EXHIBIT 28

PART 1 OF 2

CONTAINS RESTRICTED ACCESS CONFIDENTIAL MATERIAL PURSUANT TO PROTECTIVE ORDER

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

DEFENDANTS' FIFTH SUPPLEMENTAL RESPONSES AND OBJECTIONS TO PLAINTIFF AMGEN INC.'S FIRST SET OF INTERROGATORIES TO DEFENDANTS (NOS. 9-11)

Defendants F. Hoffmann-La Roche Ltd., Roche Diagnostics GmbH, and Hoffmann-La Roche Inc. (collectively "Roche") make the following further supplemental objections and responses to Plaintiff Amgen Inc.'s ("Amgen") First Set of Interrogatories (Nos. 1-15).

GENERAL OBJECTIONS

Defendants' incorporate by reference its General and Specific Objections set forth in Roche's Third Supplemental Responses and Objections to Plaintiff Amgen Inc.'s First Set of Interrogatories to Defendants (Nos. 1-15) as if fully set forth herein.

Moreover, Roche specifically reserves its right to supplement its responses to interrogatories that deal with the obviousness of the asserted claims of the patents-in-suit. As Amgen is aware, the Supreme Court just yesterday issued its opinion in *KSR International Co. v. Teleflex Inc.*, 550 U.S. __ (2007), where the Court eliminated the requirement of a specific "teaching, suggestion, or motivation" within the prior art for purposes of finding obviousness

under 35 U.S.C. § 103. Roche is still studying the ramifications of this decision. However, Roche is aware of numerous instances within the file histories of the patents-in-suit where Amgen overcame prior art by relying upon this "teaching, suggestion, or motivation" standard. As a result, those issued claims may no longer be valid because of this change in the law. In addition, the Supreme Court's decision opined on other issues which may also undermine the validity of the patents-in-suit. Roche will timely supplement its responses as soon as it has fully investigated this decision and its impact on this case.

Moreover, Amgen is still producing documents and supplemental expert reports, and as a result, Roche reserves its right to supplement these discovery responses in view of Amgen's continued production. Moreover, Amgen has had Roche's Expert Reports On Invalidity and Unenforceability since April 6, 2007, but has not made any effort to supplement its interrogatory responses regarding these issues. Therefore, Roche reserves its right to supplement these discovery responses to contend with Amgen's responses.

SUPPLEMENTAL RESPONSE

INTERROGATORY NO. 9

Separately, in claim chart form for each claim of Amgen's patents-in-suit that you contend in your Fifth and Sixth Affirmative Defenses or Tenth Counterclaim is invalid, identify:

(a) on a limitation-by-limitation basis, the legal and factual grounds on which you contend that such claim is invalid;

(b) the level of skill of a person having ordinary skill in the art to which the subject matter of the patents-in-suit pertains at the time of the claimed inventions;

(c) all evidence on which you rely in support of each contention, including all documents, testimony, prior knowledge, or public uses tending to support your contention(s), every test, experiment, and/or data upon which you rely in support of each contention that a claim is invalid;

(d) each person, other than counsel, who furnished information or was consulted regarding Roche's response to this interrogatory including the nature and substance of each such person's knowledge or information; and

(e) the three individuals affiliated with Roche, other than counsel, most knowledgeable regarding the subject matter of this interrogatory, stating the nature and substance of each such person's knowledge or information.

SUPPLEMENTAL RESPONSE:

In addition to all prior responses and subject to and without waiver of Roche's previously propounded Specific Objections and General Objections set forth above all of which are incorporated herein by reference, Defendants respond as follows.

Roche hereby incorporates by reference the Expert Report of Dr. Carolyn Bertozzi, dated 4/6/07, and supporting material; the Expert Report of Dr. Guenter Blobel, dated 4/6/07, and supporting material; the Expert Report of Dr. James W. Fisher, dated 4/6/07, and supporting material; the Expert Reports of Dr. Richard Flavell, dated 4/6/97 and 5/1/07, and supporting material; the Expert Report of Dr. Michael E. Fromm, dated 4/6/07, and supporting material; the Expert Report of Dr. Franklin Gaylis, dated 4/6/07, and supporting material; the Expert Report of Dr. Edward Everett Harlow, dated 4/6/07, and supporting material; the Expert Reports of Dr. Thomas Kadesch, dated 4/6/07 and 5/1/07, and supporting material, the Expert Report of Dr. Rodney E. Kellems, dated 4/6/07, and supporting material; the Expert Report of Dr. Robert Langer, dated 4/6/07, and supporting material, the Expert Reports of Dr. John Lowe, dated 4/6/07 and 5/1/07, and supporting material; the Expert Report of Jack Nunberg, dated 4/6/07, and supporting material; the Expert Report of Dr. Daniel Shouval, dated 4/6/07, and supporting material; the Expert Reports of Michael Sofocleus, dated 4/6/07 and 5/1/07, and supporting material, the Expert Reports of Dr. Bruce Spinowitz, dated 4/6/07 and 5/1/07, and supporting material; the Expert Report of Dr. Charles Zaroulis, dated 4/6/07.

Roche also incorporates by reference its defenses and counterclaims described in its pleadings, including Roche's First Amended Answer and Counterclaim, dated March 30, 2007.

A. Lack of Written Description, Enablement, and/or Definiteness Under Section 112

1. "human erythropoietin"

Amgen has asserted in its *Markman* briefing, and the Court has tentatively held, that "human erythropoietin" should be defined as "[a] protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." *See Amgen Inc.'s Response to Defendants' Claim Construction Brief*, dated 3/19/07, at 5. Amgen has also asserted in its expert reports that "human erythropoietin" should be even more narrowly defined to be limited to a protein having 165 amino acid residues. *See* Expert Report of Dr. Harvey Lodish, ¶ 26 ("Human EPO has a primary structure consisting of a polypeptide backbone with 165 amino acid residues. The amino acid sequence for human EPO is depicted at position +1 through +165 in Figure 6 of Amgen's patents."). Roche disagrees with these definitions. However, should the Court construe this term to adopt these definitions, then the asserted claim containing this term, namely claim 1 of the '422 patent, claims 3, 7-9, 11-12 of the '933 patent, claim 1 of the '868 patent, and claim 7 of the '349 patent, would be invalid for lack of definiteness and/or lack of written description under 35 U.S.C. § 112.

First, the claim would be indefinite because one of skill in the art, reading Amgen's written description as of their November 1984 filing date would not have known what "the amino acid sequence of human EPO" was. The patent provides a number of examples of the amino acid of human erythropoietin, but those examples are either wrong or indefinite. For example, during the prosecution of the '422 patent, Amgen told the Patent Office that:

> Human erythropoietin as recited in Claim 64 is disclosed in several examples of the application. Example 1 discloses the use of human erythropoietin isolated from the urine of patients afflicted with aplastic anemia ("urinary EPO") to produce tryptic fragments and the amino acid sequencing of those fragments. Examples 7

> and 10 disclose the production of human erythropoietin in COS-1 and CHO cells, respectively. Thus, 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. The application further discloses that the glycosylation of human urinary erythropoietin may differ depending upon the host cell used for production. Claim 64, however, excludes EPO that is isolated from human urine by the phrase "purified from mammalian cells grown in culture.

