EXHIBIT 17

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

REDACTED

DEFENDANTS' THIRD SUPPLEMENTAL RESPONSES AND OBJECTIONS TO PLAINTIFF AMGEN INC.'S FIRST SET OF INTERROGATORIES TO DEFENDANTS (NOS. 1-15)

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

The following general objections apply to all of Defendants' responses and shall be incorporated in each response as if fully set forth therein. To the extent specific General Objections are cited in response to a specific interrogatory, those specific General Objections are provided because they are believed to be particularly applicable to the specific interrogatory and are not to be construed as waiver of any other General Objections applicable to the interrogatory.

Defendants object to each and every interrogatory to the extent it seeks information protected by the attorney-client privilege, the attorney work product doctrine and/or any other applicable privilege. All answers herein shall be subject to this objection, and no provision of information herein may act as a waiver of these objections.

REDACTED

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 patents-in-suit, "are only different manifestations of the same invention." *See* Brief for the Senior Party Lin, Interference No. 102,097, dated 7/29/91 at 25-26.

In particular, during these Interference Proceedings, Amgen stated that the Counts to Interference Nos. 102,096 and 102,097 were directed to the same invention. The Count to Interference No. 102,096 was as follows, and is identical to claim 2 of the '008 patent:

> A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

The Count to Interference No. 102,097 was as follows, and covers all the essential elements of the asserted claims of the patents-in-suit:

> A process for the preparation of an in vivo biologically active glycosylated polypeptide comprising steps of 1. growing mammalian cells transformed with DNA encoding a polypeptide sufficiently duplicative of human EPO to have the in vivo biological properties of increasing red blood cells and reticulocytes, 2. transcribing the DNA to mRNA, 3. translating the mRNA into a polypeptide, 4. glycosylating the polypeptide in a manner sufficiently duplicative of the glycosylation of natural human EPO to effect the recited biological activity and 5. isolating the glycosylated polypeptide.

During the 102,097 interference, Amgen argued that the Board should adopt the findings of the District Court and the Federal Circuit regarding priority and validity issues in *Amgen, Inc. v. Chugai Pharms.*, 927 F.2d 1200 (Fed. Cir. 1991). In *Amgen*, the District of Massachusetts and the Federal Circuit found that Amgen had been the first to invent the claimed DNA sequences and host cells of the '008 patent before Genetics Institute. *Id.* Therefore, Amgen took advantage of these courts' rulings by maintaining that it should apply to the interference proceedings. Amgen argued that even though the count of the 102,097 proceeding was directed to the production of biologically active glycosylated EPO, and the litigation involved the DNA sequence and host cells of the '008 patent, this did not matter because they were the same invention. Amgen also made similar statements regarding the identity between the DNA claims and the protein claims during the prosecution of the patents-in-suit, as well as in foreign litigation.

The Patent Board agreed with Amgen's position and as a result, Amgen was allowed to proceed with the prosecution of the patents-in-suit and received a tangible benefit. As a result, Amgen is now judicially estopped from denying that the claims of the '008 invalidate the asserted claims of the patents-in-suit.

Importantly, Amgen is not shielded from this double patenting attack under 35 U.S.C. § 121 because among other things, Section 121 provides a safe harbor to patents issued from divisional applications whereas the patents-in-suit issued from continuations of the application that became the '008 patent. Moreover, Amgen did not maintain consonance with the restriction requirements *See Bristol-Myers Squibb Co. v. Research Corp. Tech.*, 361 F.3d 1343, 1348 (Fed. Cir. 2004); *Geneva,* 349 F.3d at 1381; *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1579 (Fed. Cir. 1991). ("Consonance requires that the line of demarcation between 'independent and distinct inventions' that prompted the restriction requirement be maintained. . . . Where that line is crossed the prohibition of the third sentence of Section 121 does not apply.").

