EXHIBIT B

ROCHE'S STATEMENT OF CONTESTED ISSUES OF FACT

Roche identifies the following factual issues concerning the invalidity, unenforceability, and non-infringement of the asserted patents[1]:

I. Jurisdiction and Venue

1. This Court has jurisdiction over Roche's counterclaims asserted in this action pursuant to 28 U.S.C. §§ 1331, 1337(a), 1338(a), 1367 and 2201.

2. This Court has personal jurisdiction over Amgen by virtue of its appearance as a plaintiff in this action.

3. Venue for Roche's counterclaims is also proper in this district pursuant to the provisions of 28 U.S.C. §§ 1391(b), 1391(c) and 1400(b).

II. Invalidity for Prior Art

A. The Critical Date For Prior Art Is November 30, 1984

4. Whether Amgen can establish that the effective filing date of claim 1 of the '422 patent, claims 3, 7-9, 11-12, or 14 of the '933 patent, claims 4-9 of the'698 patent, claims 1-2 of the '868 patent, or claim 7 of the '349 patent (the "Asserted Claims") is earlier than November 30, 1984.

5. Whether Amgen can establish that Dr. Lin invented the subject matter of an Asserted Claim prior to November 30, 1984.

B. The Lin Patents Are Invalid as Anticipated Under 35 U.S.C. §§ 102(a), (b), (e), and/or (g)

6. Whether product-by-process claims 3, 7, and 8 of the '933 patent are invalid as anticipated by the prior art.

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[1] Based on the evidence adduced during discovery, Amgen's admissions in pleadings, written discovery and prior cases, and the findings of fact in previous proceedings, Roche believes that facts 1-3 and 136-231 are beyond dispute or already adjudicated. Roche has listed these facts in its Statement of Contested Facts because Amgen has refused to stipulate to them.

By agreement of the parties, this preliminary statement of contested issues of fact may be modified, supplemented and/or amended, up to and including the time of final submission to the Court or thereafter should additional relevant evidence arise.

7. Whether a substance that satisfies the elements of claims 3, 7, or 8 of the ‘933 patent was known or used in the U.S. before the date of Lin’s invention.

8. Whether a substance that satisfies the elements of claims 3, 7, or 8 of the ‘933 patent was patented or described in a printed publication before the date of Lin’s invention.

9. Whether a substance that satisfies the elements of claims 3, 7, or 8 of the ‘933 patent was in public use or on sale in the U.S. more than one year prior to the effective filing date of these claims.

10. Whether a substance that satisfies the elements of claims 3, 7, or 8 of the ‘933 patent was patented or described in a printed publication more than one year prior to the effective filing date of these claims.

11. Whether a substance that satisfies the elements of claims 3, 7, or 8 of the ‘933 patent was made in the U.S. by another inventor, before the date of Lin’s invention and whether the prior inventor did not abandon, suppress, or conceal his invention.

12. Whether a substance that satisfies the elements of claims 3, 7, or 8 of the ‘933 patent was described in a patent granted on an application for patent by another, filed in the United States before the date of Lin’s invention.

13. Whether product claims 9 & 12 of the ‘933 patent and claim 1 of the ‘422 patent are anticipated by the prior art.

14. Whether a pharmaceutical composition that satisfies the elements of claims 9 or 12 of the ‘933 patent or claim 1 of the ‘422 patent was known, used, patented, or described in a printed publication before the date of Lin’s invention.

15. Whether a pharmaceutical composition that satisfies the elements of claims 9 or 12 of the ‘933 patent or claim 1 of the ‘422 patent was publicly used or sold, in the U.S., more than one year prior to the effective filing date of these claims.

16. Whether a pharmaceutical composition that satisfies the elements of claims 9 or 12 of the ‘933 patent or claim 1 of the ‘422 patent was patented or described in a printed publication more than one year prior to the effective filing date of the Asserted Claims of these claims.

17. Whether a pharmaceutical composition that satisfies the elements of claims 9 or 12 of the ‘933 patent or claim 1 of the ‘422 patent, was made in the U.S. by another inventor, before the date of Lin’s invention and whether the prior inventor did not abandon, suppress, or conceal his invention.

18. Whether a pharmaceutical composition that satisfies the elements of claims 9 or 12 of the ‘933 patent or claim 1 of the ‘422 patent, was described in a patent

granted on an application for patent by another filed in the United States before the date of Lin's invention.

C. The Asserted Patents Are Invalid as Obvious Under 35 U.S.C. § 103

19. Whether the asserted patents are obvious in view of the prior art, including prior art under 35 U.S.C. §§ 102 (a), (b), (e), (f), and/or (g).

20. Whether Dr. Lin did not himself invent the subject matter of the Asserted Claims, or derived from another any part of the claimed subject matter of the Asserted Claims.

21. Whether claim 1 of the '422 patent, claims 3, 7-9, 11-12, or 14 of the '933 patent, claims 4-9 of the'698 patent, claims 1-2 of the '868 patent, or claim 7 of the '349 patent, would have been obvious to a person of ordinary skill in the art as of Lin's invention date.

22. Whether claim 1 of the '422 patent, claims 3, 7-9, 11-12, or 14 of the '933 patent, claims 4-9 of the'698 patent, claims 1-2 of the '868 patent, or claim 7 of the '349 patent, would have been obvious to a person of ordinary skill in the art one year prior to the effective filing date of the claim.

23. Whether, based on the scope and content of the prior art, a person of ordinary skill in the art would have had a reasonable expectation of success in making and using the subject matter of claim 1 of the '422 patent, claims 3, 7-9, 11-12, or 14 of the '933 patent, claims 4-9 of the'698 patent, claims 1-2 of the '868 patent, or claim 7 of the '349 patent, as of Lin's invention date.

24. Whether, based on the scope and content of the prior art, a person of ordinary skill in the art would have had a reasonable expectation of success in making and using the subject matter of claim 1 of the '422 patent, claims 3, 7-9, 11-12, or 14 of the '933 patent, claims 4-9 of the'698 patent, claims 1-2 of the '868 patent, or claim 7 of the '349 patent, one year prior to the effective filing date of the claim.

25. Whether or not there are any considerations commensurate with the scope of the Asserted Claims that would rebut a showing of *prima facie* obviousness.

26. Whether a nexus exists between any purported secondary considerations of non-obviousness and the subject matter of the Asserted Claims.

III. Invalidity under 35 U.S.C. § 112

A. The Asserted Patents Are Invalid for Lack of Written Description

27. Whether a person of ordinary skill in the art, reading the '422 patent on the effective filing date, would have recognized that Dr. Lin was in possession of the full scope of the subject matter of claim 1 of the '422 patent.

28. Whether a person of ordinary skill in the art, reading the '422 patent on the effective filing date, would have recognized that Dr. Lin was in possession of "*human erythropoietin*" as defined by the amino acid sequence.

29. Whether a person of ordinary skill in the art, reading the '422 patent on the effective filing date, would have recognized that Dr. Lin was in possession of human erythropoietin having the structural characteristics imparted by the limitation "*purified from mammalian cells grown in culture*".

30. Whether a person of ordinary skill in the art, reading the '933 patent on the effective filing date, would have recognized that Dr. Lin was in possession of the full scope of the subject matter of the asserted claims of the '933 patent.