('197 File History, Paper 33, 4/28/99 Amendment at 4-5 (emphasis added); see also April 6, 2007 Exp. Rep. ¶196).

However, the amino acid sequence information disclosed in Table 1 of Example 1 of the patent specification does not accurately reflect the amino acid sequence of human urinary EPO. Table 1 discloses fragment T28, indicating that this portion of human urinary EPO has the amino acid sequence "E-A-I-S-P-P-D-A-A-M-A-A-P-L-R". However, subsequent to the filing of the patent application, Amgen determined that human urinary erythropoietin does not contain such a sequence. Amgen provided the amino acid sequence of human urinary EPO to the U.S. FDA in 1985 which does not include the T28 sequence. In the sequence of human urinary erythropoietin provided to the FDA, there is a glycosylated serine, "S" in place where one would expect an "M", methionine based on the T28 fragment. (Figure 4B-7 at AM-ITC 00596041 042).

A scientific article published by Amgen scientists and Eugene Goldwasser in 1986 also demonstrates that the T28 sequence described in the patent was incorrect. (Lai et al. 1986; Figure 1). This publication, like the sequence given to the FDA, indicates that T28 has a serine and not a methionine. The article states that the amino acid in position 126 of erythropoietin isolated from human urine is serine, not methionine as suggested by the patent. Regarding this amino acid the authors state

> Sequence analysis peptides T28 and 2S63 indicated a serine at position 120 and no identifiable PTH for position 126. However, amino acid composition analysis revealed the presence of 2 serine residues in this fragment. Analysis if the DNA sequence indicated that a serine is present at position 126 (10, 11). One possible explanation for these results is that position 126 is a glycosylated serine.

Id. Therefore, one of skill in the art could not have relied upon the T28 fragment of Figure 1 of the patent to know what the amino acid sequence of human erythropoietin.

As support for its claim construction, Amgen has cited to example 12 of the patent where *E. coli* host cells have been used to express a synthetic met-1-166 coding region. *See Amgen Inc.'s Response to Defendants' Claim Construction Brief*, dated 3/19/07, at 7. However, the patent states that the expression product of this DNA sequence can be one of two possible sequences, a 1-166 sequence or a 2-166 sequence. The patent states in relevant part:

> Protein sequencing revealed the product to be greater than 95% pure and the products obtained revealed two different amino terminals, A-P-P-R . . . and P-P-R . . . in a relative quantitative ratio of about 3 to 1. This latter observation of hEPO and [des Ala.sup.1]hEPO products indicates that amino terminal "processing" within the host cells serves to remove the terminal methionine and in some instances the initial alanine.

'868 patent, col. 33, ln. 43-48.

In fact, Dr. Lodish, in his Expert Report, suggests that this met-1-166 coding sequence results in a third different amino acid sequence. At paragraph 140 of this report, he states that "upon expression in E. coli, this would result in the synthesis of a human erythropoietin with an additional methionine amino acid at position -1." *See* Expert Report of Dr. Harvey Lodish, ¶ 140. Notwithstanding that there is no support for this position in the patent specification, and that Dr. Lodish is wrong in this conclusion, this only highlights the uncertainty that one of skill in the art as of November 1984 (which Dr. Lodish was), would have had no precise idea what the

amino acid sequence of human erythropoietin by relying upon the specification of the patents-in-suit.

As stated above, in defining "human erythropoietin" to the Patent Office during the prosecution of the '422 patent, Amgen also pointed the Examiner to recombinant erythropoietin produced in COS-1 and CHO cells, as predicted by the DNA and amino acid sequence of Figure 6 of the patent. However, Figure 6 of the patent shows a 166 amino acid structure, and not the 165 amino acid protein that is now known today. In fact, the Federal Circuit has already confirmed that Figure 6 describes 166 amino acid protein, and not a 165 protein. *Amgen, Inc. v. HMR/TKT*, 314 F.3d 1313, 1343 (Fed. Cir. 2003) ("If, then, as the specification states, 'the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues,' it is simply illogical for Amgen to argue that that means anything other than, at minimum, the 166 amino acids shown in Figure 6. This is verified by the fact that '080 claims 2 and 3 claim an erythropoietin glycoprotein 'compris[ing] the mature erythropoietin amino acid sequence of Fig. 6 ... .' Again, read properly in light of the term "comprising," this means that the claimed glycoprotein must have — at minimum — all 166 amino acids shown in Figure 6.").

In fact, the patent only describes monkey erythropoietin as having 165 amino acids, and explicitly states that human erythropoietin in 166 amino acids. *See* '868 patent, col. 36, ln. 44-50 ("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 FIG. 5 and the 166 residues of human species EPO in FIG. 6 ...").

As Amgen has admitted, at the time of the patent application, Amgen did not know that human erythropoietin was a 165 amino acid protein, and that the last encoded amino acid, arginine, was cleaved off during secretion of the protein. *See* Expert Statement of Harvey F. Lodish, dated 12/20/99, at ¶124 ("Although it was not known at the time the applications for Amgen's Patents were filed, it is now well-understood scientifically that mature human EPO has that 165-amino-acid sequence."); Amgen NDA at AM 17 049300, AM-ITC 00376376, Interference No. 102,096, No. 102,097, and 102,334, Ex. 399 ("The complete primary protein sequence analysis of r-HuEPO indicates that the amino acid sequence of this recombinant protein conforms to that deduced from the sequence of the coding DNA. The Arg 166, coded for by the erythropoietin gene (Section 2.8) appears to be cleaved post-translationally, resulting in a C-terminal residue of Asp 165." *See also Fritsch v. Lin*, 21 U.S.P.Q.2d 1731, 1733 (Bd. Pat. App. & Interf. 1991) ("The subject matter in issue relates to a purified and isolated DNA sequence encoding for human erythropoietin (EPO), a protein consisting of 165 amino acids which is naturally produced in the body and which stimulates the product of red blood cells.").

The correct amino acid sequence was discovered after the November 1984 filing date, when others in the field, (not Amgen), including Genetics Institute published the correct amino acid sequence of human erythropoietin. *See* Recny et al., "Structural Characterization of Natural Human Urinary and Recombinant DNA-derived Erythropoietin," *J.Biol.Chem.*, 262(35), 17156-63 (1987); Imai et al., "Physiochemical and Biological Comparison of Recombinant Human Erythropoietin with Human Urinary Erythropoietin," *J. Biochem.*, 353-359 (1990) ("The primary structure of rhEPO, consisting of 165 amino acid residues, was determined, and the C-terminal arginine predicted from the cDNA sequence was confirmed to be missing, as previously described (Recny et al., (1987) J. Biol. Chem. 262, 17156).").

Therefore, based upon the Court's tentative claim construction of "human erythropoietin" as meaning "[a] protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine," this term would have meant too many various sequences based upon the patent specification. As a result, the asserted claims containing this terms are invalid for lack of definiteness under Section 112, ¶2.

Moreover, for the same reasons stated above, the asserted claims containing this term would also be invalid for lack of written description under Section 112, ¶1. Clearly, this term cannot mean the 165 amino acid sequence that scientists today know to be correct. Figure 1 of the patent has the wrong amino acid sequence within the T28 fragment. Example 12 of the patent provides a 1-166 polypeptide and 2-166 polypeptide. Dr. Lodish argues that Example 12 of the patent actually shows a -1 to 166 protein. Figure 6 of the patent only describes a 1-166 amino acid protein, and not the correct 165 sequence, as confirmed by the Federal Circuit.

