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 REQUESTED**

DEFENDANTS' OPENING MEMORANDUM IN SUPPORT OF THEIR PROPOSED CLAIM CONSTRUCTION

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Defendants F. Hoffmann-La Roche Ltd., Roche Diagnostics GmbH, and Hoffmann-La Roche, Inc. (collectively "Roche") respectfully submit this memorandum in support of their proposed claim construction of the terms of the six patents-in-suit.

I. INTRODUCTION

In accordance with the law of claim construction, Roche's proposed claim constructions are thoroughly supported by the intrinsic evidence. In fact, many of the proposed constructions come directly from express definitions provided by the patentee in the specification common to all of the involved patents. Roche proposes that the listed terms and phrases should be construed as follows:

Claim Terms	**Roche's Proposed Construction**
human erythropoietin '422 patent, claim 1	*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.*
glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin '933 patent, claim 3.	*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.*
erythropoietin glycoprotein '080 patent, claim 3	*a protein having the amino acid sequence of erythropoietin which is glycosylated at specific amino acids naturally by a host cell.*
process for the production of a glycosylated erythropoietin polypeptide '868 patent, claim 1; '698 claims 4; 6	*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*
process for producing erythropoietin '349 patent, claims 7;	*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*

CHO cell '868 patent, claim 2; '933 patent, claim 8	*cell from the ovary of a Chinese Hamster*
effective amount of a glycoprotein product effective for erythropoietin therapy '933 patent, claims 9, 12	*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.*
purified from mammalian cells grown in culture '422 patent, claim 1	*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.* However, this is a source limitation which does not define the claimed product.
A pharmaceutical composition comprising ... and a pharmaceutically acceptable diluent, adjuvant or carrier '933 patent, claims 9, 12; '422 patent, claim 1	*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*
transformed or transfected with an isolated DNA sequence '868 patent, claim 1(a); '698 patent, claim 2	*introduction of purified exogenous DNA molecules containing the genetic instructions for human erythropoietin*
isolating said glycosylated erythropoietin polypeptide expressed by said cells; *isolating said glycosylated erythropoietin polypeptide therefrom* '868 patent, claim 1; '698 patent, claims 4, 6	*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*

II. THE LAW OF CLAIM CONSTRUCTION

Claim construction "is a matter of law exclusively for the court." *Markman v. Westview Instruments, Inc*., 52 F.3d 967, 977 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). In its most recent major decision on claim construction, the Federal Circuit has instructed that in construing disputed claim terms, "the court looks to 'those sources available to the public that show what a person of skill in the art would have understood'" the claim language to mean. *Phillips v. AWH, Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (*en banc*) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). Those sources include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Phillips*, 415 F.3d at 1314 (quoting *Innova*, 381 F.3d at 1116); *accord Markman*, 52 F.3d at 979-80. Although extrinsic evidence such as dictionaries, technical treatises, and expert testimony may be considered, their value is "less significant than the intrinsic record," and courts are cautioned to weigh them accordingly. *See Phillips*, 415 F.3d at 1317-19. Accordingly, extrinsic evidence cannot be used to vary or contradict the plain language of the claims as determined by the intrinsic evidence. *Id*. at 1324.

Furthermore, "the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Phillips*, 415 F.3d at 1317.

III. SUMMARY OF THE TECHNOLOGY

The technology of the patents-in-suit is known to the Court based on a number of prior trials and hearings. Prior decisions have provided extensive summaries of the technology. *See, e.g., Amgen v. Chugai*, 1989 WL 169006; 13 U.S.P.Q.2d 1737 (D. Mass. 1989) [hereinafter

Amgen I]; *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991) [hereinafter *Amgen II*]; *Amgen v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69 (D. Mass. 2001) [hereinafter *Amgen III*]; *Amgen v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) [hereinafter *Amgen IV*]; *Amgen v. Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126 (D. Mass. 2003) [hereinafter *Amgen V*]; *Amgen v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202 (D. Mass. 2004) [hereinafter *Amgen VI*]; *Amgen v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293 (Fed. Cir. 2006) [hereinafter *Amgen VII*].