31. Whether a person of ordinary skill in the art, reading the '933 patent on the effective filing date, would have recognized that Dr. Lin was in possession of a "*non-naturally occurring glycoprotein,*" distinguishable from naturally occurring human erythropoietin.

32. Whether a person of ordinary skill in the art, reading the '349 patent on the effective filing date, would have recognized that Dr. Lin was in possession of the full scope of the subject matter of the asserted claims of the '349 patent.

33. Whether a person of ordinary skill in the art, reading the '349 patent on the effective filing date, would recognize from the disclosure that Dr. Lin was in possession of all "*non-human DNA sequences which control transcription*" of DNA.

34. Whether a person of ordinary skill in the art, reading the '349 patent on the effective filing date, would recognize from the disclosure that Dr. Lin was in possession of all "*vertebrate cells...capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U [or 500 U, or 1000 U] of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay.*"

35. Whether the '349 patent specification fails to disclose the "*48 hour*" period within which one should measure production of "*U of erythropoietin.*"

36. Whether the '349 patent specification fails to define a standard to which "*radioimmunoassay*" data for an unknown sample could be compared.

37. Whether a person of ordinary skill in the art, reading the '698 patent on the effective filing date, would have recognized that Dr. Lin was in possession of the full scope of the subject matter of the asserted claims of the '698 patent**.**

38. Whether a person of ordinary skill in the art, reading the '698 patent on the effective filing date, would recognize from the disclosure that Dr. Lin was in possession of all "*promoter DNA other than the human EPO promoter DNA*."

39. Whether a person of ordinary skill in the art, reading the '698 patent on the effective filing date, would recognize from the disclosure that Dr. Lin was in possession of all "*viral promoter DNA*."

40. Whether a person of ordinary skill in the art, reading the patents-in-suit on the effective filing date, would recognize from the disclosure that Dr. Lin was in possession of biopolymers with EPO-like activity that can be made by chemically changing the amino acid residues of human EPO.

B. <u>The Asserted Patents Are Invalid for Lack of Enablement</u>

41. Whether the asserted patents fail to enable biopolymers with EPO-like activity that can be made by chemically changing the amino acid residues of human EPO.

42. Whether the specifications of the asserted patents fail to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date could make and use a biopolymer with EPO-like activity by chemically changing the residues of human erythropoietin via pegylation without undue experimentation.

43. Whether Dr. Lin knew of and desired the benefits of pegylation as of the effective filing date of the Asserted Claims.

44. Whether the specifications of the '933 and '422 patents fail to enable the "*pharmaceutical compositions*" claimed in the '933 and '422 patents.

45. Whether the specifications of the asserted patents fail to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date could make and use purified erythropoietin protein for pharmaceutical compositions suitable for administration to humans, without undue experimentation.

46. Whether the specification of the '933 patent fails to enable the "*Methods of treating a kidney dialysis patient*" claimed in the '933patent.

47. Whether the specification of the '933 patent fails to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date could treat a kidney dialysis patient, without undue experimentation.

48. Whether the specifications of the ‘349 and ‘698 patents fail to enable the full scope of “*vertebrate cells*” required by the claimed methods of the ‘349 and ‘698 patents.

49. Whether the specifications of the ‘349 and ‘698 patents fail to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date could practice the method(s) of producing EPO from any and all “*vertebrate cells*” claimed by the ‘349 and ‘698 patents, without undue experimentation.

50. Whether the specification of the ‘349 patent fails to enable the claimed method(s) of the ‘349 patent using all “*non-human DNA sequences which control transcription*.”

51. Whether the specification of the ‘349 patent fails to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date could practice the claimed method(s) using all “*non-human DNA sequences which control transcription*,” without undue experimentation.

52. Whether the specification of the ‘698 patent fails to enable the claimed method(s) of the ‘698 patent using all “*promoter DNA other than the human EPO promoter DNA*,” and/or all “*viral promoter DNA*.”

53. Whether the specification of the ‘698 patent fails to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date could practice the claimed methods using all “*promoter DNA other than the human EPO promoter DNA*,” without undue experimentation.

54. Whether the specification of the ‘698 patent fails to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date could practice the claimed methods using all “*viral promoter DNA*.”

55. Whether the specification of the ‘349 patent fails to enable the erythropoietin production levels required by the claims of the ‘349 patent.

56. Whether the specification of the ‘349 patent fails to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date could determine “*U[nits] of erythropoietin*” using radioimmunoassay, as required by the claims, without undue experimentation.

57. Whether the specification of the ‘349 patent fails to provide sufficient teaching that a person of ordinary skill in the art on the effective filing date would know when to measure production of “*U of erythropoietin*” using radioimmunoassay, without undue experimentation.

C. <u>The Lin Patents Are Invalid as Indefinite</u>

58. Whether the Asserted Claims of the '933 patent are indefinite under 35 U.S.C. §112.

59. Whether a person of ordinary skill in the art on the effective filing date would be unable to determine whether or not a given glycoprotein satisfies the claim limitation of the '933 patent "*a non-naturally occurring... product of expression in a mammalian host cell*."

60. Whether claim 1 of the '422 patent is indefinite under 35 U.S.C. §112.

61. Whether a person of ordinary skill in the art on the effective filing date would be unable to determine whether or not a given pharmaceutical composition satisfies the claim limitations of the '422 patent "*human erythropoietin . . . where in said erythropoietin is purified from mammalian cells grown in culture.*"

62. Whether claim 7 of the '349 patent is indefinite under 35 U.S.C. §112.

63. Whether a person of ordinary skill in the art on the effective filing date would be unable to determine whether or not a given vertebrate cell satisfies the claim limitation of the '349 patent of being "*capable of*" production of erythropoietin at the recited levels.

64. Whether a person of ordinary skill in the art on the effective filing date would be unable to determine whether or not a given cell satisfies the claimed production levels of the '349 patent because the patent fails to specify when production of "*U of erythropoietin*" is to be measured.

65. Whether a person of ordinary skill in the art on the effective filing date would be unable to determine whether or not a given cell satisfies the claimed production levels of the '349 patent because the patent fails to provide a standard to be used in the "*radioimmunoassay*" of the claim.

66. Whether a person of ordinary skill in the art on the effective filing date would be unable to determine whether or not a given cell satisfies the claim limitation of the '349 patent that requires "*non-human DNA sequences that control transcription.*"

67. Whether the Asserted Claims of the '698 patent are indefinite under 35 U.S.C. §112.

68. Whether a person of ordinary skill in the art on the effective filing date would be unable to determine whether or not a given cell satisfies the claims of the '698 patent that require promoter DNA other than human "*erythropoietin promoter DNA.*"

69. Whether a person of ordinary skill in the art on the effective filing date would be unable to determine whether or not a given cell satisfies the claims of the '698 patent that require "*viral promoter DNA.*"

By agreement of the parties, this preliminary statement of contested issues of fact may be modified, supplemented and/or amended, up to and including the time of final submission to the Court or thereafter should additional relevant evidence arise.

IV. Invalidity for Double Patenting

70. Whether subject matter covered by the Asserted Claims is obvious in view of subject matter patented in U.S. Patent No. 4,703,008 (the '008 patent).