In fact, in briefing during prior litigation with *Hoechst*, Amgen admitted that patent specification lacked a proper written description of the 165 amino acid protein, and that adding such a disclosure to the application would constitute new matter. Amgen stated:

> During the July 28 hearing, the Court questioned whether Amgen could have amended its '080 claims to expressly recite the 1-165 amino acid sequence of Figure 6. [footnote omitted] As Amgen's counsel stated at the hearing, the answer to that question is no. When Amgen drafted and filed its patent application, it was unknown and unforeseeable that the human EPO product of example 10 in the patent had 165 amino acids rather than the deduced 166 amino acid sequence shown in Figure 6. Because this fact was unknown in 1984 when the written description of Amgen's specification was drafted and submitted, the specification did not expressly recite an EPO having the 1-165 sequence. As explained more fully in Section II(A) below, the absence of an express description of that specific sequence in Amgen's application made a later claim amendment reciting that specific sequence impermissible.

Amgen Inc.'s Post-Hearing Memorandum In Support Of Its Fed. R. Civ. P. 52(c) Motion that '080 Claims 2-4 Are Infringed Under The Doctrine Of Equivalents, dated August 18, 2003, at 1., *Amgen Inc. v. Hoeschst Marion Roussel, Inc.*, Civ. Action No. 97-10814-WGY. Amgen's went on to state that:

> The applicant cannot add new written description, whether in the specification or in the claims themselves, to describe a particular equivalent that became foreseeable after the application date but before the date of an amendment. The applicant is constrained by the original written description and drawings what were in the application at the filing date [citing M.P.E.P. §§ 608.01(g) and (o), 2163(B) and 2163.05-.06] To subsequently add a description of the later-discovered equivalent - in this case, the fact that the product of example 10 has only 165 amino acids - would violate the statutory prohibition against adding new matter to the application...
>
> ...The fact that 165 human EPO was not foreseeable at the date of the application, and therefore not literally described in Amgen's specification, also explains why, even under Defendant's test, Amgen could not reasonably have been expected to submit a claim amendment that literally recited that sequence. Although the amino acid sequence of 165 human EPO is depicted within the 166 amino acid sequence shown in Figure 6, that fact alone is not sufficient to support a claim that recites the 165 human EPO sequence. Where a specification describes a genus of compounds, such as EPO having the sequence of Figure 6 and fragments thereof, a claim reciting a specific single species within that genus, (e.g., 1-165) is not supported unless the specification expressly recites that species as the applicant's invention [citing *In re Ruschig*, 379 F.2d 990, 994 (C.C.P.A. 1967].

Id. at 5-6. As to whether the 165 amino acid protein was "inherent" in Example 10 of the patent, Amgen admitted that this was irrelevant for purposes of a proper written description because the 165 sequence was not explicitly recited. *Id.* at 9 ("Even though 165 human EPO was inherently produced in Example 10, it was not expressly recited as being Amgen's invention in the '080 patent specification."). This is consistent with Federal Circuit precedent which states that a claim term must be construed to cover only what the specification recited at the time of the

application. *See Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1355 (Fed. Cir. 2000) (Schering's claims could not be construed to cover the mature polypeptide which required post-translational processes to remove extra DNA sequences because the inventor "had not identified the extraneous sequences nor the need to remove them" and thus "the district court correctly construed the claims as covering only immature polypeptides."). As the Court stated in *In re Fox*, 128 U.S.P.Q. 157, 158-59 (Bd. Pat. App. & Interf. 1957):

> three years after the application was filed, appellant inserted a new name and formula for the compound and added the claims now before us in which the base is claimed by the new name. In an amendment filed November 7, 1955, there was filed therewith an affidavit of Fox relative to experiments conducted by him to establish the correct structure of the compound...
> ...we agree with the examiner that the present disclosure is inadequate to warrant the change and to define the product by other than its method of production.

Id. Moreover, during the prosecution of the '933 patent, in order to overcome an enablement rejection, Amgen amended its claims and conceded that its invention to recombinant erythropoietin required product-by-process claims in order to "positively recite the physical properties ...and to further define the product of the subject invention since the recombinant erythropoietin claimed cannot be precisely defined except by the process by which it is produced." '933 patent application, Amendment, dated 6/2/89, at 3. Thus, Amgen told the Patent Office that its invention could not be defined by a particular amino acid sequence, but only by a particular process.

Therefore, Amgen readily admits that the patent specification does not adequately describe a 165 amino acid protein either explicitly or inherently. Given the Court's tentative construction that "human erythropoietin" means "[a] protein having the amino acid sequence of

human EPO, such as the amino acid sequence of EPO isolated from human urine," Amgen's asserted claims containing this element would be invalid for lack of written description.

2. "vertebrate cells"

Asserted claim 7 of the '349 patent, which depends from claim 1, is invalid due to lack of written description and enablement of the claim term "vertebrate cell" because the patent disclosure fails to enable and adequately describe the full scope of the claim. This claim has previously been construed by this Court to mean "cells from an animal having a backbone." As construed the claim term then covers cells from over 50,000 animal species, and millions of differentiated cells from within those species. However, the '349 patent specification discloses only two specific examples of vertebrate cells: CHO cells taken from the ovary of a Chinese Hamster, and COS-1 cells taken from the kidney of an African Green Monkey. In addition, the '349 patent provides only one working example of vertebrate cells that actually stably express the EPO gene to make human eryrthropoietin, CHO DHFR cells. (Kadesch paragraphs 47-54) (Nunberg paragraphs 35-49).

In 1983-1984, only a handful of potential mammalian host cells were being used and is was impossible to predict that promoters, transfection systems and cloning techniques would succeed in non-mammalian systems. There would not have been a reasonable expectation of success that a skilled artisan, reading the '349 patent in 1984, could produce biologically active forms of the erythropoietin glycoprotein in the full range of vertebrate cells. Further, it would require undue experimentation to practice the full scope of these claims in 1984. (Kadesch paragraphs 54-60) (Nunberg paragraphs 35-49).

3. Analogs of EPO

The Lin patents would not have enabled a person of ordinary skill in the art in the 1983-1984 timeframe to use a pegylation reaction to synthesize a new chemical having erythropoiesis

stimulating activity, through routine experimentation. Additionally, Pegylation is not disclosed in the patent or the file history and none of the prior art references cited in the Lin patents concern PEGylation of proteins.