In addition, Roche submits herewith as Exhibit G the Expert Declaration of Thomas R. Kadesch, Ph.D., Professor of Genetics at the University of Pennsylvania School of Medicine. Professor Kadesch's declaration summarizes the relevant state of the art in fields of gene cloning, protein expression, glycosylation of human proteins, and protein purification. Dr. Kadesch also provides a perspective of how one of ordinary skill in the art would have understood certain of the claim terms discussed in this memorandum.

IV. THE LIN PATENTS

There are six patents in suit -- U.S. Patent Nos. 5,441,868 (Exhibit A)[1]; 5,547,933 (Exhibit B); 5,618,698 (Exhibit C); 5,621,080 (Exhibit D); 5,756,349 (Exhibit E); and 5,955,422 (Exhibit F); (herein referred to as the '868 patent; the '933 patent; the '698 patent; the '080 patent; the '349 patent and the '422 patent, respectively, and collectively as "patents-in-suit" or the Lin patents). Amgen Amended Complaint (D.I. 52), ¶¶ 14(a)-(f). The patents can be grouped into two broad classes with claims directed to either (1) processes for producing erythropoietin

[1] Exhibits are attached to the accompanying declaration of Thomas F. Fleming.

('868, '698, and '349 patents) or (2) erythropoietin products themselves ('933, '080, and '422 patents).[2]

V. ROCHE'S CLAIM CONSTRUCTION

As indicated in Appendix A of this memorandum, this Court and the Federal Circuit have already construed several of the claim terms of the asserted patents in prior decisions. Although, Roche is not estopped from arguing the construction of those terms as it was not a party to the prior litigation, Amgen is bound by the prior rulings. *See Blonder-Tongue v. University Foundation,* 402 U.S. 313 (1971). Roche nevertheless believes that the Court's construction of these terms as modified by the Federal Circuit and identified in Appendix A is proper, and will rely upon these prior constructions in this case.

A. U.S. Patent No. 5,955,422

Although the '422 patent was the last of the series of patents to issue, it will be discussed here first because the term "human erythropoietin" is recited in the only asserted claim of that patent. Proper construction of that term sets the stage for the construction of all of the other asserted claims.[3]

There are three terms that need to be construed from this claim: (1) *human erythropoietin*; (2) *a pharmaceutical composition comprising . . . a pharmaceutically acceptable diluent, adjuvant or carrier*; and (3) *purified from mammalian cells grown in culture*

[2] The following claims have been asserted by Amgen: (a) '933 patent claims 3, 7-9, 11-12 and 14 (multiple dependent claims 7 and 9 depending only from claim 3); (b) '080 patent claims 3-4 and 6 (multiple dependent claim 4 depending only from claim 3); (c) '422 patent claim 1; (d) '868 patent claims 1-2; (e) '698 patent claims 4-9 (multiple dependent claim 9 depending from claims 2, 4 and 6); (f) claim 7 of the '349 patent (depending only from claim 1)(collectively "the asserted claims"). Pl.'s Resp. to Def.'s First Set Of Interrogs. #1.

[3] Claim 1 of the '422 patent, which is directed to a pharmaceutical composition reads "A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture."

1. human erythropoietin

This term should mean *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.* This construction is supported by the patentee's definition and use of this term in the specification and the prosecution histories.

The specification identifies erythropoietin as (1) "a polypeptide of interest"; (2) a "hormone"; and (3) "an acidic glycoprotein of approximately 34,000 dalton molecular weight, may occur in three forms: α, β, and asialo." (Ex. A at col. 5, l. 50 - col. 6, l. 21).[4]

The specification goes on to state that

> FIG. 6 thus serves to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues (estimated M.W.=18,399)....Sites for potential glycosylation of the mature human EPO polypeptide are designated in the Figure by asterisks.

(Ex. A at col. 22, ll. 6-15) (emphasis added).

Roche's proposed construction is further supported by the prosecution history. In the final amendment before allowance of the claims, the applicant unambiguously stated that

> human 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.

(Ex. H at 5).

Roche's proposed construction is also supported by definitions of erythropoietin consistent with the understanding of one of skill in the art. Dr. Eugene Goldwasser, who is indisputably a skilled artisan in this field, recently testified in this case as follows:

[4] Although all of the asserted patents have a common specification, there are minor pagination differences between the asserted patents. For convenience, all citations to specification of the asserted patents will refer to the specification of the '868 patent which is attached as Exhibit A.

