UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD ROCHE DIAGNOSTICS GmbH and HOFFMANN-LA ROCHE INC. Defendants.	CIVIL ACTION No.: 05-CV-12237WGY

ROCHE'S RESPONSE TO AMGEN'S RULE 56.1 SEPARATE STATEMENT OF UNDISPUTED FACTS IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT THAT DR. LIN'S ASSERTED CLAIMS ARE DEFINITE, ADEQUATELY DESCRIBED AND ENABLED

Pursuant to LR, Mass. 56.1, F. Hoffmann-La Roche, Ltd, Roche Diagnostics Gmbh, and Hoffmann-La Roche Inc. (collectively "Roche") hereby respond to Plaintiff Amgen Inc.'s ("Amgen") Rule 56.1 Separate Statement of Undisputed Facts in Support of its Motion for Summary Judgment That Dr. Lin's Asserted Claims are Definite, Adequately Described and Enabled ("Amgen's Facts").

I. Amgen's Undisputed Facts

Response to Amgen's Statement of Fact No. 1

1. Roche agrees that the Federal Circuit affirmed that the term "non-naturally occurring" means a product "not occurring in nature."

Response to Amgen's Statement of Fact No. 2

2. Roche agrees that the Federal Circuit stated, in reference to the '080 patent, that:

> "[T]he 'non-naturally occurring' limitation in claims 3 and 4 merely prevents Amgen from claiming the human EPO produced in the natural course. By

> limiting its claims in this way Amgen simply avoids claiming specific subject matter that would be unpatentable under § 101. This court has endorsed this approach, recognizing that patentees can use negative limitations such as 'non-human' and 'non-natural' to avoid rejection under § 101."

However, Roche clarifies that the Federal Circuit further held "..when considering obviousness and anticipation issues...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."[1]

Response to Amgen's Statement of Fact No. 3

3. Roche agrees that Amgen characterized "non-naturally occurring" as a "negative limitation" in the 12/20/95 Second Preliminary Amendment. However, Roche clarifies that Amgen stated in the amendment that "the negative limitation, 'non-naturally occurring' would, when combined with the notation of glycosylation differences...meet Section 112 specificity." (*See* Amgen Ex. 25 at AM-ITC 00941549).

Response to Amgen's Statement of Fact No. 4

4. Roche agrees that the specification purports to make a distinction between Lin's claimed recombinantly-produced products and those products that are produced without human intervention.

Response to Amgen's Statement of Fact No. 5

5. Roche agrees that the specific uses the terms "non-naturally occurring" and "human urinary erythropoietin."

Response to Amgen's Statement of Fact No. 6

6. Roche agrees that Roche did not assert that the term "non-naturally occurring" was indefinite during *Markman*. Roche also agrees that it adopted the Federal Circuit's construction

[1] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003) (citing *General Electric Co. v. Wabash Corp.*, 304 U.S. 364, 373, 58 S.Ct. 899, 82 L.Ed. 1402 (1938); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311, 4 S.Ct. 455, 28 L.Ed. 433 (1884)).

of "not occurring in nature" for the term "non-naturally occurring." However, Roche disagrees with Amgen's statement to the extent that it implies Roche waived any defenses.

Response to Amgen's Statement of Fact No. 7

7. Roche agrees that claim 7, rewritten in independent form reads as follows:

   a. "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**."** **(**DI # 542 (Declaration of Howard S. Suh in Support of Roche's Motion for Summary Judgment That Claim 7 of Patent No. 5,756,349 is Invalid Under 35 U.S.C. § 112 and is not Infringed), Ex. B, col. 38, ll. 34-36).

Response to Amgen's Statement of Fact No. 8

8. Roche agrees that claim 7, rewritten in independent form reads as shown in Roche's response to 7, and points out that the "suitable nutrient conditions" are not recited in the patent.

Response to Amgen's Statement of Fact No. 9

9. This assertion has not been previously disclosed during discovery and Roche submits that it should be stricken from the record. If it is not stricken, Roche denies on the basis that it has no information to agree or disagree.

Response to Amgen's Statement of Fact No. 10

10. This assertion has not been previously disclosed during discovery and Roche submits that it should be stricken from the record. If it is not stricken, Roche denies on the basis that it has no information to agree or disagree.

Response to Amgen's Statement of Fact No. 11

11. Roche contests Amgen statement 11 to the extent that it is intended to imply that one of skill in the art at the time of the Lin patent filing, would have known what standard to use in calculating RIA "Units" as required by claim 7.

Response to Amgen's Statement of Fact No. 12

12. Roche contests Amgen statement 12 to the extent that it is intended to imply that one of skill in the art at the time of the Lin patent filing, would have known what standard to use in calculating RIA "Units" as required by claim 7.

Response to Amgen's Statement of Fact No. 13

13. Roche contests Amgen statement 13 to the extent that it is intended to imply that one of skill in the art at the time of the Lin patent filing, would have known what standard to use in calculating RIA "Units" as required by claim 7.

Response to Amgen's Statement of Fact No. 14

14. Roche agrees that RIAs are referenced in the '349 patent. Roche disagrees with Amgen's statement 14 to the extent that it implies that RIAs can be used to measure EPO as defined by the Court or biological activity.

Response to Amgen's Statement of Fact No. 15

15. Roche disagrees with Amgen's statement 15 to the extent that it implies that one of skill in the art have considered RIAs to be capable of measuring EPO as defined by the Court or biological activity.