In 1983-1984, the science of PEGylation was not fully developed and the use a pegylation reaction to synthesize a new chemical having erythropoiesis stimulating activity was not something that could be done by routine experimentation. Dr. Lin himself testified that he was aware of PEGylation in November 1984, but did not disclose it in his patents. He further testified that he would not be able to predict whether modifications like PEGylation would result in active protein. Amgen also made numerous statements during the prosecution of patents not in suit, all of which were filed well after 1984, that support the position that PEGylation is not a task that can be performed through routine experimentation. For example, during the prosecution of Amgen's patent No. 6,586,398, Amgen argued that the prior art references did not "teach or suggest the PEGylation of hyperglycosylated or glycosylated proteins," and that "not all proteins respond equally to PEGylation and there is no guarantee of improved performance." (Langer paragraphs 25-63)

Amgen's scientists have also testified about the difficulties associated with generating EPO analogs. For example, Dr. Elliot testified that constructing viable EPO analogs is difficult, time consuming, and unpredictable. (Langer paragraphs 64-68)

Therefore, one of ordinary skill in the art in 1984 would not have been able to use a pegylation reaction to synthesize a new chemical having erythropoiesis stimulating activity and the Lin patents do not convey to a person of ordinary skill in the art that the inventor was in possession of this.

4. "non-naturally occurring"

Claim 3 of the '933 patent and claim 4 of the '080 patent claim a "non-naturally" occurring glycoprotein product. This term is indefinite under section 112. In order to determine whether a particular sample of EPO infringes upon these claims, one of skill in the art would have to compare that sample with a standard EPO which occurs in nature, or is "natural," to determine if the particular EPO sample is natural or non-natural using techniques available in 1984.

Given the microheterogeneity of EPO, EPO that occurs in nature can have a different distribution of glycoforms depending on a variety of factors, including the particular physiological condition of the human source it was taken from, whether it was taken from the human urine or plasma, and whether it was from a pooled source or not. The patents-in-suit do not specify which "naturally" occurring EPO should be used as a standard to determine whether a particular EPO sample is natural or non-natural. Nor do they define what is meant by EPO which occurs in nature. The patents-in-suit provide no guidance to a person of skill in the art as to whether a particular sample of EPO is "naturally occurring" or "non-naturally occurring," in that the patent provides no definition for "naturally occurring" EPO. Additionally, none of the prior art references to urinary human EPO preparations could serve as a standard to define "naturally occurring" EPO. Further, based on the data in example 10, which Amgen has admitted are erroneous, one of skill would not be able to determine whether a sample was "non-naturally occurring." (Bertozzi paragraphs 50-69).

Therefore, claim 3 of the '933 patent and claim 4 of the '080 patent are invalid for indefiniteness because one skilled in the art would be unable to comprehend the bounds of the claim language.

4. "100 U of erythropoietin per 106 cells in 48 hours as determined by radioimmunoassy"

Independent claims 1 and 4 of the '349 patent cover vertebrate cells capable 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." "U" or "units" refers to a measure of biological activity. Therefore, without a defined standard, one cannot determine units through a radioimmunoassay that merely quantifies the amount of protein present in a sample. This phrase is therefore indefinite because the Lin patents fail to identify the standard to be used.

To quantify the amount of biological activity presenting a sample, biochemists often develop an arbitrary measure, most often a "unit," that refers to a specific biological response obtained under a defined set of conditions. Claims 1-6 of the '349 patent specify that Units of EPO are determined using radioimmunoassay. Radioimmunoassays measure amounts in terms of numbers of molecules or weight. In order to equate units of biological activity to a specific amount or weight of a protein, it is necessary to know the specific activity of the protein sample, which is the amount of activity (units) per unit weight (milligrams). Specific activity of a protein or enzyme is a necessary conversion factor between weight and activity measurements. (Kadesch 31-36)

Different assays relying on different standards will almost certainly generate different results. Standards having different specific activities will generate different values for bioactivity in a radioimmunoassay because the conversion factor differs. While several potential standards were available for use in assays for erythropoietin, these all varied in their specific activity. (Kadesch paragraphs 37-42)

The limitation "...U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay" therefore, cannot be determined. First, the number of units of bioactivity

depends critically on conversion using a specific activity of a given standard. Because multiple standards were in use at the time of the patent, Dr. Lin should have disclosed which standard to use to make this calculation. His failure to disclose this critical information renders this determination a "moving target" that can vary depending on the standard referenced. Second, even if a standard had been disclosed, to convert results of an RIA to units of bioactivity one must either know the specific activity of the sample, or theoretically assume that the specific activity of the protein standard in the assay is equal to the specific activity of the same protein in the sample being tested. Such an assumption is improper, especially in cases where a protein in the sample may be present in an inactive form, such as a fragment or a deglycosylated variant that would report immulogical activity (amount) but not biological activity. Therefore, the claim limitation is indefinite. (Kadesch paragraphs 43-44)

5. "diluent, adjuvant, or carrier"

Amgen has argued that the limitation "diluent, adjuvant, or carrier," as contained in claim 1 of the '422 patent, and claims 9 and 12 of the '933 patent, should not be limited to ingredients that are separate and distinct from the claimed glycoprotein, but that these elements can be chemically bound to the active ingredient. For example, Amgen argued that "the specification exemplifies diluents, adjuvants, or carriers that interact with and bond to the recited 'human erythropoietin' 'active ingredient.'" *See* Amgen Inc.'s Response To Defendants' Claim Construction Brief, dated March 19, 2007, at 13.

Roche disagrees with this claim interpretation and believes that "diluent, adjuvant, or carrier" should mean separate and distinct ingredients within a mixture. However, should the Court adopt Amgen's construction, then the asserted claims that contain these elements would be invalid for lack of written description and enablement.

Excipients from several different classes of ingredients are commonly used in making pharmaceutical formulations. These classes include ingredients known as diluents, adjuvants and carriers. Diluents are mixed with an active drug substance and act as vehicles or bulking agents aiding in the formulation, storage and delivery of the drug. Adjuvants are mixed with an active drug substance and act to separately and independently enhance the activity of the active drug substance. Carriers are mixed with an active drug substance to help carry the active drug substance into the body. None of these excipients possess therapeutic activity. After a pharmaceutical formulation containing these ingredients in administered, they are broken down and removed by the body separately from the active drug substance.

There is no description in the patent specification of any diluent, adjuvant, or carrier being chemically bound or reacted to erythropoietin. While the patent does describe covalent bonding of erythropoietin with radio-labeled detectable markers (e.g., '868 patent, col. 12, ln. 51-65), these are not diluents, adjuvants, or carriers, and the resulting products are described as useful "reagents," not erythropoietin polypeptides.

The patent does not teach or describe anywhere that the diluent, adjuvant or carrier used in the pharmaceutical composition can form a variety of bonds with the active ingredient. Nowhere in the patent is there an indication that saline, which is listed as a standard carrier, can form a complex with the active ingredient through the formation of covalent bonds. Nor does the patent describe that albumin, a standard diluent, can be covalently attached to the active ingredient.

Amgen's expert, Dr. Torchilin, has stated in his expert declaration in support of Amgen's claims construction papers, that some of the standard diluents, adjuvants and carriers listed in the specification can interact or form a variety of bonds with the active ingredient, and relies

upon a reference by Poznansky, for the proposition that one of skill in the art in 1984 would know that albumin could be chemically bound to erythropoietin in a pharmaceutical composition. See *Enzyme-Protein Conjugates: New Possibilities for Enzyme Therapy*, Pharmac Ther Vol 21, pp 53-76, 1983. However, the Poznansky reference does not even mention albumin forming a reaction with erythropoietin. Instead, the Poznansky reference describes non-EPO enzyme conjugates and non-EPO enzyme-albumin polymers as a means of prolonging the half-life of the enzyme in the circulation, and how albumin can be polymerized by cross-linking with glutaraldehyde. The process is extremely complex as Poznansky readily admits. However, no such description is presented in the patent, and the Poznansky article is not even referenced in the patent. In fact, Amgen has failed to demonstrate anything in the prior art that show erythropoietin chemically bound to an adjuvant, diluent, or carrier in a pharmaceutical composition.