71. Whether subject matter covered by the Asserted Claims is obvious in view of subject matter patented in U.S. Patent No. 4,667,016 (the '016 patent).

72. Whether subject matter covered by the Asserted Claims is obvious in view of claim 1 of the '868 patent.

73. Whether Amgen can show that 35 U.S.C.§ 121 applies to any of its asserted patents.

74. Whether the asserted claims of the '868 and '698 patents are consonant with the Group II claims of the June 16, 1986 Restriction Requirement within U.S. Patent Application No. 675,298.

V. 103(b)

75. Whether under 35 U.S.C. 103(b) the Asserted Claims of the '868 patent, the '698 patent, or the '349 patent expired in 2004, when the '008 patent or the '016 patent expired.

76. Whether under 35 U.S.C. 103(b) claim 7 of the '349 patent loses a presumption of validity if any of claims 1-6 of the '349 patent are found to be invalid.

VI. Non-Infringement

A. No Literal Infringement

Roche Does Not Literally Infringe Any Asserted Claim of the '933 Patent or the '422 Patent.

77. Whether Roche infringes or will infringe claims 3, 7-9, 11-12 or 14 of the '933 patent by making, using, importing, selling, or offering to sell MIRCERA®.

78. Whether MIRCERA® has as any of its ingredients a substance that is the "*glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin*," as required by claims 3, 7-9, 12 or 14 of the '933 patent.*

* Impacted by the Court's current claim construction, to which Roche objects.

79. Whether MIRCERA® has as any of its ingredients a substance that is a "*non-naturally occurring glycoprotein*" as required by claims 3, 7-9, 11, 12, or 14 of the '933 patent.

80. Whether the substance that Amgen alleges is a glycoprotein product of expression is "*non-naturally occurring*."

81. Whether Roche practices the "*method[s] for treating a kidney dialysis patient...*" recited in claims 11 and 14 of the '933 patent.

82. Whether MIRCERA® is a "*pharmaceutical composition comprising an effective amount [of] a glycoprotein product effective for erythropoietin therapy...and a pharmaceutically acceptable diluent, adjuvant or carrier,*" as required by claims 9 and 12 of the '933 patent (and their dependent claims).

83. Whether MIRCERA® contains just one "*diluent, adjuvant, or carrier*" as required by claim 9 (and its dependent claims) of the '933 patent.*

84. Whether MIRCERA® has as any of its ingredients a substance that is the "*glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin,*" as required by the asserted claims of the '933 patent.*

85. Whether Roche infringes or will infringe any of the Asserted Claims of the '422 patent by making, using, importing, selling, or offering to sell MIRCERA®.

86. Whether MIRCERA® has as any of its ingredients a substance meeting the limitations of "*human erythropoietin,*" as required by claim 1 of the '422 patent.

87. Whether the substance that Amgen contends is human erythropoietin is or is not present in a "*therapeutically effective amount*."

88. Whether MIRCERA® has as any of its ingredients a substance that constitutes a "*therapeutically effective amount of human erythropoietin*" as required by the limitations of claim 1 of the '422 patent.

89. Whether MIRCERA® is a "*pharmaceutical composition comprising an effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant, or carrier*" as required by claim 1 of the '422 patent.

90. Whether MIRCERA® contains just one "*diluent, adjuvant, or carrier*" as required by claim 1 of the '422 patent.*

By agreement of the parties, this preliminary statement of contested issues of fact may be modified, supplemented and/or amended, up to and including the time of final submission to the Court or thereafter should additional relevant evidence arise.

Roche Does Not Literally Infringe Any Asserted Claim of the '868 Patent, '698 Patent, or '349 Patent.

91. Whether Roche practices any process of claims 1-2 of the '868 patent, claims 4-9 of the '698 patent, or claim 7 of the '349 patent, in Europe.

92. Whether the cells used by Roche in the production of MIRCERA® are "*transformed or transfected with an isolated DNA sequence*," as required by claims 1 and 2 of the '868 patent.

93. Whether the cells used by Roche in the production of MIRCERA® "*comprise promoter DNA,... operatively linked to DNA encoding the mature erythropoietin amino acid sequence of Fig. 6*," as required by claims 4 and 5 of the '698 patent.

94. Whether the cells used by Roche in the production of MIRCERA® "*comprise amplified DNA encoding the mature erythropoietin amino acid sequence of Fig. 6*," as required by claims 6-9 of the '698 patent.

95. Whether the cells used by Roche in the production of MIRCERA® are "*vertebrate cells...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*," as required by claim 7 of the '349 patent.

Assuming, *arguendo*, that Amgen Can Prove that Roche Uses the Patented Process(es) of the Asserted Claims of the '868, '698, or '349 Patents ("the Patented Processes") in the Production of MIRCERA® in Europe, the Following Factual Questions Remain:

96. Whether CERA is or will be imported into the United States prior to being formulated as a final product.

97. Whether Roche imports the direct product of any of the Patented Processes into the United States.

98. Whether any product of the Patented Processes is not materially changed in the manufacture of MIRCERA®.

99. Whether or not the steps conducted by Roche in Europe to isolate epoetin beta from crude cell harvest are subsequent processes that materially change any product of the patented process.

100. Whether or not the chemical reaction of epoetin beta and activated PEG reagent used in the manufacture of MIRCERA® is a subsequent process performed by Roche that materially changes epoetin beta.

101. Whether or not the purification of CERA following the chemical reaction of epoetin beta and activated PEG reagent is a subsequent process that materially changes the product of that reaction.

102. Whether or not the formulation of CERA into MIRCERA® is a subsequent process that materially changes the product of the Patented Processes.

103. Whether the clinical trials for MIRCERA® establish that CERA is materially changed from the product of the Patented Processes.

104. Whether MIRCERA® is a unique compound, different from epoetin and Aranesp®, that achieves clinical advantages because it works in a substantially different way to get a substantially different and better result.

B. No Infringement under the Doctrine of Equivalents

Assuming, *arguendo,* that the Court Decides that Amgen Is Not Barred from Asserting that Roche Infringes Under the Doctrine of Equivalents and the Amgen has not waived the issue, the Following Factual Questions Remain:

105. Whether any limitation of claim 1 of the '422 patent or claims 3, 7-9, or 12 of the '933 patent, not literally present in MIRCERA®, is infringed equivalently.

106. Whether an element found in MIRCERA® that Amgen alleges is equivalent to a limitation of claim 1 of the '422 patent, claims 3, 7-9, 11-12, or 14 of the '933 patent, claims 4-9 of the'698 patent, claims 1-2 of the '868 patent, or claim 7 of the '349 patent performs the same function, in the same way, with the same result, as the element(s) of these claims.

107. Whether MIRCERA® has as any of its ingredients a substance that is an obligate glycoprotein.

108. Whether any element or step of claims 4-9 of the '698 patent, claims 1-2 of the '868 patent, or claim 7 of the '349 patent that is not literally present in Roche's processes performs the same function, in the same way, achieving the same result as the step or element recited in these claims.

109. Whether any element or step of claims 11 or 14 of the '933 patent that is not literally present in Roche's processes performs the same function, in the same way, achieving the same result as the step or element recited in these claims.

