Amgen Inc. v. F. Hoffmann-LaRoche LTD et al Doc. 501 Att. 65

EXHIBIT Q
Part 2 of 2

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57. The language of Claim 10 from the '016 patent reads as follows:

> A process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid, said process comprising the following steps in sequence:
>
> (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.9, thereby to selectively bind erythropoietin in said sample to a DEAE agarose cationic resin;
>
> (2) stabilizing materials bound to said resin against degradation by acid activated proteases through treatment with urea;
>
> (3) selectively eluting bound materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of about 4.3.
>
> (4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0;
>
> (5) subjecting erythropoietin-containing eluent fractions to reverse phase liquid chromatographic separation involving an immobilized C4 resin, thereby to selectively bind erythropoietin in said fluid to said resin;
>
> (6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of about 60 percent at a pH of about 7.0; and,
>
> (7) isolating erythropoietin-containing fractions of the eluent.

58. For claim 10, I considered two ways to define the meaning of recombinant erythropoietin. In the first, I examined the '016 patent itself and found a concise statement on how to practice the '016 invention:

> Practice of the present invention is believed to be suitably illustrated by the following examples practiced on pooled CHO cell supernatants prepared in the manner described in Example 10 of the aforementioned U.S. patent application Ser. No. 675,298 [now the '008 patent].

'016 patent, at col. 4, lines 33-39. Example 10 set forth in the patents-in-suit (set forth at col. 26, line 35 – col. 30, line 29 of the '008 patent, for example), concludes:

> Glycoprotein products provided by the present invention are thus comprehensive of products having a primary structural conformation sufficiently duplicative of

> that of a naturally occurring erythropoietin to allow possession of one or more of the biological properties thereof....

'008 patent, col. 30, lines 22-27. The person of ordinary skill in the art would understand from the '016 patent that the recombinant erythropoietin in claim 10 encompasses the product of Example 10, which is grown in CHO cell culture, glycosylated, and biologically active. Example 10 describes DHFR-mediated amplification, detection by RIA, amino acid correspondence to the EPO sequence described in Figure 6, and detection of biological activity including increased hematocrit. This same Example 10 is in each of the patents-in-suit. This means that the recombinant erythropoietin set forth in claim 10 of the '016 patent must overlap the products described in all of the claims-in-suit.

59. Second, I also considered the meaning of recombinant erythropoietin to a person of ordinary skill in the art in 1983. The person of ordinary skill in the art would have the understanding of recombinant DNA technology as described in paragraphs 15-54 above. In the following paragraphs, I discuss how the person of ordinary skill in the art would understand the claims-in-suit.

60. I also considered other terms in claim 10. Supernatant is well known in the art to be the liquid/fluid from media from the cell culture. Any cells, cellular debris, membranes, insoluble proteins, etc. may be removed by methods such as centrifugation or filtration of the cell media.

61. The '016 patent claims the recovery of recombinant EPO from the culture of mammalian host cells. The steps taught and claimed in the '016 patent allow one of ordinary skill in the art to provide acceptable EPO for pharmaceutical purposes.

62. Any solid portions of the mammalian host cells (e.g., disturbed cells, cellular debris, etc.) are removed using techniques so well known in the prior art that the techniques are

not described in any detail in either the '016 patent or the patents-in-suit. The remaining liquid – the supernatant – includes the recombinant EPO (rEPO) as well as many other molecules. Since it is highly undesirable to deliver to a human many of these other molecules (e.g., DNA fragments, mRNA fragments and proteins endogenous to the mammalian host cell), the rEPO is isolated from the supernatant.

63. The isolation of the rEPO from the undesirable molecules of the host cell's supernatant is absolutely essential to providing a rEPO that is a pharmaceutically acceptable product. If the rEPO is not properly isolated from the supernatant, it cannot be used for its intended purpose.

64. The amino acid sequence shown in FIG. 6 of the patents-in-suit is the primary translation product of the erythropoietin gene used in the '016 claims. I understand that a final rEPO product may not have all 166 amino acids shown in FIG. 6.

