants would read into Lin's claims to exclude or preclude the presence of other structural elements, such as the polyethylene glycol that Defendants attach to recombinant human EPO to

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[4] *Please see generally* Docket No. 252, Exh. C at Exhibit A.

[5] *Id.*

[6] *See Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 1350-1351 (Fed. Cir. 2001); *A.B. Dick Co. v. Burroughs Corp.*, 713 F.2d 700, 703 (Fed Cir. 1983);

produce their accused peg-EPO. The second issue is whether Dr. Lin's process claims should be construed to preclude the performance of steps beyond those recited in the claims, such as the pegylation step used by Defendants after they isolate the recombinant human EPO produced by Dr. Lin's claimed process.

II. DR. LIN'S PIONEERING INVENTIONS

The patents-in-suit describe and claim Dr. Fu-Kuen Lin's pioneering EPO inventions. By inventing the means to produce and use human recombinant EPO, Dr. Lin's inventions provided the first – and to date only − therapeutically effective pharmaceutical treatment for millions of patients suffering from debilitating chronic anemia. Recognizing the multitude of inventions disclosed in Dr. Lin's patent applications, the United States Patent and Trademark Office ("Patent Office") issued seven separate patents, each assigned to Amgen. Dr. Lin's patents include claims directed to novel EPO products, pharmaceutical compositions, vertebrate cells that produce high levels of EPO, processes for making recombinant EPO products, and methods of using the claimed EPO products to treat kidney dialysis patients.

Human EPO is produced in the kidneys of healthy adults and secreted into the blood. EPO circulates in the blood until it reaches the bone marrow, where it stimulates the production of red blood cells. Kidney disease can impair the body's ability to produce EPO, resulting in a debilitating chronic anemia. Cancer chemotherapy can also interfere with normal red cell production, and similarly produce a debilitating anemia. For decades prior to Dr. Lin's path-breaking inventions, the medical community searched in vain for a product with the biological properties of EPO to treat patients suffering from severe forms of anemia. Although the medical need for these patients was great, a solution proved elusive.

Prior to Dr. Lin's first patent application, EPO had been identified as a naturally

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Dow Chem. Co. v. Sumitomo Chem. Co., 257 F.3d 1364, 1380-81 (Fed. Cir. 2001).

occurring 34,000 Dalton glycoprotein hormone that was postulated to stimulate the production of red blood cells, as needed, in the bone marrow.[7] As explained in Dr. Lin's patents, a great need existed for a product having the biological activity of stimulating red blood cell production that could be used clinically to treat anemia.[8]

Using the sources and techniques available before Dr. Lin's inventions, scientists had obtained tiny quantities of naturally occurring EPO from sheep plasma or human urine. But none of these preparations of naturally occurring EPO could be produced in sufficient quantity for therapeutic use in treating anemia.[9] Nor did any of these preparations possess the chemical structure required to treat anemia effectively. In particular, Goldwasser deemed the administration of his prior art urinary EPO ("uEPO") preparation to be a "failure" – it appeared to degrade rapidly upon administration, was rapidly cleared from the body, failed to increase red blood cell mass or hematocrit in patients and may, in fact, have been impure and toxic.[10] Prior art attempts to produce human EPO from other sources proved similarly fruitless.[11] A therapeutically effective solution remained elusive: that is, until Dr. Lin made his breakthrough inventions.

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[7] Appendix B at 5:48-52. The prior art disclosed a number of different EPO preparations having different activities and molecular weights based on differences in preparation and methods of detection. *Id.* at 6:60-7:42.

[8] Appendix B ('933 Patent at 6:20-24, 35-38). All citations to the column and line numbers of the specification will be to the '933 patent. Although all six patents share a common specification, citations to the specification in the '933 patent will not precisely track the columns and line numbers of the specifications in the other patents.

[9] Appendix B at 6:60-65.

[10] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d at 112 n.27; *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d at 333-34 (D. Mass. 2004); Exhibit 4 at AM-ITC 01008871 (providing that shortly after uEPO injected into patients, 25% of uEPO molecules degraded into fragments half the size of fully active human EPO); Exhibit 5 at AM-ITC 00952087)(same); Exhibit 6 at AM-ITC 00991063 (Goldwasser observed fragments having a molecular weight of 14 kD while native EPO weighs 34 kD).

[11] Appendix B at 6:60-65, 8:67-9:9.