Therefore, to the extent that the Court adopts Amgen's construction of "adjuvant, diluent, or carrier" to cover substances that chemically bond or interact with the erythropoietin glycoprotein, Amgen's asserted claims containing these elements would be invalid for lack of written description and enablement under 35 U.S.C. § 112.

6. "pharmaceutical composition"

Amgen has argued and the Court has tentatively decided that the element "a pharmaceutical composition," as set forth in claim 1 of the '422 patent, and claims 9 and 12 of the '933 patent, should be limited to "a composition suitable for administration to humans." Roche disagrees with this construction. However, should the Court ultimately adopt this definition, then the asserted claim containing this element would be invalid for a lack of written description.

There are no examples of any human clinical trials within the patent. In fact, the only *in vivo* data within the patent which purportedly demonstrates a therapeutic effect is limited to mice studies involving 7 mice. The patent states:

> To determine the in vivo effect of the EPO-CCM upon hematocrit levels in normal Balb/C mice, the following experiment was conducted. Cell conditioned media from untransfected CHO cells (CCM) and EPO-CCM were adjusted with PBS. CCM was used for the control group (3 mice) and two dose levels of EPO-CCM--4 units per injection and 44 units per injection--were employed for the experimental groups (2 mice/group). Over the course of 5 weeks, the seven mice were injected intraperitoneally, 3 times per week. After the eighth injection, average hematocrit values for the control group were determined to be 50.4%; for the 4U group, 55.1%; and, for the 44U group, 67.9%.

'868 patent, col. 29, ln. 49-63. The patent does have a general description of using the claimed invention in human therapy, but there are no working examples. Moreover, these passages state that the claimed invention can be administered in human "to the extent that these polypeptide products of the intention share the in vivo activity of natural EPO isolates." '868 patent, col. 34, ln. 48-51. However, Amgen specifically asserts in this case that these pharmaceutical composition claims of the '422 and '933 patent are distinct over prior art which showed natural erythropoietin pharmaceutically administered in patients. As a result, should the Court ultimately adopt Amgen's construction that "pharmaceutical composition" should be limited to "a composition suitable for administration to humans," then Amgen's asserted claims containing this limitation would be invalid for lack of written description.

7. "purified from mammalian cells grown in culture"

Amgen has argued that "purified from mammalian cells grown in culture," as recited in claim 1 of the '422 patent, imparts structural distinctions over the prior art, and therefore should not be read out for purposes of patentability. *See* Amgen Inc.'s Response to Defendants' Claim

Construction Brief, dated March 19, 2007, at 9 ("such source or process limitations can and do serve to define the structure of a claimed product where such limitations are the best means to distinguish a claimed product over the prior art." Roche disagrees with this position, and contends that this limitation should be read out for purposes of patentability because it does not impart any structural distinction over the prior art.

The Federal Circuit stated that for this limitation, the district court should be "cognizant of the rule that a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations." *Amgen, Inc. v. HMR/TKT*, 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003). Moreover, this Court has also already established that this limitation does not impart structural distinctions over the prior art. In *Amgen v. HMR/TKT*, 339 F.Supp.2d 202, 317 (D. Mass. 2004), the Court held that:

> Amgen argues in defense that Sugimoto does not suggest purification *from mammalian cells grown in culture* specifically. The Federal Circuit made clear in *Amgen II*, however, that when considering obviousness with respect to the '422 and '080 product claims, "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 II*, 314 F.3d at 1354 n. 20 (citing *General Electric Co. v. Wabash Corp.*, 304 U.S. 364, 373, 58 S.Ct. 899, 82 L.Ed. 1402 (1938), and *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311, 4 S.Ct. 455, 28 L.Ed. 433 (1884)). Therefore, this argument fails.

Id. (emphasis added). In fact, this Court and the Federal Circuit has determined on numerous occasions that Lin's EPO glycoprotein and urinary EPO, which was in the prior art, are the same, and that it was "impossible" to distinguish the products.

"By clear and convincing evidence Dr. Lin's disclosure fails adequately to describe an EPO glycoprotein whose glycosylation differs from that of human urinary erythropoietin" *Amgen v. HMR/TKT*, 126 F.Supp.2d 69, 155 (D. Mass. 2001).

"Making comparisons between the glycosylation of recombinant EPO and that of urinary EPO is virtually impossible." *Id* (emphasis added).

"Amgen argues that the uEPO is a different product that the rEPO...However, the overwhelming evidence, including Amgen's own admissions, establishes that uEPO and rEPO are the same product...Amgen's own scientists have concluded that by all criteria examined, rEPO is the 'equivalent to the natural hormone.'...Amgen's Product License Application to the FDA states that all 'physical tests performed on both rHuEPO and uHuEPO...show these proteins to be indistinguishable'...Therefore, Amgen has failed to demonstrate by clear and convincing evidence a difference between the two products." *Amgen v. Chugai*, 1989 WL 169006, *84 (D. Mass. Dec. 11, 1989).

Therefore, "purified from mammalian cells grown in culture" does not impart any structural characteristics for purposes of patentability. However, should the Court adopt Amgen's reasoning that this limitation does provide a structural difference over the part art, then claim 1 of the '422 patent would be invalid for lack of written description.

There is no adequate description in the patent showing any differences between Lin's invention and natural isolates of erythropoietin. In fact, the only data within the patent that supports such a proposition has now been determined to be wrong, as already conceded by Amgen. *See Fritsch v. Lin*, 21 U.S. P.Q.2d 1739, 1741 (Bd. Pat. App. & Inter. 1991) ("Lin concedes that the hexose value reported in his involved application (Example 10)is probably incorrect.");

Therefore, to the extent that "purified from mammalian cells grown in culture" is construed to impart structural distinctions over the prior art, then claim 1 of the '422 patent

would be invalid for lack of written description because the patent fails to describe any real structural differences over the prior art.

Even if Amgen were to demonstrate that this limitation has a structural distinction over the prior art, this claim would still fail because the patent specification fails to describe purification techniques of human erythropoietin. Claim 1 of the '422 patent, claims 4 and 6 of the '080 patent and claims 9, 11, 12 and 14 of the '933 patent are invalid for lack of written description and/or enablement because the Lin patents do not contain any disclosures of purification techniques that could be applied to successfully make the pharmaceutical compositions recited in the claims without undue experimentation.

