IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

AMGEN, INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD., ROCHE DIAGNOSTICS GMBH, and HOFFMANN-LA ROCHE, INC. Defendants.	Civil Action No. 05 CV 12237 WGY **ORAL ARGUMENT SCHEDULED FOR APRIL 17TH, 2007**

DEFENDANTS' MEMORANDUM IN OPPOSITION TO AMGEN, INC.'S CLAIMS CONSTRUCTION BRIEF

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Defendants (collectively "Roche") respectfully submit this memorandum in opposition to Amgen, Inc.'s ("Amgen") Claims Construction Brief.

I. INTRODUCTION

Amgen has filed a claims construction brief that ignores the plain meaning of the claims in a transparent attempt to cover products and processes that Amgen did not invent.[1] When construing some of the same claims at issue here, the Federal Circuit cautioned that "[j]ust as the prosecution record cannot enlarge the claims beyond what the inventor has presented as his invention, so the court cannot enlarge the claims beyond the limitations imposed by the patentee." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1042 (Fed. Cir. 2006). Amgen's proposed construction violates this fundamental maxim of patent law.

Certain Lin product patent claims are directed to a "glycoprotein product of the expression in a mammalian host cell." Following the plain meaning of the claims, Roche proposed in its opening brief that this means "a protein that is the expression product of the mammalian host cell ...." (Roche Op. Br. at 11) (emphasis added). However, Amgen would have this Court disregard this essential limitation that the claimed glycoprotein must be the "product of the expression in a mammalian host cell."

Similarly, certain Lin process patent claims cover methods for making "glycosylated erythropoietin polypeptides" by following steps which end with "isolating said glycosylated erythropoietin polypeptide." However, Amgen proposes a claim construction so open-ended that it would cover an infinite number of steps beyond the isolation of the polypeptide defined by the

[1] Roche attempted to narrow the subject matter of the Markman briefs by offering to meet and confer over certain terms that Roche believed were not in serious dispute. By letter, dated February 27, 2007, Roche offered Amgen with a list of definitions of claim limitations that Roche would agree, some subject to slight modifications which were to be further negotiated (Ex. T). Amgen never responded to Roche's offer. Roche's claims construction of these and other terms are attached hereto as Appendix B. Amgen tactically chose only to address a few claim terms in its brief, despite knowing that Roche had issues with other terms. Roche therefore has no opportunity to address any new terms or arguments that Amgen may discuss for the first time in its opposition brief.

claim. Notwithstanding that this construction would make these claims facially invalid for lack of written description and indefiniteness, Amgen seeks to vitiate the express limitations of the claim language that define the product of the process as a substance that is isolated from cells. Amgen's open-ended reading of its process claims would vitiate the purpose and intent of the "materially changed" provision of 35 U.S.C. § 271(g)(1).

CERA, the active ingredient in Roche's new drug MIRCERA™ is produced in the laboratory through a complex reaction that chemically changes epoietin β by reacting it with an acylating agent of polyethylene glycol. This chemical synthesis creates an entirely new molecule possessing different chemical, physical and biological properties from the glycosylated erythropoietin polypeptide claimed by Amgen's patents. Amgen seeks to improperly expand its claims to encompass Roche's new molecule, grasping at a claim construction that ignores the plain language of the claims. CERA is not made in a cell (and indeed cannot be produced in a cell) but artificially created in the laboratory. Thus, CERA is not and cannot be "the product of the expression in a mammalian host cell," as recited in the product claims. Likewise, CERA is not the "said glycosylated erythropoietin polypeptide" of the process claims because it is not a substance that is isolated from a host cell as required by those claims.

Amgen's claims should be limited to the glycosylated erythropoietin polypeptide described in those claims, and not expanded to cover analogs or derivatives of erythropoietin that have some, but not all, of the biological properties of the natural hormone. Amgen tried to secure such broad claims in the past but failed. For example, in 1986, during prosecution of the parent application of the patents-in-suit, Amgen originally had claims to DNA sequences encoding any "polypeptide analog of naturally-occurring erythropoietin." Amgen had to relinquish these claims during prosecution because the Patent Office deemed them too broad and

unsupported by the specification. In 1987, Amgen similarly tried to obtain from the Patent Office claims to a "synthetic polypeptide having part or all of the amino acid sequence" of human erythropoietin. However, Amgen had to abandon these claims when the Patent Office rejected them for lack of enablement.

Later that year, Amgen was eventually awarded U.S. Patent No. 4,703,008 ("the '008 patent") (Ex. U) with claims directed to DNA sequences encoding a polypeptide "sufficiently duplicative of that of erythropoietin." (*See e.g.* claim 7). But by 1991, this Court and the Federal Circuit found that these claims were also invalid for lack of an enabling disclosure. As the Federal Circuit stated in *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1214 (Fed. Cir. 1991), "[i]t is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity."

Amgen's overreaching is also evident from its existing patent monopoly. The claims within the '008 patent that were not invalidated for over breadth were directed to the isolated DNA sequence encoding human erythropoietin, and mammalian host cells transformed with this DNA sequence "in a manner allowing" these cells to express erythropoietin ("EPO"). *See, e.g.*, (Ex. U at claim 4). Amgen told the Patent Office that these previously patented host cell claims and those of the patent-in-suit are the same invention. Yet, even though the host cell claims of the '008 patent expired in 2004, Amgen continues to extend its patent monopoly by asserting patents that also should have already expired against products it clearly has no rights over.[2]

[2] Amgen makes much of the fact that cell lines belonging to Roche's licensor, Genetics Institute ("G.I.") were found to infringe certain claims of the '008 patent. However, Amgen's argument is misleading and has no relevance to claim construction. First, Roche is not a successor-in-interest of G.I. Second, Roche developed its own master cell bank with culture conditions different from those of G.I. Third, Amgen could not assert the '008 patent in this case because it expired in 2004. Fourth, to the extent that Amgen is suggesting that Roche's product be enjoined because of the '008 patent, this only underscores Amgen's overreaching. Amgen already had 17 years of patent protection under the '008 patent, but it still craves for more. In fact, Amgen's reliance on the G.I. cell lines only confirms that the patents-in-suit are the same invention as the '008 patent and therefore should have also expired in 2004.

II. ROCHE'S PRODUCT MIRCERA™

Roche is developing a novel drug for treating anemia named MIRCERA™, which contains the active ingredient CERA (short for Continuous Erythropoiesis Receptor Activator). CERA is produced in the laboratory through complex chemical mechanisms, which uses epoietin β and a specific type of polyethylene glycol (PEG) reagent as raw materials. CERA differs considerably from erythropoietin, both in its chemical and biological properties. CERA is substantially more complex and has twice the molecular weight and more than twice the physical size of erythropoietin. MIRCERA™ also has a substantially longer circulating half-life in the human body than epoietin ά, the active ingredient in Amgen's EPOGEN. Laboratory studies indicate that CERA interacts with the cellular receptor for erythropoietin in a way that suggests the biological mechanism of action of CERA and erythropoietin differ. Indeed, the FDA has recognized these differences, and accordingly MIRCERA™ is under review as a "new chemical entity". 21 C.F.R. § 314.108(a) (April 1, 2003) (containing "no active moiety that has been approved by the FDA."). The Patent Office has also determined that CERA is a novel and non-obvious composition of matter by granting Roche U.S. Patent No. 6,583,272 (Ex. V), which covers this molecule. Critically, CERA cannot be formed by the expression of any DNA sequence in any mammalian host cell.