> Q. Well, what is the chemical definition of epo?
> A. It's a glycoprotein of a molecular size, at least human erythropoietin, a molecular size of about 30,000 consisting of 165 amino acids in linear array and about 39 or 40 percent polysaccharide attached to the protein.
> Q. Okay. And what's your biological definition?
> A. It's a hormone that regulates the rate of red blood cell formation in mammals.
> Q. And can you just again tell us what a hormone is?
> A. A hormone is a substance made in one part of a complex organism like a mammal, secreted into the circulation and acts at another part.

(Ex. I at 40:21 - 41:11).

Moreover, Roche's proposed construction comports with prior judicial determinations. For example, this Court has found that:

> EPO is a hormone which is produced naturally in healthy individuals, and is the only hormone required for regulating the level of red blood cells which are found in the normal individual. A hormone is a protein (also called a polypeptide) which is made in one cell, is secreted from that cell, and then acts in another organ.

Amgen I, 1989 WL 169006 at *6.[5]

The phrase "human erythropoietin" of claim 1 of the '422 must also be part of a pharmaceutical composition, as defined in the next section.

2. "A pharmaceutical composition comprising . . . and a pharmaceutically acceptable diluent, adjuvant or carrier"

This phrase should mean *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*.

These claim terms are supported by their ordinary meaning. The term "composition" is a term of art in both chemistry and patent law which "generally refers to mixtures of substances."

[5] The Federal Circuit also characterized erythropoietin in substantially the same way: "EPO is a naturally occurring protein that initiates and controls erythropoiesis, the production of red blood cells in bone marrow." *Amgen IV*, 314 F.3d at 1321.

PIN/NIP, Inc. v. Platte Chemical Co., 304 F.3d 1235, 1243-44 (Fed. Cir. 2002). The Federal Circuit has repeatedly stated that a "composition" in a patent claim is a mixture of specified components. *Mars, Inc., v. H.J. Heinz Co., L.P.*, 377 F.3d 1369, 1374 (Fed. Cir. 2004) (citing *PIN/NIP, Inc. v. Platte Chemical Co.*, 304 F.3d 1235 (Fed. Cir. 2002) and *Exxon Chemical Patents, Inc., v. Lubrizol Corp.*, 64 F.3d 1553 (Fed. Cir. 1995)). A composition specifically refers to claimed ingredients after they are mixed together. *Id.*; *PIN/NIP*, 304 F.3d at 1244.

A pharmaceutical composition meeting the limitations of claim 1 of the '422 patent must have, 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.

This second component of the pharmaceutical composition is recited in the format "A, B or C," which is the same as using Markush language to indicate a closed group of those members. (Ex. R at § 2173.05(h)(I)). As such, diluent, adjuvant and carrier are three different alternatives each of which must be supported in the specification. (Ex. S at § 608.01(p)). The Lin patents provide neither a working example of a pharmaceutical composition nor a specific reference to suitable materials, which could shed light on the meaning of these claim terms. The only diluent disclosed in the Lin patent specification is human serum albumin and the only carrier is saline. (Ex. A at col.35 ll.24-27). Thus, the claim requires the second component of the pharmaceutical composition to be one that acts a diluent, an adjuvant or a carrier as recognized by a person of skill in the art at the time of the invention.

Claims 9 and 12 of the '933 patent are also directed to a pharmaceutical composition and therefore should be construed in the same manner. Similarly, claim 4 of the '080 patent is also to a pharmaceutical composition but does not contain the diluents, adjuvants and carriers limitation.

3. "purified from mammalian cells grown in culture"

Unlike the two prior phrases discussed above with respect to the '422 patent, this phrase does not provide any physical characteristics that define the claimed pharmaceutical composition. The Court's prior construction of "*purified from mammalian cells grown in culture*" was:

> 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.

Amgen III, 126 F. Supp. 2d at 89.