The Lin patents do not adequately describe methods or instruct the public how to obtain large quantities of erythropoietin sufficient for production and of the purity necessary to produce pharmaceutical compositions. None of the twelve examples provided in the common specification describe a pharmaceutical composition. Additionally, the specification provides no disclosure which one of skill could use on its own to purify EPO protein in order to achieve the degree of homogenous, contaminant-free protein necessary to make a pharmaceutical composition. The only method of purification in the patent, HPLC (C_4), would not work to achieve the needed level of purity of rEPO needed to make a pharmaceutical composition. The Lin patents do not describe the parameters to be applied to the disclosed purification process, and Amgen itself was not able to use the teachings of the Lin patents to devise a purification method sufficient to make any pharmaceutical compositions. (Flavell paragraphs 33-58)

After the time of filing of the specification in the Lin patents in November 1984, Amgen encountered a variety of difficulties purifying EPO, and continued to modify their purification schemes. Amgen's scientist, Dr. Strickland, later developed a new purification method outside

the teachings of the Lin patents, which was used in the production of Amgen's rEPO product, Epogen. Amgen believed this new process was a novel development over the method for purification described in the Lin patents that Amgen had applied for and obtained a patent on the new purification method, U.S. Patent no. 4,667,016 by Lai and Strickland. Dr. Strickland testified that his purification work was more than routine and required more than just "a pair of hands." Additionally, the purification method Amgen disclosed in its PLA consists of 4 successive column chromatography steps, only one of which is disclosed in the Line patents. The process disclosed in the PLA is similar to the method described in example 2 of the '016 patent. (Flavell paragraphs 59-104).

8. "comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3,4, 5 or 6

Claim 7 of the '349 patent is invalid for lack of enablement and written description because it possesses a single means for carrying out the claimed process. As such, this claim is overly broad as a matter of law because it seeks to cover every possible means to producing erythropoietin while the specification discloses at best only one or a few methods. As stated in M.P.E.P. § 2164.08(a):

> A single means claim, i.e., where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. *In re Hyatt*, 708 F.2d 712, 714-715, 218 USPQ 195, 197 (Fed. Cir. 1983) (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor.). When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor.

Id; see also infra at subsection A.10, "capable upon growth."

9. "non-human DNA sequences which control transcription of DNA encoding human erythropoietin"; "other than human erythropoietin transcription control sequences," and "other than human erythropoietin promoter DNA."

Claims 1 and 4 of the '349 patent, and claim 4 and 5 of the '698 patent are invalid for lack of written description because they claim, among other things, a broad genus of transcription control DNA while the patent specification only recites the use of one control region, namely the SV40 promoter for use in vertebrate cells. Claims 1 and 4 of the '349 patent cover vertebrate cells comprising "non-human DNA sequences which control transcription of DNA" and "transcription DNA sequences, other than human erythropoietin transcription control sequences" respectively. Claim 4 of the '698 patent covers a process for making a glycosylated erythropoietin polypeptide by growing vertebrate cells "promote DNA, other than human erythropoietin promoter DNA." Such transcription control regions cover a vast array of possible DNA sequences.

In the human genome there are approximately 30,000 genes. Each gene has its own control region DNA sequences. By rough approximation, there are 30,000 DNA sequences that control transcription in human cells. The number of animals that are classified as vertebrates is enormous. All of the genes in all of those species also have DNA sequences that control their transcription. Viruses that infect vertebrate cells also have DNA sequences that can control transcription in vertebrate host cells. The number of viruses that infect vertebrate cells number in the hundreds.

Moreover, a DNA sequence is a large chemical molecule. The claims of the '349 and '698 patent cover vertebrate cells that comprise a hundreds of thousands if not millions of different structures. If one considers combinations of different regulatory elements that could be made to create hybrid sequences, the number of possible DNA sequences is so astronomical that

one can only begin to imagine the number of different DNA sequences that would fall within these definitions.

In the "Background" section of the patent specification, there is a general discussion about promoters and regulators, but this does not describe particular DNA sequences. *See* '868 patent, col. 2, ln. 5-19. Even with today's understanding of biotechnology, transcription control sequences are very hard to define based on sequence alone. The background discussion says nothing about any specific DNA sequences that are included or excluded from the invention of the application. It provides no practical information from which a person of the skill in the art could determine what DNA sequences Dr. Lin had possession of for producing erythropoietin from vertebrate cells.

The only disclosed non-human DNA sequences that initiate and/or regulate transcription of DNA encoding human erythropoietin in *vertebrate cells* are the sequences from SV40. SV40 is a virus that has been studied and used to express foreign DNA in proteins even before the filing date of the patents-in-suit. However, one example of SV40 does not provide a written description of the large genus of all viral promoter sequences that control transcription in vertebrate cells, let alone provide a written description of a complete genus of sequences that are covered by the other broader phrases relating to transcription control sequences recited in the claims of the '349 patent and '698 patent (claims 4 and 5).

The promoters used in Example 12 of the specification to control transcription in *E. coli* and yeast are not sequences that would control transcription in vertebrate cells. The cellular machinery, such as trans-acting transcription factors, in *E. coli* and yeast are different from the machinery of vertebrate cells. The lambda P_L promoter and α-factor promoter disclosed in this example will not effectively control transcription of DNA in vertebrate cells.

Moreover, claim 4 of the '349 patent covers "transcription DNA sequences, other than human erythropoietin transcription control sequences," and claim 4 of the '698 patent covers the use of "promote DNA, other than human erythropoietin promoter DNA." These are negative limitations requiring at the very least a description of "human erythropoietin transcription control sequences" and "human promoter DNA." *See* M.P.E.P. §2173.05(i) ("Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ('[the] specification, having described the whole, necessarily described the part remaining.')."

The specification gives no description of the human DNA sequences from the human genome that control transcription of erythropoietin. The fact the human promoter for erythropoietin is somewhere within the sequence disclosed in Figure 6 does not provide a precise description of human DNA sequences that control transcription of the human EPO gene. A person of skill in the art is not provided with a written description of the DNA sequences from the human genome for the promoter or any of the regulatory elements that control expression of the erythropoietin gene. Since the patent does not provide a written description of the human DNA sequences that control transcription of erythropoietin, it does not provide an adequate written description of all such "non-human" sequences.

10. "capable upon growth"

Claim 1 of the '349 patent is directed to vertebrate cells which can be propagated in vitro "and which are capable upon growth" in culture. Claims 2, 3, 5, and 6 are directed to vertebrate cells that are "capable of producing" in excess of certain amounts.

However, the use of the term "capable" in this context makes these claims vague and indefinite under Section 112, ¶2. During the prosecution of the '868 patent, certain pending claims directed to "host cells capable of effecting post-translational glycosylation of polypeptides" were rejected by the Patent Office. The Examiner stated:

> It is not clear what relationship applicant intends between the glycosylation of polypeptides the recited cell. A cell capable of effecting post-translational glycosylation of polypeptides is not necessarily effecting post-translational glycosylation and so it not clear if applicants intend to claim said a cell which is in fact effecting post-translational glycosylation, said cell which is not effecting post-translational glycosylation, or both. It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation in any patentable sense. *In re Hutchinson*, 69 USPQ 138. It is noted that the instant ground of rejection may be overcome by deleting the recitation of the hosts capability.

('179 Application, Office Action, Paper No. 29, at 11, dated 9/1/93) (emphasis added). As a result of this rejection, Amgen eliminated the "capable of " language from the pending claims. Applied here, claims 1-3, and 5-6 are similarly indefinite and vague in using the term "capable." It would not have been clear to one of skill in the art whether Amgen was claiming cells that actually did grow under certain condition, cells that did not grow, or both. Similarly, one of skill in the art would not know whether Amgen was claiming cells that actually produced erythropoietin at certain levels, cells that did not, or both. "Capable of" is not combined with any other specific elements or steps, as was pointed out above with respect to the fact that these claims only recite a single means step in violation of M.P.E.P. § 2164.08(a). As a result, these claims should be held invalid for lack of definiteness under Section 112, ¶2.