III. THE LIN PATENTS

All of the patents-in-suit stem from the same parent application, filed in 1984, that was based on a single discovery: the human DNA coding sequence of natural erythropoietin and host cells transformed with this DNA sequence allowing for the production of recombinant EPO. Amgen did not invent the EPO protein, as that natural protein had been isolated by others, such as Dr. Goldwasser, for many years prior to Amgen's work. *See Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006, *12 (D. Mass. Dec. 11, 1989). While the first patent which issued as part

of this discovery, the '008 patent, already expired on October 27, 2004, Amgen has asserted the patents-in-suit, which, absent Court intervention, will not expire until the years 2012 to 2015. By the time the last of these patents expires, Amgen's single invention will have enjoyed monopoly protection for over twenty-seven years. Industry analysts have described Amgen's EPO as "the second best monopoly of our generation (behind Microsoft's Windows)."[3] In fact, even Amgen's current CEO, Mr. Sharer, was at a loss for words when asked why the life of the patents-in-suit lasted so long beyond the statutory prescribed periods. He could only answer by confessing, "It's an obvious question; I've had it myself."[4]

Up until now, Amgen has asserted its patents against others attempting to sell EPO. Now however, Amgen goes farther. Amgen now seeks to stop U.S. patients from obtaining a new and different drug neither disclosed in the patents-in-suit nor commercialized by Amgen. To do so, Amgen must contort its patents' plain meaning in unprecedented ways to cover a product it clearly did not invent. Thus, this case presents novel claim construction issues not previously decided by this Court.

IV. THE LIN PATENTS CANNOT COVER EPO ANALOGS

In its attempt to expansively broaden its claims to cover Roche's MIRCERA™, Amgen proposes a claim construction that would cover any analog or derivative of erythropoietin, regardless of whether that polypeptide is the expression product of the mammalian host cell (as required by the product claims) or whether that polypeptide is isolated from a mammalian host cell (as required by the process claims). However, even if the language of the claims was open to Amgen's interpretation (which it is not), Amgen is estopped from taking such a position

[3] Morgan Stanley Equity Research, Amgen: Some Setbacks for Competitors in EU, Feb. 23, 2006. (Ex. LL).
[4] Andrew Pollack, Rivals Laying Siege to Amgen's Near Monopoly in Anemia Drugs, N.Y. Times, Dec. 23, 2005, Ex. W at 6.

because it expressly surrendered claims to EPO analogs and derivatives during the prosecution of the patents-in-suit.

A. Amgen Surrendered Claims To DNA Sequences Encoding Analogs

Specifically, during the prosecution of Application No. 675,298, which is the purported parent application to all of the patents-in-suit, Amgen submitted original claim 34 which read: "A DNA sequence coding for a polypeptide fragment or polypeptide analog of naturally-occurring erythropoietin." (Ex. X at 100) (emphasis added).

The Patent Office made numerous rejections of this claim as being too vague and meaningless, and therefore indefinite in violation of 35 U.S.C. § 112. *See, e.g.*, (Ex. Y at 4-5). As a result, Amgen amended this claim as new claim 96 by describing the DNA sequence as "purified and isolated." However, the Patent Office maintained its rejection for lack of definiteness. In particular, the Patent Office stated that this new claim 96 "appear[ed] to embrace substantially all known DNA sequences since the isolated DNA sequence is not designated as encoding for erythropoietin." *See* (Ex. Z at 3-4).

Amgen eventually cancelled its EPO analog claim in favor of a new claim 110. *See* (Ex. AA at 14-15) ("In order to expedite prosecution of this application [sic] has reconstituted prior claims 77 and 96 as new claim 110."). New claim 110 read:

> A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

Id. at 6. This new claim 110 eventually became issued claim 7 of the '008 patent. However, even this much more narrowed claim was held invalid for lack of enablement by the Federal Circuit in *Amgen v. Chugai*, 927 F.2d at 1214. The Federal Circuit concluded that:

> In affirming the district court's invalidation of claims 7, 8, 23-27, and 29 under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs .... Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.

Id. (emphasis added). Therefore, not only did Amgen surrender its claim to EPO analogs because the Patent Office consistently maintained that this claim was indefinite, but Amgen's replacement of this claim was later found to be invalid for lack of enablement by this Court and the Federal Circuit.

B. Amgen Abandoned Claims To "Synthetic Polypeptides"

During the prosecution of the '933 patent, Amgen sought claims to a "synthetic polypeptide having part or all of the amino acid sequence set forth in Figure 6 ... and having a biological property of naturally-occurring human erythropoietin." (Ex. BB at 102). The Patent Office rejected this and similar claims to "synthetic polypeptides" by stating:

> Claims to "synthetic polypeptides" are not enabled by this disclosure. "Synthetic," as opposed to "recombinant," is an art recognized term which indicates a chemically derived rather than genetically engineered protein. No support for chemical synthesis of EPO or EPO fragments is shown by this disclosure.

(Ex. CC at 5). As a result, Amgen abandoned all claims to "synthetic polypeptides."

C. Amgen Again Surrenders Claims To Proteins "Sufficiently Duplicative" of EPO

Similarly, during prosecution of the '933 patent, Amgen tried unsuccessfully to obtain claims to erythropoietin analogs "sufficiently duplicative of that of naturally occurring human erythropoietin." For example, Amgen wanted to claim:

> A glycoprotein product of the expression of an exogenous DNA sequence in a eucaryotic host cell, said product having a primary structural conformation and glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells to increase production of reticulocytes and red blood cells...

(Ex. DD at 1) (emphasis added). The PTO rejected this claim pursuant to 35 U.S.C. § 112 ¶¶ 1 and 2, on grounds of nonenablement and indefiniteness. (Ex. EE at 3). However, driven by its desire to capture any glycoprotein analog that contains the "primary structural conformation" of erythropoietin, Amgen pressed on. Amgen argued that the disclosure of the exact amino acid sequence of erythropoietin entitled it to inventions that were slightly different but sufficiently duplicative of human EPO. Amgen stated:

> Claims 67-75 stand rejected under 35 U.S.C. 112, first and second paragraphs. Reconsideration is requested.
>
> Regarding point 1 raised by the Examiner, the phrase "a primary structural conformation" particularly points out the subject matter which applicant regards as the invention, and is defined at page 19, line 2, of the subject specification as a "continuous sequence of amino acid residues." Further, page 90, lines 10-17 state "While the deduced sequences of amino acid residues of mammalian EPO provided by the illustrative examples essentially define the primary structural conformation of mature EPO, it will be understood that the specific sequence of 165 amino acid residues of monkey species EPO in Figure 5 and the 166 residues of human species in Figure 6 do not limit the scope of useful polypeptides provided by the invention." Thus, it can be seen that the phrase "primary structural conformation" as used in the specification and claims, relates to amino acid sequence.

(Ex. FF at 3) (emphasis added). The Patent Office rejected this argument and continued to reject Amgen's claims. (Ex. GG) ("Applicant to amend claims to overcome rejections of 112").