Response to Amgen's Statement of Fact No. 16

16. Roche agrees that the Lin specification at Example 2 contains the text cited by Amgen. Roche disagrees with Amgen's statement 16 to the extent that it implies that RIAs can be used to measure EPO as defined by the Court or biological activity.

Response to Amgen's Statement of Fact No. 17

17. Roche disputes this statement.

- At the time of the invention of the '349 patent, there were a variety of EPO standards that could be used in RIA testing, each of which would yield a different result, and, during its EPO project, Amgen relied upon several different EPO standards for its assays. (DI # 542, Suh Decl., Ex. O at AM-ITC 00558660, AM-ITC 00558662; *Id,* Ex. Q; *Id,* Ex. I at 45:18-25, 134:9-11; 170:17-171:20; 183:20-184:3; 184:14-185:2, 194:7-16).

- In the RIA protocol, Dr. Egrie used CAT-1 urinary EPO as the assay standard, and not the standard International Reference Standard. (DI # 542, Suh Decl., Ex. I at 45, 52, 134-136, 172, 183-184, 194; *Id* at Ex. CC AM-ITC 00550777).
- CAT-1 was not calibrated against IRP #2. (DI # 542, Suh Decl., Ex. Z at AM-ITC 00550542).
- George Rathmann, Amgen's then CEO, confirmed that "if one expressed international units in the time period of 1985-87, it might be assumed that the reference standard was IRP #2, but unless the precise method to be used was defined, there would be no basis for stating international units." (DI # 542, Suh Decl., Ex. O at AM-ITC 00558660).
- In a March 15, 1990 memo George Rathmann wrote the following about the measurement of EPO activity:

> I think we should be absolutely fastidious in reporting specific activity in arbitrary (Amgen) units ***until we can establish an excellent correlation with international units*** . . . . I think we should understand how any standard can deviate from 'parallelism' trying to relate to international units. It is absolutely imperative that we learn as early as possible what the international (NIBSAC) committee that is conducting round robin studies is finding. My prediction is that the information will be absolute chaos. Discrepancies between laboratories is likely to far exceed their predicted accuracy or precision . . . .
>
> (DI # 542, Suh Decl., Ex. T at AM-ITC 00558619).

Response to Amgen's Statement of Fact No. 18

18. Roche disputes this statement.

- Dr. McLawhon, the RIA "says nothing about the biological activity directly." (DI # 542, Suh Decl., Ex. J at 133:24-25).
- Amgen's expert, Dr. Goldwasser stated:

> "An RIA is used to measure erythropoietin in a sample based on its immunological reactivity with an antibody raised against EPO. An RIA to measure EPO cannot distinguish between, for instance, unmodified erythropoietin and erythropoietin that has been desialated and has no in vivo biological activity. . . ."
>
> (DI # 542, Suh Decl., Ex. at ¶ 48; *see Id,* Ex. AA at 281: 3-5, 8-10).

- A 1987 Amgen validation report regarding RIA for EPO similarly states that the "RIA activity is a quantitative measure of native protein structure but not a direct measure of its in vivo potency." (DI # 542, Suh Decl., Ex. M at AM ITC 00156691).
- The claim requires measurement of EPO Units, which since before the time of the invention has been universally understood to be a measure of biological activity. (DI # 542, Suh Decl., Ex. E at 50:20-51:21, 52:7-16, 52:20-54:1, 56:1-6; Ex. F at ¶ 75).

- Converting the measured amount of protein to "U of erythropoietin" requires reference to a standard. (DI # 542, Suh Decl., Ex. H at ¶ 32).
- The '349 patent does not prescribe what standard is to be used as the basis for comparison in the RIA of the claims. (DI # 542, Suh Decl., Ex. B col. 16, line 43).

Response to Amgen's Statement of Fact No. 19

19. Roche disputes this statement.

- RIA does not distinguish between biologically active EPO and inactive EPO. (DI # 542, Suh Decl., Ex. G at ¶ 48).
- The antibody used in an RIA may bind not only EPO but also certain EPO fragments. (DI # 542, Suh Decl., Ex. J at 151:18-152:8, 220:4-15; *Id,* Ex. E at 49-50).
- The RIA does not distinguish EPO from whatever else may bind to the antibodies. (DI # 542, Suh Decl., Ex. J at 151:18-152:8, 220:4-15; *Id,* Ex. E at 49-50).

Response to Amgen's Statement of Fact No. 20

20. Roche agrees that the Court's April 17, 2007 tentative construction for "human erythropoietin" is "a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine."

Response to Amgen's Statement of Fact No. 21

21. Roche agrees that it did not assert that the term "human erythropoietin" was indefinite during the *Markman* proceedings. However, Roche disagrees with Amgen's statement to the extent that it implies Roche waived any defenses.

Response to Amgen's Statement of Fact No. 22

22. Roche agrees that the specification contains the text reproduced by Amgen. Roche disagrees with Amgen's statement to the extent it implies that "human erythropoietin" as construed by the Court includes allelic variants.

Response to Amgen's Statement of Fact No. 23

23. Roche agrees that Example 10 of the specification purports to describe a method for producing human erythropoietin. Roche disagrees with Amgen's statement to the extent it

implies that Example 10 discloses, describes or enables an amino acid sequence for human erythropoietin.