After years of exacting effort, Dr. Lin succeeded in 1983 in isolating, identifying, and characterizing the DNA sequence that encodes human EPO. Using this initial discovery, between 1983 and 1984, Dr. Lin also deduced the sequence of amino acid residues of human EPO; invented genetically engineered cells that produced recombinant EPO in abundance; used his genetically engineered cells to produce a recombinant human EPO; demonstrated that his recombinant EPO differed from the prior naturally-occurring EPO isolates obtained from human urine; and demonstrated that his recombinantly produced human EPO not only possessed the biological activity of the prior EPO isolates, but also increased hematocrit levels in mammals.

The first step in Dr. Lin's quest for a therapeutic solution was the identification and isolation of the DNA that encodes human EPO. Dr. Lin disclosed this invention in his very first application, filed on December 13, 1983, in which he described the isolation and initial characterization of DNA sequences encoding human EPO.[12]

Another critical step was the elucidation of the sequence of amino acid residues that constitute the primary structure of human EPO. After all, while the DNA sequence for EPO held tremendous scientific significance, it was the protein — not the DNA — that patients around the world desperately needed. Once Dr. Lin obtained and confirmed the correct nucleotide sequence of the DNA encoding human EPO, he used that nucleotide sequence to deduce the sequence of amino acid residues that make up the human EPO polypeptide.[13]

A third important step was the invention of genetically engineered cells that would produce a biologically active and therapeutically effective recombinant EPO glycoprotein, and do so in sufficient quantity for therapeutic use. To achieve this result, host cells needed to be selected and manipulated not only to produce human EPO, but to do so in a form and at a level

[12] *See, e.g.*, Appendix B at Examples 4 and 5, Figure 6.

[13] *See generally* Appendix B at Example 5.

of production that would prove to be therapeutically effective when administered to humans. Dr. Lin's specification discloses how to manipulate a range of host cells, including mammalian cells, bacterial cells, and yeast cells, to produce EPO, and he specifically describes the genetic manipulations, cell types, and culture conditions that combine to produce a therapeutically effective EPO composition.[14]

The natural EPO "promoter"[15] does not promote high levels of transcription,[16] and thus can only produce limited quantities of EPO. In the examples disclosed in the specification, however, Dr. Lin overcame this problem by placing the DNA encoding EPO under the transcriptional control of a non-human promoter − a viral promoter.[17] Likewise, Dr. Lin discloses and teaches in the specification the use of "amplification" techniques to further increase the production of EPO by these cells.[18] Thus, the specification disclosed the first cells capable of continuously producing therapeutically effective amounts of EPO in a cell culture.[19]

Based on these genetic manipulations, Dr. Lin then showed that EPO, an "obligate" glycoprotein,[20] could be recombinantly produced using genetically manipulated cells to achieve a biologically active form of the protein.[21] Before Dr. Lin's disclosure, it was unknown whether any obligate glycoprotein could be expressed in such form in transformed cells grown in

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[14] *See generally* Appendix B at Examples 6, 7, and 10.

[15] A "promoter" is a regulatory site where an enzyme called RNA polymerase binds and interacts to initiate transcription. Appendix B at 2:3-5.

[16] "Transcription" is the first step in gene expression. During transcription, DNA is transcribed into RNA. 1:52-55. RNA polymerase binds to a promoter, separates the two strands of DNA, "reads" the sequence of one of the strands as it moves, and joins RNA nucleotides into a primary RNA transcript based on the underlying DNA sequence. Appendix B at 2:12-15.

[17] Appendix B at 22:19-27, 24:12-14.

[18] Appendix B at 26:19-65, 25:39-45.

[19] Appendix B at 10:42-49.

[20] An "obligate" glycoprotein is a protein whose *in vivo* activity depends on its proper glycosylation.

culture.[22]

But Dr. Lin's inventions went well beyond the discovery of EPO DNA, of EPO protein sequences, and genetically engineered host cells and processes for making biologically active human EPO. In addition, Lin invented novel human EPO products, products that are not only structurally and functionally distinct from the naturally-occurring uEPO isolates that preceded Dr. Lin's inventions, but which also possess the unprecedented and novel ability to correct the anemia of desperately ill patients by elevating their hematocrit levels. Before Dr. Lin, a few scientists possessed minute amounts of therapeutically ineffective uEPO. As a result of Dr. Lin's inventions, the medical profession today possesses therapeutically effective pharmaceutical compositions for treatment of anemia.[23]