In fact, Amgen's Expert Report of Dr. Ronald W. McLawhon, which was served just yesterday, only underscores that this "capable of" limitation renders these claims indefinite. Dr. McLawhon alleges the under certain conditions (thawed and grown in media containing

methotrexate for 24hr before being harvested and re-grown in media containing methotrexate for 48hr), the accused DN2-3ά3 cells, grown as the M-3 04/19/2007 aliquots, produced 1377 units of EPO per 10^6 cells in 48 hours. *See* McLawhon Report, ¶32. Amgen would claim that these alleged results would fall within the parameters of at least claims 3 and 6 of the '349 patent. However, Dr. McLawhon also states that these same cells were grown under different starting condition as M-5 04/21/2007 aliquots. These were thawed and grown in media containing methotrexate for 24hr before being harvested and re-grown in media containing methotrexate for 48hr, and then harvested and regrown a second time in media containing methotrexate for 48hr. These cells produced completely different results - 712 units of EPO per 10^6 cells in 48 hours, and therefore could not fall within the limitation of claim 3 and 6 of the '349 patent. *See* McLawhon Report, ¶33. This demonstrates the indefiniteness of the "capable" language because it does not provide any guidance to one of skill in the art to what initial condition are necessary to practice the invention. As Amgen's expert report even indicates, one can allegedly practice the invention under certain starting conditions, yet fall completely outside of certain claims under different conditions. This makes these claims indefinite and therefore invalid under Section 112, ¶2.

B. Improper Dependency Under Section 112, ¶4

Amgen has argued and the Court has tentatively decided that the element "a pharmaceutical composition," as set forth in claims 9 and 12 of the '933 patent, should be limited to "a composition suitable for administration to humans." Roche disagrees with this construction. However, should the Court ultimately adopt this definition, then these claims, as well as their dependent claims 10 and 13, would be invalid for lack improper dependency under Section 112, ¶4.

Section 112, ¶4 states in relevant part that "a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed...A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim in which it refers."

As construed by Amgen, claims 9 and 10 of the '933 patent would be limited to "a composition suitable for administration to humans." However, dependent claims 10 and 13 are directed to a "method for providing erythropoietin therapy to a *mammal,*" and as a result, would be broader in scope then their antecedent claims in violation of Section 112, ¶4. As a result, should the Court ultimately adopt Amgen's claim construction that claims 9 and 10 of the '933 patent be limited to a "composition suitable for administration to humans," then these claims, as well as dependent claims 10 and 13, should be held invalid. *See Pfizer, Inc. v. Ranbaxy Laboratories Ltd.*, 457 F.3d 1284, 1292 (Fed. Cir. 2006) ("Although the district court was reluctant to find the fourth paragraph of § 112 to be an invalidating provision, doing so does not exalt form over substance. Rather, it is consistent with the overall statutory scheme that requires applicants to satisfy certain requirements before obtaining a patent, some of which are more procedural or technical than others. ").

Moreover, claim 9 of the '698 patent is to "The process according to claims 2, 4 ***and*** 6 wherein said cells are mammalian cells." This is also invalid for improper multiple dependency. Claims 2, 4, and 6 are different processes. Therefore, claim 9 is invalid because it refers back to three different processes simultaneously, and not in the alternative. As stated in M.P.E.P. § 608.01(i), "Any dependent claim which refers to more than one other claim ("multiple dependent claim") shall refer to such other claims in the alternative only." As a result, claim 9 of the '698 patent is invalid under Section 112, ¶4.

C. Anticipation and/or Obviousness Under Sections 102/103

1. "non-naturally occurring"

Claims 3, 7-9, 11-12 and 14 of the '933 patent, claim 3 of the '080 patent and claim 1 of the '422 patent are invalid as anticipated or rendered obvious by prior art disclosing the isolation and purification of human urinary EPO.

If Amgen contends that claim 3 of the '933 patent, which contains a limitation to a "non-naturally" occurring glycoprotein, (a) is limited to human erythropoietin produced through recombinant expression; and if Amgen maintains that (b) the expression product of this claim is not limited to the product of transcription and translation, then this claim would cover any product containing one or more of the possible glycoforms of human erythropoietin that could be produced in any particular mammalian host cell. Limiting the claimed product to a human erythropoietin product from a recombinant source would not distinguish the claimed product from human EPO described and existing in the prior art.

Glycoforms of human erythropoietin expressed in at least some mammalian host cells are all encompassed within the naturally occurring human erythropoietin glycoforms found in human urinary erythropoietin. Therefore, claim 3 of the '933 patent would be anticipated by prior art describing uEPO preparations made from different sources and using different purification schemes, for example: Chiba et al. U.W. Patent 4, 465,624; Dukes, P.P. (1982) (abs.); Espada (1982) (abs. 5192); Lange (1984); Takaji Miyake, Charles Kung, and Eugene Goldwasser, "Purification of Human Erythropoietin," J. Biol. Chem., 252, 5558-64 (1977) (Miyake 1977); Spivak et a., "Use of Immobilized Lectins and Other Ligands for the Partial Purification of Erythropoietin," Blood 52(6):11178-1188 (1978); Webber and Clemens, "Purification of Erythropoietin from Human Urine," Fed. Proceed. 42(7):1872 (1983);

Yanagawa et al., "Isolation of human erythropoietin with monoclonal antibodies," J. Biol. Chem., 259(5):2707-10 (1984). (Bertozzi paragraphs 70-72).

Additionally, available methods for carbohydrate analysis cannot distinguish recombinant human erythropoietin as something different from human urinary erythropoietin. Amgen's own studies and data, as well as the testimony of Amgen scientists, demonstrate that every glycan that had been identified in the rEPO expression product was a glycan that had been observed in uEPO. (Bertozzi paragraphs 73-86).

Dependent claims 9, 11, 12 and 14 of the '933 patent, which all depend from claim 3 of the '933 patent, do not add any novel elements to the claims. It would have been obvious to use EPO in the pharmaceutical composition and to use that pharmaceutical composition to treat kidney dialysis patients. Such pharmaceutical compositions could also be used in mammals. By 1983-984, the desirability of treating dialysis patients with human EPO was widely recognized and appreciated. As early as 1971, it was appreciated that human EPO could be important for "possible therapeutic use in some types of refractory anemia...." (Goldwasser 1971). Moreover, Eschbach's studies demonstrating a correction of anemia in sheep receiving administration of erythropoietin enriched plasma, implies that EPO therapy should correct anemia observed in patients with chronic renal failure. (Bertozzi paragraphs 87-91)

Claim 3 of the '080 patent is also anticipated or made obvious by the prior art relating to purification of human uEPO. To the extent Amgen asserts that '080 claim 3 covers a recombinant 165 amino acid human erythropoietin product, the claim would similarly be anticipated or made obvious by the prior art describing the purification and use of uEPO. Further, for the reasons discussed for the '933 dependent claims, it would have been obvious to use a therapeutically effective amount of the recombinant human erythropoietin product claimed

by '080 claim 3 in a pharmaceutical composition recited in '080 claim 4, and consequently to use such a pharmaceutical composition in a method for treating a dialysis patient, as recited in '080 claim 6. (Bertozzi paragraphs 92-93)