Amgen eventually withdrew all claims directed to "a primary structural conformation and glycosylation sufficiently duplicative," and replaced them with claims that were defined by the exact DNA sequence encoding human erythropoietin disclosed and claimed in the now expired '008 patent. For example, new claim 76 read:

> A non-naturally occurring glycoprotein product of the expression in a non-human eucaryotic host cell of an exogenous DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing human bone marrow cells to increase production of reticulocytes and red blood cells.

(Ex. HH at 1). In that same Amendment, Amgen characterized its new claims as follows:

> The Applicant has added new claims 76-83, which are similar to cancelled claims 67-75, but which specify that the DNA sequences encode human erythropoietin. These new claims parallel claim 2 of U.S. Patent No. 4,703,008 (Lin. '008 patent), the parent of the instant application.

Id. at 5 (emphasis added). Thus, Amgen withdrew its broad claims directed to EPO analogs, and defined its new protein claims to "parallel" Amgen's earlier issued '008 patent claims, which were directed to specific DNA sequences encoding only a specific human erythropoietin.

Critically, in this same amendment, Amgen argued that the '933 patent application should not be suspended in view of interference proceedings between Amgen (party Lin) and Genetics Institute (party Fritsch) because this Court had allegedly resolved the priority issue between these parties regarding the claimed subject matter in its decision *Amgen Inc. v. Chugai Pharm. Co.,* Civ. Action No. 87-2617-Y (Dec. 11, 1989) (M.J. Saris).

> In determining that claims 2 and 4 of the Lin '008 patent are valid, the Court recognized that Lin is the first inventor of the DNA sequence encoding human erythropoietin and of the use thereof in a host cell to make recombinant erythropoietin...The decision is thought to be fully dispositive of not only the priority of the invention issues in both interferences, and [sic] any priority issue in the subject application. Therefore, it is submitted that if Lin was the first to invent the DNA encoding erythropoietin, and the use of that DNA in a host cell to produce recombinant erythropoietin, then clearly he was the first to invent a recombinant erythropoietin product produced using such a host cell.

(Ex. HH at 6) (emphasis in original). Thus, in surrendering its claims to broad EPO analogs, Amgen subsequently defined its glycoprotein EPO polypeptides in terms of the inventions claimed in its prior and now expired '008 patent. Amgen argued that the host cell claims of the '008 patent and the glycoprotein polypeptide claims of the product patents were "parallel" inventions, and that priority of one determined the priority of the other.

As a matter of law, when a patent applicant surrenders or disavows a claim for the purpose of obtaining a patent, the patent claims will be limited "so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution." *Spectrum Int'l v. Sterilite Corp.,* 164 F.3d 1372, 1378 (Fed. Cir. 1998). Therefore, because Amgen surrendered its claims to EPO analogs and synthetic polypeptides in the course of obtaining a patent, it cannot now make the argument that the asserted claims of the patents-in-suit cover synthetic EPO analogs and derivatives and certainly not Roche's CERA product.

V. AMGEN'S PRODUCT CLAIMS TO THE GLYCOPROTEIN SHOULD BE LIMITED TO THE EXPRESSION PRODUCT OF THE HOST CELL

Notwithstanding that Amgen is estopped from arguing its broad claim construction, Amgen's proposed construction for its product claims also ignores a fundamental aspect of Amgen's invention - namely, that the recombinant glycosylated erythropoietin is the expression product of the host cell. Amgen is proposing an impermissible litigation-based construction in an attempt to ensnare CERA. As the common specification and prosecution histories of the asserted patents make clear, Amgen's inventions were restricted to expression of a protein in a host cell, a purely biological process. Significantly, nowhere in the common specification was there any mention or examples of a chemically-made molecule for stimulating erythropoiesis. In fact, as discussed above, the Federal Circuit has held that the common specification did not

support claims to biologically made analogs much less chemically derived analogs. *Amgen v. Chugai,* 927 F.2d at 1213-1214.

A. The Specification and File Histories Require That The Claimed Polypeptide Be Identical To The Expression Product Of the Host Cell

The plain meaning of the claims require that the "glycoprotein product" be identical to the expression product of the host cell. For example, claim 3 of the '933 patent is to a "non-naturally occurring glycoprotein product of the expression in a mammalian cell." There is no "comprising" language of the claimed glycoprotein product which would permit the protein to possess additional structures. The "comprising" language of this claim refers to genetic elements within the mammalian host cell, and not to the claimed glycoprotein product. "Of" is not an open ended modifier such as "comprising," but actually defines the claimed product.[5]

As described in more detail in Roche's Opening Brief *e.g.,* at page 11, the patent specification clearly defines the claimed glycoproteins by the biological process of making them. The specification states that "[t]hese polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast and mammalian cells in culture) ..." (Ex. A at col. 10, ll. 23-26) (emphasis added). Referring to the "Brief Summary" section of the patent specification, the inventor Dr. Lin described his claimed erythropoietin polypeptides as follows during trial testimony:

> I said that: These polypeptides are uniquely characterized by being the product of microbial expression (e.g., by mammalian cells in culture) of an exogenous DNA sequence. I say that because at the time the only way we can characterize the product is by the way they were making, that's why this is described this way.

[5] The Patent Office does not recognize "of" by itself as term of art in patent claim drafting. See M.P.E.P. § 2111.03. (Ex. NN). Thus, it must be interpreted by the Court based on the plain meaning and the intrinsic evidence, which in this case it used in connection with "product of." The dictionary definition of "product" is "[s]omething produced by human or mechanical effort or by a natural process." American Heritage Dictionary 1399 (4th ed. 2006). (Ex. OO). So "product of . . ." means "something produced by . . . ".

Amgen Inc v. Hoechst Marion Roussel Inc., No. 97-10814 (D. Mass.), Trial Tr. (June 7, 2000) at 965:8-14 (emphasis added). (Ex. MM). Thus, Amgen specifically defined the glycoprotein polypeptides of the present invention in terms of the process for making them and repeatedly stated that production in a host cell was a critical feature of the invention. Under these circumstances, these "process-based limitations" become part of the claim construction for that product. *See Andersen Corp. v. Fiber Composites, LLC,* 474 F.3d 1361 (Fed. Cir. 2007).

In arguing that the claimed erythropoietin glycoproteins should not be limited to the expression product of the host cell, Amgen points the Court to sections of the specification that discusses "polypeptide products having part or all of the primary structural confirmation" or "DNA sequences encoding part or all of the polypeptide sequence of human and monkey species erythropoietin." (Amgen Op. Br. at 16) (emphasis changed). However, as stated above, the Patent Office and the Court discredited these and similar sections of the specification and claims based on such passages when ruling that Amgen's claims to polypeptide analogs were invalid for being too broad and indefinite. *See* (Ex. FF at 3) ("Regarding point 1 raised by the Examiner, the phrase "a primary structural conformation" particularly points out the subject matter which applicant regards as the invention, and is defined at page 19, line 2, of the subject specification ...") (emphasis added); *Amgen v. Chugai*, 927 F.2d at 1213 ("polypeptide product having at least a part of the primary structural conformation...") (emphasis added).