Response to Amgen's Statement of Fact No. 24

24. Roche disputes this statement. See section III below.

II. Roche Undisputed Facts

1. The Claim Limitation "Non-Naturally Occurring" Renders The Asserted Claims Of The '933 Patent Indefinite

25. The Federal Circuit agreed 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 II* at 1354. This is consistent with another recent Federal Circuit decision which held that "a prior art disclosure of a product precludes a future claim to that same product, even if it is made by an allegedly novel process." *SmithKline Beecham Corp. v. Apotex Corp.,* 439 F.3d 1312, 1319 n.7 (Fed. Cir. 2006).

26. The '933 patent describes only one supposed physical distinction between the non-naturally occurring erythropoietin glycoproteins of the claims and naturally occurring erythropoietin, *i.e.*, glycosylation. (DI # 507, Suh Decl., Ex. A at col. 10:28-40; 28:51-29:7).

27. Amgen attempted to claim "recombinant EPO" without any structural limitation during the prosecution of its U.S. Patent No. 5,955,422. This attempt was rejected by the Examiner as failing "to impose any definitive **physical limitation** on the claimed compositions." (DI # 507, Suh Decl., Ex. G).

28. In *Amgen I*, this Court held that because the glycosylation of naturally occurring EPO varies, claims 1, 2 and 9 of the '933 patent, which distinguish the claimed non-naturally occurring erythropoietin glycoproteins from naturally occurring erythropoietin based on the "glycosylation" or "average carbohydrate composition," were not infringed or, alternatively,

were invalid for indefiniteness ("one of ordinary skill would be unable to determine whether a particular erythropoietin has a glycosylation which differs from that of human urinary erythropoietin") and lack of written description ("the patent fails to convey to one of ordinary skill in the art as of 1984 that Dr. Lin invented in erythropoietin product having glycosylation which differs from human urinary erythropoietin"). *Amgen I* at 155-56.

29. In *Amgen, Inc. v. Hoescht Marion Roussel, Inc*., Civil Action No. 97-10814-WGY (D. Mass), Amgen fully litigated whether the glycosylation of human urinary erythropoietin varies such that one of ordinary skill in the art as of 1984 reading the '933 patent would have understood that Dr. Lin invented an erythropoietin product having glycosylation which differed from the glycosylation of human urinary erythropoietin.

30. In *Amgen Inc. v. Hoechst Marion Roussel, Inc*., Civil Action No. 97-10814-WGY (D. Mass.), Amgen fully litigated whether one of ordinary skill in the art reading the claims of the '933 patent would have been able to determine whether the glycosylation of a particular erythropoietin glycoprotein differed from the glycosylation of human urinary erythropoietin.

31. In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003), the Federal Circuit affirmed this Court's holding that claims 1, 2 and 9 of the '933 patent were invalid for indefiniteness.

2. <u>The Claim Limitation "Human Erythropoietin" As Construed By The Court Is Indefinite When Read In Light Of The Specification Of The Patents-In-Suit</u>

32. Human erythropoietin (EPO) is a glycoprotein hormone in the body that regulates the production of red blood cells. (DI # 485, Rycroft Decl., Ex. 14, at ¶26; See also Amgen v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1321 (Fed. Cir. 2003) ("EPO is a naturally occurring protein that initiates and controls erythropoiesis, the production of red blood cells in bone marrow.")).

33. Human EPO has a specific 165-amino acid sequence starting with an alanine at the 1 position and ending with aspartic acid at the 165 position. (DI # 485, Rycroft Decl., Ex. 5; Id, Ex. 14, at ¶27).

34. The '422 patent issued on September 21, 1999 from application Ser. No. 08/100,197 ("the '197 application") filed on August 2, 1993. The '197 application:

a. is a continuation of application Ser. No. 07/957,073, filed Oct. 6, 1992, abandoned, which is a continuation of application Ser. No. 07/609,741, filed Nov. 6, 1990, now abandoned, which is a continuation of application Ser. No. 07/113,179, filed Oct. 23, 1987, now U.S. Pat. No. 5,441,868, which is a continuation of application Ser. No. 06/675,298, filed Nov. 30, 1984, now U.S. Pat. No. 4,703,008, which is a continuation in part of application Ser. No. 06/655,841, filed Sep. 28, 1984, now abandoned, which is a continuation in part of application Ser. No. 06/582,185, filed Feb. 21, 1984, now abandoned, which is a continuation in part of application Ser. No. 06/561,024, filed Dec. 13, 1983, now abandoned. (DI # 485, Rycroft Decl., Ex. 1, Related U.S. Application Data).

35. The '422 patent shares a specification or disclosure with the other Amgen patents-in-suit ("the Lin disclosure"), originating from continuation-in-part application Ser. No. 06/675,298 filed November 30, 1984. *Amgen v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 79 (D. Mass. 2001).

36. Claim 1 of the '422 patent claims: "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." (DI # 485, Rycroft Decl., Ex. 1, col. 38:37-41).

37. The Court has adopted Amgen's construction of the term "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." (DI # 485, Rycroft Decl., Ex. 3, at 39:7-10; Id, Ex. 2, at 5).

38. Lin's disclosure expressly acknowledges that at the time the common specification was filed on November 30, 1984 "no substantial amino acid sequence information has been published" for human urinary erythropoietin. (DI # 485, Rycroft Decl., Ex. 1, '422 col. 8:46-49).

39. The Lin disclosure explains to one of skill in the art that "FIG. 6 thus serves to identify the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues (estimated M.W.=18,399)." (DI # 485, Rycroft Decl., Ex. 1, at 20:66-21:2; See also Id, col. 13:32-34).