Roche seeks a clarification that the correct reading of claim 1 of the '422 patent is that because this phrase is merely a source limitation, it should be read out of the claim because it does not define the claimed product. As the Federal Circuit instructed in this case, in dealing with validity of the '422 patent, the Court should be "cognizant of the rule that a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations." *Amgen IV*, 314 F.3d at 1354, n.20. This rule was also followed in *Smithkline Beecham Corp v. Apotex Corp.*, 439 F.3d 1312 (Fed. Cir. 2006), there the Federal Circuit invalidated a patent to a pharmaceutical composition that recited process steps as the only distinguishing feature over a prior art tablet.[6] The Federal Circuit stated:

> It makes no difference here whether the '944 patent's product-by-process claims are construed broadly to cover the product made by any process or narrowly to cover only the product made by a dry admixing process. Either way, anticipation by an earlier product disclosure (which disclosed the product itself) cannot be avoided. While the process set forth in the product-by- process claim may be new, that novelty can only be captured by obtaining a process claim. We agree

[6] The patent at issue claimed "[a] pharmaceutical composition in tablet form containing paroxetine, produced on a commercial scale by a process which comprises the steps of: a) dry admixing... b) dry admixing ...and c) compressing mixture into tablets." *Id.* at 1314.

> with the district court's conclusion that the '723 patent disclosure anticipated the identical product claimed by the '944 patent even though that product was produced by an allegedly novel process.

Smithkline, 439 F.3d at 1318-19.[7]

This phrase "*purified from mammalian cells grown in culture*" is merely a source limitation for at least the following reasons. The plain meaning of the claim language itself indicates that this is identifying a source of a component of the already defined claimed pharmaceutical composition. The Federal Circuit confirmed as much. *See Amgen IV*, 314 F.3d at 1330 n.5 ("Accordingly, they limit only the source from which the EPO is obtained, not the method by which it is produced.") (emphasis added).

Moreover, there is nothing in the patent specification that informs the skilled worker which forms of human erythropoietin are obtainable from mammalian cells grown in culture and which forms are not. In fact, the specification leaves open the possibility by saying that the forms of erythropoietin will depend on the host cell employed. (Ex. A at col. 10, ll. 65-68). The PTO examiner understood this when he rejected claims to "recombinant" EPO. (*See* Ex. J) ("While the declaration indicates that some forms of recombinant EPO may be alternatively glycosylated, the use of the generic term 'recombinant' fails to impose any definitive physical limitation on the claimed compositions.").

Critically, Amgen cannot argue that the term *"purified from mammalian cells grown in culture"* should be defined to exclude urinary EPO. This Court has already made a legal determination that it is impossible to determine whether a form of EPO differs from urinary

[7] At the district court level, the patentee tried to distinguish the physical characteristics of the product made by the process from the product of the prior art. *SmithKline,* 2002 U.S. Dist. LEXIS 25275 at 19-20. The district court stated that these characteristics were not required by the patent claims or the specification and therefore insufficient to distinguish the tablets in the earlier patent. *Id.* at 20-21 ("Moreover, we decline to recognize product properties that are not required by the patent claims or specification.").

EPO. *See Amgen III,* 126 F. Supp. 2d 69, 155 (D. Mass. 2001) ("making comparisons between the glycosylation of recombinant EPO and that of human urinary EPO is virtually impossible."). In fact, Amgen's '933 patent claims based on this distinction were invalidated for lack of definiteness for this very reason. *Id.* at 156-57. Therefore, as supported by this judicial finding of fact, this phrase should be construed as nothing more than a source limitation.

B. U.S. Patent No. 5,547,933

1. Glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin

This phrase should be construed to mean *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.*[8]

Roche's proposed construction is based on the claim language and the intrinsic evidence. There is no limiting structural feature of the claimed compound other than it being the product of the expression in a mammalian host cell. Thus, the claim language itself requires a glycoprotein product having a structure that is produced by expression of a gene encoding human erythropoietin and glycosylated by the mammalian cells.

This meaning is supported by the common specification of the asserted patents. For example, the specification states that the existing machinery for gene expression in the 'transformed' or 'transfected' microbial host cells operates to construct the desired product . . . ." (Ex. A at col. 2, ll. 33-36) (emphasis added). The specification further states that "[t]hese polypeptides are also uniquely characterized by being the product of procaryotic or eucaryotic

[8] This phrase appears at claim 3 of the '933 patent which reads "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells."

host expression (e.g., by bacterial, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis." (Ex. A at col.10 ll.52-57) (emphasis added). Moreover, the specification states "[d]epending upon the host employed, polypeptides of the invention may be glycosylated with mammalian or other eucaryotic carbohydrates or may be non-glycosylated." (Ex. A col.10 ll.28-31).