The prosecution history is consistent with the specification because Amgen represented to the PTO that its invention was limited to the expression of a specific erythropoietin in host cells, solely a biological process, and not to chemical or synthetic production of a protein conjugate. Original claim 1 of the '298 application, which was the progenitor application of all of the asserted patents claims, reads:

> 1. A purified and isolated polypeptide having part or all of the primary structural conformation and one or more of the biological properties of naturally-occurring erythropoietin and characterized by being the product of procaryotic or eucaryotic expression of an exogenous DNA sequence

(Ex. X at 97) (emphasis supplied).

Likewise, during the prosecution of the '933 patent, the patentee amended all the claims to product-by-process claims stating that "[t]hese product-by-process claims are presented in an effort to positively recite the physical properties of recombinant erythropoietin, and to further define the product of the subject invention since recombinant erythropoietin claimed cannot be precisely defined **except** by the process by which it is produced." (Ex. DD at 4) (emphasis added).

B. The Glycoprotein Product Must Possess All Of The Structural Elements Of Erythropoietin Produced By The Host Cell

In its opening brief, Roche defined "human erythropoietin" as used in the '422 patent as "a glycoprotein having the amino acid sequence of erythropoietin isolated from human urine having the structure that would be produced in mammalian cells as of the invention date." (Roche Op. Br. at 1). Amgen does not contest this since it admits in its opening brief that "the essential structural attributes of the claimed glycoprotein product are defined by reference to the DNA and cells used to produce the product." (Amgen Op. Br. at 13) (emphasis added). Therefore, both parties agree that the claimed erythropoietin glycoprotein is limited to those structural elements that are present in erythropoietin produced by mammalian host cells.

As provided in more detail in the accompanying Supplemental Declaration of Thomas R. Kadesch, (Ex. PP) erythropoietin produced by mammalian host cells has an N-terminal residue where the alpha amino group is un-substituted. (See also Ex G at ¶31). Similarly, erythropoietin produced in mammalian cells also has eight residues derived from the amino acid lysine. (Ex. PP at ¶10). The side chains of these residues have a four carbon chain attached to a primary

amino group. Consequently, any compound that does not have these essential structural attributes is not within the scope of a claim to limited erythropoietin produced by mammalian cells.

VI. AMGEN'S PROCESS CLAIMS SHOULD BE LIMITED TO THE PROCESS FOR MAKING THE CLAIMED PRODUCTS

A. The Process Claims of the '868 and '698 Patents Should Be Limited To Claimed "Said Glycosylated Erythropoietin Polypeptide"

Independent claim 1 of the '868 patent and independent claim 4 of the '698 patent are directed to a process of making a glycosylated erythropoietin polypeptide wherein the last step in the process requires the isolation of that claimed product from host cells.

Claim 1 of the '868 patent	Claim 4 of the '698 patent
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 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, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and	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 therefrom.	b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

As is apparent from the plain language of these claims, these inventions are limited to the process for making a particular compound - the glycosylated erythropoietin polypeptide - by following certain steps in the process. While Amgen would have this Court construe these claims to cover additional subsequent steps not recited by these claims, including the complex chemical pegylation reactions Roche developed and undertook to create CERA, such an open ended interpretation of the claims is not supported by the plain language. The last step of the

claimed process must end with the isolation of the product from the host cell (step (b)). After all, the process is limited to the making of a particular protein, and step (b) describes the isolation of that **"said"** product.

In fact, in an attempt to overcome prior art during the prosecution of the '868 patent, Amgen clearly stressed the importance of the final isolation step because it determined that the pattern of glycosylation was allegedly necessary to have *in vivo* biological activity of the claimed polypeptide. Amgen stated that:

> Further required by claim 65 is the glycosylation processing of the translated polypeptide at sites directed by the order of amino acids of the translated polypeptide so that the resulting product, **upon isolation, will have the pattern of glycosylation which is also required for in vivo biological activity.**

(Ex. II at 7) (emphasis added); *see also* (Ex. JJ at 3) (same language).

Moreover, as discussed in more detail in Roche's opening brief (Roche Op. Br. at 16), Amgen overcame an indefiniteness rejection during prosecution of the '868 patent by limiting the claimed processes to the expression of an isolated DNA sequence encoding human erythropoietin. Applicants stated that:

> Reference to such DNA constitutes a positive limitation of the claim and specifically characterizes the product obtainable through practice of the process. In any event, new claims 70 and 71 specifically refer to preparation [sic, of] *erythropoietin* polypeptides.

(Ex. O at 5).

Thus, Amgen limited the scope of the claim to processes that result in a glycosylated erythropoietin polypeptide that is obtainable through the two step process recited in the claim. Having relied upon the isolation step in order to overcome prior art and make definite its claim, Amgen should not now be allowed to distance itself from these statements and argue that these processes now claim additional subsequent unrecited steps.

Amgen's citation to the specification of examples of post isolation steps, such as the creation of pharmaceutical compositions or covalent association of detectable markers is of no moment. (Amgen Op. Br. at 20). Nowhere within the language of the claims is there any mention of these post isolation products.

As to Amgen's citation to covalent association of a detectable marker, such as radioactive iodine, an accurate reading of the patent specification actually contradicts Amgen's argument that these claims cover subsequent processes that can be employed to chemically modify the expression product. The specification clearly designates these products as radio-labeled materials; not as erythropoietin. (Ex. A at col. 17, ll. 30-68). For the same reason that an EPO analog (such as [His7]EPO) is not EPO, iodinated-EPO is also not EPO. (Ex. A at col. 30, ll. 43-46). This comports with basic laws of chemistry which dictate that once a chemical reaction occurs, the original substance ceases to exist and a different substance is created. Dr. Goldwasser readily acknowledged this in his recent deposition when he stated that iodination creates a completely new molecule, and that "by putting the bulky iodine in, you . . . change[] the structure so that it no longer ha[s] any biological activity." (Ex. KK at 178: 3-11).

B. Amgen's Open Ended Claim Construction Of The Process Claims Would Vitiate The "Materially Changed" Doctrine of Section 271(g)(1)

Amgen's open-ended construction of process steps would completely undermine the "materially changed" law of noninfringement under 35 U.S.C. § 271(g)(1). Under Section 271(g)(1), it is not an act of infringement if the product made by the patented process is "materially changed by subsequent processes" before it is imported into the United States. 35 U.S.C. § 271(g)(1). Under Amgen's open ended construction of process claims, litigants could never demonstrate non-infringement based upon a material change because patentees could always maintain that their process claims covered a multitude of subsequent steps beyond that

which was actually claimed. Obviously, this has not been the case. Courts have found no liability under Section 271(g) because the accused imported products had been materially changed from the product of the claimed process.

1. Case law In *Genentech, Inc. v. Boehringer Mannheim GmbH*, 47 F. Supp. 2d 91, 112 (D. Mass. 1999), which also involved process claims using the "comprising" language, the Court rejected essentially the same argument that Amgen proposes here - that even though patentee's claim was to a process for making a particular product (plasmid), additional unrecited process steps would not itself foreclose a finding of infringement. However, under Section 271(g)(1), there is no liability if the subsequent process steps materially change the product. The Court stated:

> Genentech cites the well-established patent doctrine that performance of additional steps not found in the patent does not absolve an infringer from liability. *See Amstar Corp. v. Envirotech Corp.*, [internal citations omitted]. Although *Amstar* governs a determination of whether the process for producing the expression plasmid violated claim 1, this reliance is misplaced in the context of an analysis of whether pePA98.1 was materially changed under Section 271(g). The additional steps, which were not covered by the patent, did change the physical and chemical properties of the plasmid 98.1 and its expression product t-PA in material ways.