Evidence supporting this contention can be found at Interference File History Nos. 102,096 and 102,097, *Fritsch v. Lin*, 21 U.S.P.Q.2d 1731 (Bd. Pat. App. & Interf. 1991), *Fritsch v. Lin*, 21 U.S.P.Q. 2d 1737 (Bd. Pat. App. & Interf. 1992), and *Amgen, Inc. v. Chugai Pharms.*, 927 F.2d 1200 (Fed. Cir. 1991).

B. Lack Of Inventorship and Derivation Under Sections 102(f) and 116

As stated above, Defendants have maintained that the DNA and host cell claims of the '008 render obvious the asserted claims of the patents-in-suit. To the extent that Amgen denies this contention and argues that the asserted claims require separate inventive contribution, then those asserted claims would be invalid for lack of inventorship and derivation under 35 U.S.C. §§ 102(f) and 116.

Specifically, during Interference Proceedings Nos. 102,096 and 102,097, it was adduced that all of the work done at Amgen relating to expression of the EPO gene in mammalian host cells was directed and supervised by Dr. Browne and Dr. Smalling, and not Dr. Lin. *See Fritsch*

v. Lin, 21 U.S.P.Q. 2d 1737 (Bd. Pat. App. & Interf. 1992). In fact, during those proceedings, Amgen did not dispute that Lin's contribution was directed towards isolating the EPO gene, but rather stated that once the gene was isolated, it would have been obvious to express that gene into a biologically active protein. *Id.*

C. Prior Inventorship By Fritsch Under 102(g)/103

Similarly, during the above referenced interference proceedings and in *Amgen, Inc. v. Chugai Pharms.*, 13 U.S.P.Q.2d 1737 (D. Mass. 1989), *aff'd in relevant part*, 927 F.2d 1200 (Fed. Cir. 1991), it was established that Fritch had reduced to practice the isolation of the EPO gene in May 1984. *See Amgen*, 927 F.2d at 1205-1206.

This was several months before November 1984, the earliest effective filing date of the patents-in-suit. Therefore, for all the reasons stated above with respect to Defendants' invalidity contentions on obviousness-type double patenting, Fritsch's reduction to practice of the EPO gene in May 1984 was a prior invention and renders obvious the asserted claims of the patents-in-suit.

D. Derivation Under Section 102(f) – Goldwasser

The asserted claims of U.S. Patent Nos. 5,955,422 ("the '422 patent") and 5,547,933 ("the '933 patent") are invalid under 35 U.S.C. §102(f) as derived from others. In particular, before Amgen's alleged invention of the subject matter of these claims, Dr. Eugene Goldwasser had conceived and reduced to practice a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier. These elements are evident in at least the following documents produced by Amgen: *See e.g.*, AM-ITC 00849306-341; AM-ITC 01006613-756; AM-ITC 00081365-75; AM-ITC 00053532.

Further, the claim limitation "wherein said erythropoietin is purified from mammalian cells grown in culture" is a source or process limitation which the Federal Circuit stated would not confer patentability to the claimed product over human erythropoietin isolated from a

different source. *See Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003) ("[T]he 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.").

E. Obviousness Under Section 103

The claims of the patents-in-suit are invalid under 35 U.S.C. § 103 because they would have been obvious to one of ordinary skill in the art at the time of the invention.

Roche may rely on at least the following prior art, alone or in combination, as rendering the claims of the patents-in-suit obvious, and to provide support for the above contentions:

United States Patent No. 4,377,513

United States Patent No. 4,399,216

United States Patent No. 4,393,133

United States Patent No. 4,558,006

United States Patent No. 4,757,006

Japanese Patent Application Kokai Number SHO 54-55790, published May 4, 1979.

European Patent Application No. 093,619, published November 9, 1983.

All underlying work of inventors named in the above patents and patent applications.

Anderson, S., and Kingston, I.B., "Isolation Of A Genomic Clone For Bovine Pancreatic Trypsin Inhibitor By Using A Unique-Sequence Synthetic DNA Probe," *Proc. Natl. Acad. Sci. USA*, 80:6838-6842 (1983).