65. I am told that courts specifically created the doctrine of obviousness-type double patenting to preclude applicants from extending the duration of their patent term to a single invention by claiming obvious variants of that invention in later patents. To protect the public from an unwarranted extension of the patent monopoly, a terminal disclaimer limiting the patent terms of these patents to the full life of the earlier '016 patent should have been required. Since the '016 patent has now expired, the patents-in-suit should likewise be expired or invalidated.

66. All of the limitations of the six Amgen patents-in-suit would have been considered routine and obvious to those of skill in the art once they were in possession of the process for recovering purified recombinant EPO from a mammalian cell culture claimed in the '016 patent.

VII. THE CLAIMS-IN-SUIT WERE ANTICIPATED OR OBVIOUS OVER '016 PATENT CLAIM 10

A. '933 Patent

1. Claim 3

67. Claim 3 of the '933 patent reads as follows:

> 3. A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.

68. All of the elements of claim 3 are either found within claim 10 of the '016 patent or would be obvious to a person of ordinary skill in the art with knowledge of claim 10 of the '016 patent. Without limitation, I note the product claimed by claim 3 of the '933 patent would have been obvious over the product formed by the process set forth in claim 10 of the '016 patent.

69. Claim 3 of the '933 patent is directed to the recombinant EPO product of claim 10 of the '016 patent. Although I have not considered how one could distinguish a "naturally occurring" protein from a "non-naturally occurring" protein, it is my opinion that *non-naturally occurring erythropoietin*, if it means anything, would have been obvious in view of the "recombinant erythropoietin." Erythropoietin grown in a mammalian cell culture as called for in claim 10 of the '016 patent is *a glycoprotein product of the expression in a mammalian host cell.* Mammalian derived cells, such as CHO cells, were known at the time of the '016 patent submission to glycosylate secreted proteins. Such cells were specifically known to glycosylate other recombinant secreted proteins. Since EPO is naturally glycosylated, there is every expectation that the rEPO recovered in claim 10 of the '016 patent would be glycosylated as well. The cell culture of the '016 patent uses a DNA sequence encoding erythropoietin. *Human*

EPO was and remains the EPO of greatest interest to scientists and pharmaceutical companies. Claim 3 also calls for the "in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." Recombinant EPO from the cell culture of claim 10 of the '016 patent would have every expectation to inherently exhibit this property. I base this belief on several facts. First, as I discussed above, it was well known in 1983 that other active recombinant proteins could be isolated from the supernatant of mammalian cells manipulated to express other recombinant proteins. Second, based on what was known in 1983, someone of ordinary skill in the field would have had a reasonable expectation that recombinant erythropoietin would be appropriately glycosylated through expression in a mammalian host cell and thus would be erythropoietic, i.e., that it would have the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells. Third, to one skilled in the art in 1983, it would be obvious to test purified or partially purified preparations of rEPO for biological activity. In fact, if this were not done the ultimate goals of this purification could not be achieved. The purified rEPO was only useful if it had biological activity. It is inconceivable to me that one of ordinary skill in the art would purify rEPO without making sure they were purifying biologically active rEPO. Indeed, I note that throughout the '016 patent, it is claimed that the isolated rEPO is biologically active. For example, see Abstract, Background, and Brief Summary. Finally, I note that Amgen has conceded in discourse with the Patent and Trademark Office that once a clone for the human EPO gene was isolated, all of the steps to synthesize, purify, and prepare active rEPO for clinical trials followed in a straightforward manner. (See discussion below.) Therefore, there would have been a reasonable expectation that the rEPO purified in the '016 patent possessed the *in vivo biological property (or activity) of causing bone marrow cells to increase production of*

reticulocytes and red blood cells. Thus, the glycoprotein product of claim 3 was the same as the EPO produced by the process of claim 10 of the '016 patent or would have been obvious in view of it.

2. Claim 7

70. Claim 7 of the '933 patent reads as follows:

> 7. The glycoprotein product according to claim 3, 4, 5 or 6 wherein the host cell is a non-human mammalian cell.

