UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

AMGEN'S RESPONSE TO
ROCHE'S RULE 56.1 STATEMENT OF UNDISPUTED MATERIAL FACTS
IN SUPPORT OF ROCHE'S MOTION FOR SUMMARY JUDGMENT
THAT CLAIM 1 OF THE '422 PATENT IS INVALID UNDER 35 U.S.C. § 112

Pursuant to LR, D. Mass. 56.1, Plaintiff Amgen Inc. hereby responds to Defendants F. Hoffmann-La Roche LTD, Roche Diagnostics GmbH and Hoffmann-La Roche, Inc.'s ("Roche's") Rule 56.1 Statement of Undisputed Material Facts in Support of its Motion for Summary Judgment that Claim 1 of the '422 Patent is Invalid Under 35 U.S.C. § 112 ("Roche's Facts").

1. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 1 provided that the discussion is limited to human EPO that occurs naturally in the body.

2. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 2 as it pertains to the human EPO described in Recny *et al.*, but considers that the "human erythropoietin" of '422 claim 1 encompasses allelic variants. (*See infra at* ¶¶ 48-51).

3. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 3, except to correct the typographical errors in the "Related U.S. Application Data" section of the '422 Patent:

> Continuation of application No. 07/957,073, Oct. 6, 1992, abandoned, which is a continuation of application No. 07/609,744, Nov. 6, 1990, abandoned, which is a continuation of application No. 07/113,179, Oct. 23, 1987, Pat. No. 5,441,868, which is a continuation of application No. 06/675,298, Nov. 30, 1984, Pat. No. 4,703,008, which is a continuation-in-part of application No. 06/655,841, Sep. 28, 1984, abandoned, which is a continuation-in-part of application No. 06/582,185, Feb. 21, 1984, abandoned, which is a continuation-in-part of application No. 06/561,024, Dec. 13, 1983, abandoned.

4. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 4 except to the extent that "originating" is intended to mean that all of Dr. Lin's specification was first submitted on November 30, 1984. As set forth above, Dr. Lin's specification arose from four separate filings made with the U.S.P.T.O.

5. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 5.

6. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 6.

7. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 7, except to clarify that the Lin disclosure describes erythropoietin as "a substance for which no substantial amino acid sequence information has been published" and is not limited to human urinary erythropoietin only.

- '422 Patent, at col. 8:49.

8. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 8, except to clarify that the Lin disclosure also states that "[i]t should be noted that the

deduced human and monkey EPO sequences reveal an 'additional' lysine (K) residue at (human) position 116."

- '422 Patent, at col. 21:24-26.

9. Amgen contests the statement of fact contained in Roche's Facts paragraph 9. Figure 9 shows the then ***deduced*** amino acid sequence of human EPO.

- '422 Patent, at col. 21: 24-26.

10. Amgen contests the statement of fact contained in Roche's Facts paragraph 10 because Example 10 of Dr. Lin's specification describes a 165 amino acid sequence.

- '422 Patent, at Example 10.

11. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 11, except to correct typographical errors and to provide the full quotation from Dr. Lodish's expert statement:

> I understand this reference to "the mature erythropoietin amino acid sequence of FIG. 6" to mean the amino acids numbered 1-165 as set forth in Figure 6 of Amgen's Patents. 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. This is the final form of human EPO that is produced by recombinant human cells, CHO cells and other mammalian cells. It is also the final form of human EPO found in human urine. As described in Amgen's Patents, the amino acids shown in Figure 6 were deduced from the EPO DNA that was cloned and sequenced by Dr. Lin. Amgen's Patents correctly identify the 27-amino-acid signal peptide (or "leader sequence"), and confirm its cleavage from the translated amino acid residue at position 166, while based on the correct DNA sequence for the EPO gene, is cleaved off of the EPO polypeptide during post-translational processing. (internal citations omitted)

12. Amgen contests the statement of fact in Roche's Facts paragraph 12. Figures 4B-6 and 4B-7 submitted to the FDA disclose the ***deduced*** 166 amino acid sequence for human EPO.