MIRCERA® Does Not Have as Any of Its Ingredients a Substance that Is the Equivalent of Any Product of the Asserted Claims of the Lin Patents.

110. Whether MIRCERA® has as any of the ingredients in its formulation a substance that performs the same function, in the same way, achieving the same result as

does a "*glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin*" in claim 3 of the '933 patent.

111. Whether MIRCERA® has as any of the ingredients in its formulation a substance that performs the same function, in the same way, achieving the same result as of does a "*non-naturally occurring glycoprotein*" in claim 3 of the '933 patent.

112. Whether MIRCERA® performs the same function, in the same way, achieving the same result as does "*human erythropoietin*" in claim 1 of the '422 patent.

Roche's Processes Are Not Equivalent to the Processes of the Asserted Claims .

113. Whether Roche uses cells in the production of MIRCERA® that are or have been created by an equivalent process to "*transform[ation] or transfect[ion] with an isolated DNA sequence.*"

114. Whether Roche uses cells in the production of MIRCERA® that comprise the equivalent of "*amplified DNA encoding the mature erythropoietin amino acid sequence of Fig. 6.*"

115. Whether Roche uses cells in the production of MIRCERA® that comprise the equivalent of "*promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of Fig. 6.*"

116. Whether Roche uses processes in the manufacture of MIRCERA® that perform the same function, in the same way, achieving the same result as the Patented Processes.

C. <u>No Infringement Under the Reverse Doctrine of Equivalents</u>

MIRCERA® Is So Far Changed from Lin's Invention that, Even if Roche Literally Infringes, a Judgment of Infringement Would Be Inappropriate.

117. Whether MIRCERA® has as any of its ingredients a substance that is encompassed by the originally intended scope of claim 1 of the '422 patent or claims 3, 7-9, or 12 of the '933 patent.

118. Whether, based on the context of the patent, the prior art, and the particular circumstances of this case, the spirit and intent of the asserted patent claims was to cover inventions uniquely characterized as being the product(s) of a host cell.

119. Whether MIRCERA® is so far changed from Dr. Lin's invention(s), which, according to the patents, are uniquely characterized as being the product of a host cell, that a judgment of infringement would be inappropriate.

120. Whether MIRCERA® has as any of its ingredients a substance that is an obligate glycoprotein.

121. Whether Roche obtained patent protection for MIRCERA® in 2003.

D. No Inducement of Infringement

122. Whether any third party has infringed or will infringe the Asserted Claims.

123. Whether Roche has engaged or will engage in any culpable conduct directed to encouraging infringement by any third party whom Amgen contends has infringed or will infringe of any of the Asserted Claims .

E. Roche's Activities Prior to Commencement of this Civil Action Do Not Constitute Infringement Under 35 U.S.C §271(e)1

124. Whether Roche had actually infringed any of the Asserted Claims as of November 5, 2005 or prior to the commencement of this Civil Action.

125. Whether Roche's activities prior to November 5, 2005 or prior to the commencement of this Civil Action were not acts of infringement.

VII. Unenforceability for Inequitable Conduct

A. Information Material To The Lin Patents Was Misrepresented, Omitted, and/or Buried to United States Patent And Trademark Office (USPTO)

126. Whether any material information was misrepresented, omitted and/or buried during the prosecution of the Lin Patents.

127. Whether the following information is material and, if so, was it misrepresented, omitted and/or buried during the prosecution of the Lin Patents.

a. 1/28/93 Goldwasser Declaration

b. 1/6/94 Cummings declaration (*e.g.*, AM-ITC 00903238-501)

c. 10/30/1987 Amgen Product License Agreement

d. 2/13/92 Strickland Declaration (*e.g.* AM-ITC 00326183-98)

e. 5/19/92 Heckler Declaration (*e.g.*, AM-ITC 00311601-18)

f. 5/19/94 Strickland Declaration (*e.g.*, AM-ITC 00312260-71)

g. 9/27/85 Notice of Claimed Investigational Exemption for Recombinant-Human Erythropoietin (r-HuEPO)

h. Amgen's positions and statements in proceedings of *Amgen v. U.S. Int'l Trade Comm'n*; before the Board of Patent Appeals and Interferences during the *Fritsch v. Lin* interferences; in the EP 411 678 Opposition Proceedings; and the European Patent Office Board of Appeals regarding EP 0 148 605.

i. Amgen publications and industry presentations, including Browne, "Erythropoietin: Gene Cloning, Protein Structure, and Biological Properties," *Cold Spring Harbor Symposium* (1986); Egrie *et al.*, 1986, Characterization and Biological Effects of Recombinant Human Erythropoietin, *Immunobiol*., vol. 172, pp. 213-224 (1986); Egrie *et al*., Abstract (1984) from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA, October 2, 1984; Egrie *et al*., Characterization Of Recombinant Monkey And Human Erythropoietin, *Proc Clin Biol Res*. 1985;191:339-50; Egrie *et al*., Presentation (1984) from 10th Annual Fredrick Stohlman Memorial Symposium on Stem Cell Physiology, Boston, MA, October 2, 1984; Egrie, Presentation Transcript "Cloning of Human & Monkey EPO" (1984) from Hemoglobin Switching Meeting, Airlie House, Virginia, September 1984; Eschbach *et al.* Correction Of The Anemia Of End-Stage Renal Disease With Recombinant Human Erythropoietin, *NEJM* 316:73-78 (1987); Vapnek *et al*., "Comparative Studies of Natural and Recombinant Erythropoietin," *Banbury Reports 29:Therapeutic Peptides and Proteins*, 241-56 (1988)**.**

j. Egrie Input Data File (*e.g.*, AM-ITC 01072474-501); and errors in the carbohydrate analysis of CHO rEPO and urinary EPO in example 10 ('933 patent 28:51-67)

k. Garcia, JF, and JC Schooley, "Disassociation of Erythropoietin from Erythropoietin-Antierythropoietin Complex," *Proc. Soc. Biol. Med.* 138:213-215 (1971).

l. the Baron-Goldwasser IND and study

m. rejections made by examiners during pendency of Ser. No. 113,178 (including Ser. Nos. 202,874, 487,774 and 468,556) from examiners of co-pending Ser. No. 113,179 (including Ser. Nos. 609,741, 957,073 and 100,197)

n. the decisions of the Board of Patent Appeals and Interferences in *Fritsch v. Lin*

o. the relevance of Lai U.S. 4,667,016 patent to obviousness-type double patenting, including the correct test for obviousness and information relating to delays in prosecution

p. the relevance of prior art, including Yokota et al. (U.S. 4,695,542), to obviousness-type double patenting in light of U.S. 4,703,008

q. the identity and unavailability of the EPO standard used to support Lin's claims in the '349 patent; that results in an RIA are dependent on the EPO standard used; the lack of correlation between Amgen units ("U") and International Units ("IU")

r. the Examiner's restriction requirement in Ser. No. 675,298 requiring process claims to be included in Group II (which issued as the '008 patent)

s. patents and patent applications: Goeddel EP 0 093 619 and/or Goeddel U.S. 4,766,075; McCormick et al. U.S. 4,966,843 and/or McCormick et al. Ser. No. 438,991

t. information about EPO-producing cell lines, including the existence and testing of the 1411 cell line.