71. The use of a mammalian cell culture as set forth in claim 10 of the '016 patent would have suggested to one of ordinary skill in the art in 1983 that *non-human mammalian cells* could have been used. See paragraph 32 above for a description of the state of the art as to the routine use of non-human mammalian cells for protein expression. Thus, claim 7 depending from claim 3 recites a glycoprotein that would have been obvious over the EPO produced by the process of claim 10 of the '016 patent.

3. Claim 8

72. Claim 8 of the '933 patent reads as follows:

> 8. The glycoprotein product according to claim 7 wherein the non-human mammalian cell is a CHO cell.

73. As explained above at paragraphs 22-27, *CHO cells* would have been a routine choice for those of ordinary skill in the art in 1983 for use as the host cell. Therefore, claim 8 would have been obvious over claim 10 of the '016 patent.

4. Claims 9 and 12

74. Claims 9 and 12 read as follows:

> 9. A pharmaceutical composition comprising an effective amount a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

> 12. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 7 and a pharmaceutically acceptable diluent, adjuvant or carrier.

75. One of ordinary skill in the art in 1983 would have understood the purified recombinant EPO of the '016 patent was intended for use in *pharmaceuticals*. As in any pharmaceutical, one of ordinary skill in the art would have found it routine to combine an effective amount of the recombinant EPO purified according to claim 10 of the '016 patent with a *diluent, adjuvant or carrier*. Therefore, claim 9 depending from claim 3 and claim 12 would have been obvious in view of the purification of recombinant EPO as claimed in the '016 patent.

5. Claims 11 and 14

76. Claims 11 and 14 read as follows:

> 11. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient.
>
> 14. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product.

77. As discussed above at paragraphs 38-45, it was well known in the art in 1983 that EPO could be used for *treating kidney dialysis patients to increase a patient's hematocrit level*. The growing demands for these treatments led Amgen and others to seek a method to produce recombinant EPO. Based on the state of the art in recombinant DNA technology at that time, there was a reasonable expectation of success in producing rEPO useful for such treatment. Therefore, it would have been obvious in 1983 to one of ordinary skill in the art to use the purified recombinant EPO produced in claim 10 of the '016 patent to make a pharmaceutical composition for treating a kidney dialysis patient and inherently increase the hematocrit levels.

B. '080 Patent

1. Claim 3

78. Claim 3 of the '080 patent reads as follows:

> 3. A non-naturally occurring erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.

79. Claim 3 of the '080 patent would have been obvious from claim 10 of the '016 patent. Although I have not considered how one could distinguish a "naturally occurring" protein from a "non-naturally occurring" protein, it is my opinion that non-naturally occurring erythropoietin, if it means anything, would have been obvious in view of the "recombinant erythropoietin." Erythropoietin grown in a mammalian cell culture as called for in claim 10 of the '016 patent is a *glycoprotein.* As discussed above in connection with claim 3 of the '933 patent, there would have been a reasonable expectation that the rEPO purified in the '016 patent possessed *the in vivo biological property (or activity) of causing bone marrow cells to increase production of reticulocytes and red blood cells.* FIG. 6 depicts a 166 amino acid sequence. I understand that a final EPO product may not have all 166 amino acids shown in FIG. 6. To the extent claim 3 of the '080 patent could be construed to cover a 165 amino acid sequence, claim 3 would have been obvious in light of claim 10 of the '016 patent.

2. Claim 4

80. Claim 4 of the '080 patent reads as follows:

> 4. A pharmaceutical composition comprising a therapeutically effective amount an erythropoietin glycoprotein product according to claim 1, 2 or 3.

81. I understand that the Federal Circuit Court of Appeals recently interpreted *therapeutically effective amount* to mean an amount "that elicits any one or all of the effects

often associated with *in vivo* biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals." *Amgen Inc. v. Hoeschst Marion Roussel, Inc.*, 457 F.3d 1293, 1303 (Fed. Cir. 2006).