- Roche's June 11, 2007 Memorandum in Support of its Motion for Summary Judgment that Claim 1 of the '422 Patent is Invalid Under 35 U.S.C. § 112 (Docket No. 483) (hereinafter "Roche's Br."), Ex. 7 at AM-ITC 00596041-42, AM-ITC 00595293.

13. Amgen contests the statement of fact in Roche's Facts paragraph 13. A 1985 article co-authored by Lin states that "[t]he Epo gene encodes a preprotein probably comprised of a 27-amino acid signal peptide and a 166-amino acid mature protein."

- Roche's Br., Exh. 8 (Lin *et al.*, *Proc.Nat'l Acad. Sci.*, 82:7580-84 (1985)).

14. Amgen contests the statement of fact in Roche's Facts paragraph 14. In 1986, during prosecution of a parent application to the '422 patent, in Lin's argument regarding three potential amino acid sequences for EPO based on Figure 6, one was the 165 amino acid sequence of human EPO now claimed.

- Roche's Br., Exh. 9 ('298 File History, Paper 12, Ex. 8 of 10/2/86 Amendment and Reply);

- Roche's Br., Exh. 10 ('298 File History, Paper 12, 10/2/86 Amendment and Reply), at pp. 35-37.

15. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 15, except to correct a typographical error in the language of and provide the full quotation from Roche's Br., Exh. 5 (Recny *et al.*, "Structural Characterization of Natural Human Urinary and Recombinant DNA-derived Erythropoietin," *J. Biol. Chem.*, 262(35); 17156-17163 (1987)), at 17161:

> Our discovery that the natural hormone purified from urine and the recombinant hormone purified from CHO cell-conditioned media are both des-Arg^{166} EPO indicates that each is apparently processed by an enzyme that specifically removes COOH-terminal basic residues. Since natural EPO exerts its biological effect as a circulating plasma hormone prior to excretion into urine, COOH-terminal processing of the natural hormone to des-Arg^{166} EPO can occur at one of three stages.

16. Amgen disputes the heading between paragraphs 15 and 16 of Roche's Facts and directs the Court's attention to Amgen's Opposition, filed herewith, for each of the bases for the dispute.

17. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 16 except for the characterization that the quoted language is an "admission."

18. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 17 except for the characterization that the quoted language is an "admission."

19. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 18 except for the characterization that the quoted language is an "admission," and because the statement implies that the claims limitations for the '080 patent and the patents-at-issue in this litigation are the same.

20. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 19, except for the characterization that the quoted language is an "admission" and also to correct a typographical error in the language of and provide the full quotation from Roche's Br., Exh. 4 (Amgen's Post-Hearing Memo.), at p. 4:

> As the *Festo* Court stated, "What is claimed by the patent application must be the same as what is disclosed in the specification; otherwise the patent should not issue." 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 that were in the application at the filing date. 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. That is why it is the date of the application, not the date of the amendment, that is the appropriate point in time at which to judge whether the applicant could have foreseen, and therefore could have described, a particular equivalent.

21. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 20 except to clarify that the statements were made in the context of the '080 patents under a hypothetical claim analysis. (*See* Roche's citations in support of Fact 20).

22. Amgen disputes the heading between paragraphs 20 and 21 of Roche's Facts and directs the Court's attention to Amgen's Opposition, filed herewith, for each of the bases for the dispute.

23. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 21.

24. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 22.

25. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 23.

26. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 24 except to clarify that Dr. Lin refers to the T28 sequence elsewhere in his specification as an example of a possible natural variant.

- '933 Patent, at col. 21:3-19.