In short order, Dr. Lin's inventions revolutionized the treatment of millions of severely anemic patients, virtually eliminating the need for blood transfusions and greatly reducing the chronic fatigue and other complications that accompanied their anemia. In recognition of his discoveries, Dr. Lin received the Pharmaceutical Research and Manufacturers Association Discovery Award — an award presented each year to scientists whose research and development of pharmaceuticals have greatly benefited humankind. In recognition of Amgen's contribution in making EPO therapy a reality for millions of patients throughout the world, the United States awarded Amgen the National Medal of Technology.

In addition, after years of thorough examination and *inter partes* proceedings, the Patent Office granted Dr. Lin seven separate patents on the different inventions made and disclosed in his patent applications. The inventions claimed in Dr. Lin's patents have been subjected to an

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[21] *See* Appendix B at Examples 6-10.

[22] *See*, *e.g.*, Exhibit 7 at AM-ITC-00953219-224 (U.S. Appln. 113,179 File History, 5/26/88 Second Preliminary Amendment (Paper No. 8) at 15-20).

[23] Appendix B at 10:28-41; 28:33-29:7.

unprecedented degree of scrutiny in patent offices and courtrooms around the world, including a District of Massachusetts action resulting in a finding of infringement of Dr. Lin's EPO DNA claims by the same cells now used by Defendants to make their accused peg-EPO product.[24] Time and time again, the validity and enforceability of Dr. Lin's patents have been upheld.[25]

III. THE SEVEN PATENTS AWARDED TO DR. LIN FOR HIS INVENTIONS

Dr. Lin filed his first U.S. patent application directed to some of his inventions on December 13, 1983. Over the course of the next year, Dr. Lin filed three additional patent applications describing and claiming additional inventions, culminating in a continuation-in-part application filed on November 30, 1984. All of the patents-in-suit originate from these applications and share the same specification as the November 30 application. However, because the November 30 application described and claimed at least six related, but distinct, classes of invention, the Patent Office issued a "restriction requirement,"[26] requiring Amgen to file and prosecute a separate application for each distinct class of invention.

The first patent issued to Dr. Lin was U.S. Patent No. 4,703,008. The '008 patent claimed inventions directed to a purified and isolated DNA encoding EPO and shares the same specification as the later issued patents-in-suit. Because the '008 patent expired in late 2004, it is not at issue in this case. Nonetheless, in a litigation involving multiple validity challenges by Defendants' licensor and predecessors-in-interest (the "GI/Chugai litigation"), this Court (as affirmed by the Federal Circuit) previously determined that some claim of the '008 patent were valid,[27] and that the cells made and used by Genetics Institute to produce recombinant EPO

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[24] *See, e.g.*, *Amgen Inc. v. Chugai Pharm. Co.*, 13 U.S.P.Q.2d 1737 (D. Mass. 1989) (Saris, M.J.), *aff'd in part, rev'd in part*, 927 F.2d 1200 (Fed. Cir. 1991).

[25] *See supra* n. 1.

[26] *See, e.g.*, Exhibit 1 at AM-ITC 00901994-995 (U.S. Appln. 675,298 File History, 7/3/86 Office Action at 2-3).

[27] *See, e.g.*, *Amgen Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d at 1219 (affirming finding that

(which are the same cells now used by Defendants to produce the recombinant EPO contained in peg-EPO),[28] infringed claims 4 and 6 of the '008 patent.[29]

At the same time as the GI/Chugai litigation, Dr. Lin's inventions were also being contested in the Patent Office in three extended interference proceedings involving Defendants' licensor, GI, to determine whether Dr. Lin was the first to invent the subject matter disclosed and claimed in his patent applications. During these proceedings, all further examination of Dr. Lin's patents was suspended by the Patent Office until the interference proceedings were resolved. Ultimately, once the interferences and follow-on litigation were resolved in Amgen's favor in 1992 and 1995, the examination of Dr. Lin's remaining applications continued, culminating with the issuance of the six patents-in-suit between 1995 and 1999.[30]

The six patents-in-suit are U.S. Patent Nos. 5,441,868 (the '868 patent), 5,547,933 (the '933 patent), 5,618,698 (the '698 patent), 5,621,080 (the '080 patent), 5,756,349 (the '349 patent) and 5,955,422 (the '422 patent).[31] In this suit, Amgen seeks a declaratory judgment that the importation, sale and use of Defendants' peg-EPO product in the United States will infringe

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'008 claims 2, 4, and 6 are valid and enforceable).