Id. at 111-12 (emphasis added). Similarly, in *Eli Lilly & Co. v. American Cyanamid Co.*, 66 F. Supp. 2d 924, 937 (S.D. Ind. 1999), the Court determined that the accused imported product, "compound 10" or cefaclor, was materially changed from the product of the claimed process, "compound 6." Here again, the Court looked to the accused imported product and compared it to the product of the process defined by the claim, not to processes of additional steps beyond those recited in the claim. The Court stated:

> ... for purposes of this motion, the parties agree that Opos manufactures cefalcor in a nine step process, beginning with a starting material called "compound 1" and continuing through eight distinct intermediates and producing a final end product called "compound 10," which is cefaclor. The focus of this motion and Lilly's infringement claim is step 5 of the Opos process, in which compound 5 is

> converted into compound 6. Step 5 is claimed in Lilly's Shionogi patents. The issue before the Court is whether compound 6 is 'materially changed by subsequent processes' when converted into cofactor so as to preclude liability against Defendants for infringement of Lilly's patents.

Id. at 926 (emphasis added). In fact, had the Court in *Lilly* followed Amgen's proposed "open ended" claim construction, there could not have been any material change because the claim would have been construed to cover not only the process of making compound 6, but additional steps towards the construction of compounds 7, 8, 9, and 10.[6]

2. Legislative History The legislative history of Section 271(g) makes clear that the steps of a patented process explicitly recited in the patent claim actually define the product of the process. Any additional processing steps that are outside the claim must be examined to determine if the final product is materially changed from the product of the claimed process. For example, the Senate report accompanying the enactment of 271(g) states that "a product will be considered to have been made by a patented process if the additional processing steps which are not covered by the patent do not change the physical or chemical properties of the product ..." S. Rep. No. 100-83, at 50 (1987) (emphasis added). Additional process steps are just that - additional steps after production of the product of the claimed process, and not as Amgen argues, part of the patented process itself.

Indeed, the Senate Report further explains that one purpose of enacting Section 271(g) was to bring U.S. patent law more in accord with that of other industrialized nations which traditionally afforded greater protection to process patents than the United States. S. Rep. No. 100-83, at 29-31. The Senate report states that "another point of difference ... is the limitation in

[6] Importantly, the method steps in the *Lilly* patents also contained "comprising" language. For example, claim 1 of U.S. Patent No. 4,160,085 reads: "A process for cyclizing a compound represented by the formula ##STR157## ... **which comprises the step** of treating the said compound with a member of the group consisting of acid, base, solvent and a solvent together with a catalyzer selected from the group of a neutral or basic silica gel, alumina, diatomaceous earth and fluorisil to give a compound represented by the formula ##STR159##." (emphasis added)

the process patent laws of most industrialized nations to products made 'directly' from the process." *Id.* at 36 (emphasis added). Foreign patent laws "use the word 'directly' to exclude as an infringement the importation, use or sale of a product which is materially changed from the product resulting from the patented process by subsequent steps or processes." *Id.* at 49. Rather than use the word 'directly', Section 271(g) "introduces a new phrase, 'materially changed by subsequent processes'... to serve the same general purpose of restricting the scope of the bill to exclude ultimate products that, because of intervening manufacturing steps, cease to have a reasonable nexus with the patented process." *Id.* at 36 (emphasis added).[7] Thus, subsequent manufacturing steps are properly seen as outside the steps claimed in a process patent claim, which can make the final product materially changed from the product of the process. If the subsequent manufacturing steps are part of producing the product of the claimed process, there can never be a material change and this part of Section 271(g) becomes completely meaningless, in contradiction of the explicit language of the statute and Congress' intent in enacting it.

Finally, adhering to Amgen's open-ended claim construction would render those claims facially invalid for lack of enablement and written description, and indefiniteness. If Amgen is allowed to capture additional steps beyond the isolation of the claimed compound, the public at large would no longer be on notice as to the metes and boundaries of the claims to prevent infringement of the patent. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1560 (Fed. Cir. 1991); M.P.E.P. § 2173. "A claim that is interpreted too broadly will run into validity issues, providing motivation for the construing court to choose a narrower interpretation if possible."

[7] *See also* H.R. Rep. No. 100-60, at 13-14, accompanying enactment of 35 U.S.C. § 271(g), which clearly indicates that subsequent manufacturing steps after the claimed steps of a process patent are outside the patented process ("The [patented] process may produce chemical X, which is subsequentially subjected to further processing or manufacturing steps. If the subsequent modifications change the basic structure of chemical X so that a clearly different chemical Y results, the connection between the patented process and the product chemical Y is broken." and "The Committee intends that liability for infringement exists of the **immediate product of the process** becomes an integral important or essential feature of the second product.") (emphasis added).

See MBO Labs. v. Becton, Dickinson & Co., 474 F.3d 1323. 1332 (Fed. Cir. 2007). Roche's construction provides the Court with such a narrower construction that prevents Amgen from claiming products and processes it did not claim or invent.

C. The Process Claim of the '349 Patent Should Also Be Limited To The Claimed "Erythropoietin"

Claim 7 of the '349 patent reads:

> 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.

Claim 1 of the '349 patent reads:

> 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.sup.6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin.

Based upon its plain meaning, claim 7 of the '349 patent should be limited to the process for making the claimed "erythropoietin," which is defined by the vertebrate host cells that are producing them at certain levels. For the same reasons stated above with respect to the process claims of the '868 and '698 patents, claim 7 of the '349 patent should not be construed to cover additional process steps which materially change the claimed product. *See Genentech, Inc.*, 47 F. Supp. 2d at 112 ("The additional steps, which were not covered by the patent, did change the physical and chemical properties of the plasmid 98.1, and its expression product t-PA, in material ways.").

VII. CONCLUSION

Based on the foregoing, Roche respectfully requests that the Court adopt Roche's proposed construction of the claim terms discussed above and in Roche's Opening Brief.

DATED: Boston, Massachusetts
March 19, 2007

Respectfully submitted,

F. Hoffmann-La Roche Ltd,
ROCHE DIAGNOSTICS GMBH, and
HOFFMANN-LA ROCHE INC.

By their Attorneys,

/s/ Thomas F. Fleming
Leora Ben-Ami (*pro hac vice*)
Mark S. Popofsky (*pro hac vice*)
Patricia A. Carson (*pro hac vice*)
Thomas F. Fleming (*pro hac vice*)
Howard S. Suh (*pro hac vice*)
Kaye Scholer LLP
425 Park Avenue
New York, New York 10022
Tel. (212) 836-8000
tfleming@kayescholer.com

Lee Carl Bromberg (BBO# 058480)
Julia Huston (BBO# 562160)
Keith E. Toms (BBO# 663369)
Nicole A. Rizzo (BBO# 663853)
Bromberg & Sunstein LLP
125 Summer Street
Boston, MA 02110
Tel. (617) 443-9292

CERTIFICATE OF SERVICE

I hereby certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on the above date.