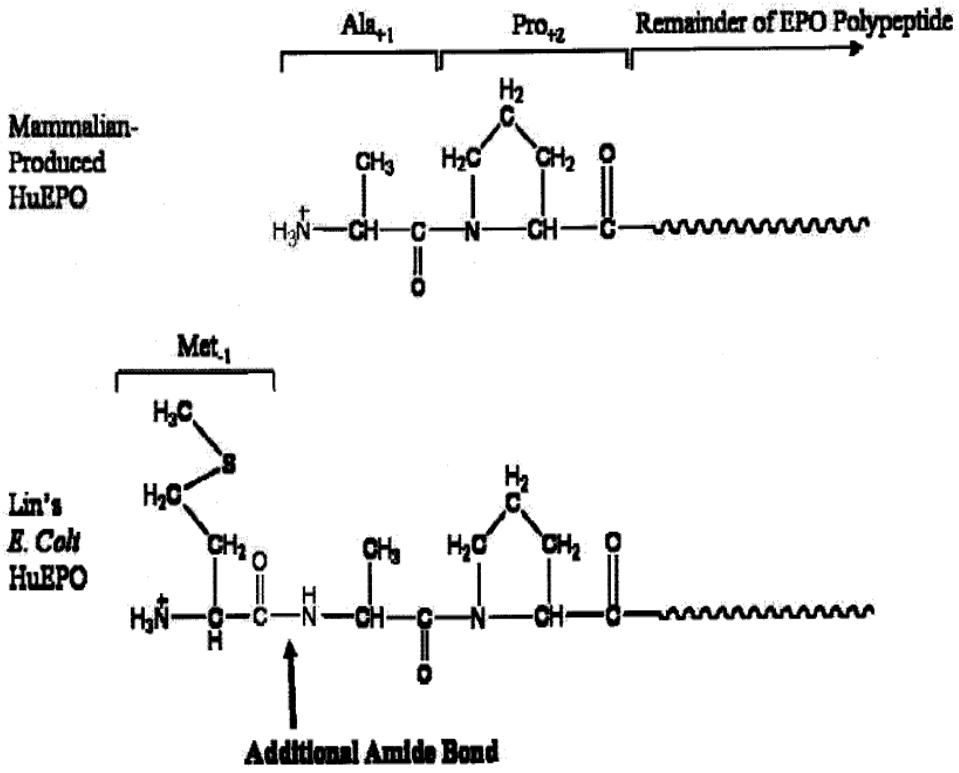
27. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 25 except as set forth above in Amgen's response to Roche's Facts paragraph 24.

28. Amgen does not contest the statement of fact contained in Roche's Facts paragraph 26 except to the extent that Roche's statement that Amgen "defined" certain terms in its specification is intended to imply that Amgen acted as a lexicographer to assign a meaning other than a plain meaning to a term.

29. Amgen contests the statement of fact contained in Roche's Facts paragraph 27. Paragraphs 32-33 of Roche's Br., Exh. 14 (3/19/07 Lodish Decl.) state:

32. In addition to differences in glycosylation state, the patent specification also contemplates human erythropoietin with other differences in structure as compared to the "structure that would be produced in mammalian cells as of the invention date." In particular, the patent specification states that human erythropoietin can include a methionine residue linked to the amino-terminus of human erythropoietin by an amide bond: "Polypeptides of the invention may also include an initial methionine amino acid residue (at position 01)." In the context of Example 11, the patent specification further states: "FIGS. 10 through 15 and 7 illustrate the design and assembly of a manufactured gene encoding a human EPO translation product lacking any leader or presequence but including an initial methionine residue at position -1." This passage in particular makes plain that according to Lin (as well as the common understanding at the time), that even when an additional molecule, here methionine, is added to the polypeptide sequence of human EPO, it is still a "human EPO." Again, like glycosylation, if a bond to a hydrogen atom from the nitrogen atom in the amino group of Ala+1 is replaced by an amide bond to a methionine, this does not change the identity of that amino acid as alanine, nor does it change the identity of the polypeptide as human erythropoietin.