Ascensao, J.L., Gaylis, F., Bronson, D. et al., "Erythropoietin Production By A Human Testicular Germ Cell Line," *Blood* 62(5):1132-1134 (1983).

Breslow et al., "Isolation and characterization of cDNA clones for human apolipoprotein A-1" *Proc. Natl. Acad. Sci. USA*, 79:6861-6865 (1982).

Caro, J., Hickey J. and Erslev, A.J., "Erythropoietin Production By An Established Kidney Proximal Tubule Cell Line ($LLCPK_1$)," *Exp. Hematol.* 12(6):375A (July 1984).

Colman et al., "Cells That Secrete Foreign Proteins," TIBS, (December): 435-437 (1982).

Dukes P.P., "Preparation of High Specific Activity Erythropoietin by a Four Step Procedure," *Blood*, 60(5):86a (Abstract 270) (1982).

Erslev, A.J., Caro, J., Kansu, E. et al., "Plasma Erythropoietin In Polycythemia," *Am. J. Med.* 66(2):243-247 (1979).

Eschbach, J.W., Mladenovic, J., Garcia, J.F. et al., "The Anemia Of Chronic Renal Failure In Sheep," J. Clin. Invest. 74:434-441 (August 1984).

Eschbach, J.W. and Adamson, J.W., "Correction By Erythropoietin (EPO) Therapy Of The Anemia Of Chronic Renal Failure (CRF) In Sheep," *Clin. Res.* 29(2):69 (Abstract 578A) (1981).

Essers, U., Muller, W. and Brunner, E., "Weitere Untersuchungen zur Wirksamkeit von Erythropoetin bei Patienten mit Niereninsuffizienz," *Deutsche Medizinische Wochenschrift* 99:1618-1624 (1974).

Essers, U., Muller, W. and Heintz, R., "Effect Of Erythropoietin In Normal Men And In Patients With Renal Insufficiency," European Dialysis and Transplant Association Proceedings, *Biomed W1 EU715*, v. 11:398-402 (1975).

Farber, N.M., and Zanjani, E.D., Abstract, "Translation Of mRNA From Human Kidneys Into Biologically Active Erythropoietin Following Microinjection Into *Xenopus Laevis Oocytes," J. Lab. Clin. Med.* 102(4) 681 (1983)

Farber, N.M., and Zanjani, E.D., Abstract, "Translation Of mRNA From Human Kidneys Into Biologically Active Erythropoietin Following Microinjection Into *Xenopus Laevis Oocytes," Clin. Res.* 31: A769 (1983).

Farber, N.M., and Zanjani, E.D., Int. Soc. Exp. Hem. (July 1983) Abstract 101, "Translation Of mRNA From Anemic Baboon Kidney into Biologically Active Erythropoietin," *Expt. Hematology* 11: S14.

Feodorov, N.A., Rozenberg, G.Y., Kakhetelidze, M.G. et al., "Extraction Of Erythropoietin From Placental Blood And Study Of Its Hemopoietic Properties," *Nouvelle Revue Francaise d'Hematolgie* 11(4):595-608 (1971).

Gasser C.S. et al., "Expression of Abbreviated Mouse Dihydrofolate Reductase Genes in Cultured Hamster Cells, *Proc. Natl. Acad. Sci. USA* 79:6522-6526 (1982).

Goldberg, M.A., Glass, G.A., Cunningham J.M. et al., "The Regulated Expression Of Erythropoietin By Two Human Hepatoma Cell Lines," *Proc. Natl. Acad. Sci. USA* 84:7972-7976 (1987).

Goldwasser E. "Biochemical Control of Erythroid Development," in Current Topics in Developmental Biology, ed. A. Monroy and A.A. Noscona, pp. 173-211, Academic Press, NY (1966).

Goldwasser, E. et al., "Further Purification of Sheep Plasma Erythropoietin," *Bioch. Biophys. ACTA* 64: 487-496 (1962).

Goldwasser, E. and Kung, C.K. "Progress In The Purification Of Erythropoietin," *Annals of the N.Y. Acad. Sci.* 149:49-53 (1968).