[28] *Compare* Exhibit 2 at AM-ITC-00166687 (*Amgen v. Chugai* Trial Exhibit PX19 at A120084 providing that "EPO expressed in ***DN2-3α3*** cells was prepared exactly as described for the production lots." (emphasis added)), *with* Docket No. 252, Exh. C at Exhibit A, page 8, *citing* ITC-R-BLA-00004667 (excerpt from Defendants' Biologics License Application ("BLA") providing that "Epoetin beta (EPO) is produced by the recombinant CHO cell line ***DN2-3α3*** in suspension culture." (emphasis added)).

[29] *Amgen Inc. v. Chugai Pharm.*, 927 F.2d at 1219.

[30] Notwithstanding the Patent Office's grant of six patents, Amgen disclaimed the terminal end of any patent term for patents directed to similar subject matter. Thus, Amgen's claims to processes for making EPO products ('868 and '698 claims), claims to novel EPO products and pharmaceutical compositions comprising these products and their use to treat patients ('933, '080, and '422 claims), and claims directed to novel vertebrate cells and processes using those cells (the '349 claims) will expire 2012, 2013 and 2015, respectively.

[31] All but the '868 Patent were at issue in the *Amgen Inc. v. Hoechst Marion Roussel, Inc.* litigation ("Amgen v. HMR") (the '868 Patent is directed to processes for making a "glycosylated erythropoietin polypeptide" using "exogenous" EPO DNA).

Amgen's patents, and that the process used by Defendants to produce their imported peg-EPO product also infringe Amgen's patents.[32]

IV. LEGAL PRINCIPLES OF CLAIM CONSTRUCTION

Claim construction is a question of law that is reviewed *de novo* on appeal.[33] In reviewing a court's claim construction, the Federal Circuit has adopted a framework that favors intrinsic evidence, including the claims, specification, and prosecution history, over extrinsic evidence, such as expert testimony.[34]

Under this framework, the first step is to look to the words of the claims themselves, both asserted and unasserted, to define the patented inventions.[35] The words of the claim are "generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention . . . ."[36] However, the "[c]laims must be read in view of the specification, of which they are a part."[37] As set forth in the Federal Circuit's *en banc* decision in *Phillips*, the specification is "the primary

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[32] In their documents, Defendants refer to their peg-EPO product as PEG-EPO, peg-epoetin beta, RO0503821, CERA, and MIRCERA.

[33] *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (*en banc*); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Amgen is challenging the Federal Circuit's application of this standard of review in a petition for certiorari to the Supreme Court on the ground that claim construction is a mixed question of law and fact that requires a measure of deference by an appellate court to the claim construction of a district court.

[34] *Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) (*en banc*) ("We have viewed extrinsic evidence in general as less reliable than the patent and its prosecution history in determining how to read claim terms . . . ."); *Vitronics*, 90 F.3d at 1583 (holding that it is improper to rely on extrinsic evidence when analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term).

[35] *Vitronics*, 90 F.3d at 1582; *Masco Corp. v. United States*, 303 F.3d 1316, 1329 (Fed. Cir. 2002); *see also Phillips*, 415 F.3d at 1312 ("It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'") (citations omitted); *id.* at 1314 ("Other claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment as to the meaning of a claim term.").

[36] *Phillips*, 415 F.3d at 1312-13 (citing numerous cases).

[37] *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*) (citing

basis" for construing claims because it is "the best source for understanding a technical term in the specification from which it arose . . . ."[38]

This is in part because the specification may "reveal a special definition given to a claim term by the patentee. . . . ."[39] Such lexicography, when it occurs, requires a clear and express statement or manifestation by the patentee that he or she intends to use a term of art in a manner other than its ordinary and customary meaning to those skilled in the art.[40] The specification may also act as a dictionary when it explicitly defines terms used in the claims.[41] By expressly defining a claim term, a patentee may specifically disavow a meaning that would otherwise comport with the ordinary and customary meaning of the term.[42]

Notwithstanding this emphasis on the specification, the Federal Circuit, in its *en banc* decision in *Phillips*, explicitly recognized "the danger of reading limitations from the specification into the claim,"[43] noting that the "distinction between using the specification to interpret the meaning of a claim and importing limitations from the specification into the claim can be a difficult one to apply in practice."[44] To avoid importing limitations from the specification into the claims, the court must focus its inquiry on "understanding how a person of

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Autogiro Co. of Am. v. United States, 384 F.2d 391, 399 (Ct. Cl. 1967)).