33. Example 11 describes construction of a synthetic gene for human erythropoietin that has been optimized for production in *E. coli* by, among other things, the replacement of the codons for the normal 23 amino acid signal sequence found in the native EPO gene with a methionine codon. Upon expression in *E. coli*, this would result in the synthesis of a human erythropoietin with an additional methionine amino acid at position -1. I set forth below a comparison of the chemical structures between the human EPO produced by mammalian cells (such as the CHO cells of Lin's Example 10) and the human EPO produced by *E. coli* cells as described in Examples 11 and 12, which has an additional amide bond between Ala+1 and Met-1 which is not present in human EPO produced by mammalian cells:



Paragraphs 26-27 of Roche's Br., Exh. 15 (6/4/07 Supplemental Expert Report of Harvey F. Lodish) state:

> 26. As to Dr. Flavell's discussion of the amino acid sequences described in Example 12 of the patent, which concerns expression of human erythropoietin in *E. coli*, I believe that these examples support the Court's interpretation of "human erythropoietin." Example 12 demonstrates that the specification intended the term "human erythropoietin" to allow for additional structure, even in the form of an amino acid (Lin Example 12 at the amino terminus).
>
> 27. Dr. Flavell contends that I wrongly characterized Example 12 as producing a -1 to 166 protein in my Infringement Expert Report. Dr. Flavell is correct that the Lin's *E. coli* host cell example in the specification shows that a terminal methionine, and in some instances the initial alanine, were cleaved off after *E. coli* synthesis. My point is not that human EPO recovered from the *E. coli* cells in Examples 11-12 must have a methionine attached. Rather, my point is that the specification explicitly includes polypeptides that have an additional methionine residue in its description of "human EPO." For example, the specification states: "Polypeptides of the invention may also include an initial methionine amino acid residue (at position -1)." In addition, the specification describes Figures 10-15 and 7 as illustrating the "design and assembly of a manufactured gene encoding a ***human***

> ***EPO translation product*** lacking any leader or presequence but including an initial ***methionine residue at position -1***." A polypeptide containing methionine at position -1 was made by the *E. coli* cells in Examples 11-12, and the specification describes that polypeptide as "human EPO translation product" and "polypeptides of the invention" because, in my opinion, the polypeptide backbone of the protein produced by *E. coli*. in this Example contained the human EPO amino acids sequence. The fact that the methionine at position -1 was subsequently cleaved off in the cells after initial synthesis of the polypeptide, does not change this fact. Thus, in my opinion, one of ordinary skill in the art reading the specification in 1984 would have understood Lin's definition of "human EPO" did not exclude the presence of additional molecules attached to the amino acid sequence of human EPO such as a methionine. Such a polypeptide was still human EPO. (emphasis in original, internal citations omitted)

30. Amgen contests the statement of fact contained in Roche's Facts paragraph 28.

The '422 Patent, at col. 31:56-32:24, states:

> Cells were harvested, lysed, broken with French Press (10,000 psi) and treated with lysozyme and NP-40 detergent. The pellet resulting from 24,000 xg centrifugation was solubilized with guanidine HCl and subjected to further purification in a single step by means of C_4 (Vydac) Reverse Phase HPLC (EtOH, 0-80%, 50 mM NH_4 Ac, pH 4.5). 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^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. Radioimmunoassay activity for the isolates was at a level of 150,000 to 160,000 U/mg; in vitro assay activity was at a level of 30,000 to 62,000 U/mg; and in vivo assay activity ranged from about 120 to 720 U/mg. (Cf., human urinary isolate standard of 70,000 U/mg in each assay.) The dose response curve for the recombinant product in the in vivo assay differed markedly from that of the human urinary EPO standard.

31. Amgen contests the statement of fact contained in Roche's Facts paragraph 29.

The '422 Patent, at col. 32:22-24, states: "The dose response curve for the recombinant product in the in vivo assay differed markedly from that of the human urinary EPO standard."

32. Amgen contests the statement of fact contained in Roche's Facts paragraph 30 to the extent that it misstates the arguments made by Amgen during prosecution of the '422 patent.

- Roche's Br., Exh. 11 ('422 File History, Paper 2, 11/6/90 Preliminary Amendment), at p. 2;
- Roche's Br., Exh. 12 ('197 File History, Paper 33, 4/28/99 Amendment), at pp. 4-5.