Claim 1 of the '422 patent is also similarly anticipated or made obvious by prior art relating to the purification of human uEPO for the reasons discussed for the '933 dependent claims. By all available means in 1983-1984, uEPO was indistinguishable in terms of its immunological, biological, and physical properties from CHO cell produced rEPO. Therefore, it would have been obvious to use uEPO in the claimed pharmaceutical composition, and to use that composition for treating a kidney dialysis patient. This is confirmed by Dr. Strickland's conclusions that "one of ordinary skill in the art in the 1983-84 timeframe could have repeated the purification method described in the Miyake/Goldwasser procedure to consistently obtain the high specific activity, purified human urinary EPO of Fraction II described herein." Amgen also admits that the uEPO purified by Miyake and Goldwasser "caused increased hemoglobin synthesis after *in vivo* administration to mice." (Amgen's Response to Defendants' Third Set of Requests for Admission No. 32.). Therefore, it would have been obvious to provide a therapeutically effective amount of human erythropoietin in the claimed pharmaceutical composition. (Bertozzi paragraphs 94-96)

2. Baron and Goldwasser Hamster Study

Claim 1 of the '422 patent is invalid as anticipated or as obvious in light of the toxicology study on hamsters conducted by Drs. Baron and Goldwasser in 1978.

In connection with the IND, Dr. Baron and Dr. Goldwasser conducted a toxicology study in 1978 on hamsters. AM-ITC 01006678-6752. This toxicology study included measures of general effects of large doses of the proposed pharmaceutical composition on a test animal. The toxicology study showed that administration of a pharmaceutical composition comprising

purified human urinary EPO in two hamsters produced a significant increase in hematocrit. This is a clear demonstration of therapeutic effectiveness for this composition that includes an increase in hematocrit and red blood cell count.

The EPO administered to the four hamsters was the same pharmaceutical composition comprising urinary EPO and human serum albumin, a pharmaceutically acceptable diluent, administered in the Baron Clinical Study. The average hematocrit of the hamsters receiving EPO was increased 40% compared to the average hematocrit of the control hamsters.

The Goldwasser and Baron Hamster Study disclosed a pharmaceutical composition suitable for administration in humans, containing a therapeutically effective amount of human erythropoietin, and a pharmaceutically acceptable diluent adjuvant or carrier. Therefore, the Goldwasser and Baron Hamster Study disclosed every element of claim 1 of the '422 patent in 1978. Based on the results of the Goldwasser and Baron Hamster Study, it also would have been obvious to one skilled in the art prior to 1983 to a use a pharmaceutical composition in a human comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier.

3. Essers Clinical Study Using EPO-Rich Human Plasma

Claim 1 of the '422 patent is anticipated and rendered obvious by the Essers EPO-rich plasma studies because they disclose every relevant element of that claim. The Essers EPO-rich plasma study disclosed a "therapeutically effective amount of human erythropoietin" as that term has been construed by the Federal Circuit, with a diluent, adjuvant, or carrier, as required by the claim. The studies demonstrate convincingly that an increase in reticulocytes follows administration of EPO-rich plasma, a pharmaceutical composition produced by plasmapheresis. The claim term "wherein said erythropoietin is purified from mammalian cells grown in culture" is a source or process limitation that is irrelevant for determining whether a piece of prior art

anticipates a patent claim. Nevertheless, Essers discloses enriched plasma containing EPO that is ultimately derived from mammalian kidney cells.

4. Eschbach Clinical Study Using EPO-Rich Human Plasma

Claim 1 of the '422 patent is anticipated and rendered obvious by the Eschbach EPO-rich plasma study because that study discloses every relevant element of that claim. The Eschbach EPO-rich plasma study disclosed a "therapeutically effective amount of human erythropoietin" as that term has been construed by the Federal Circuit, along with a diluent, adjuvant, or carrier. The studies demonstrate convincingly that an increase in reticulocytes follows administration of EPO-rich plasma. The claim term "wherein said erythropoietin is purified from mammalian cells grown in culture" is a source or process limitation that is irrelevant for determining whether a piece of prior art anticipates a patent claim. Nevertheless, Eschbach discloses enriched plasma containing EPO that is ultimately derived from mammalian kidney cells.

5. Eschbach Sheep Study

Claim 1 of the '422 patent is invalid as obvious in light of the Eschbach Sheep Study which discloses the administration of a pharmaceutical composition containing a therapeutically effective amount of erythropoietin to sheep.

Prior to April 1983, Dr. Eschbach and his team conducted sheep studies in which they administered EPO-rich plasma to uremic sheep. (ESCH 0000008; 0000060; 0000022-24 at 24). In these studies Dr. Eschbach and his team developed a protocol to determine if erythropoietin is effective in sheep with chronic renal failure (CRF) as compared to normal state sheep, and if the anemia of CRF sheep could be corrected by administration of erythropoietin. (ESCH 0000025-31 at 29). Dr. Eschbach and his team determined that anemia in uremic sheep was corrected by administering EPO-rich sheep plasma to the uremic sheep. (ESCH 0000008; 0000022-24 at 24). Based on the results of these studies, Dr. Eschbach "predicted that if and when human Epo

became available in sufficient quantities it would correct the anemia...." (ESCH 0000022-24 at 24). In fact, Dr. Eschbach states that he later "confirmed the sheep study in a human by observing that Epo-rich plasma obtained by plasmapherisis from a patient with secondary polycythemia resulted in significant reticulocytosis and an increase in plasma iron turnover when infused into an ABO compatible dialysis patient." *Id.*

The erythropoietic response in sheep to the EPO-rich plasma infusions was measured by reticulocyte response, ferrokinetics (plasma iron turnover and marrow transit time) and by hemoglobin C synthesis. (ESCH 0000025-31 at 25 & 26).

Drs. Eschbach observed that infusion of EPO-rich plasma resulted in increases in reticulocytes, plasma iron turnover, and erythrocyte mass changes. (ESCH 0000025-31 at 25). While Drs. Eschbach and Adamson did not infuse purified erythropoietin, they concluded that the erythropoietic response detected in sheep was due to erythropoietin because only "EP is known to produce these all of the following: reticulocytosis, increased PIT, shortening on MTT HbC activation, and the production of polycythemia." (ESCH 0000025-31 at 29).

Additionally, Dr. Eschbach and his team concluded that they had demonstrated the administration of approximately 10 units/ml of EPO-rich sheep plasma given daily or every other day, corrected the anemia of uremic sheep. (ESCH 0000024; ESCH 0000025 ("The anemia was corrected in the uremic sheep after 15-40 daily infusions of Ep-rich plasma...")). Eschbach additionally concluded that "....anemia could be corrected completely by daily infusions of Ep-rich plasma" (ESCH 0000025-31 at 29; *see also* ESCH 0000042 ("When these animals were treated with EP-rich plasma, red cell production increased, and anemia was corrected in all (Fig. 2).")). Dr. Eschbach's results also show a significant increase in the hematocrit of uremic sheep after continued infusions of EPO-rich plasma. (ESCH 0000042).