[38] *Phillips*, 415 F.3d at 1315 (quoting *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985)).

[39] *Id.* at 1316.

[40] *Markman*, 52 F.3d at 980 ("As we have often stated, a patentee is free to be his own lexicographer. The caveat is that any special definition given to a word must be clearly defined in the specification.") (citation omitted); *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996) ("A technical term used in a patent document is interpreted as having the meaning that it would be given by persons experienced in the field of the invention, unless it is apparent from the patent and the prosecution history that the inventor used the term with a different meaning."); *Vitronics*, 90 F.3d at 1582.

[41] *Vitronics*, 90 F.3d at 1582.

[42] *Phillips*, 415 F.3d at 1316.

[43] *Id.* at 1323.

ordinary skill in the art would understand the claim terms" in light of the specification.[45] This principle of avoiding importing limitations has been long-recognized by the Federal Circuit. As articulated in *Amstar v. Envirotech*, in the context of deciding infringement the presence of an unrecited structure or step is "simply and totally irrelevant" to infringement.[46]

In addition to the specification, a review of the prosecution history is also of "primary significance."[47] The prosecution history includes both the complete record of the proceedings before the Patent and Trademark Office and the prior art cited during examination of the patent.[48] The prosecution history "limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution."[49] As with the specification, a disclaimer in the prosecution history must be express.[50]

V. CONSTRUCTION OF DR. LIN'S PRODUCT AND PROCESS CLAIMS

A. DR. LIN'S PRODUCT CLAIMS DO NOT EXCLUDE UNRECITED STRUCTURE

Eight of the asserted claims in the patents-in-suit claim EPO glycoprotein products and pharmaceutical compositions containing these products. For purposes of this brief, Amgen will refer to six representative product claims:[51]

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[44] *Id.*

[45] *Id*. Keeping in mind that "the purposes of the specification are to teach and enable those of skill in the art to make and use the invention and to provide a best mode for doing so," the Federal Circuit has warned that "persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the embodiments." *Id.*

[46] *Amstar Corp. v. Envirotech Corp.*, 730 F.2d at 1482 (Fed. Cir. 1984); *see also Amgen v. Hoechst Marion Roussel*, 314 F.3d at 1347.

[47] *Markman*, 52 F.3d at 980 ("This 'undisputed public record' of proceedings in the Patent and Trademark Office is of primary significance in understanding the claims."); *see also Vitronics*, 90 F.3d at 1582.

[48] *Phillips*, 415 F.3d at 1317 (citing *Autogiro*, 384 F.2d at 399).

[49] *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995).

[50] *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1367 (Fed. Cir. 2003).

[51] '080 claims 3 and 4 are the remaining two "product" claims at issue in this litigation. Unlike

> '933 claim 3: A non-naturally occurring ***glycoprotein product*** of the expression in a mammalian host cell of an exogenous DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.
>
> '933 claim 7: The ***glycoprotein product*** according to claim 3, 4, 5, or 6 wherein the host cell is a non-human mammalian cell.
>
> '933 claim 8: The ***glycoprotein product*** according to claim 7 wherein the non-human mammalian cell is a CHO cell.
>
> '933 claim 9: A pharmaceutical composition comprising an effective amount 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.
>
> '933 claim 12: A pharmaceutical composition comprising an effective amount of ***glycoprotein product*** effective for erythropoietin therapy according to claim 7 and pharmaceutically acceptable diluent, adjuvant or carrier.
>
> '422 claim 1: A pharmaceutical composition comprising a therapeutically effective amount of ***human erythropoietin*** and a pharmaceutically acceptable diluent, adjuvant to carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

Claims 3, 7 and 8 of Lin's '933 patent are directed to a "non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence encoding human erythropoietin." In each of these claims, the essential structural attributes of the claimed glycoprotein product are defined by reference to the DNA and cells used to produce the product. In contrast, the essential structural attributes of the "non-naturally occurring erythropoietin glycoprotein" of '080 claim 3 are defined by reference to a sequence of amino acid residues depicted in Figure 6 of the specification and their distinct glycosylation, rather than the DNA and cells used to produce the product. Both the asserted '933 and '080 claims also include the limitation of "having the in vivo biological activity of causing bone marrow cells to increase