Gordon, A.S. et al., "A Plasma Extraact with Erythropoietic Activity," *Proc. Soc. Expt. Biol. Med.* 86: 255-268 (1954).

Gray et al., "Expression of Human Interferon cDNA in E. Coli and Monkey Cells," *Nature* 295: 503-508 (1982).

Hagiwara, M., I-Li Chen, McGonigle, R. et al., "Erythropoietin Production By Cultured Human Renal Carcinoma Cells," (April 1983) (Abstract 2818).

Hagiwara, M., Chen, I., McGonigle, R. et al., "Erythropoietin Production In A Primary Culture of Human Renal Carcinoma Cells Maintained In Nude Mice," *Blood* 63(4):828-835 (April 1984).

Hagiwara, M., Chen, I.L., Fisher J.W., "Erythropoietin Production In Long-Term Cultures Of Human Renal Carcinoma Cells," *Exp. Cell Res.* 154(2):619-624 (October 1984).

Hauser et al., "Induction of Human B-interferon in Mouse L cell Clones," *Nature* 297:650-654 (1982).

Haynes and Weissman, "Production of a Glycosylated Human Protein by Recombinant DNA Technology," Humoral Factors Host Def., *Proc. Takeda Sci. Found. Symp. Biosci.* (1982 Meeting): 111-29 (1983).

Jacobsen, L.O. "Role of the Kidney in Erythropoiesis," *Nature* 179: 633-634 (1957).

Jacobs et al., Isolation and characterization of genomic and cDNA clones of human erythropoietin. *Nature* 313(6005):806-10 (1985).

Katsuoka, Y., McGonigle, R., Rege, A.B. et al., "Erythropoietin Production In Human Renal Carcinoma Cells Passaged In Nude Mice And In Tissue Culture," *GANN* 74:534-541 (1983).

Knowles, B.B., Howe, C.C., Aden, D.P., Human Hepatocellular Carcinoma Cell Lines Secrete The Major Plasma Proteins And Hepatitis B Surface Antigen," *Science* 209 (4455):497-499 (1980).

Kornblihtt, A.R. et al., "Isolation and Characterization of cDNA Clones for Human and Bovine Fibronectins," *Proc. Natl. Acad. Sci. USA* 80: 3218-3222 (1983).

Kuraowska, Z., Kowalski, E., Lipinski, B. et al., "Human Blood As A Source For Preparatiohn Of Erythropoietin," In *Erythropoiesis* (Jacobson, L.P., ed.), 58-63 Grune and Stratton, New York (1962).

Lai et al., "Ovalbumin is Synthesis in Mouse Cells Transformed with the Natural Chicken Ovalbumin Gene," *Proc. Natl. Acad. Sci. USA* 77:244-248 (1980).

Matsuya, Y., Green, H. and Basilico, C., "Properties And Uses Of Human-Mouse Hybrid Cell Lines," *Nature* 220:1199-1202 (1968).

McCormick, F., Trahey, M., Innis, M. et al., "Inducible Expression Of Amplified Human Beta Interferon Genes In CHO Cells," *Mol. Cell. Biol.* 4(1):166-172 (1984).

Miyake, T. et al., "Purification of Human Erythropoietin," *J. Biol. Chem.* 252: 5558-5564 (1977).

Nielsen, O.J., Schuster, S.J., Caro, J. et al., "Erythropoietin Production In A Human Hepatoblastoma Cell Line," *Blood* 66:158a (Abstract 519) (1985).

Saito, T., Saito, K., Trent D.J. et al., "Translation Of Human Erythropoietin-mRNAs," *Exp. Hematol.* 11(14):228 (Abstract 409) (1983).

Saito, T., Saito K., Trent D. et al., "Translation Of Messenger RNA From A Renal Tumor Into A Product With The Biological Properties Of Erythropoietin," Exp. *Hematol.* 13:23-28 (1985).