B. Persons Substantially Involved In the Prosecution of the Lin Patents Had the Intent to Mislead the USPTO.

128. Which individuals at Amgen or acting on behalf of Amgen owed the USPTO a duty of good faith and candor and a duty of disclosure during the pendency of the applications leading to the Lin Patents.

129. Whether at least Michael Borun, Stuart Watt and Steven Odre, Fu-Kuen Lin, Thomas Strickland and Joan Egrie each owed a duty of candor to the patent office with respect to the prosecution of the patents-in-suit.

130. Whether individuals with a duty of candor regarding the Lin Patents had the intent to deceive the USPTO.

C. Amgen Committed Inequitable Conduct And Fraud On The USPTO To Obtain The Lin Patents

131. Whether any of the Lin Patents is unenforceable for inequitable conduct.

132. Whether any of the Lin Patents would have issued but for Amgen's inequitable conduct.

133. Whether any Lin Patents claiming priority to the '868 patent, including the '698, '349 and '422 patents, are unenforceable for infectious unenforceability.

134. Whether any Lin Patents claiming a product inherent to the '868 process claims, including the '933 patent is unenforceable for infectious unenforceability.

135. Whether any of the Lin patents claiming priority to Ser. No. 675,298 is unenforceable for infectious unenforceability.

A complete explanation of Roche's positions on issues of contested facts relevant to invalidity, unenforceability and non-infringement was set forth in its interrogatory responses and expert reports served in this action.

VIII. Additional Facts

136. U.S. Patent No. 5,621,080 ("the '080 patent") issued on April 15, 1997.

137. Roche's counterclaims are an actual and justiciable controversy within the meaning of 28 U.S.C. §§ 2201 and 2202 between Counterclaim-Plaintiff Roche and Counterclaim-Defendant Amgen with respect to the infringement of the '868, '933, '698, '080, '349, and '422 patents.

138. Erythropoietin ("EPO") is a naturally occurring hormone found in human blood. EPO is produced in the kidneys and stimulates red blood cell production in the bone marrow.

139. Anemia is the condition of having less than the normal number of red blood cells.

140. Any party seeking to market or sell a drug in the U.S. must obtain approval from the United States Food and Drug Administration ("FDA").

141. As of the date of this pretrial memorandum, Roche's MIRCERA™ product has not yet been approved for sale in the U.S. by the FDA.

142. As of the date of this pretrial memorandum, Roche's MIRCERA™ product has been approved for sale in the European Union.

143. Amgen's erythropoiesis stimulating agent "ESA" sold under the brand name EPOGEN® was introduced into the United States marketplace in 1989, and is used by healthcare providers to treat anemia. Amgen sold more than $2.4 billion worth of EPOGEN® worldwide in 2005.

144. EPOGEN® was approved for sale by the FDA and introduced to the market in 1989 prior to the issuance of any of the patents-in-suit.

145. Amgen's ESA sold under the brand name ARANESP® was introduced into the United States marketplace in 2001, and is used by healthcare providers to treat anemia. Amgen sold more than $2.1 billion worth of ARANESP® worldwide in 2005.

146. ARANESP® and the process for making ARANESP® is not covered by any of the asserted claims of the patents-in-suit.

147. The United States Patent and Trademark Office ("PTO") has issued patents assigned to Amgen regarding erythropoietin and processes related to erythropoietin.

148. The patents-in-suit are each patents that have been issued based on U.S. Application Nos. 561,024 (filed 12/13/83), 582,185 (filed 2/21/84); 655,841 (filed 9/28/84), and 675,298 (filed 11/30/84).

149. The linear methoxy polyethyleneglycol ("peg") molecule that is integrated with an amino group of RO0503821 is not expressed by mammalian host cells.

150. The linear methoxy polyethyleneglycol ("peg") molecule that is integrated with an amino group of RO0503821 is not isolated from mammalian host cells.

151. CERA is not expressed by mammalian host cells.

152. CERA is not isolated from mammalian host cells.

153. MIRCERA™ is not expressed by mammalian host cells.

154. MIRCERA™ is not isolated from mammalian host cells.

155. Amgen stated in its Brief for the Senior Party in Interference No. 102,097 the following sentences: "The close relationship of the three interferences has been acknowledged by Fritsch et al in preliminary motions and in their Briefs at Final Hearing in this interference and in Interference No. 102,334. Thus, Fritsch et al in earlier motions urging the combination of the Interference Nos. 102,096 and the present interference characterized these two interferences as 'different manifestations of the same invention.' Additionally, in their briefs at final hearing in this interference and Interference No. 102,334, Fritsch et al state: 'Accordingly, as in the '096 Interference, priority turns upon the first conception of the purified and isolated gene.' Fritsch et al thus admit that the priority issue is identical in all three interferences." (emphasis in original).

156. Amgen stated in its Interference Brief in Interference No. 102,097 (AM-ITC00337664) that "as in motion (G) in Interference No. 102,096, to combine the two interferences because the two interferences represent "different manifestations of the same invention."

157. Amgen stated in its Interference Brief in Interference No. 102,097 (AM-ITC00337677-78) that "[w]hile the count is directed to a process for preparing in vivo biologically active EPO using a mammalian host cell transected or transformed with an isolated DNA sequence encoding human EPO, and the litigation was directed to the purified and isolated DNA sequence in host cells transected or transformed thereby, it is evident that these are only different manifestations of the same invention acknowledged by Fritsch et al in their motion Q herein (and in Motion G in interference No. 102,096)."

158. Amgen stated in its Interference Brief in Interference No. 102,097 (AM-ITC00337678) that "Clearly the whole purpose and intent of the purified and isolated DNA sequence encoding human EPO (and host cells transected therewith) at issue in the litigation was to express in vivo biologically active human EPO."

159. Only erythropoiesis stimulating agents approved by the FDA for the treatment of anemia associated with chronic renal failure can be marketed for that indication in the United States.

160. Amgen Executive Vice President of Global Operations George Morrow stated on a conference call concerning "Commercial Perspectives on Amgen's Late Stage Product Pipeline" that "When I joined Amgen, the company had tremendous success launching Epogen and Neupogen, in essence monopoly products, and was focused mainly on the U.S. market." (AM47 903658, at 59.)

161. United States Patent Application No. 693,258 by scientists at Genetics Institute discloses a DNA sequence encoding human erythropoietin, and discloses the cloning of the erythropoietin gene by Genetics Institute scientists.

162. United States Patent Application No. 693,258 by scientists at Genetics Institute sets forth a DNA sequence encoding human erythropoietin.

163. There are oligosaccharide structures in the recombinant human erythropoietin glycoprotein products produced by following the teachings of Example 10 in Lin's patents that are also contained in human urinary erythropoietin preparations, and there are oligosaccharide structures in recombinant human urinary erythropoietin preparations that are also contained in the recombinant human erythropoietin glycoprotein products produced by following the teachings of Example 10 in Lin's patents.

164. The recombinant human erythropoietin products from Lin's patents and the human urinary erythropoietin preparation purified by Drs. Miyake and Goldwasser as described in Miyake, et al., *J. Biol. Chem.* 252, 5558-5564 (1977) have caused increased hemoglobin synthesis after in vivo administration to mice.