Additionally, the specification states:

> Novel DNA sequences of the invention include all sequences useful in securing expression in procaryotic or eucaryotic host cells of polypeptide products having at least a part of the primary structural conformation and one or more of the biological properties of erythropoietin.

(Ex. A col. 12, ll. 16-21). The specification clearly shows that the patentee linked the glycoproteins of the present invention to the biological process of making them. Thus, the patentee not only specifically defined the polypeptides of the present invention in terms of the process of making them, Amgen also repeatedly stated that production in a host cell is an essential feature of the invention. *See, e.g.*, *Phillips*, 415 F.3d at 1316 (Where the specification reveals "a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess," then the "inventor's lexicography governs"); *see also, Andersen Corp. v. Fiber Composites, LLC,* 474 F.3d 1361, 1366, 1374 (Fed. Cir. 2007).

That the human erythropoietin be glycosylated at specific amino acids is also supported by the intrinsic evidence. The patent specification identifies three potential cites for glycosylation of the erythropoietin protein. (Ex. A at col. 22, ll. 6-15). The specification provides a comparison of the carbohydrate constitution of recombinant CHO cell-produced erythropoietin and purified human urinary erythropoietin. The same types of carbohydrates are found on both forms. Amgen now admits that the ratios of these carbohydrates are incorrectly reported in the patent. (*Fritsch et al. v. Lin*, Interference No. 102,334, 21 U.S.P.Q.2d 1739, 1741

(Bd. Pat. App. & Interf. 1992) ("Lin concedes that the hexose value reported ... is probably incorrect")). Nevertheless, the patent specification makes clear the human erythropoietin produced in mammalian cells has the amino acid sequence of Figure 6 wherein naturally occurring sugars are attached to three specific asparagine residues. No other amino acid residue is described in the patent specification as being post translationally modified.

Roche's proposed definition also finds support in the prosecution file history. During prosecution of the '933 patent, the Examiner required patentee to positively recite in the claim the glycosylation pattern (structure) he asserts the native species does not possess. (Ex. K at 3). 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. L at 4) (emphasis added).

2. CHO cell

This term should be construed to mean "*a cell from the ovary of a Chinese hamster*." The specification makes clear that "CHO" means a "Chinese hamster ovary"" (Ex. A at col. 15, l. 64). A "cell" in common parlance is the smallest metabolically functional unit of life and, except for sex cells, contains a diploid or full complement of paired chromosomes. Additionally, as the specification indicates, the CHO cells can be grown in culture. (Ex. A at col. 26, l. 50 – col. 30, l. 45). This Court made a similar ruling in prior litigation when it construed mammalian cells to mean "cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands" *Amgen III,* 126 F. Supp. 2d at 86 (D. Mass. 2001).

Claim 2 of the '868 patent also has the term "CHO cells," and should be defined accordingly.

3. Effective amount of a glycoprotein product effective for erythropoietin therapy [‘933 patent, claims 9 and 12]

Roche contends that this phrase should be given the same construction as the limitation “therapeutically effective amount.” The Federal Circuit recently interpreted “therapeutically effective amount” as used in the ‘422 patent to mean:

> 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.

Amgen VII, 457 F.3d at 1303.

Based on its plain meaning, an “effective amount...for erythropoietin therapy” cannot substantially differ from a “therapeutically effective amount” of erythropoietin. Moreover, because the ‘933 and ‘422 patent specifications are identical, these claims should be construed the same. *See NTP, Inc., Inc., v. Research in Motion, LTD.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005) (“Because NTP’s patents all derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents.”). The Federal Circuit determined that “therapeutic,” as used in the specification, covers more than just an increase in hematocrit of the recipient. *Amgen VII*, 457 F.3d at 1303. The Federal Circuit’s decision rested on express statements in the specification. *Id.* Likewise “erythropoietin therapy,” as used in the claims of the ‘933 patent, should also not be limited to just increasing hematocrit but should cover all of the indicated responses listed in the specification.