Schulze et al. "Identification of the cloned Gene For the Murine Transplantation Antigen H-2K by Hybridization with Synthetic Oligonucleotides," *Mol. Cell. Biol.* 3:750-755 (1983).

Sherwood, J.B. and Goldwasser, E. " Extraction of Erythropoietin from Normal Kidneys," *Endo* 103: 866-870 (1978).

Sherwood, J.B., Burns, E. and Shouval, D. "Establishment Of A Human Erythropoietin-Producing Renal Carcinoma Cell Line," *Clin. Res.* 31(2):323A (1983).

Sherwood J.B. and Goldwasser, E., "Erythropoietin Production By Human Renal Carcinoma Cells In Culture," *Endocrinology* 99(2):504-510 (1976).

Sherwood J.B. and Shouval D., "Continuous Production Of Erythropoietin By An Established Human Renal Carcinoma Cell Line: Development Of The Cell Line," *Proc. Natl. Acad. Sci. USA* 83:165-169 (1986).

Spier, R., "The Use Of Animal Cell Cultures In Pharmaceutical Production Processes," *Topics In Pharmaceutical Sciences* (D.D. Breimer and P. Speiser eds.) 511-533 Elsevier/North-Holland, New York (1981).

Sue, J.M., and Sytkowski, A.J., "Site-Specific Antibodies To Human Erythropoietin Directed Toward The NH2-Terminal Region," *Proc. Natl. Acad. Sci. USA* 80(12):3651-55 (1983).

Suggs, S.V. et al., "Use of Synthetic Oligonucleotides as Hybridization Probes: Isolation of Cloned cDNA Sequences for Human B2-microglobulin," *Proc. Natl. Acad. Sci. USA* 78: 6613-6617 (1981).

Suggs, S.V. et al., "Use of Synthetic Oligodeoxy-ribonucleotides for the Isolation of Specific Cloned DNA Sequences," in *Developmental Biology Using Purified Genes,* D. Brown, Ed., (1981).

Toyama, K., Noritoyo, F., Suzuki, H. et al., "Erythropoietin Levels In The Course OF A Patient With Erythropoietin-Producing Renal Cell Carcinoma And Transplantation Of This Tumor In Nude Mice," *Blood* 54(1):245-253 (1979).

Ullrich et al., "Isolation of the Human Insulin-like Growth Factor I Gene Using a Synthetic DNA Probe," EMBO J. 3: 361-364 (February 1984).

Urlaub et al., "Isolation of Chinese Hamster Ovary Cell Mutants Deficient in Dihydrofolate Reductase Activity," *Proc. Natl. Acad. Sci. USA* 77: 4216-4220 (1980).

Wallace et al., "The Use of Synthetic Oligonucleotides as Hybridization Probes," *Nucleic Acids Res.* 9: 879-895 (1981).

Weiss, T.L., Kavinsky, C.J., and Goldwasser, E., "Characterization Of A Monoclonal Antibody To Human Erythropoietin," *Proc. Natl. Acad. Sci. USA* 79:5465-5469 (1982).

Yanagawa, S., Hirade, K., Ohnota, H. et al., "Isolation Of Human Erythropoietin With Monoclonal Antibodies," *J. Biol. Chem.* 259(5): 2707-10 (March 1984).

All underlying work by the authors of such publications, including, to the extent Amgen contends for any claim of the patents-in-suit an invention date prior to the publication date of any of the above publications, any underlying work conducted by the authors before such an invention date.

F. Anticipation Under Section 102

The claims of the '422 and '933 patents (and the '080 patent, so far as Amgen improperly contends that the claimed subject matter would cover a 165 amino acid glycoprotein) are invalid under 35 U.S.C. §102 as anticipated by any one of several prior art publications describing use of various sources of EPO, including EPO expressing cells, as well as urine from anemic subjects, for isolating and purifying a therapeutically effective amount of human erythropoietin. (See art cited above in Sections D and E).