/s/ *Thomas F. Fleming*
Thomas F. Fleming

Index of Exhibits

Exhibit A	U.S. Patent Nos. 5,441,868
Exhibit B	U.S. Patent Nos. 5,547,933
Exhibit C	U.S. Patent Nos. 5,618,698
Exhibit D	U.S. Patent Nos. 5,621,080
Exhibit E	U.S. Patent Nos. 5,756,349
Exhibit F	U.S. Patent Nos. 5,955,422
Exhibit G	Expert Declaration of Thomas R. Kadesch, Ph.D., Professor of Genetics at the University of Pennsylvania School of Medicine, and attached exhibits.
Exhibit H	May 5, 1999, Amendment, 08/100,197-33.
Exhibit I	Goldwasser Depo. Tr. February 14, 2007
Exhibit J	March 31, 1995, Office Action, 08/100,197-26
Exhibit K	February 10, 1989, Office Action, 07/113,178-9.
Exhibit L	June 2, 1989, Amendment Under Rule 116, 07/113,178-11
Exhibit M	May 24, 1988, Second Preliminary Amendment, 07/113,179-8.
Exhibit N	September 1, 1993, Office Action, 07/113,179-29.
Exhibit O	January 10, 1994, Amendment and Response, 07/113,179-33.
Exhibit P	Brief for Lin in Interference No. 102,097.
Exhibit Q	U.S. Patent No. 4,399,216.
Exhibit R	MANUAL OF PATENT EXAMINING PROCEDURE § 2173.05(h) I.
Exhibit S	MANUAL OF PATENT EXAMINING PROCEDURE § 608.01(p) Completeness [R-3].
Exhibit T	February 27, 2007 Letter From Thomas Fleming to Deborah E. Fishman.
Exhibit U	U.S. Patent No. 4,703,008.
Exhibit V	U.S. Patent No. 6,583,272.
Exhibit W	Pollack, A., "Rivals Laying Siege to Amgen's Near Monopoly in Anemia Drugs," The New York Times, Dec. 23, 2005.
Exhibit X	November 30, 1984, Application No. 06/675,298.
Exhibit Y	June 16, 1986, Office Action, 06/675,298-8.
Exhibit Z	June 18, 1987 Office Action, 06/675,298-17.
Exhibit AA	July 10, 1987, Amendment and Reply, 06/675,298-20.
Exhibit BB	October 23, 1987, Application No. 07/113,178.
Exhibit CC	June 2, 1988, Office Action, 07/113,178-4.
Exhibit DD	June 2, 1989, Amendment Under Rule 116, 07/113,178-11.
Exhibit EE	June 20, 1989, Office Action, 07/113,178-13.
Exhibit FF	July 12, 1989, Amendment, 07/113,178-15.
Exhibit GG	December 12, 1989, Examiner Interview, 07/113,178-17.
Exhibit HH	January 1, 1990, Amendment Under Rule 116, 07/113,178-19.
Exhibit II	May 24, 1988, Second Preliminary Amendment, 07/113,179-8.
Exhibit JJ	September 27, 1988, Applicant's Reply, 07/113,179-14.
Exhibit KK	Goldwasser Depo. Tr. February 14, 2007
Exhibit LL	Morgan Stanley Equity Research, "Amgen: Some Setbacks for Competitors in EU," Feb. 26, 2006.

Exhibit MM	*Amgen Inc. v. Hoechst Marion Roussel Inc.*, No. 97-10814 (D. Mass.), Trial Tr. (June 7, 2000).
Exhibit NN	MANUAL OF PATENT EXAMINING PROCEDURE § 2111.03 [R-3].
Exhibit OO	THE AMERICAN HERITAGE DICTIONARY 1399 (4th ed. 2006).
Exhibit PP	Supplemental Expert Declaration of Thomas R. Kadesch, Ph.D., Professor of Genetics at the University of Pennsylvania School of Medicine, and attached exhibits.
Exhibit QQ	December 11, 1996, Interview Summary, 0-8/468,381-7.

APPENDIX B

ROCHE'S PROPOSED CLAIM CONSTRUCTION

Proposed Claim Construction for U.S. PATENT NO. 5,441,868 CLAIM 1		
Claim Limitations	**ROCHE**	**EVIDENCE**
A process for the production of a glycosylated erythropoietin polypeptide	**"Process for the production of a glycosylated erythropoietin polypeptide having the amino acid sequence and carbohydrate modifications obtainable through the process steps (a) and (b) of these claims"**	**See Roche's Proposed Claim Construct Brief, Section I, filed March 5, 2007, 16 [hereinafter "Roche Opening Brief"].**
having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells	**"causing bone marrow cells to increase production of reticulocytes and red blood cells in a living organism."**	***'868 Patent:*** **col. 6, ll. 42-57; col.6, l. 58 - col. 7, l. 3; col. 10, ll. 45-52; col. 14, l. 41; col. 26, ll. 41-45; col. 29, l. 18; col. 33, l. 57; col. 34, ll. 48-59; col. 35, l. 18; col. 36, l. 2; col. 36, l. 41; col. 37, l. 55.** ***Prosecution History:*** **Roche Exhibit P at 48; Roche Exhibit M; Roche Exhibit JJ at 3-5; Amgen Exhibit 16 at 5; Amgen Exhibit 17 at 3.**
comprising the steps of:		
(a) growing, under suitable nutrient conditions, mammalian host cells	**"growing, under conditions appropriate for mammalian host cell growth, which are cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands"**	***Case Law:*** ***Amgen v. Hoechst,*** **126 F. Supp. 2d 69, 86 (D. Mass. 2001).** ***'868 Patent:*** **col. 11, ll. 46-53; col. 22, ll. 45-50; col. 27, ll. 3-7; col. 28, l. 33 - col. 29, l. 15.**

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Proposed Claim Construction for U.S. PATENT NO. 5,441,868 CLAIM 1		
Claim Limitations	**ROCHE**	**EVIDENCE**
transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and	**"introduction of purified exogenous DNA molecules containing the genetic instructions for human erythropoietin"**	**See Roche Opening Brief at 18-19.**
(b) isolating said glycosylated erythropoietin polypeptide therefrom.	**"separating the glycosylated erythropoietin polypeptide having the defined activity from the growth medium, cellular lysates or cellular membrane fractions of the cells that produce it"**	**See Roche Opening Brief at 17-18.**

Proposed Claim Construction for U.S. PATENT NO. 5,441,868 CLAIM 2		
Claim Limitations	**ROCHE**	**EVIDENCE**
The process according to claim 1		
wherein said host cells are CHO cells.	**"cell from the ovary of a Chinese Hamster"**	**See Roche Opening Brief at 13.**

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Proposed Claim Construction for U.S. PATENT NO. 5,441,698 CLAIM 2		
Claim Limitations	**ROCHE**	**EVIDENCE**
transformed or transfected with an isolated DNA sequence.	**"introduction of purified exogenous DNA molecules containing the genetic instructions for human erythropoietin"**	**See Roche Opening Brief at 18-19.**