82. One of ordinary skill in the art in 1983 would have understood the purified recombinant EPO of the '016 patent was intended for use in *pharmaceuticals*. It would have been obvious to one of ordinary skill in the art to use a sufficient amount of EPO so as to elicit at least one of the effects characterizing *therapeutically effective*. Thus, claim 4 depending from claim 3 would have been obvious over claim 10 of the '016 patent.

3. Claim 6

83. Claim 6 of the '080 patent reads as follows:

> 6. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 4 in an amount effective to increase the hematocrit level of said patient.

84. As discussed above at paragraphs 38-45, it was well known in the art in 1983 that EPO could be used for *treating kidney dialysis patients to increase a patient's hematocrit level.* The growing demands for these treatments led Amgen and others to seek a method to produce recombinant EPO. Based on the state of the art in recombinant DNA technology at that time, there was a reasonable expectation of success in producing rEPO useful for such treatment. Therefore, it would have been obvious in 1983 to one of ordinary skill in the art to use the purified recombinant EPO produced in claim 10 of the '016 patent to make a pharmaceutical composition for treating kidney dialysis patient and inherently increase the hematocrit levels.

C. '422 Patent Claim 1

85. Claim 1 of the '422 patent reads as follows:

> 1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

86. One of ordinary skill in the art in 1983 would have understood the purified recombinant EPO of the '016 patent was intended for use in *pharmaceuticals*. As in any pharmaceutical, one of ordinary skill in the art would have found it routine to combine a therapeutically effective amount of the recombinant EPO purified according to claim 10 of the '016 patent with a *pharmaceutically acceptable diluent, adjuvant or* carrier. As explicitly covered by the '016 patent, *erythropoietin is purified from mammalian cells grown in culture.* Given that it would have been obvious to use the process of claim 10 of the '016 patent to produce human EPO, claim 1 of the '422 patent would have been obvious over claim 10 of the '016 patent.

D. '698 Patent

1. Claim 4

87. Claim 4 of the '698 patent reads as follows:

> 4. A process for the production of a glycosylated erythropoietin polypeptide having the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> (a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> (b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

88. Claim 4 of the '698 patent recites the same process as the process of claim 10 of the '016 patent but in different words and specifically for the obvious selection of human EPO.

89. As explained above in paragraphs 24-26 and 49 by expressing EPO in a mammalian cell culture as covered in claim 10 of the '016 patent, the resultant EPO will have been *glycosylated.* The EPO produced by claim 10 of the '016 patent is a *polypeptide.* Recombinant EPO from a mammalian cell culture as claimed in claim 10 of the '016 patent would have inherently exhibited the *in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.* Given that claim 10 of the '016 patent produces recombinant EPO, it necessarily follows that the mammalian cell culture was provided *suitable nutrient conditions.* Mammalian cells are *vertebrate* cells because mammals have backbones. As explained above in paragraphs 28-32 and 52, *promoter DNA other than human erythropoietin promoter DNA* was routinely used in recombinant protein synthesis in 1983. *FIG. 6* depicts the amino acid sequence of the primary expression product of human erythropoietin. This is the original complete 166 amino acid sequence that would have been formed in the mammalian cells of claim 10 of the '016 patent when used to produce human EPO. Given that it would have been obvious to use the process of claim 10 of the '016 patent to produce human EPO, such use would necessarily involve *promoter DNA operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6. Isolating said glycosylated erythropoietin polypeptide expressed by said cells* corresponds to step 7 of claim 10 of the '016 patent. The elements of claim 4 are all thus covered by or obvious from the claimed process of claim 10 of the '016 patent.

2. Claim 5

90. Claim 5 of the '698 patent reads as follows:

> 5. The process of claim 4 wherein said promoter DNA is viral promoter DNA.

91. As discussed above at paragraph 31, it was routine in the art in 1983 to make use of *viral promoter DNA* during synthesis of recombinant proteins in a method such as that claimed in claim 10 of the '016 patent. In view of the discussion with respect to claim 4 and for this reason, claim 5 would have been obvious over claim 10 of the '016 patent.