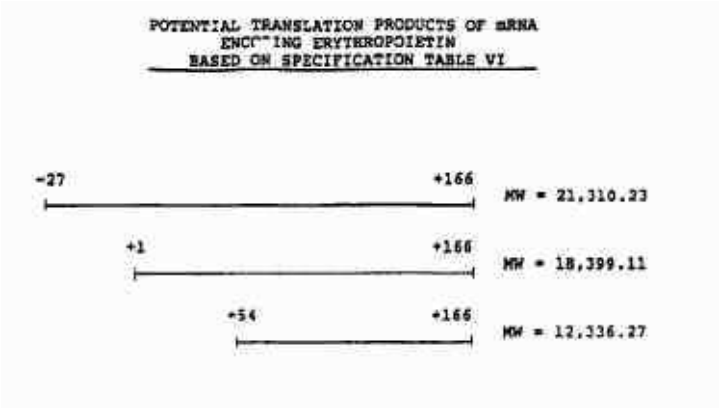
40. Similarly, Figure 9 also shows the amino acid sequence of human EPO as 166 amino acids (+1 through +166) and its leader sequence (shown as -27 through -1). (DI # 485, Rycroft Decl., Ex. 1, Figure 9 & col. 19:28-36, 21:2-5, 35:4-11).

41. Amgen has admitted that, at the time the Lin disclosure was submitted to the Patent Office on November 30, 1984, Lin did not know that human erythropoietin was a protein with a 165 amino acid sequence. (DI # 485, Rycroft Decl., Ex. 6, at ¶124 ("Although it was not known at the time of the applications for Amgen's Patents were filed, it is no well-understood scientifically that mature human EPO has a 165-amino-acid sequence.")); *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d. 1313, 1343 (Fed. Cir. 2003) ("later research demonstrated that the full sequence of human EPO was actually 165 amino acids")).

42. On September 27, 1985, Amgen told the U.S. Food and Drug Administration ("FDA") "that the amino acid sequence of natural (urine derived) human erythropoietin and r-HuEPO are identical, and that both conform to the amino acid sequence deduced from DNA sequence analysis of the gHuEPO [genomic human EPO] clone." (DI # 485, Rycroft Decl., Ex. 7, at AM-ITC 00595293. Figures 4B-6 and 4B-7 submitted to the FDA disclose a 166 amino acid sequence for human EPO. *Id*. at AM-ITC 00596039-042).

43. Similarly, in 1985, an article co-authored by Lin reported that human EPO was a "166-amino acid mature protein". (DI # 485, Rycroft Decl., Ex. 8.).

44. In 1986, during prosecution of a parent application to the '422 patent, Lin argued that there were three potential amino acid sequences for EPO based on Figure 6 — none of which is the 165 amino acid sequence of human EPO now claimed:



(DI # 485, Rycroft Decl., Ex. 9; *Id*, Ex. 10, at 35-37).

45. On June 26, 1987, Recny et al. submitted a paper that was subsequently published in December 1987, describing the amino acid sequence of human erythropoietin isolated as having a 165 amino acid sequence. (DI # 485, Rycroft Decl., Ex. 5) ("Our discovery that the natural hormone purified from urine and recombinant hormone purified from CHO cell-conditioned media are both des-Arg^{166} EPO ....).

46. Amgen admitted that: "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." (DI # 485, Rycroft Decl., Ex. 4, Amgen's Post-Hearing Memo. at 6, 7-8 (AM-ITC 00852571)). Because the '422 patent specification shares the same disclosure as the '080 patent, the 165 amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine, also "was not expressly recited as being Amgen's invention" in the

‘422 patent. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d at 79 (each patent-in-suit, including the ‘422 patent shares a common disclosure and specification).

47. Furthermore, Amgen admitted that: “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.” (DI # 485, Rycroft Decl., Ex. 4, at 5).

48. During the prosecution of the ‘422 patent, Amgen told the Patent Office that:

a. 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. (DI # 485, Rycroft Decl., Ex. 12, at 4-5).

49. Example 1 of the Lin specification discloses 17 discrete fragments of human urinary erythropoietin that were analyzed for amino acid sequence. (DI # 485, Rycroft Decl., Ex. 1, col. 15:21-53).

50. Lin discloses that two of the 17 fragments, T30 and T38, were “not un ambiguously determined.” (DI # 485, Rycroft Decl., Ex. 1, col. 15:28-53).

51. The ‘422 specification also discloses an amino acid sequence for another fragment, T28, as E-A-I-S-P-P-D-A-A-M-A-A-P-L-R. (DI # 485, Rycroft Decl., Ex. 1, col. 15:47). However, it was subsequently determined by 1985 that the disclosed amino acid sequence for fragment T28 was wrong because of human urinary EPO included a glycosylated serine (“S”) instead of the expected methionine (“M”) reported in the T28 fragment disclosed by Lin. (DI # 485, Rycroft Decl., Ex. 7, Figure 4B-7 at AM-ITC 00596041-42); Ex. 7, at AM-ITC 00595293

("The complete amino acid sequence for human urinary-derived EPO protein in [sic] shown in Figure 4B-7")).

52. A scientific article published by Amgen scientists and Eugene Goldwasser in 1986 also demonstrates that the T28 sequence described in the patent was incorrect. (DI # 485, Rycroft Decl., Ex. 13, Figure 1). This publication, like the sequence submitted to the FDA in 1985, indicates that T28 — including the amino acid in position 126 of human erythropoietin — has a serine and not a methionine as disclosed by the '422 patent.