Proposed Claim Construction for U.S. PATENT NO. 5,618,698 CLAIM 4		
Claim Limitations	**ROCHE**	**Evidence**
A process for the production of a glycosylated erythropoietin polypeptide	**"Process for the production of a glycosylated erythropoietin polypeptide having the amino acid sequence and carbohydrate modifications obtainable through the process steps (a) and (b) of these claims"**	**See Roche Opening Brief at 16.**
having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells	**"causing bone marrow cells to increase production of reticulocytes and red blood cells in a living organism."**	**See '868 patent, claim 1**
comprising the steps of:		
a) growing, under suitable nutrient conditions, vertebrate cells comprising	**"growing under conditions appropriate for vertebrate cell growth, which are cells from an animal having a backbone"**	*Amgen,* **126 F. Supp. 2d 69 at 85 (D. Mass. 2001).**

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Proposed Claim Construction for U.S. PATENT NO. 5,618,698 CLAIM 4		
Claim Limitations	**ROCHE**	**Evidence**
promoter DNA, other than human erythropoietin promoter DNA,	**"DNA sequences not part of the human genome that initiate and may regulate the process of transcription"**	***Amgen* 126 F. Supp. 2d at 87-88 (D. Mass. 2001).**
operatively linked to	**"the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA."**	***Amgen v. Hoechst,* 126 F. Supp. 2d 69 at 89-90 (D. Mass. 2001).**
DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and	**"the genetic instructions for"** **"the fully realized form of amino acid sequence of Figure 6"**	***Amgen,* 339 F. Supp. 2d 202 at 92 (D. Mass. 2003); *Amgen* 126 F. Supp. 2d at 86-87 (D. Mass. 2001).** *Amgen,* **457 F.3d at 1312-17 (Fed. Cir. 2006).**
b) isolating said glycosylated erythropoietin polypeptide expressed by said cells	**"separating the glycosylated erythropoietin polypeptide having the defined activity from the growth medium, cellular lysates or cellular membrane fractions of the cells that produce it"**	**See Roche Opening Brief at 17-18.**

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Proposed Claim Construction for U.S. PATENT NO. 5,618,698 CLAIM 6		
Claim Limitations	**ROCHE**	**Evidence**
A process for the production of a glycosylated erythropoietin polypeptide	**"Process for the production of a glycosylated erythropoietin polypeptide having the amino acid sequence and carbohydrate modifications obtainable through the process steps (a) and (b) of these claims"**	**See Roche Opening Brief at 16.**
having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells	**"causing bone marrow cells to increase production of reticulocytes and red blood cells in a living organism."**	**See '868 patent, claim 1**
comprising the steps of:		
a) growing, under suitable nutrient conditions, vertebrate cells comprising	**"growing under conditions appropriate for vertebrate cell growth, which are cells from an animal having a backbone"**	***Amgen,* 126 F. Supp. 2d 69 at 85 (D. Mass. 2001).**
amplified DNA	**"an increased number of copies of a particular gene relative to the number of copies inserted by transformation or transfection, and which results in an increased production of the gene product by the cell."**	***'868 Patent:* col. 15, ll. 8-12; col. 22, ll. 56-60; col. 27, ll. 42-44; col. 29, ll. 37-39; col. 31, ll. 14-16.** ***Prosecution History:* Roche Exhibit OO; Amgen Exhibit 18 at 9-10.**

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Proposed Claim Construction for U.S. PATENT NO. 5,618,698 CLAIM 6		
Claim Limitations	**ROCHE**	**Evidence**
[DNA] encoding the mature erythropoietin amino acid sequence of FIG. 6,	**"the genetic instructions for"** **"the fully realized form of amino acid sequence of Figure 6"**	***Amgen* 339 F. Supp. 2d at 92 (D. Mass. 2003); *Amgen* 126 F. Supp. 2d at 86-87 (D. Mass. 2001);** *Amgen,* **457 F.3d at 1312-17 (Fed. Cir. 2006).**
b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.	**"separating the glycosylated erythropoietin polypeptide having the defined activity from the growth medium, cellular lysates or cellular membrane fractions of the cells that produce it"**	**See Roche Opening Brief at 17-18.**

Proposed Claim Construction for U.S. PATENT NO. 5,618,698 CLAIM 7		
Claim Limitations	**ROCHE**	**Evidence**
The process of claim 6		

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Proposed Claim Construction for U.S. PATENT NO. 5,618,698 CLAIM 7		
Claim Limitations	**ROCHE**	**Evidence**
wherein said vertebrate cells further comprise amplified marker gene DNA.	**"cells from an animal having a backbone"** **"an increased number of copies of a particular gene relative to the number of copies inserted by transformation or transfection, and which results in an increased production of the gene product by the cell."**	***Amgen* 126 F. Supp. at 85 (D. Mass. 2001).** **See '698 patent, claim 6**

Proposed Claim Construction for U.S. PATENT NO. 5,618,698 CLAIM 9		
Claim Limitations	**Roche**	**Evidence**
The process according to claims 2, 4 and 6	Multiple dependent claims not drafted in the alternative are invalid under 35 U.S.C. § 112 par. 5.	
wherein said cells are mammalian cells.	**"cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands"**	***Amgen* 126 F. Supp. 2d at 86-87 (D. Mass. 2001).**

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Proposed Claim Construction for U.S. PATENT NO. 5,756,349 CLAIM 7		
Claim Limitations	**Roche**	**Evidence**
A process for producing erythropoietin	**"Process for producing a glycoprotein having the amino acid sequence and glycosylation structure of a naturally occurring hormone that is produced in a cell and secreted from that cell, and that controls the formation of red blood cells in bone marrow"**	**See Roche Opening Brief at 19.**
comprising the step of		
culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5 or 6.	**"culturing under conditions appropriate for vertebrate cell growth, which are cells from an animal having a backbone"**	***Amgen* 126 F. Supp. 2d at 85 (D. Mass. 2001).**

Proposed Claim Construction for U.S. PATENT NO. 5,756,349 CLAIM 1		
Claim Limitations	**ROCHE**	**Evidence**
Vertebrate cells	**"cells from an animal having a backbone"**	***Amgen* 126 F. Supp. 2d at 85 (D. Mass. 2001).**
which can be propagated in vitro and	**"which can be grown in culture outside of a living body"**	**No disagreement with Amgen.**

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Proposed Claim Construction for U.S. PATENT NO. 5,756,349 CLAIM 1		
Claim Limitations	**ROCHE**	**Evidence**
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,	**This term is vague and ambiguous and defies claim construction.**	**See Defendants' Opposition To Amgen's Motion To Enforce The Court's January 23, 2007 Order And Memorandum In Support Of Defendants' Cross Motion To Compel Production Of Amgen's Cell Lines And Related Documents (D.I. # 297).**
said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin.	**"DNA sequences not part of the human genome that initiate and may regulate the process of transcription"** **"the genetic instructions for"**	***Amgen* 126 F. Supp. 2d at 87-88 (D. Mass. 2001); *Amgen* 339 F. Supp. 2d at 251 (D. Mass. 2004).**