165. No scientific tests were performed in connection with or in furtherance of this action, by, for, or on behalf of Dr. Harvey Lodish or Amgen in connection with the generation of the graphics attached to Dr. Lodish's April 6, 2007 expert report in this case.

166. Optimal pegylation is product-specific, and can vary depending on the site of attachment, the chemistry used to create the conjugate, and the characteristics of the PEG used. *See* Molineux 2002 at 15.

167. The products of pegylation reactions have different physiochemical properties from the starting reagents including changes in conformation, electrostatic binding properties and hydrophobicity. *See* Molineux, Anti-Cancer Drugs (2003) at 260.

168. The products of pegylation reactions have different physicochemical and formulation properties and different pharmacokinetic and pharmacodynamic properties. *See* Molineux, Anti-Cancer Drugs (2003) at 259.

169. Epoietin alpha, the active ingredient in EPOGEN and PROCRIT, has a different structure than epoietin beta, the active ingredient in Neorecormon.

170. Epoietin alpha, the active ingredient in EPOGEN and PROCRIT, has different glycosylation than epoietin beta, the active ingredient in Neorecormon.

171. Amgen's U.S. Patent No. 4,703,008 ("the '008 patent") is now expired.

172. As used in claim 7 of the '008 patent, the phrase "to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake" refers to red blood cell production.

173. Claim 7 of the '008 patent thus defines the activity in biological terms of the hormone erythropoietin; that is, it causes the bone marrow to increase production of red blood cells.

174. Claim 23 of the '008 patent reads "A prokaryotic or eukaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide."

175. Claim 23 of the '008 patent differs from the previous host cell claims of the '008 patent in that it refers specifically to cDNA and, as well, refers specifically to the exact biological property of the protein encoded by either the cDNA or the gDNA sequence.

IX. Findings of Fact from Proceedings in the United Kingdom

176. That Dr. Lin was "able by patient but conventional methods to identify the whole of [the EPO gene's] structural region, its introns, exons and splicing sites and a fair amount of the upstream and downstream sequences as well." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶6 (Oct. 21, 2004).

177. "Once the sequence of the EPO gene had been discovered, it was possible to make it by methods of recombinant DNA technology which were well known in 1983." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶8 (Oct. 21, 2004).

178. "To get it into the DNA of the CHO cell, it had first to be incorporated into a bacterial plasmid vector. To improve the chances of expression, the gene's natural promoter was removed and a more powerful viral promoter substituted. To increase the rate of expression, cells in which the gene had been multiplied ("amplified") were selected by a technique which involved treating them with methotrexate. Indeed, the CHO cell had been chosen as host because it had a gene mutation which made it particularly suitable for amplification by methotrexate. But these were all tricks of the trade well known among practitioners of the art." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶9 (Oct. 21, 2004).

179. "During the 1970s, recombinant DNA technology was developed. This is a technique which involves isolating or synthesising the gene which codes for the desired protein, combining the gene with other ("vector") DNA, inserting this "recombinant" DNA into a "host cell", which then expresses the protein." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶71 (Apr. 11, 2001).

180. "As at the priority date, a genomic DNA library of repute was the Lawn library disclosed in 1978 by Lawn et al in Cell 15:1174. Its use was described in the standard work in the field, the so-called Maniatis Manual (Molecular Cloning, A Laboratory Manual, by Maniatis, Fritsch and Sambrook 1982, especially in Chapter 7)." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶75 (Apr. 11, 2001).

181. "In 1984 the types of mammalian cells which were thought to be suitable host cells was limited. Those in conventional use included the Chinese Hamster Ovary ("CHO") cell, the baby hamster kidney ("BHK") cell, and the COS monkey ("COS") cell, as well as certain types of human cells." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶86 (Apr. 11, 2001).

182. "By 1983, it was known that the level of protein expression depended on the number of copies of the relevant gene present in the cell and the expression level of those genes. There were also techniques available to select cells which

contained multiple -- or "amplified" -- copies of a particular gene." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶95 (Apr. 11, 2001).

183. "[T]here is and was in 1984, no reason to think that the introduction of a mutation in CHO cells to produce cells which are DHFR -- would suffer any other mutation." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶112 (Apr. 11, 2001).

184. "SDS-PAGE is (and was in 1984) a well-established form of an experimental technique called electrophoresis; it enables the apparent molecular weights of proteins or glycoproteins to be assessed." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶122 (Apr. 11, 2001).

185. "In 1983, Ascensao et al (Blood 62(5):1132) described an EPO-producing human testicular germ cell that had been sustained in culture for two years; it had a biological activity of 100-600 milliunits/ml of cell culture." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶134 (Apr. 11, 2001).

186. "A similar level of production was reported by Sherwood et al, in Clinical Research 31(2): 323A, in 1983 for an EPO-producing human renal carcinoma cell line which was cultured for over 3 years." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶134 (Apr. 11, 2001).

187. "[U]sing recombinant DNA techniques then available, Dr Lin inserted a fragment of DNA containing these human EPO sequences into a plasmid, and, before transfecting this recombinant plasmid into vertebrate cells, he inserted a strong viral promoter, a DNA fragment from the simian virus known as "SV40", upstream from the EPO gene structural region of the fragment in the plasmid. This resulted in a recombinant gene in which the SV40 viral promoter was able to control the expression of human EPO from the human EPO gene." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶138 (Apr. 11, 2001).

188. "Using recombinant techniques then available, Dr Lin inserted the genetic construct created as described above in the chromosomal DNA of a host cell line (in Example 10, a CHO cell line) by transfecting the cell with the DNA of the construct." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶140 (Apr. 11, 2001).

189. "After the filing of the application for 605, it was discovered that the final amino acid residue in the human EPO polypeptide (the arginine residue at position 166), is removed during or following the secretion of the polypeptide from the cell to

generate the fully mature human EPO polypeptide ....” *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶142 (Apr. 11, 2001).

190. “The paragraph which was included in Example 10 in 605A and 605B, but was not followed through into the patent in its present form, namely 605, is to be found immediately after the first paragraph, and immediately before the second paragraph, of Example 10.... The paragraph in question which was deleted (and which I shall refer to as “the deleted matter”) was on page 65 of 605A (and on page 29 of 605B). It was in these terms:

> Purified human urinary EPO and a recombinant, CHO cell-purified, EPO according to the invention were subjected to carbohydrate analysis according to the procedure of Ledeen, et al. Methods in Enzymology, 83 (Part D), 139-191 (1982) as modified through use of the hydrolysis procedures of Nesser, et al., Anal.Biochem., 142, 58-67 (1984). Experimentally determined carbohydrate constitution values (expressed as molar ratios of carbohydrate in the product) for the urinary isolate were as follows: Hexoses, 1.73; N-acetylglucosamine, 1; N-acetylneuraminic acid, 0.93; Fucose, O; and N-acetylgalactosamine, O. Corresponding values for the recombinant product (derived from CHO pDSVL-gHuEPO 3-day culture media at 100 nM MTX) were as follows: Hexoses, 15.09; N-acetylglucosamine, 1; N-acetylneuraminic acid, 0.998; Fucose, O; and N-acetylgalactosamine, O. These findings are consistent with the Western blot and SDS-PAGE analysis described above.”