53. In addition to arguing that "human erythropoietin" has the same amino acid of human EPO such as the sequence of EPO isolated from human urine, Amgen has also relied upon examples 11 and 12 of the '422 patent as defining the claim limitation human erythropoietin to one of ordinary skill in the art. (DI # 485, Rycroft Decl., Ex. 2, at 7, fns. 22 & 23; *Id*, Ex. 3 at 32:15-22).

54. Amgen's expert, Dr. Lodish, admits, however, the products of examples 11 and 12 include "an additional methionine amino acid residue (at position -1)" which is not found in the 165 amino acid sequence of EPO isolated from human urine but, rather, results in a "human erythropoietin" with a 167 amino acid sequence. (DI # 485, Rycroft Decl., Ex. 14, at ¶¶32-33; *Id*, Ex. 15 at ¶¶ 26-27; *Id,* Ex. 1, at col. 29:42-45).

55. Example 12 of the '422 patent purports to describe a human erythropoietin in which the terminal methionone and the initial alanine (at position +1) is not present. (DI # 485, Rycroft Decl., Ex. 1, 32:10-17). Therefore, while this product of example 12 has a 165 amino acid sequence of +2 through +166, it has a different 165 amino acid sequence than that of EPO isolated from human urine.

56. The Lin disclosure states that in vivo the product of example 12 "differed markedly from the human urinary EPO standard." (DI # 485, Rycroft Decl., Ex. 1, col. 32:22-24).

57. In 1986, Lin argued that there actually were two other amino acid sequences for human erythropoietin (1) a 193 amino acid sequence of -27 to +166 and (2) a 113 amino acid sequence of +54 to +166. (DI # 485, Rycroft Decl., Ex. 12, at 35-37; *Id*, Ex. 11).

3. Claim 7 Of The '349 Patent Is Invalid As A Matter Of Law On The Grounds Of Indefiniteness, Lacks Written Description And Lack Of Enablement

58. "U of erythropoietin" is a measure of EPO biological activity that cannot be measured by RIA. DI # 542, Suh Decl., Ex. E at 56:7-10; *Id,* Ex. I at 64:22-65:25; *Id,* Ex. F at ¶ 51).

59. Many standards for RIA were known at the time of the invention, each of which would have reported different values for "U of erythropoietin" in a test sample. DI # 542, Suh Decl., Ex. E at 53:5; Id, Ex. I at 45:18-25, 134:9-11; 170:17-171:20; 184:14-185:2.

60. Amgen then CEO George Rathman stated:

> "[Amgen] should be absolutely fastidious in reporting specific activity in arbitrary (Amgen) units until we can establish an excellent correlation with international units. I do not believe such correlation exists today … I think we have also been careless with respect to what is the precision or uncertainty (accuracy) of our data … I think we should understand how any standard can deviate from 'parallelism' trying to relate to international units." (DI # 542, Suh Decl., Ex T at AM-ITC 00558618).

61. Amgen's own experts confirm that test specified by the claim cannot determine the claimed biological activity of a sample because biological activity is not measured by RIA. (DI # 542, Suh Decl. Ex. J at 133:24-25, Id, Ex. E at 50:20-51:21, 52:7-16, 56:1-6; Id, Ex. F at ¶ 75).

62. Amgen's own experts confirm that RIA does not necessarily detect "erythropoietin" in its entirety, and in fact, could recognize "relevant portions" of EPO including EPO fragments. (DI # 542, Suh Decl. Ex. J at 151:18-152:8, 220:4-221:9).

63. Claim 7 covers the cellular production of EPO, without regard to how much is actually being produced, as long as the cells employed in the process are capable, under unspecified set of circumstances, of producing EPO at the levels prescribed in claims 1-6. (DI # 542, Suh Decl. Ex. B col. 38, ll. 34-36).

64. EPO production capability of cells will vary depending on the growth conditions. New cell culture techniques and growth media conditions are constantly being developed. (DI # 542, Suh Decl. Ex. U at ¶¶ 46, 49).

III. Roche Disputed Facts

1. Lack Of Written Description And Lack Of Enablement For Pegylated Proteins

65. During the prosecution of Application No. 675,298, which is the parent application to all of the patents-in-suit, the Patent office rejected Amgen's claims to DNA sequences "coding for a polypeptide fragment or polypeptide analog of naturally-occurring erythropoietin" as being indefinite in violation of 35 U.S.C. § 112. (Ex. D at 100, November 30, 1984, Application No. 06/675,298 (emphasis added) and Ex. E at 4-5, June 16, 1986, Office Action, 06/675,298-8).

66. Amgen cancelled its EPO analog claim in favor of a new narrower claim 110. *See* Ex. F at 14-15, July 10, 1987, Amendment and Reply, 06/675,298-20) ("In order to expedite prosecution of this application [sic] has reconstituted prior claims 77 and 96 as new claim 110.").

67. New claim 110, which eventually issued as claim 7 of the '008 patent, read:

> A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow to increase production of reticulocytes and red blood cells, and to

increase hemoglobin synthesis or iron uptake. (*See* Ex. F at 14-15, July 10, 1987, Amendment and Reply, 06/675,298-20) at 6).