In addition to the facts set forth above, Amgen affirmatively offers the additional statement of undisputed, or indisputable, facts that support its opposition to Roche's motion:

33. On April 17, 2007, the Court construed "human erythropoietin" to mean "a protein having the amino acid sequence of human EPO, ***such as*** the amino acid sequence of EPO isolated from human urine."

- Docket No. 514, Exh. 40 (4/17/07 *Markman* Hearing Tr.), at 23:17-39:10 (the Court took under advisement whether the term should include reference to glycosylation as well as human erythropoietin's amino acid sequence) (emphasis added).

34. Throughout his specification, Dr. Lin affirmatively states that the products of his invention include "human erythropoietin" or "human EPO."

- *See*, *e.g.*, '933 Patent, at col. 27:47-51.

35. To demonstrate that he in fact possessed "human erythropoietin/human EPO," Dr. Lin's specification offers at least the following evidence regarding the products he obtained:

a) the products were obtained using a DNA sequence encoding human erythropoietin ('933 Patent, at Examples 7, 10, and 11);

b) the N-terminal amino acid sequence of his products corresponds to the N-terminal sequence of human urinary EPO (*id.* at 28:11-12);

c) the products possess the expected biological activity of human erythropoietin, as measured using a variety of *in vivo* and *in vitro* assays (*id.* at 28:1-10; 28:13-28); and

d) the products of his invention are appropriately glycosylated (*id.* at 28:1-10; 28:13-28).

36. Dr. Lin's specification expressly states that "human EPO" is exemplified in Example 10.

- *See, e.g.*, '933 Patent, at col. 26:11-18.

37. The human erythropoietin produced in Example 10 contains a 1-165 amino acid polypeptide.

- *See*, *generally*, *e.g.*, Roche's Br., Exh. 5.

38. Goldwasser's human urinary erythropoietin has the same 165 amino acid sequence as the human EPO product of Example 10.

- Roche's Br., Exh. 5.

39. Dr. Lin's specification states that the 166 amino acid sequence disclosed in Dr. Lin's specification is a "deduced" sequence (a sequence derived from the DNA sequence that Dr. Lin had isolated and not from actual sequencing of the entire product).

- '933 Patent, at col. 21:20-27 ("FIG. 9 illustrates the extent of polypeptide sequence homology between human and monkey EPO. In the upper continuous line of the Figure, single letter designations are employed to represent the deduced translated polypeptide sequences of human EPO commencing with residue -27 and the lower continuous line shows the deduced polypeptide sequence of monkey EPO commencing at assigned residue number -27.");

- '933 Patent, at col. 10:64-11:2;

- Declaration of Linda A. Sasaki-Baxley in Support of Amgen Inc.'s Opposition to Roche's Motion for Summary Judgment that Claim 1 of the '422 Patent is Invalid Under 35 U.S.C. § 112 ("Sasaki-Baxley Decl."), Exh. A (3/28/07 Lin Depo. Tr.), at pp. 77-78.

40. Example 10 of Dr. Lin's specification inherently yields a 1-165 amino acid product, or that the product's inherent amino acid sequence corresponds to the amino acid sequence of a human urinary EPO preparation.

- Sasaki-Baxley Decl., Exh. A (3/28/07 Lin Depo. Tr.), at 223:16-20;
- Roche's Br., Exh. 5 (Recny *et al. J. Biol. Chem*. 262(35): 17156-163 (1987)).

41. In Amgen's Rule 52(c) motion in the *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, Civil Action No. 97-10814-WGY (D. Mass. 2001) ("*TKT* case"), Amgen argued that the *Festo* presumption against the application of the doctrine of equivalents did not apply to the '080 patent claims.

- Roche's Br., Exh. 4, at p. 9 (Docket No. 485-7, at p. 3).

42. In that motion, Amgen argued that the written description requirement prevented Amgen from amending its '080 patent claims to recite a hypothetical claim limitation ("human EPO having the specific 1-165 amino acid sequence of Figure. 6."). Amgen's arguments were limited to whether there was support for that hypothetical limitation in a hypothetical claim.