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Proposed Claim Construction for U.S. PATENT NO. 5,547,933 CLAIM 3		
Claim Limitations	**ROCHE**	**Evidence**
A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising	**"not occurring in nature"** **"a protein that is the expression product of the mammalian host cell having the amino acid sequence of human erythropoietin which is glycosylated naturally by the host cell at specific amino acids."**	***Amgen* 126 F. Supp. 2d at 91 (D. Mass. 2001).** **See Roche Opening Brief at 11-13.**
a DNA sequence encoding	**"the genetic instructions for"**	***Amgen* 339 F. Supp. 2d at 251 (D. Mass. 2004).**
human erythropoietin	**"a glycoprotein having the amino acid sequence of erythropoietin isolated from human urine having the structure that would be produced in mammalian cells as of the invention date."**	**See Roche Opening Brief at 6-7.**
said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.	**"causing bone marrow cells to increase production of reticulocytes and red blood cells in a living organism."**	**See '868 patent, claim 1**

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Proposed Claim Construction for U.S. PATENT NO. 5,547,933 CLAIM 7		
Claim Limitations	**ROCHE**	**Evidence**
The glycoprotein product according to claim 3, 4, 5, or 6	**"a glycoprotein product according to claim 3"**	Amgen is only asserting claim 7 as depending from claim 3
wherein the host cell is a non-human mammalian cell.	**"cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands"**	*Amgen*, **126 F. Supp. 2d at 86 (D. Mass. 2001).**

Proposed Claim Construction for U.S. PATENT NO. 5,547,933 CLAIM 8		
Claim Limitations	**ROCHE**	**Evidence**
The glycoprotein product according to claim 7		
wherein the non-human mammalian cell is a CHO cell.	**"cell from the ovary of a Chinese Hamster"**	**See Roche Opening Brief at 13.**

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Proposed Claim Construction for U.S. PATENT NO. 5,547,933 CLAIM 9		
Claim Limitations	**ROCHE**	**Evidence**
A pharmaceutical composition comprising	**"a mixture having in addition to the active ingredient (as defined by the claim), an additional distinct and separate ingredient that acts as a diluent, an adjuvant or a carrier"**	**See Roche Opening Brief at 7-8.**
an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and	**"therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals."**	**See Roche Opening Brief at 14.**
a pharmaceutically acceptable diluent, adjuvant or carrier.	**See preamble**	**See Roche Opening Brief at 7-8.**

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Proposed Claim Construction for U.S. PATENT NO. 5,547,933 CLAIM 11		
Claim Limitations	**ROCHE**	**Evidence**
A method for treating a kidney dialysis patient		
which comprises		
administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient.	*Compare to* **"therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals."**	**See Roche Opening Brief at 14.**

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Proposed Claim Construction for U.S. PATENT NO. 5,547,933 CLAIM 12		
Claim Limitations	**ROCHE**	**Evidence**
A pharmaceutical composition comprising	**"a mixture having in addition to the active ingredient (as defined by the claim), an additional distinct and separate ingredient that acts as a diluent, an adjuvant or a carrier"**	**See Roche Opening Brief at 7-8.**
an effective amount of glycoprotein product effective for erythropoietin therapy according to claim 7	**"therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals."**	**See Roche Opening Brief at 14.**
and a pharmaceutically acceptable diluent, adjuvant or carrier.	**See preamble**	**See Roche Opening Brief at 7-8.**

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Proposed Claim Construction for U.S. PATENT NO. 5,547,933 CLAIM 14		
Claim Limitations	**ROCHE**	**Evidence**
A method for treating a kidney dialysis patient		
which comprises		
administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product.	*Compare to* **"therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals."**	**See Roche Opening Brief at 14.**

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Proposed Claim Construction for U.S. PATENT NO. 5,955,422 CLAIM 1		
Claim Limitations	**ROCHE**	**Evidence**
A pharmaceutical composition	**"a mixture having in addition to the active ingredient (as defined by the claim), an additional distinct and separate ingredient that acts as a diluent, an adjuvant or a carrier"**	**See Roche Opening Brief at 7-8.**
comprising		
a therapeutically effective amount of	**"A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing heatocrit levels in mammals."**	***Amgen v. Hoechst.*, 457 F.3d 1293 (Fed. Cir. 2006).**
human erythropoietin	**"a glycoprotein having the amino acid sequence of erythropoetin isolated from human urine having the structure that would be produced in mammalian cells as of the invention date."**	**See Roche Opening Brief at 6-7.**

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Proposed Claim Construction for U.S. PATENT NO. 5,955,422 CLAIM 1		
Claim Limitations	**ROCHE**	**Evidence**
and a pharmaceutically acceptable diluent, adjuvant or carrier,	**See preamble**	**See Roche Opening Brief at 7-8.**
wherein said erythropoietin is purified from mammalian cells grown in culture.	**"obtained in substantially homogeneous form from the mammalian cells, using the word "from" in the sense that it originates in the mammalian cells, without limitation to it only taking it directly out of the interior of the cells, which have been grown in the in vitro culture."** **"cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands"**	**See Roche Opening Brief at 9-11.** *Amgen,* **126 F. Supp. 2d at 86 (D. Mass. 2001).**

Proposed Claim Construction for U.S. PATENT NO. 5,621,080 CLAIM 3		
Claim Limitations	**ROCHE**	
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	**"not occurring in nature"**	***Amgen* 126 F. Supp. 2d at 91 (D. Mass. 2001).**

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Proposed Claim Construction for U.S. PATENT NO. 5,621,080 CLAIM 3		
Claim Limitations	**ROCHE**	
wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6	**"a protein having the amino acid sequence of erythropoietin which is glycosylated at specific amino acids naturally by a host cell."** **"the fully realized form of amino acid sequence of Figure 6"**	**See Roche Opening Brief at 15** ***Amgen* 126 F. Supp. 2d at 86-87 (D. Mass. 2001); *Amgen* 457 F.3d at 1312-17 (Fed. Cir. 2006).**

Proposed Claim Construction for U.S. PATENT NO. 5,621,080 CLAIM 4		
Claim Limitations	**ROCHE**	**Evidence**
A pharmaceutical composition	**"a mixture having in addition to the active ingredient (as defined by the claim), an additional distinct and separate ingredient "**	**See Roche Opening Brief at 7-8.**
comprising		

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Proposed Claim Construction for U.S. PATENT NO. 5,621,080 CLAIM 4		
Claim Limitations	**ROCHE**	**Evidence**
a therapeutically effective amount [of]	**"A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing heatocrit levels in mammals."**	***Amgen* 457 F.3d at 1303 (Fed. Cir. 2006).**
an erythropoietin glycoprotein product according to claim 1, 2, or 3.		

Proposed Claim Construction for U.S. PATENT NO. 5,621,080 CLAIM 6		
Claim Limitations	**ROCHE**	**Evidence**
A method for treating a kidney dialysis patient		
which comprises		

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Proposed Claim Construction for U.S. PATENT NO. 5,621,080 CLAIM 6		
Claim Limitations	**ROCHE**	**Evidence**
administering a pharmaceutical composition of claim 4 in an amount effective to increase the hematocrit level of said patient.	*Compare to* **"therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals."**	**See Roche Opening Brief at 14.**