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the asserted '933 and '422 patent claims, which Amgen asserts Defendants infringe literally, Amgen asserts that Defendants infringe the '080 claims under the doctrine of equivalents. Because Amgen is currently seeking certiorari to appeal the scope of equivalents that can be properly asserted under the '080 claims, this Brief will not specifically address construction of the '080 claims.

production of reticulocytes and red blood cells." The required expression in a mammalian cell from a DNA sequence encoding human erythropoietin imparts essential structural characteristics that must be present in the "glycoprotein product" of the asserted '933 claims, and the recited biological activity is an essential functional requirement that the claimed "glycoprotein product" must also satisfy.[52]

Claims 9 and 12 of the '933 patent, claim 1 of the '422 patent, and claim 4 of the '080 patent are each directed to pharmaceutical compositions – compositions that are suitable (*e.g.*, safe) for administration to patients.[53] Each differs from the other by the essential structural characteristics that comprise its active ingredient. For example, in '933 claims 9 and 12 the product's essential structural characteristics are specified by the process and cells recited in the claims from which claims 9 and 12 depend. In '080 claim 4 the essential structural characteristics are the sequence of amino acid residues and corresponding glycosylation recited in the claims from which it depends. In '422 claim 1, "human erythropoietin … purified from mammalian cells grown in culture" recites the essential structural characteristics of the claimed pharmaceutical composition.

Terms Likely To Be In Dispute. Based on the parties' communications and interrogatory responses to date, it appears that the following claim terms should be construed by the Court:[54]

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[52] Appendix B at 10:34-40.

[53] *See generally* Appendix B at 12:1-7 (describing pharmaceutical compositions generally); Appendix B at 33:39-43 (describing the pharmaceutical compositions as being free of pyrogens and natural inhibitory substances).

[54] *See* Notes 1 and 3, *supra*. In this brief, Amgen addresses the claim terms it believes require construction by the Court in this litigation. In Appendix A, Amgen provides, for each of the remaining terms in each of the asserted claims of the patents-in-suit, the claim construction that it previously provided to Defendants in response to Defendants' Interrogatory No. 1, and the supporting citations to the intrinsic record.

Claim Term	Patent Claim
Terms directed to the structural characteristics of the claimed product or process	
"erythropoietin"	'349 claim 7 (as it depends on claim 1)
"human erythropoietin"	'422 claim 1
"glycosylated erythropoietin polypeptide" and "said glycosylated erythropoietin polypeptide" (contained in the same claim)"	'868 claims 1 and 2, '698 claims 4-9
"non-naturally occurring human erythropoietin glycoprotein product of the expression of a mammalian host cell" and "non-naturally occurring human glycoprotein product" (as contained in dependent claims)	'933 claims 3, 7-9, 11-12, and 14

Based on Defendants' pleadings and discovery responses, Amgen anticipates that Defendants will assert that Amgen's glycoprotein and EPO product claims exclude EPO products to which molecules like polyethylene glycol ("peg") have been attached to EPO. Based on their responses to Amgen's interrogatories, it appears that Defendants' will argue that the recitation of "erythropoietin" or "human erythropoietin" in the asserted claims — such as "human erythropoietin" in "non-naturally occurring human erythropoietin glycoprotein" (*e.g.* '933 claim 4) or "human erythropoietin" in '422 claim 1 − requires the exclusion of any structure other than or in addition to the structure of erythropoietin. In addition, Defendants will apparently argue that the "source" or "process" limitations in certain claims requires the exclusion of any additional step performed on such products, including the attachment of additional structures to the product of the claimed process.

