(b) the purpose(s) of each such use; and

(c) each document (excluding only patient-specific information) recording or reflecting any communication, agreement, or understanding between each such individual or entity and Roche or its agents or attorneys regarding such use; and

(d) each person, other than counsel, who furnished information or was consulted regarding your 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.

RESPONSE:

See Objections and Response To Interrogatory No. 7 above.

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.

RESPONSE:

Defendants object to this interrogatory as unduly vague, ambiguous and overly broad. Moreover, Defendants object to this interrogatory to the extent that it calls for information protected by the attorney-client privilege or work-product immunity. Defendants also object to

this interrogatory because it constitutes multiple interrogatories and should be counted against Amgen as such for purposes of the 40 interrogatory limit imposed by the Court.

Defendants also object to this interrogatory because it is premature and calls for expert testimony. The asserted claims of the patents-in-suit have not been construed and the Court does not expect a *Markman* hearing on these claims until April 2, 2007.

Defendants reserve the right to modify or supplement this response at any time upon receipt of relevant materials from any source during discovery.

Subject to and without waiver of these Specific Objections and General Objections set forth above which are incorporated herein by reference, Defendants respond as follows.

A. Obviousness-Type Double Patenting and Same Invention Double Patenting under Section 101

All of the asserted claims of the patents-in-suit are invalid for obviousness-type double patenting over Amgen's now expired U.S. Patent No. 4,703,008 ("the '008 patent"). The '008 patent claims, among other things, the isolated DNA sequence encoding EPO as well as mammalian host cells transformed with this DNA sequence in a manner allowing these cells to express biologically active and glycosylated EPO protein. The '008 patent and the patents-in-suit all share the same specification and single inventor, and demonstrate that Amgen possessed only a single invention with minor obvious variations: mammalian host cells that can express the EPO protein using recombinant DNA technology to produce reliable quantities of EPO.

Amgen already convinced the Board of Patent Appeals of PTO during interference proceedings with Genetics Institute and Chugai, that once the skilled worker had isolated the EPO gene - as claimed in the '008 patent - there was nothing novel or inventive in the process of expressing that gene in host cells and then isolating the biologically active glycoprotein - as claimed in the patents-in-suit. In those same proceedings, Amgen categorically stated that the EPO gene of the '008 patent and the process for making biologically active EPO, as claimed by

the claim phrase. The specification does not define "U of erythropoietin" nor does it disclose any method for measuring "U of erythropoietin." Without further guidance that the specification fails to provide, the proper metes and bounds of this limitation cannot be determined. Because claim 7 depends from claims 1-6, each of which contains this limitation, claim 7 itself is indefinite under § 112 for failing to distinctly claim the subject matter in a manner that enables one skilled in the art to understand its true scope.

SUPPLEMENTAL RESPONSE

Roche supplements this response with the following chart showing which of the asserted claims of the patents-in-suit are invalid by certain defenses.

Claims Asserted by Roche to Be Invalid

'080 Patent Claim	35 U.S.C. §102	35 U.S.C. §103	35 U.S.C. §112	Double Patenting / 35 U.S.C. § 101
3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.	✓	✓	✓	✓
4. A pharmaceutical composition comprising a therapeutically effective amount an erythropoietin glycoprotein product according to claim 1, 2 or 3	✓	✓	✓	✓
6. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 4 in an amount effective to increase the hematocrit level of said patient.		✓	✓	✓

'868 Patent Claim	35 U.S.C. §102	35 U.S.C. §103	35 U.S.C. §112	Double Patenting / 35 U.S.C §101
1. 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:		✓	✓	✓

'868 Patent Claim	35 U.S.C. §102	35 U.S.C. §103	35 U.S.C. §112	Double Patenting / 35 U.S.C §101
(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..				
2. The process according to claim 1 wherein said host cells are CHO cells.		✓	✓	✓

'698 Patent Claim	35 U.S.C. §102	35 U.S.C. §103	35 U.S.C. §112	Double Patenting / 35 U.S.C §101
4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps 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.		✓	✓	✓
5. The process of claim 4 wherein said promoter DNA is viral promoter DNA.		✓	✓	✓
6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.		✓	✓	✓
7. The process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA.		✓	✓	✓
8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.		✓	✓	✓
9. The process according to claims 2, 4 and 6 wherein said cells are mammalian cells		✓	✓	✓

'349 Patent				
Claim	**35 U.S.C. §102**	**35 U.S.C. §103**	**35 U.S.C. §112**	**Double Patenting/ 35 U.S.C §101**
7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5 or 6.		✓	✓	✓

'422 Patent				
Claim	**35 U.S.C. §102**	**35 U.S.C. §103**	**35 U.S.C. §112**	**Double Patenting / 35 U.S.C §101**
1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.	✓	✓	✓	✓

CONTAINS RESTRICTED ACCESS CONFIDENTIAL BLA/IND MATERIAL
PURSUANT TO PROTECTIVE ORDER

'933 Patent Claim	35 U.S.C. §102	35 U.S.C. §103	35 U.S.C. §112	Double Patenting / 35 U.S.C §101
3. 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.	✓	✓	✓	✓
7. The glycoprotein product according to claim 3, 4, 5 or 6 wherein the host cell is a non-human mammalian cell.	✓	✓	✓	✓
8. The glycoprotein product according to claim 7 wherein the non-human mammalian cell is a CHO cell.	✓	✓	✓	✓
9. A pharmaceutical composition comprising an effective amount [sic. of] a gylcoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.	✓	✓	✓	✓
11. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient.		✓	✓	✓
12. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 7 and a pharmaceutically acceptable diluent, adjuvant or carrier.	✓	✓	✓	✓
14. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product [sic. patient?].		✓	✓	✓

With respect to double patenting, Roche contends that at least claims 1, 2, 4, 5, 6, 7, 8, 23, 24, 25, 26, and 27 of U.S. Patent No. 4,703,008 render the asserted claims of the patents-in-suit invalid as identified above.

INTERROGATORY NO. 10

Separately, in claim chart form for each claim of Amgen's patents-in-suit that you contend is invalid under 35 U.S.C. § 102, identify and describe on a limitation-by-limitation basis for each claim:

(a) where, on a limitation-by-limitation basis, you contend each claim limitation is disclosed in the prior art;

(b) how each such limitation is disclosed in the prior art, including specific references to pages, claims, columns and/or line numbers (if applicable) in each document supporting such contention;

(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), and 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 your 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.

RESPONSE:

See Objections and Response To Interrogatory No. 9 above.

INTERROGATORY NO. 11

Separately, in claim chart form for each claim of Amgen's patents-in-suit that you contend is invalid under 35 U.S.C. § 103 or for double patenting, identify and describe for each claim and for each asserted defense:

(a) where, on a limitation-by-limitation basis, you contend each claim limitation is found or disclosed in the prior art or earlier Lin patent claims;

(b) why the claim would have been obvious, including where the motivation to combine prior art disclosures or earlier Lin patent claims may be found;

(c) why 35 U.S.C. § 121 does not bar the application of the doctrine of obviousness-type double patenting;

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,	:	Civil Action No.: 05-12237 WGY
Defendants.	:	

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

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

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.