In the Matter of European Patents (UK) Nos. 148,605 and 411,678, 2001 WL 273001, Judgment ¶186 (Apr. 11, 2001).

191. “During the [1994] hearing before the Appeal Board [the Technical Board of Appeal of the European Patent Office], Amgen conceded that the carbohydrate analysis of the recombinant EPO as contained in the penultimate sentence of the second paragraph could not be supported, in that it was clearly mistaken. In those circumstances, Amgen accepted that the second paragraph should be deleted from Example 10 of the Patent.” *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶19 (Mar. 21, 2002).

192. Claim 19 of EP 0 148 605 B2 claiming

> A recombinant polypeptide having part or all of the primary structural conformation of human or monkey erythropoietin as set forth in Table VI or Table V or any allelic variant or derivative thereof possessing the biological property of causing bone marrow

> cells to increase production of reticulocytes and red blood cells to increase hemoglobin synthesis or iron uptake and characterized by being the product of eucaryotic expression of an exogenous DNA sequence and which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources.

was held invalid in the United Kingdom. *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶¶ 14, 132 (Oct. 21, 2004).

193. "Claim 19 distinguishes the product falling within the claim on the ground that it has a 'higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources'." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶121 (Oct. 21, 2004).

194. Amgen was "determined to try to patent the protein itself, notwithstanding that, even when isolated, it was not new." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶132 (Oct. 21, 2004).

195. "[T]he last-minute amendment to distinguish the product from the natural EPO turned out to based upon the false premise that all uEPO had the same molecular weight." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶132 (Oct. 21, 2004).

196. "The claim appeared to assume that all uEPOs had effectively the same molecular weight, irrespective of source and method of isolation. This had been shown not to be the case." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶124 (Oct. 21, 2004).

197. "There were variations [in urinary EPO] which might have been attributable to the source of the urine and the method of purification or might have been purely random." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶121 (Oct. 21, 2004).

198. "Simply to use the first uEPO which came to hand would turn the claim into a lottery. On the other hand, it would be burdensome to have to work one's way through several specimens of uEPO ... and even then the result would be inconclusive because *non constat* that some untried specimen did not have a different molecular weight." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶124 (Oct. 21, 2004).

199. "It did not merely throw up the possibility of doubtful cases but made it impossible to determine in any case whether the product fell within the claim" requiring EPO which has higher molecular weight by SDS-PAGE from erythropoietin isolated from urinary sources. *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶125 (Oct. 21, 2004).

200. "The glycosylation of any protein is and was known in 1984 to be heterogeneous. In other words, the glycans were known to consist of a combination or combinations of monosaccharides, attached to the polypeptide chain of the protein ("the back bone"), which vary from molecule to molecule." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶107 (Apr. 11, 2001).

201. "[U]rinary EPOs can vary depending on their source, and even urinary EPOs from the same source, albeit from different fractions during the purification process, can vary from each other." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶546 (Apr. 11, 2001).

202. "Amgen's work involved three types of urinary EPO and two types of recombinant EPO. The three types of uEPO were:

1. "Goldwasser uEPO", which was uEPO isolated from pooled urinary sources by Dr Goldwasser in accordance with the teaching of Miyake;
2. "Lot 82 uEPO" which was uEPO isolated substantially in accordance with the teaching of Miyake, but in respect of which there was a single source (i.e. the urine all came from one patient);
3. Alpha Therapeutics uEPO, which was uEPO from urinary sources, by a method of isolation which was not specified.

The two types of recombinant EPO used in Amgen's experiments were expressed substantially in accordance with the teaching of 605, in COS and CHO cells respectively (i.e. "COS rEPO" and "CHO rEPO")." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶458 (Apr. 11, 2001).

203. "Dr. Egrie ran a number of comparative SDS-PAGE experiments. She ran various urinary EPOs against each other, most notably Lot 82 uEPO against Goldwasser uEPO on a number of occasions, and also Alpha Therapeutic uEPO against Goldwasser uEPO. She also ran CHO rEPO against Lot 82 uEPO on at least three occasions and COS rEPO against Goldwasser uEPO on at least three occasions." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶459 (Apr. 11, 2001).

204. "The results of the Amgen experiments, at least as interpreted by Dr. Egrie at the time, were:

1. Lot 82 uEPO had a higher apparent molecular weight than Goldwasser uEPO;
2. COS rEPO had the same apparent molecular weight as Goldwasser uEPO;
3. CHO rEPO had the same apparent molecular weight as Lot 82 uEPO;

4. Alpha Therapeutics uEPO had the same apparent molecular weight as Lot 82 uEPO."

In the Matter of European Patents (UK) Nos. 148,605 and 411,678, 2001 WL 273001, Judgment ¶459 (Apr. 11, 2001).

205. "These views were repeated in the articles to which I have referred, and those articles were not written by Dr Egrie alone, but included more senior scientists working for Amgen. Most of the articles were in prestigious journals or books, and they were all peer-reviewed." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶461 (Apr. 11, 2001).

206. "Each of the papers contained an unambiguous statement to the effect that one or other of the two types of rEPO migrated on SDS-PAGE effectively identically to one of the types of uEPO." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶461 (Apr. 11, 2001).

207. "In addition, in its own submissions to the FDA, Amgen stated that 'the r-HuEPO migrates identically to the pure urinary EPO'." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶461 (Apr. 11, 2001).

208. "At some point before he drafted the fourth US Patent application, it seems pretty clear that Mr Borun had a discussion with Dr. Egrie about her work relating to the performance of various types of EPO's on SDS-PAGE, as a result of which she agreed to send him copies of relevant pages of her notebook." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶95 (Mar. 21, 2002).

209. "In relation to COS rEPO, she expressed the conclusion that:

> Recombinant monkey and human EPO produced by COS cells have the same molecular weight as native urinary EPO [Goldwasser's [urinary] EPO]. This result indicates that the recombinant EPO is glycosylated to the same extent as the native protein.

Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc., [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶97 (Mar. 21, 2002).

210. "[I]n Dr Egrie's view, the position was tolerably clear and was as follows. If one confined oneself to comparing recombinant EPOs with Goldwasser uEPO, CHO rEPO had a somewhat higher molecular weight than urinary EPO, but COS rEPO had the same apparent molecular weight as urinary EPO. On the other hand, once one extended the comparison to two other urinary EPOs, namely Lot 82 uBPO and Therapeutics uEP0, CHO rEPO had the same apparent molecular weight as

those two urinary EPOs." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶99 (Mar. 21, 2002).

211. "Dr. Egrie would have been unlikely to depart from the views expressed in her notebooks." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶103 (Mar. 21, 2002).

212. That Mr. Borun "conceded that there were at least parts of the [Egrie] File which were inconsistent with what he had written in the first paragraph of Example 10." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶105 (Mar. 21, 2002).

213. "There is no indication in any documentation or in any oral evidence ... which even suggests that anyone from Amgen (or indeed anyone else) gave any information or opinion in 1984 to Mr. Borun which was inconsistent with that of Dr. Egrie as contained in the Files." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶106 (Mar. 21, 2002).