Properly framed, the issue for the Court is whether the intrinsic record as a whole defines Dr. Lin's claimed inventions as expressly or necessarily excluding any structural characteristics

that are not expressly recited in the claims. The intrinsic record demonstrates that Lin claimed his inventions by reference to certain essential structural characteristics that must be present in a claimed product or composition, not by reference to structural characteristics that must be missing or excluded from his claimed products and compositions. Because the intrinsic record does not support such a restrictive reading of Lin's claimed inventions, Defendants' attempt to construe Lin's claims to exclude such unrecited structures ignores the intrinsic record and misapplies the law. [55]

1. "Human erythropoietin . . . purified from mammalian cells grown in culture" ('422 claim 1)

The intrinsic record demonstrates that "human erythropoietin" means "a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine."[56] As used in the specification, "erythropoietin" refers to polypeptides having the same sequence of amino acid residues as naturally occurring erythropoietin:

> The present invention provides, for the first time, novel purified and isolated polypeptide products having part or ***all of the primary structural conformation (i.e., continuous sequence of amino acid residues***) and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof.[57]
>
> According to the present invention, DNA sequences encoding part or ***all of the polypeptide sequence of human and monkey species erythropoietin (hereafter, at times, 'EPO'***) have been isolated and characterized.[58]

The prosecution history of the '422 patent makes plain that "human erythropoietin" includes any polypeptide that has the same sequence of amino acid residues as EPO isolated from human urine:

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[55] *Crystal Semiconductor*, 246 F.3d at 1351; *A.B. Dick*, 713 F.2d at 703.

[56] *See* Appendix A at 1-2, 15.

[57] Appendix B at 10:9-15 (emphasis added).

[58] Appendix B at 13:50-53 (emphasis added).

> [H]uman erythropoietin is understood to include any polypeptide having the amino acid sequence of EPO isolated from human urine and may be produced in human cells or in other mammalian cells.[59]

"Human erythropoietin" also includes any naturally occurring allelic variations in human EPO's amino acid sequence.[60]

Significantly, the specification does not define "erythropoietin" or "human erythropoietin" by reference to the presence or absence of any attached molecules, such as the carbohydrate that can be attached to EPO proteins to form glycosylated EPO:

> Depending upon the host employed, ***polypeptides of the invention may be glycosylated with mammalian or other eucaryotic carbohydrates or may be non-glycosylated***. Polypeptides of the invention may also include an initial methionine amino acid residue (at position -1).[61]

Thus, not only does the specification expressly contemplate that molecules in addition to the required sequence of amino acid residues, such as carbohydrate or amino acid molecules, ***may*** be attached to "human erythropoietin," but nowhere does the specification limit or exclude the attachment of additional structures to the essential amino acid structure that comprises Lin's claimed products.

The limitation "purified from mammalian cells grown in culture" does not alter this "open" construction of the term "human erythropoietin." Rather, it recites the source from which the "human erythropoietin" component of the claimed composition may be obtained and necessarily imparts a further structural requirement that the product also be glycosylated.[62] The

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[59] Exhibit 8 at AM-ITC-00899474 (U.S. Appln. 100,197 File History, 4/28/99 Amendment (Paper 33) at 5).

[60] Appendix B at 21:11-19; 35:10-20; 35:27-39.

[61] Appendix B at 10:28-33 (emphasis added).

[62] *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d at 1347-49; Exhibit 8 at AM-ITC-00899474 (U.S. Appln. 100,197 File History, 4/28/99 Amendment (Paper 33) at 5 (in contrasting '422 claims 1 and 2, Amgen provided that "purified from mammalian cells in culture" is a source limitation and relied on the recombinant process by which Amgen made EPO to structurally distinguish rEPO from uEPO)); Exhibit 9 at AM-ITC-00899180 (U.S. Appln. 100,197 File

claim is silent as to the presence or absence of any structural characteristic beyond the required sequence or amino acid residues and glycosylation, and for that reason cannot be construed to require the exclusion of additional structural characteristics.[63]

2. "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence. . . encoding human erythropoietin" ('933 claims 3, 7, 8, 9, and 12)

The term "non-naturally occurring glycoprotein product" means "a protein not occurring in nature having carbohydrate groups attached to the polypeptide." Based on this Court's past constructions of the terms "DNA sequence encoding"[64] and "mammalian cells,"[65] the further limitation, "product of the expression in a mammalian host cell of an exogenous DNA sequence . . . encoding human erythropoietin," means that the product is "produced by a mammalian cell transformed or transfected with a DNA sequence that does not have its origin from the genome of the host and which contains at least the genetic instructions for human erythropoietin."[66]

As with '422 claim 1, the intrinsic record defines the claimed "glycoprotein product" of the '933 claims by reference to the essential structural characteristics that must be found in the product, not by reference to structural characteristics that must be absent.