68. This Court and the Federal Circuit held new claim 110 invalid for lack of enablement.[2]

> In affirming the district court's invalidation of claims 7, 8, 23-27, and 29 under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs …. Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.(emphasis added). *Amgen v. Chugai*, 927 F.2d 1200, 1214 (Fed. Cir. 1991).

69. Amgen sought claims to a "synthetic polypeptide having part or all of the amino acid sequence set forth in Figure 6 ... and having a biological property of naturally-occurring human erythropoietin." (DI # 593, Toms Decl., Ex. 1 at 102).

70. The Patent Office rejected this and similar claims to "synthetic polypeptides" stating:

> Claims to "synthetic polypeptides" are not enabled by this disclosure. "Synthetic," as opposed to "recombinant," is an art recognized term which indicates a chemically derived rather than genetically engineered protein. No support for chemical synthesis of EPO or EPO fragments is shown by

this disclosure. (Ex. G at 5, June 2, 1988, Office Action, 07/113,178-4).

71. Amgen tried to obtain claims to erythropoietin analogs "sufficiently duplicative of that of naturally occurring human erythropoietin." (DI # 593, Toms Decl., Ex. 2). The PTO rejected these claims pursuant to 35 U.S.C. § 112 ¶¶ 1 and 2, on grounds of nonenablement and indefiniteness. (DI # 593, Toms Decl., Ex. 3 at 3).

72. CERA is the culmination of nearly a decade of research by Roche scientists, directed to creating improved drugs to treat anemia. Those years, chronicled in the notebooks of Roche scientists, reflect how unpredictable pegylation technology was and remains today. The U.S. Patent Office recognized Roche's accomplishment by awarding it U.S. patent No. 6,883,272 in 2003, which covers CERA. (DI # 610, Decl. of Dr. Klibanov at ¶177; DI # 609, Decl. of Dr. Longmore at ¶65).

73. Pegylation reactions are not predictable, routine or conventional and scientists cannot predict the properties of the resulting compounds. (DI # 610, Decl. of Dr. Klibanov at ¶131).

74. Pegylation reactions are complex, multi-step processes which require and depend on the evaluation of numerous variables and factors. (DI # 610, Decl. of Dr. Klibanov at ¶ 137).

75. Successful pegylation greatly depends on numerous factors, including the protein's concentration and primary structure, as well as the activated PEG reagent's concentration, molecular weight, distribution, activation site, and structure; and also reaction time, temperature, pH, and ionic strength. Chemical reactions between proteins and activated PEG reagents invariably produces a mixture of distinct molecules. Precisely characterizing products of a pegylation reaction is arduous and sometimes impossible because of the presence of multiple different products, or species. (DI # 610, Decl. of Dr. Klibanov at ¶141).

76. As demonstrated in numerous publications, when Roche developed CERA pegylation was still being developed as an experimental technique. The chemical reagents used to carry out pegylation reactions available in the mid-1980's were few and inadequate. The pegylation reactions using the chemical reagents of that era were generally unpredictable with respect to the structure and activity of the products that would be produced. (DI # 610, Decl. of Dr. Klibanov at ¶146).

77. Pegylation procedures employed during the late 1970s and 1980s were plagued by difficulties, including restriction to PEGs with low molecular weights, relatively unstable activated PEGs, and lack of selectivity in protein modification. This gave rise to impure and heterogeneous substances difficult to purify. (DI # 610, Decl. of Dr. Klibanov at ¶148; DI # 603, Toms Decl., Ex. 263, at 462). Researchers at the time considered pegylation to be "a failing technology". (DI # 610, Decl. of Dr. Klibanov at ¶148; DI # 603, Toms Decl., Ex. 263, at 474).

78. Moreover, PEG molecules available in the mid-1980's widely varied in structure and molecular weight. There were many uncertainties in the art of pegylation in the mid-1980's that had to be experimentally determined without direction from the art:

> Enzymes used as pharmacological agents for systemic therapy offer promise in the treatment of several diseases, but have considerable limitations because of problems of protein immunogenicity, instability and, often, rapid elimination. One method overcoming these difficulties appears to be the masking of the polypeptide structure by linking polymers to the protein surface (Holcenberg 1982). This technique is still in its early stages concerning choice of polymer, method of coupling and long-term toxicity. (DI # 603, Toms Decl., Ex. 284, at 757).

79. During the late 1970s and 1980s, pegylation technology was in its infancy. PEG reagents were non-selective and would react at various sites of protein starting materials, producing heterogeneous substances difficult to purify, and led to inactivation. (DI # 610, Decl.

of Dr. Klibanov at ¶148; DI # 603, Toms Decl., Ex. 56, at 3579; DI # 603, Toms Decl., Ex. 102, Chapter 4 at 76-77; DI # 603, Toms Decl., Ex. 216, at 93; DI # 603, Toms Decl., Ex. 91 at 31).

80. Reacting the ε-amino groups of Lys residues, as done by Roche, was specifically discouraged and considered a potential problem in the art during the early 1980s. (DI # 610, Decl. of Dr. Klibanov at ¶136; DI # 603, Toms Decl., Ex. 216, at 95).

81. In the 1990s, researchers still considered pegylation difficult and unpredictable:

> This type of modification often leads to inactivation of proteins containing amino groups important for their biological activity or of proteins unstable in alkaline conditions. (DI # 603, Toms Decl., Ex. 222, at 644).
>
> The first-generation pegylation methods were fraught with difficulties. With first-generation pegylation, the PEG polymer was generally attached to the ε amino groups of lysine. This resulted in the modification of multiple lysines, and gave mixtures of PEG isomers with different molecular masses. The existence of these isomers makes it difficult to reproduce drug batches, and can contribute to the antigenicity of the drug and poor clinical outcomes. (DI # 603, Toms Decl., Ex. 121, at 215).