3. Claim 6

92. Claim 6 of the '698 patent reads as follows:

> 6. A process for the production of a glycosylated erythropoietin polypeptide having the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> (a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and
>
> (b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

93. Claim 6 of the '698 patent recites the same process as the process of claim 10 of the '016 patent but in different words and specifically for the obvious selection of human EPO.

94. As explained above in paragraphs 24-26 and 49, by expressing EPO in a mammalian cell culture as covered in claim 10 of the '016 patent, the resultant EPO will have been *glycosylated.* The EPO produced by claim 10 of the '016 patent is a *polypeptide.* Recombinant EPO from a mammalian cell culture as claimed in claim 10 of the '016 patent would have inherently exhibited the *in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.* Given that claim 10 of the '016 patent produces recombinant EPO, it necessarily follows that the mammalian cell culture was provided *suitable nutrient conditions.* Mammalian cells are *vertebrate* cells because mammals have backbones. As explained above in paragraphs 33-35 and 52, *amplified DNA* was routinely used in recombinant protein synthesis in 1983. *FIG. 6* depicts the amino acid sequence of the primary

expression product of human erythropoietin. This is the original complete 166 amino acid sequence that would have been formed in the mammalian cells of claim 10 of the '016 patent when used to produce human EPO. Given that it would have been obvious to use the process of claim 10 of the '016 patent to produce human EPO, such use would necessarily involve *amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6. Isolating said glycosylated erythropoietin polypeptide expressed by said cells* corresponds to step 7 of claim 10 of the '016 patent. The elements of claim 6 are all thus covered by or obvious from the claimed process of claim 10 of the '016 patent.

4. Claim 7

95. Claim 7 of the '698 patent reads as follows:

> 7. The process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA.

96. As discussed above in paragraphs 33-35 and 52, *amplified marker gene DNA* was routinely used in 1983 during synthesis of recombinant proteins in a method such as that claimed in claim 10 of the '016 patent. In view of the discussion with respect to claim 6 and for this reason, claim 7 would have been obvious over claim 10 of the '016 patent.

5. Claim 8

97. Claim 8 of the '698 patent reads as follows:

> 8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.

98. As discussed above in paragraphs 33-35 and 52, *Dihydrofolate reductase (DHFR) gene DNA* was routinely used as an amplified marker gene DNA in 1983 during synthesis of recombinant proteins in a method such as that claimed in claim 10 of the '016 patent. In view of

the discussions with respect to claims 6 and 7 and for this reason, claim 8 would have been obvious over claim 10 of the '016 patent.

6. Claim 9

99. Claim 9 of the '698 patent reads as follows:

> 9. The process according to claims 2, 4 and 6 wherein said cells are mammalian cells.

100. The use of mammalian cells is explicitly covered by claim 10 of the '016 patent. In view of the discussions with respect to claims 4 and 6, claim 9 would have been obvious over claim 10 of the '016 patent.

E. '868 Patent

1. Claim 1

101. Claim 1 of the '868 patent reads as follows:

> 1. A process for the production of a glycosylated erythropoietin polypeptide having the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:
>
> (a) growing, under suitable nutrient conditions, mammalian host cells transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and
>
> (b) isolating said glycosylated erythropoietin polypeptide therefrom.

102. Claim 1 of the '868 patent recites the same process as the process of claim 10 of the '016 patent but in different words and specifically for the obvious selection of human EPO.

103. As explained above in paragraphs 24-26 and 49, by expressing EPO in a mammalian cell culture as covered in claim 10 of the '016 patent, the resultant EPO will have been *glycosylated.* The EPO produced by claim 10 of the '016 patent is a *polypeptide.* Recombinant EPO from a mammalian cell culture as claimed in claim 10 of the '016 patent would have inherently exhibited the *in vivo biological property of causing bone marrow cells to*

increase production of reticulocytes and red blood cells. Given that claim 10 of the '016 patent produces recombinant EPO, it necessarily follows that the mammalian cell culture was provided *suitable nutrient conditions.* As explained above in paragraphs 17-19, it was routine in the art in 1983 when synthesizing recombinant proteins in mammalian cells *to transform or transfect the cells with the isolated DNA sequence* encoding the desired protein. It would have been a mere obvious choice to use the process of the '016 patent to produce *human erythropoietin.* The elements of claim 4 are all thus covered by or obvious from the claimed process of claim 10 of the '016 patent. *Isolating said glycosylated erythropoietin polypeptide* corresponds to step 7 of claim 10 of the '016 patent. The elements of claim 1 are all thus covered by or obvious from the claimed process of claim 10 of the '016 patent.