B. DR. LIN'S PROCESS CLAIMS DO NOT PRECLUDE FURTHER PROCESS STEPS

Eight of the asserted claims in the patents-in-suit are directed to processes for making

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History, 3/2/95 Amendment (Paper 25) at 2). Because Lin's specification teaches that mammalian cells will glycosylate EPO, the limitation "purified from mammalian cells grown in culture" provides that the human erythropoietin comprising the claimed pharmaceutical composition will be glycosylated.

[63] *Amstar*, 730 F.2d at 1482; *NeoMagic Corp. v. Trident Microsystems, Inc.*, 287 F.3d 1062, 1074 (Fed. Cir. 2002); *Crystal Semiconductor*, 246 F.3d at 1351; *A.B. Dick*, 713 F.2d at 703; *Dow Chemical*, 257 F.3d at 1381.

[64] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d at 251.

[65] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d at 86.

[66] *See* Appendix A at 19-20 (citing to intrinsic record supporting proposed construction).

EPO products, with the asserted '868 and '698 patent claims directed to novel processes for making "glycosylated erythropoietin polypeptide products" and '349 claim 7 directed to a process for making large quantities of EPO using novel vertebrate cells.[67]

The '868 and '698 process claims are distinguished in part by the novel genetic composition of the cells used to produce a "glycosylated erythropoietin polypeptide." Claim 7 of the '349 patent is similarly distinguished by the novel genetic composition of the vertebrate cells used to produce "erythropoietin" as well as the amount of EPO the cells must produce. Because the process used by Defendants to produce their EPO product meets every limitation of Lin's claimed processes,[68] Defendants predictably resort to claim construction to argue that their accused MIRCERA product is not "a 'glycosylated erythropoietin polypeptide' as properly construed."[69] At bottom, it appears that Defendants are asserting that Amgen's process claims should be narrowly construed to exclude processes used to manufacture EPO products to which additional molecules have been attached. This position is contrary to the plain meaning of the asserted process claims, each of which include the transitional phrase "comprising" when reciting the steps of the claimed process.[70]

As the Federal Circuit held in the context of Amgen's claims, "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***."[71] Thus, the

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[67] The text of these claims is set forth at Appendix A.

[68] *See* Docket No. 252, Exh. C at Exhibit A, pages 1-12, 13-21, and 21-2 (providing infringement charts for '868 claims 1 and 2, '698 claims 4-9 and '349 claim 1, respectively).

[69] Exhibit 13 at 20 (non-confidential excerpt from Defendants' February 9, 2007 Supplemental Responses and Objections to Plaintiff Amgen Inc.'s First Set of Interrogatories to Defendants (Nos. 1-15), Response to Interrogatory No. 2); s*ee also id.* at 27 (regarding similar assertion regarding '349 claim 7 and "erythropoietin").

[70] *See Dow Chemical*, 257 F.3d at 1380-81.

[71] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d at 1344-45 (emphasis added).

asserted process claims cover the practice of process steps in addition to the claimed process steps.

The specification is consistent with this plain meaning. It discloses additional processes for making Amgen's EPO product that are not required steps in Amgen's process claims. For example, Example 10 includes the precursor step of actually transforming the cells used in the claimed process with EPO DNA, as well as amplifying such DNA.[72] At the other end of the process, the specification describes steps that follow the isolation of the expression product. For example, the specification describes the step of formulating an isolated product into a pharmaceutical composition.[73] It further identifies the step of labeling the expressed product by the covalent association of a detectable marker substance to EPO after its isolation.[74] Finally, as set forth above, there is no basis in either the terms' plain meaning or the intrinsic record to limit the terms "erythropoietin" and "glycosylated erythropoietin polypeptide" to exclude EPOs to which an additional molecule has been attached.

VI. CONCLUSION

Claim construction in this case should focus on a handful of terms and whether Amgen, either in its specification or during prosecution, expressly disclaimed EPO products to which additional molecules have been attached and processes that would allow for the conduct of additional steps to allow for such attachment. Defendants' burden to show such disclaimer is high and is unsupported by the plain meaning and intrinsic record.

[72] Appendix B at 25:39-26-65.

[73] Appendix B at 33:60 to 34:27.

[74] Appendix B at 12:8-12. The file histories for these patents are silent as to this issue and thus do not change the claims' plain meaning, as supported by the specification.

Respectfully Submitted,

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By its attorneys,

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