82. Even in 2006, pegylation is still considered to be a developing technology:

> [t]he organic and polymer chemistry of PEG activation has now matured, and protein pegylation is becoming viable commercially. However, the technique needs significant know-how, and the modified protein is considered to be a new chemical entity from a regulatory point of view. (DI # 603, Toms Decl., Ex. 90, at 205).

A. Amgen Witnesses Acknowledge The Difficulty In Successfully Reacting PEG Reagents With Proteins

83. During his deposition, Dr. Lin, named inventor of the patents-at-suit acknowledged that pegylation of erythropoietin is unpredictable:

> Q. So you understood that modifications, like pegylation, could be done to EPO?
>
> A. Yes. Yes.

> Q. But the book didn't tell you whether or not, when you made those modifications, the protein would be active; correct?
>
> . . . .
>
> THE WITNESS: You had to do it yourself. For any particular procedure, you had to do it yourself to see if the end product that you modified—the way you did it—would be active or not. You had to check it out, experimentary [sic]. Yes. (DI # 603, Toms Decl., Ex. 225, at 100:9-22; *see also* 94:2-95:12).

84. Mr. Boone, Amgen's spokesman in this litigation on Amgen's efforts to create a product from the reaction of erythropoietin and PEG reagents, has stated that pegylation is unpredictable:

> Do you have any reason to believe that scientists at Amgen were able to predict the in vivo biological activity of a PEG-EPO compound prior to testing?
>
> . . . .
>
> THE WITNESS: I don't know.
>
> You don't know if you have any reasons or not?
>
> I have no reason to believe that Amgen scientists would be able to predict in vivo biological activity of a PEG-EPO compound. (DI # 603, Toms Decl., Ex. 94, at pp. 46:10-22).
>
> * * *
>
> So, in the assays that Amgen was using at the time, they found that PEGylation of the amino groups of CHO-EPO would cause a loss of in vivo activity, right?
>
> THE WITNESS: Based on your definition of in vivo activity, I would say that the assays that Amgen run—ran at that time were not very predictable.
>
> Q. Was Amgen able to predict from the structure of its PEG-EPO whether or not the compound would be in vivo active?

No, we were not able to predict from the structure.

(DI # 603, Toms Decl., Ex. 94, at pp 93:1-10)

Q. So, with the information Amgen had available to it in 1991, they were not able to predict whether an EPO produced in CHO cells which was modified at the amines to contain PEG would be activity in vivo as I defined it?

A. I believe—I believe the assay that we were using for in vivo activity would not, with a hundred percent guaranty, predict the activity as you defined it.

(DI # 603, Toms Decl., Ex. 94, at pp 94:21-95:4)

So every time you attach a PEG to EPO, you don't necessarily end up with a biologically active compound; right?

. . . .

THE WITNESS: All I can say is there's no guaranty that if you attach a PEG to EPO you will have a biologically active material as defined in your assay.

(DI # 603, Toms Decl., Ex. 94, at pp 96:12-21).

85. Amgen scientist, Dr. Elliott testified that pegylation is unpredictable and there is no way to know what properties the product of the pegylation reaction will have unless you perform the experiments:

Q. So this would be another instance where you just have to do the test, the trial and see what happens?

A. With a given molecule, looking at the variable nature of the human population and what we know, if we're going to speak about erythropoietin specifically . . . .

Q. Yes.

A. We know that there's a potential for immunogenicity which is caused by whole bunch of variables, some of which have to do with manufacturing processes.

And so one could imagine that if you were to do pegylation of EPO, there might be some conditions under

> which you pegylate that would result in immunogenicity and other conditions where it might be less likely to get immunogenicity.
>
> It's a combination not only of whether peg is there or not, but also how you make the protein.
>
> So because of all of these variables, one would need to do an experiment to find out.
>
> And, then, even when you do the experiment, it's not necessarily conclusive because you might only have a limited number of samples or time that is involved in the experiment.
>
> (DI # 603, Toms Decl., Ex. 104, at 198:12-199:11).

86. Amgen patent for pegylated NESP (Novel Erythropoietin Stimulating Protein) calls the results of the pegylation reactions "surprising". (DI # 603, Toms Decl., Ex. 52, col. 2). Amgen argued at the PTO that its PEG-NESP was novel and not obvious and pegylation was unpredictable:

> [N]ot all proteins respond equally to PEGylation and there is no guarantee of improved performance.
>
> Initial experiments designed to evaluate and optimize PEG-NESP reaction stoichiometries revealed that PEGylation by reductive alkylation using PEG-aldehyde was surprisingly somewhat inefficient, requiring substantially higher molar ratios of PEG to protein than typically observed with non-glycosylated proteins. Similarly, acylation with PEG-NHS esters was also slower and less efficient than expected. It was thus evident that the PEGylation of non-glycosylated proteins was not necessarily predictive of the PEGylation of glycosylated proteins and that further optimization of reaction conditions was necessary.
>
> The oligosaccharide...content of NESP represents over 65% of the total molecular mass. It was not immediately obvious that the intrinsic activity of NESP would tolerate further modification by PEGylation, or that such modification would further

> enhance *in vivo* half-life and performance. (DI # 603, Toms Decl., Ex. 27, at 5).