214. "[T]he only experiments, records and expert views which appear to have existed [in 1984] were those contained in the File, and they showed a clear record of COS rEPO having the same apparent molecular weight as the urinary EPO upon which Amgen effectively rely, namely Goldwasser uEPO." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶109 (Mar. 21, 2002).

215. "[T]here was nothing to support the statement in the first paragraph of Example 10 so far as it related to the performance of COS rEPO against urinary EPO on SDS-PAGE, either by way of experiments or by way of any scientists views of experiments." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶115 (Mar. 21, 2002).

216. "[W]hile CHO rEPO had a higher apparent molecular weight by SDS-PAGE than Goldwasser uEPO, it had the same apparent molecular weight by SDS-PAGE as Lot 82 and Therapeutics uEPOs." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶127 (Mar. 21, 2002).

217. "[W]hile CHO rEPO has a higher apparent molecular weight than uEPO prepared strictly in accordance with the teaching of Miyake, it has approximately the same, and if anything a lower, apparent molecular weight than uEPO isolated in accordance with the teaching of Miyake subject to a small, almost trivial, modification." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶478 (Apr. 11, 2001).

218. "There is no specific teaching in the patent to the effect that some or all recombinant EPOs differ in their glycosylation characteristics from some or all EPO isolated from urinary sources." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶487 (Apr. 11, 2001).

219. "The disclosure that CHO rEPO had a 'somewhat higher molecular weight' than COS rEPO, which in turn had a 'slightly larger' molecular weight than pooled urinary EPO would be understood to suggest that the aggregate apparent molecular weight of the glycans on the two types of recombinant EPO was greater (albeit not by much) than on urinary EPO. Beyond that, however, the patent gives no guidance as to the nature of the difference in the 'average carbohydrate composition' between the 'glycoprotein polypeptide' and the 'human erythropoietin isolated from urinary sources'." *In the Matter of European Patents (UK) Nos. 148,605 and 411,678*, 2001 WL 273001, Judgment ¶487 (Apr. 11, 2001).

220. Claim 26 of EP 0 148 605 B2 claiming

> A polypeptide product of the expression in a eucaryotic host cell of a DNA sequence according to any of claims 1, 2, 3, 5, 6 and 7.

was held invalid as anticipated in the United Kingdom. *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶¶ 15, 101, 132 (Oct. 21, 2004).

221. Independent claim 1 from which claim 26 of EP 0 148 605 B2 depends is

> A DNA sequence for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least part of the primary structural [conformation] of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase [haemoglobin] synthesis or iron uptake, said DNA sequence selected from the group consisting of:
>
> (a) the DNA sequences set out in Tables V and VI or their complementary strands;
>
> (b) DNA sequences which hybridize under stringent conditions to the protein coding regions of the DNA sequences defined in (a) or fragments thereof; and
>
> (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).

Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd., [2005] R.P.C. 9, Judgment ¶13 (Oct. 21, 2004).

222. "The important point is that the [European Patent] Office found that rEPO according to claim 26 was a new product because its glycosolation pattern would necessarily be different from that of uEPO. Once this finding of fact was removed, there was no basis for allowing claim 26." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶99 (Oct. 21, 2004).

223. "It is true that glycosylation occurs only in eucaryotic cells, but that is no distinction from the prior art because human cells are eucaryotic." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶95 (Oct. 21, 2004).

224. "Neuberger J. ... found as a fact that there was no difference between uEPO and EPO made according to claim 26. He drew no distinction between EPO made in accordance with claim 19 and EPO made in accordance with claim 26, calling them both recombinant EPO ("rEPO"). He found (at [545] to [557]) that there was no necessary distinction between rEPO and uEPO." *Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd.*, [2005] R.P.C. 9, Judgment ¶96 (Oct. 21, 2004).

225. "Mr. Steven Odre, senior vice president and general counsel of Amgen, ... had the in-house supervisory responsibility for the prosecution of the US and European patent applications." *Hoechst Marion Roussel Ltd. v. Kirin-Amgen Inc.*, [2002] EWHC 471, Judgment (AM-ITC01066841-925), ¶92 (Mar. 21, 2002).

X. Findings of Fact from Proceedings Before the European Patent Office Technical Board of Appeal

226. "No process is disclosed in the patent [EP 0148 605] for making a mRNA from which a cDNA coding for human Epo could be made or identified. Method (i) could yield a human cDNA only in the instance the skilled worker were lucky enough to pick up the full-length cDNA and this possibility is very remote in view of the experimental evidence provided by the appellants. Should the skilled worker, though, pick up a defective cDNA as it is more likely, the task of turning it into a complete cDNA susceptible of expression in mammalian cells would possibly require a further invention." *Kirin Amgen v. Genzyme*, [1995] E.P.O.R. 629, ¶26 (Nov. 21, 1994).

227. "Complete synthesis of the cDNA...would require the skilled person first to know what he had to synthesise, and secondly to have a practical method of synthesising it. To identify a partial sequence in Table VI [of EP 0148 605] as being the cDNA would be mere guesswork. Neither is there an unambiguous information of the start nor an indication of where the end should be. Thus the

skilled person would be unable to use this approach." *Kirin Amgen v. Genzyme*, [1995] E.P.O.R. 629, ¶28 (Nov. 21, 1994).

228. "Whether [a] product claim can stand for the purposes of Article 83 depends on whether what is claimed can be identified and whether a reliable method existed for making it, using the teaching of the patent and common general knowledge available at the priority." ..."Consequently, Claim 3 of the main request does not comply with Article 83, EPC, so that the main request is not allowable." *Kirin Amgen v. Genzyme*, [1995] E.P.O.R. 629, ¶¶20 and 29 (Nov. 21, 1994).

229. "In the context of the description the term cDNA, in accordance with usual scientific usage, refers to the product obtained by *in vitro* synthesis of a double-stranded DNA sequence by enzymatic 'reverse transcription'of mRNA" "The reference to cDNA in Claim 3 must be interpreted in the same way." *Kirin Amgen v. Genzyme*, [1995] E.P.O.R. 629, ¶19 (Nov. 21, 1994).

230. That there is "no certainty of getting a particular r-Epo glycosylation pattern," and that "The glycosylation pattern for u-EPO would also appear to depend on the time of day, and physiological status of the patient from whom it is obtained. r-Epo thus appears to share with u-EPO the characteristic that the carbohydrate composition is to a considerable degree a matter of chance....Claim 19 thus lacks novelty over the u-Epo of the prior art and is not allowable." *Kirin Amgen v. Genzyme*, [1995] E.P.O.R. 629, ¶¶39 and 41 (Nov. 21, 1994).

231. That Claim 19 "does not comprise any indication of the technical feature or the degree of difference on which non-identity of r-Epo with u-Epo should be based, but rather leaves this to the reader's imagination. This puts the claim clearly in the category of claims which are not clear....Claim 19 of auxiliary request 5 is thus not allowable as no being in accordance with Article 84 EPC, and auxiliary request 5 must therefore be refused." *Kirin Amgen v. Genzyme*, [1995] E.P.O.R. 629, ¶¶45 and 46 (Nov. 21, 1994).