- Roche's Br., Exh. 4, at pp. 8-9 (Docket No. 485-7, at pp. 2-3).

43. Amgen's Rule 52(c) Motion explicitly stated that claim 1 of the '422 patent encompassed the 165-amino-acid EPO product, for which there was ample written descriptive support:

> Defendants argue that Amgen cannot rebut the presumption of estoppel unless it shows that it could not have drafted a claim that encompasses 165 human EPO. As Amgen has explained, the dispositive issue is not whether Amgen could have drafted *any* claim that would cover 165 human EPO. If that were the dispositive issue, the Federal Circuit would not have remanded the issue of rebuttal for decision by this Court. As this Court previously found and the Federal Circuit affirmed, Amgen drafted another claim that encompasses Defendants' 165 amino acid product (claim 1 of the '422 patent). If the only question was whether Amgen could have drafted a claim that encompassed 165 human EPO, the Federal Circuit would have held that Amgen had already done so in the '422 claim 1 and therefore could not rebut the presumption.

- Roche's Br., Exh. 4, at pp. 8-9 (Docket No. 485-7, at pp. 2-3).

44. In an October 2, 1986, Amendment and Reply to a Patent Office action during prosecution of the '422 patent, Amgen argued that Dr. Lin's pending claims were not obvious over the cited prior art.

- Roche's Br., Exh. 10, at 24-37 (Docket No. 485-16, p. 4 – 485-17, p.7).

45. Amgen's arguments centered on the failed prior-art attempt by Dr. Sylvia Lee-Huang and her colleagues to clone the human EPO gene.

- Roche's Br., Exh. 10, at pp. 29-37 (Docket No. 485-16, p. 9 – 485-17, p.7) (*discussing* Lee-Huang *et al*., *Proc. Nat'l Acad. Sci. USA* (1984) 81: 2708-2712).

46. In the action, the Patent Office cited an article by Dr. Lee-Huang and her colleagues in which they suggested that they had cloned the human EPO gene based on the production of translation products (made by translating cDNAs produced from RNA isolated from human kidney tumor tissue) in an *in vitro* bacterial translation system.

- Roche's Br., Exh. 10, at pp. 13-14, 16-18 (Docket No. 485-15, at pp. 3-4, 6-8).

47. In response, Amgen argued that the DNA sequence described for the first time in Figure 6 of Dr. Lin's patent application, along with computer-assisted modeling, showed that Dr. Lee-Huang and her colleagues could not possibly have cloned the human EPO gene.

- Roche's Br., Exh. 10, at 29-37 (discussing Docket No. 485-16, p. 9 – 485-17, p.7).

48. Amgen showed that the DNA sequence encoding human EPO described by Dr. Lin in Figure 6 has a limited number of cleavage sites recognized by the restriction enzymes employed by Dr. Lee-Huang to cleave purported cDNA molecules created in her *in vitro* system, and that none of Dr. Lee-Huang's purported cDNA clones could have been an authentic cDNA encoding the EPO polypeptide.

- *Id.*

49. Amgen argued that Dr. Lee-Huang's "translation products" could not possibly have been authentic human EPO proteins because none of their purported lengths matched the length of a protein that could hypothetically have been produced if an authentic EPO mRNA had been translated in Dr. Lee-Huang's *in vitro* bacterial translation system.

- Roche's Br., Exh. 10, at pp. 33-37 (Docket No. 485-17, at pp. 3-7 of 9).

50. In Dr. Lin's specification, "erythropoietin" refers to polypeptides having the same sequence of amino acid residues as naturally occurring erythropoietin:

> The present invention provides, for the first time, novel purified and isolated polypeptide products having part or ***all of the primary structural conformation (i.e., continuous sequence of amino acid residues)*** and one or more of the biological properties (e.g., immunological properties and in vivo and in vitro biological activity) of naturally-occurring erythropoietin, including allelic variants thereof.

- '933 Patent, at col. 10:9-15 (emphasis added).