2. Claim 2

104. Claim 2 of the '868 patent reads as follows:

> 2. The process according to claim 1 wherein said host cells are CHO cells.

105. Because glycosylation of EPO was necessary for the desired biological activity, and because *CHO cells* were readily available and well characterized, one of ordinary skill in the art in 1983 would have naturally chosen *CHO cells* as a host. In view of the discussion with respect to claim 1 and for this reason, claim 2 would have been obvious over claim 10 of the '016 patent.

F. '349 Patent Claim 7

106. Claim 7 depends from any of claims 1-6. In order to present all elements of the claim, claim 7 can be read as follows:[21]

> A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells [which can be propagated in vitro

[21] The bracketed text corresponds to what is claimed in claims 1-6.

> and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100, 500, or 1000 U of erythropoietin per 10^6 cells in 48 hours as determined by radioimmunoassay, said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin].

107. Claim 7 of the '349 patent recites the same process as the process of claim 10 of the '016 patent but in different words and an obvious selection of human EPO. The claim also specifies that the cells are capable of being propagated in vitro and are capable of producing human erythropoietin in excess of 100, 500 or 1000 U per 10^6 cells in 48 hours, although the claims does not require that any specific rate of EPO growth be attained in the process.

108. However, the standard used in the radioimmunoassay (RIA) described in the '349 patent, as well as all the other parameters necessary to ensure a repeatable and consistent RIA, are not clearly set forth in the '349 patent. Thus, the claims of the '349 patent appear indefinite.

109. The relevant examples given in the '349 patent do not appear to provide greater than ordinary rates of production of a protein. Thus, I conclude that, whatever rate of production is enabled by the '349 patent, it is no more than what someone of ordinary skill in the field would have reasonably expected from a cell line expressing a recombinant protein.

110. Given that claim 10 of the '016 patent produces recombinant EPO, it necessarily follows that the mammalian cell culture was provided *suitable nutrient conditions.* Mammalian cells are *vertebrate* cells because mammals have backbones.

111. Whether the mammalian cells of claim 10 of the '016 patent would have been capable of producing EPO at a rate on the order of what is enabled by the '349 patent was well within the ordinary skill in the art as of 1983. The techniques for amplifying production as described in paragraphs 33-35 and 52 were readily available. The '349 patent does not disclose or claim any unknown method for making its rate of production possible. Since the scope of

claim 7 of the '349 patent—which appears indefinite—must be limited to what was enabled in the '349 patent, and since such a scope would have been obvious over the claim 10 of the '016 patent, claim 7 must have been obvious over claim 10 of the '016 patent, if it were somehow capable of being construed to have a definite scope.

VIII. AMGEN PRIOR STATEMENTS AND ACTIONS SUPPORT MY OPINION THAT THE CLAIMS-IN-SUIT WOULD HAVE BEEN OBVIOUS OVER '016 PATENT CLAIM

112. I am told that Patent and Trademark Office (PTO) has recognized that just given the isolation of the EPO gene needed for use in the mammalian cell culture, the process steps for making glycosylated biologically active EPO "d[id] not require the exercise of inventive skill." *Fritsch v. Lin*, 21 U.S.P.Q.2d 1739, 1740 (BPAI 1992) (emphasis supplied).