87. Amgen's testifying expert Dr. Katre agrees that pegylation is not conventional and is unpredictable: For example, during the prosecution of U.S.S.N. 06/866,459, a patent application directed to chemical reactions of proteins, Dr. Katre asserted,

> one cannot predict [without experimentation with the particular protein] whether selective conjugation of a given protein with a given chemical reagent such as PEG or POG will be successful to retain biological activity and confer water solubility. (DI # 603, Toms Decl., Ex. 275).
>
> [i]t is impossible to predict with any degree of certainty the outcome of a chemical reaction involving different proteins and a given reagent.
>
> Hence, the only obvious feature of chemical reactions involving proteins is the unobvious nature of modified proteins obtained from such reactions. (DI # 603, Toms Decl., Ex 275 at 6).
>
> "It is not a priori possible to predict which selected proteins would be favorably responsive to treatment with polymers due to the vast difference in the pharmacokinetics and physical properties among different proteins." (DI # 603, Toms Decl., Ex 275 at 7).
>
> "[u]ntil actual empirical data are obtained, it is impossible to predict that any given protein will remain active after conjugation." (DI # 603, Toms Decl., Ex 275 at 9).
>
> "it is impossible to predict the outcome of a chemical conjugation of a different protein, as regards to water solubility, in vivo half-life, biological activity, stability, and immunogenicity." (DI # 603, Toms Decl., Ex 275 at 10).

Moreover, discussing prior art to her patent application for PEG CSF-1, Dr. Katre stated:

> Furthermore, it is not generally possible to predict the extent of protein modification or the nature of the reaction conditions that are desirable, because some proteins are much more susceptible to inactivation through conjugation

than others. (emphasis added) (DI # 603, Toms Decl., Ex 42, at col. 4, ll.4-12).

B. Amgen Failed To Successfully React PEG Reagents and Epoetin Alfa.

88. As part of its erythropoietin program, Amgen tried to develop a product through the chemical reactions of erythropoietin and activated PEG reagents. (DI # 610, Decl. of Dr. Klibanov at ¶169).

89. Amgen did not attempt to react erythropoietin with PEG reagents until after 1985. (DI # 610, Decl. of Dr. Klibanov at ¶169).

90. Amgen experimented with different reagents, including branched and linear activated PEG reagents of different molecular weights, such as 30 kDa PEG-NHS, 10 kDa branched PEG-NHS, and 30 kDa PEG-Ald., without success. (DI # 610, Decl. of Dr. Klibanov at ¶169; DI # 603, Toms Decl., Ex. 61).

91. Amgen also tried to pegylate sialic acid groups and galactose residues of asialo-erythropoietin (erythropoietin that lacks sialic acids), but found that the resultant compound was inactive. (DI # 610, Decl. of Dr. Klibanov at ¶170; DI # 603, Toms Decl., Ex. 70 at 327.)

92. Dr. Lin's own attempts at pegylation failed to produce a molecule with any significant biological activity. (Ex J at AM-ITC-01089076-9096).

93. Amgen found that the "PEG modification of EPO having normal sialic acid content had no effect on in vivo activity," and decided to stop pursuing reactions of erythropoietin and activated PEG reagents. (DI # 610, Decl. of Dr. Klibanov at ¶170; DI # 603, Toms Decl., Ex. 89.)

94. Amgen's 30(b)6 witness Mr. Boone testified that Amgen attempted between 1985 and approximately 2000 to react erythropoietin and PEG reagents. Amgen did not advance any product into development. (DI # 610, Decl. of Dr. Klibanov at ¶171.)

95. Further, he stated, "I have no reason to believe that Amgen scientists would be able to predict *in vivo* biological activity of a PEG-EPO compound" (DI # 603, Toms Decl., Ex. 94, at 46:20-22) and that "…[T]here's no guaranty that if you attach a PEG to EPO you will have a biologically active material as defined in your assay." (DI # 603, Toms Decl., Ex. 94, at 96:18-21).

Dated: July 5, 2007
Boston, Massachusetts

Respectfully submitted,

F. HOFFMANN-LA ROCHE LTD,
ROCHE DIAGNOSTICS GMBH, and
HOFFMANN-LA ROCHE INC.

By its Attorneys,

/s/ Nicole A. Rizzo

Lee Carl Bromberg (BBO# 058480)
Julia Huston (BBO# 562160)
Keith E. Toms (BBO# 663369)
Nicole A. Rizzo (BBO# 663853)
Kimberly J. Seluga (BBO# 667655)
BROMBERG & SUNSTEIN LLP
125 Summer Street
Boston, MA 02110
Tel. (617) 443-9292
nrizzo@bromsun.com

Leora Ben-Ami (*pro hac vice*)
Mark S. Popofsky *(pro hac vice)*
Patricia A. Carson (*pro hac vice*)
Thomas F. Fleming (*pro hac vice*)
Howard S. Suh (*pro hac vice*)
Peter Fratangelo (BBO# 639775)
Vladimir Drozdoff (*pro hac vice*)
David L. Cousineau (*pro hac vice*)
KAYE SCHOLER LLP
425 Park Avenue
New York, New York 10022
Tel. (212) 836-8000

CERTIFICATE OF SERVICE

I hereby certify that the redacted version of this document was filed through the ECF system and was sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies were sent to those indicated as non registered participants on the above date.

/s/ Nicole A. Rizzo
Nicole A. Rizzo