C. U.S. Patent No. 5,621,080

1. erythropoietin glycoprotein

Erythropoietin glycoprotein, as used in claim 3 of the '080 patent[9], should not be construed any differently from *glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin,* as this phrase exists in claim 3 of the '933 patent. Both claims use these terms to describe the same chemical substances that possess the same biological activity. As such, this phrase should be construed as *a protein having the amino acid sequence of erythropoietin which is glycosylated at specific amino acids naturally by a host cell.*

D. United States Patent Nos. 5,441,868 and 5,618,698

The '868 and '698 patents claim processes for the production of "*a glycosylated erythropoietin polypeptide."* The three independent claims at issue from these two process patents are claim 1 of the '868 patent; and claim 4 and claim 6 of the '698 patent.[10]

[9] Claim 3 of the '080 patent reads "A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6."

[10] Claim 1 of the '868 patent reads "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 (b) isolating said glycosylated erythropoietin polypeptide therefrom."
Similarly, Claim 4 of the '698 patent reads: "A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and b) isolating said glycosylated erythropoietin polypeptide expressed by said cells."

1. process for the production of glycosylated erythropoietin polypeptide

This phrase means a *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*.

Based on its plain meaning, *glycosylated erythropoietin polypeptide* should be construed to be a synonym of the terms *glycoprotein product of the expression* and *erythropoietin glycoprotein*, which were defined above for the '933 and '080 patents, respectively.

Second, during prosecution of the '868 patent, Amgen submitted claims to a process for the preparation of an in vivo biologically active glycosylated polypeptide without reference to an *erythropoietin* polypeptide. (Ex. M). The examiner rejected these claims for lack of enablement and indefiniteness. (Ex. N). In response, Amgen argued that the rejection was improper in view of the recitation in the claims to an isolated DNA sequence encoding human erythropoietin. Applicants went on to state 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).

This exchange shows that 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. Thus, any material that is not obtainable through the practice of the process is not a glycosylated erythropoietin polypeptide for the purposes of this claim. Moreover, as discussed below, the claim requirement that the "*said glycosylated erythropoietin polypeptide*" be expressed from the "said cells" further supports this construction that the erythropoietin be obtainable through the process steps (a) and (b) of these claims.

2. isolating said glycosylated erythropoietin polypeptide therefrom; isolating said glycosylated erythropoietin polypeptide expressed by said cells

These phrases should be construed to mean *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.*

This construction is supported by the patent specification and from positions Amgen successfully maintained before the Patent Office. The specification states that "provided by the invention are novel methods for the production of useful polypeptides comprising . . .isolation of the desired polypeptides from the growth medium, cellular lysates or cellular membrane fractions." (Ex. A at col. 11, ll. 46-53) (emphasis added). Thus, the patent specification clearly uses "isolation" as a means of separating the desired polypeptide from other aspects of the growth medium.

Moreover, during Interference Proceedings involving the priority of Dr. Lin's inventions, Amgen advocated a similar construction when it stated that "[t]he isolation step (b) means nothing more than separating the expressed product from the cells (LR 229) and would obviously be necessary to determine the *in vivo* biological activity of the expression product." (Ex. P at 48). Amgen argued successfully that "isolating" the polypeptides as required by this process claims was not a purification step and therefore non-inventive. (Ex. P at 58) ("As for the isolating step, there is clearly nothing separately inventive in this. Fritsch et al again try to equate isolation with purification, but as noted earlier, these two are not the same..."). Upon Amgen's urging, the Patent Office found that there was "no evidence suggesting that the work done at Amgen relating to expression of the EPO gene in mammalian host cells and isolation of the resulting glycoprotein product involved anything other than the exercise of ordinary skill by practitioners in that field. *Fritsch v. Lin,* Interference No. 102,097, 1991 WL 332571, *3 (Bd.

Pat. App. & Interf. 1991) (emphasis added). Amgen should not be able to argue for a different claim construction now, especially since it previously persuaded the Patent Office that this phrase merely means "separating the expressed product from the cells" and not "purification."