113. I further note that during the prosecution of the '868 patent, Amgen argued to the PTO that as of the time of the then asserted filing date of December 13, 1983, it was well known by those skilled in the art to obtain glycosylated proteins expressed in mammalian host cells. The Patent and Trademark Office rejected the pending claims as non-enabled and lacking adequate written description under Section 112. In particular, the PTO stated that:

> Applicant claims a method of preparing EPO, in part, by growing a host "capable of effecting post-translational glycosylation of polypeptides expressed therein." Applicant has provided no guidance for, and no working examples of, any test or procedure for determining which host cells have such capability and which do not. Without such a procedure, one of ordinary skill in the art would have no way to determine operable from inoperable embodiments of the claimed invention...Accordingly, it would require undue experimentation by one of ordinary skill in the art to practice the invention as claimed. (Office Action, dated 9/1/93, '868 patent prosecution)

Amgen traversed this rejection in part by arguing that it would have been obvious to the skilled worker to be able to make glycosylated proteins from available host cells. In particular, Amgen argued that "numerous other mammalian cells [in addition to CHO and COS] capable of

effecting glycosylation of expressed polypeptides were known to those skilled in the art at the time of the present invention." Applicant Amendment and Response, dated January 3, 1994, '868 patent prosecution AM-IT 00953641 (emphasis supplied). Thus, Amgen conceded during the prosecution of the '868 patent that the process for using host cells capable of effecting post-translational glycosylation was obvious at the time of the invention.

114. Amgen has admitted and has successfully argued in a prior proceeding that the patents-in-suit are to the same invention. Indeed, Amgen successfully argued to the Board of Patent Appeals that the composition claims and the process claims "are only different manifestations of the same invention" and that "the whole purpose and intent of the purified and isolated DNA sequence encoding human EPO (and host cells transfected therewith)...was to express *in vivo* biologically active human EPO." Brief for the Senior Party Lin, Interference No. 102,097, dated 7/29/91 at 26, AM-ITC 00337678. Thus, it would have been obvious to one of skill in the art in 1983 to use the mammalian cell culture to recover recombinant EPO (as claimed in the '016 patent) thereby producing glycosylated, biologically active EPO protein (as claimed in the '868, '698, '933 and '080 patents) at levels exceeding 100-1000 U (as claimed in the '349 patent) for incorporation into a pharmaceutical composition (as claimed in the '422, '080 and '933 patents) to be used to treat kidney dialysis patients (as claimed in the '080 and '933 patents). Thus, the processes, proteins, compositions and use of same in treatments described in the asserted claims are just a rewording or obvious variation of the process claims of the '016 patent.

IX. DOUBLE PATENTING OF THE CLAIMS-IN-SUIT OVER U.S. PATENT NO. 4,703,008 TO LIN, ISSUED OCTOBER 27, 1987

115. I have reviewed the claims of the U.S. Patent No. 4,703,008 to Lin (the '008 patent). The claims of the '008 patent are generally directed to purified and isolated DNA

sequences encoding erythropoietin and to host cells transformed or transfected with such sequences. For the reasons discussed above in connection with the '016 patent, it is also my opinion that the claims-in-suit would have been considered obvious over the claims of the '008 patent. In addition, Amgen's arguments in the Patent and Trademark Office, including those made to the Board of Patent Appeals, referred to above, are consistent with this opinion.

116. Claims 2, 4, 5, 6, 7, 11, 12, 23, 24, 25 and 27 of the '008 patent read as follows:

> 2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.
>
> 4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.
>
> 5. A biologically functional circular plasmid or viral DNA vector including a DNA sequence according to claim 1, 2, or 3.
>
> 6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.
>
> 7. 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 cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.
>
> 11. A genomic DNA sequence according to claim 7.
>
> 12. A human species erythropoietin coding DNA sequence according to claim 11.
>
> 23. A procaryotic or eucaryotic 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.
>
> 24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.
>
> 25. A transformed or transfected mammalian host cell according to claim 24.
>
> 27. A transformed or transfected CHO cell according to claim 25.