> According to the present invention, DNA sequences encoding part or ***all of the polypeptide sequence of human and monkey species erythropoietin (hereafter, at times, "EPO"***) have been isolated and characterized.

- '933 Patent, at col. 13:50-53 (emphasis added).

51. The prosecution history of the '422 Patent similarly makes plain that "human erythropoietin" includes any polypeptide that has the same sequence of amino acid residues as EPO isolated from human urine:

> [H]uman 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.

- Roche's Brief, Exh. 12 (U.S. Appln. 100,197 File History, 4/28/99 Amendment (Paper 33)), at p. 5.

52. "Human erythropoietin" also includes any naturally occurring allelic variations in the amino acid sequence of human EPO.

- '933 Patent, at cols. 21:11-19; 35:10-20; 35:27-39.

53. Roche offered a similar construction for "human erythropoietin" at *Markman* except that Roche sought to further limit the term by also requiring the presence of particular glycosylation (carbohydrate structures) attached to the amino acid sequence by mammalian cells as of Lin's invention date:

> a glycoprotein having the amino acid sequence of erythropoietin isolated from human urine having the same structure that would be produced by mammalian cells as of the invention date.

- Defs.' Opening Mem. in Supp. of Their Proposed Claim Construction (Docket No. 311), at p. 1.

54. Roche argued that its proffered definition "was supported by the patentee's definition and use of this term in the specification and the prosecution histories," and was consistent with the understanding of an ordinarily skilled artisan.

- *Id.* at 6.

55. Roche's expert witnesses have acknowledged that human erythropoietin contains the same amino acid sequence as human urinary erythropoietin, which has the 1-165 amino acid sequence.

- *See e.g.*, Sasaki-Baxley Decl., Exh. B (6/6/07 Bertozzi Depo. Tr.), at pp. 96:17-97:17.

56. As the specification specifically contemplates, "human erythropoietin" may include proteins with an amino acid sequence that corresponds to allelic variants.

- '933 Patent, at col. 21:11-19; *see also* '933 Patent col. 35:17-39.

57. Example 10 of the specification, describing a method for producing "human erythropoietin," discloses products that have a 1-165 amino acid sequence.

- Sasaki-Baxley Decl., Exh. C (9/28/99 Decl. of Jeffrey K. Browne, Ph.D.).

Respectfully Submitted,

AMGEN INC.,
By its attorneys,

/s/ Patricia R. Rich

D. DENNIS ALLEGRETTI (BBO#545511)
MICHAEL R. GOTTFRIED (BBO#542156)
PATRICIA R. RICH (BB#640578)
DUANE MORRIS LLP
470 Atlantic Avenue, Suite 500
Boston, MA 02210
Telephone: (857) 488-4200
Facsimile: (857) 488-4201

LLOYD R. DAY, JR. (*pro hac vice*)
DAY CASEBEER
MADRID & BATCHELDER LLP
20300 Stevens Creek Boulevard, Suite 400
Cupertino, CA 95014
Telephone: (408) 873-0110
Facsimile: (408) 873-0220

WILLIAM GAEDE III (*pro hac vice*)
McDERMOTT WILL & EMERY
3150 Porter Drive
Palo Alto, CA 94304
Telephone: (650) 813-5000
Facsimile: (650) 813-5100

KEVIN M. FLOWERS (*pro hac vice*)
MARSHALL, GERSTEIN & BORUN LLP
233 South Wacker Drive
6300 Sears Tower
Chicago IL 60606
Telephone: (312) 474-6300
Facsimile: (312) 474-0448

Of Counsel:

STUART L. WATT
WENDY A. WHITEFORD
MONIQUE L. CORDRAY
DARRELL G. DOTSON
KIMBERLIN L. MORLEY
ERICA S. OLSON
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789
(805) 447-5000

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CERTIFICATE OF SERVICE

I hereby certify that this document, filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing and paper copies will be sent to those indicated as on-registered participants.

/s/ Patricia R. Rich
Patricia R. Rich