3. transformed or transfected with an isolated DNA sequence encoding human erythropoietin

The phrase is recited only in claim 1 of the '868 patent. It also appears in a number of non-asserted claims. This phrase should be construed to mean *introduction of a purified exogenous DNA molecules containing the genetic instructions for human erythropoietin.*

This construction is supported by the patent specification, the file history, and the understanding of a person of skill in the art. The patent specification describes two examples where mammalian cells are either transformed or transfected with DNA encoding human erythropoietin. Example 7A reports that the vector pSVgHUEPO "was propagated in E.coli and vector DNA isolated," (Ex. A at col. 25, l. 5), and the isolated DNA was used to transfect COS-1 cells. These same procedures were later used to transform CHO cells as disclosed in Example 10 of the Lin patents. Both these examples demonstrate that purified exogenous DNA molecules are introduced into the host system.

As further intrinsic evidence, the patent specification defines the transformation and transfection techniques of the invention by reference to U.S. Patent No. 4,399,216. (Ex. A at col. 26, ll. 62-65) (Ex Q; "the '216 patent"). The '216 patent defines transformation as "the process for changing the genotype of a recipient cell mediated by the introduction of purified DNA." (Ex. Q at col. 4, ll. 15-17).

Amgen's Responses to Interrogatories proposed the claim construction for this term: "*[said cells] receiving purified genetic instructions for human erythropoietin*." Therefore, both

Amgen and Roche agree that the isolated DNA sequence encoding erythropoietin must be purified and not to be introduced with other genetic material.

Roche's proposed construction is further supported by the file history. During the prosecution of the '868 patent, Amgen told the PTO that the pending claims containing this limitation were addressing a preparative process involving erythropoietin DNA corresponding to the DNA of claim 2 of the '008 patent. (Ex. O at 6) Claim 2 of the '008 patent requires "purified and isolated DNA sequences." Therefore, the file history also supports the proposition that the introduced material be purified and exogenous DNA.

E. United States Patent No. 5,756,349[11]

1. process for producing erythropoietin

This phrase should be construed to mean the product of the process is erythropoietin. The definition of erythropoietin was discussed above in reference to the terms "human erythropoietin" and "erythropoietin glycoprotein."

VI. CONCLUSION

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

DATED: Boston, Massachusetts
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[11] 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 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin."

Respectfully submitted,

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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.

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APPENDIX A

	Term or Phrase	Claim Construction	Relates to Claims
	non-human DNA sequences which control transcription	"DNA sequences not part of the human genome that initiate and may regulate the process of transcription" *Amgen I*, 126 F. Supp. 2d at 87-88 (D. Mass. 2001).	'349 patent, claim 1
	DNA encoding	"the genetic instructions for" *Amgen IV*, 339 F. Supp. 2d at 251 (D. Mass. 2004).	'349 patent, claim 1; '698 patent, claims 4, 6
	glycosylation which differs from	"Glycosylation as to which there is a detectable difference based upon what was known in 1983-1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." *Amgen I*, 126 F. Supp. 2d at 92 (D. Mass. 2001).	Not in asserted claims.
	human urinary erythropoietin	"erythropoietin derived from human urine" *Amgen I*, 126 F. Supp. 2d at 93 (D. Mass. 2001).	Not in asserted claims.
	mammalian cells	"cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands" *Amgen I*, 126 F. Supp. 2d at 86 (D. Mass. 2001).	'698 patent, claim 9
	mature erythropoietin amino acid sequence of FIG. 6	"the fully realized form of amino acid sequence of Figure 6" *Amgen I*, 126 F. Supp. 2d at 86-87 (D. Mass. 2001). This is limited to the 166 amino acid erythropoietin of Figure 6. No equivalents are allowed. *Amgen V* 457 F.3d at 1312-17 (Fed. Cir. 2006).	'080 patent, claims 3; '698 patent, claim 4, 6

APPENDIX A

	non-naturally occurring	"not occurring in nature" *Amgen I* 126 F. Supp. 2d at 91 (D. Mass. 2001).	'080 patent, claim 3; '933 patent, claim 3
	operatively linked	"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 I*, 126 F. Supp. 2d at 89-90 (D. Mass. 2001).	'698 patent, claim 4
	therapeutically effective amount	"A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals." *Amgen V*, 457 F.3d at 1303 (Fed. Cir. 2006).	'422 patent, claim 1; '080 patent, claim 4
	vertebrate cells	"cells from an animal having a backbone" *Amgen I*, 126 F. Supp. 2d at 85 (D. Mass. 2001).	'349 patent, claims 1, 7; '698 patent, claims 4, 6, 7

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].