For example, the Goldwasser clinical study meets all of the relevant limitations of the claims of the '422 and '933 patents. Goldwasser disclosed a pharmaceutical composition of EPO prepared from the urine of patients with aplastic anemia. This pharmaceutical composition contained human serum albumin. In addition, the results of Goldwasser's clinical study demonstrate that the pharmaceutical composition comprised a "therapeutically effective amount of human erythropoietin" as that term is properly construed. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1303 (Fed. Cir. 2006). For example, the patients participating in the clinical study showed an increase in reticulocyte count, an increase in erythroid cells in the

marrow and an increase in red cell mass, all of which are signs that the pharmaceutical composition had therapeutic effects. Accordingly, the EPO disclosed by Goldwasser also had "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells" as that phrase is properly construed.

Further, the claim limitation "wherein said erythropoietin is purified from mammalian cells grown in culture" is a source or process limitation which the Federal Circuit stated would not confer patentability to the claimed product over human erythropoietin isolated from a different source. *See Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003). Similarly, any source or process limitations found in the '933 claims or in the '080 claims would not confer patentability to those claimed products over human erythropoietin isolated from a different source.

G. Lack of Written Description and Enablement Under Section 112 – Pegylated Compounds

Amgen has taken the position that the asserted claims of the patents-in-suit cover and claim pegylated compounds, which Amgen contends MIRCERA™ to be. The asserted claims of the patents-in-suit are invalid for lack of written description and enablement because it is undisputed that there is no written description of the techniques for pegylating proteins within the patent specifications. As a result, Amgen has failed to adequately describe its contended full scope of its asserted claims.

H. Lack of Written Description and Enablement Under Section 112 – DNA Claims

To the extent that Amgen contends that the patents-in-suit cover proteins expressed from cDNA, those claims are invalid for failure to provide an adequate written description and lack of enablement. Amgen's claims directed to the production of EPO are only supported by examples to human genomic DNA, rather than screening a human cDNA library.

The German Federal Patent Court (BPG) held in December 2000 that Amgen's European patent disclosure, which is identical to the specification of the patents-in-suit, does not

adequately teach cDNA encoding human EPO and required an express disclaimer in the DNA claims in that case stating that they were "excluding [the] cDNA sequence encoding human EPO." *See* BPG Decision, dated December 14, 2000.

I. Lack of Definiteness Under Section 112 – "Glycosylated Erythropoietin"

The asserted claims of the patents-in-suit that contain the terms "glycosylated erythropoietin," "erythropoietin glycoprotein," and similar variants, are invalid under 35 U.S.C. § 112 as indefinite because one skilled in the art is unable to comprehend the bounds of the claim language considering that multiple glycosylation forms can exist from a single host cell when cultured under different conditions.

A particular glycoprotein may occur in forms that differ in the structure of one or more of its carbohydrate units, especially when cultured under differing conditions, including a different glucose concentration, a different ammonium ion concentration, or the addition of hormones. The language "a glycosylated erythropoietin" and its variants are vague and indefinite in light of the microheterogeneity of glycoproteins and therefore Amgen has failed to set out with the requisite degree of precision and particularity the bounds of the invention which it has claimed and has failed to provide the necessary clear warning to others as to what constitutes infringement of the patent.

J. Lack of Definiteness Under Section 112 – "capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay"

Asserted claim 7 of the '349 patent depends from claims 1-6, each directed to vertebrate cells capable of producing erythropoietin in the medium of their growth. The claims require that claimed cells produce a specified number of "U of erythropoietin," either 100, 500, or 1000, per 100,000 cells in 48 hours. Claims 1-6 further require that "U of erythropoietin" be determined by radioimmunoassay. It is Roche's contention that the phrase as used in the claims is indefinite, cannot be properly defined in view of the patent specification and is otherwise scientifically inaccurate, as radioimmunoassay alone cannot measure erythropoietin units ("U") as required 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.	✓	✓	✓	✓

'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.

REDACTED

DATED: April 2, 2007

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CERTIFICATE OF SERVICE

I hereby certify that a copy of this document was served upon the attorneys of record for the plaintiff (as listed below) via email on the above date.

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