117. Claims 2, 4, 6, 12, 25 and 27, and perhaps other claims, of the '008 patent render the claims of the patents in suit obvious. For example, Claim 2 sets forth a *DNA sequence*

encoding human erythropoietin. Claim 12 sets forth a *human species erythropoietin coding DNA sequence* that encodes *an amino acid sequence sufficiently duplicative 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 hemoglobin synthesis or iron uptake.* In my opinion, having a gene sequence as defined by claim 2 or 12, the person of ordinary skill would have found the subject matter of the claims-in-suit obvious.

118. Claims 4 and 6 set forth a eucaryotic host cell. Claim 27 sets forth a CHO cell that is capable of glycosylating [a] polypeptide and that is transformed or transfected with a DNA sequence that encodes the polypeptide so that it has an amino acid sequence sufficiently duplicative 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 hemoglobin synthesis or iron uptake. In my opinion, having a host cell as defined by claim 4, 6 or 27, the person of ordinary skill would have found the subject matter of the claims-in-suit obvious.

X. AMGEN'S ASSERTION THAT LIN IS THE SOLE INVENTOR OF ALL THE CLAIMS IN THE PATENTS-IN-SUIT AND THE '008 PATENT SUPPORTS THE INVALIDITY OF THE CLAIMS-IN-SUIT FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

119. I am informed that the Board of Patent Appeals and Interferences stated in their Final Judgment of December 3, 1991, in an Interference proceeding in which Amgen was a party-in-interest and which involved the subject matter of the claims-in-suit, that:

> The record indicates that all the work at Amgen relating to expression of the EPO gene in mammalian host cells was directed and supervised by Dr. Browne, assisted by Ralph Smalling. Dr. Lin does not recall giving any instructions or suggestions as to how such expression should be carried out (PF V-3, 4). The effort to isolate the EPO glycoprotein expression product was carried out by Dr. Strickland, and Dr. Lin gave no specific instructions for accomplishing that task (PF V-6). (*Fritsch v. Lin,* 21 USPQ 2d 1739, 1991 WL 332571 *2 (BPAI 1991))

120. From reading the foregoing, I conclude that Dr. Lin only provided Dr. Browne and Ralph Smalling with the DNA sequence and provided them with no further instructions. Thus, in my opinion, the expression of recombinant human EPO would have been obvious to one skilled in the art at the time, once the gene sequence for EPO was known. Otherwise, Dr. Lin should not have been listed by Amgen as the sole inventor on each of the patents-in-suit, since he provided no instructions for expressing EPO within a mammalian cell line to the people working on this aspect of the project. Similarly, Dr. Lin provided no instructions for isolating the EPO glycoprotein expression product. Therefore, the other people working with Dr. Lin on the EPO project must have relied simply on the techniques and operating conditions known to those of ordinary skill in the art for expressing recombinant proteins in mammalian cells and isolating EPO therefrom.

121. Thus, Dr. Lin's lack of involvement in expression and isolation of EPO supports my opinion that the claims-in-suit would have been obvious over the claims of the '008 patent. This also supports my opinion of the level of skill in the field and my opinion of what someone of ordinary skill in the field would have found to be obvious. Thus, this supports my opinion that the claims-in-suit would have been obvious over the claims of the '016 patent.

XI. THE INADEQUACY OF DISCLOSURE IN THE PATENTS-IN-SUIT

122. As set forth above, it is my opinion that the subject matter of the claims-in-suit would have been obvious over the claims of either the '016 patent or the '008 patent. In other words, it is my opinion that someone of ordinary skill in the field had a level of skill that was high enough that the differences between the claims-in-suit and the claims of either the '016 patent or the '008 patent would have been obvious to such a person. If, however, these differences would not have been obvious to one of ordinary skill – or, in other words, if the level

of skill in the field was not sufficiently high for these differences to have been obvious – then it is my opinion that the patents-in-suit would not have enabled one of ordinary skill to purify the rEPO from the mammalian host cell material. The purification (or isolation) of EPO from host cell material is a critical step to making an EPO that is useful. The purpose of EPO is to be used as a pharmaceutical composition. In order to make a pharmaceutically acceptable EPO, it must be purified, because it would be unacceptable to provide the patient with host cell material (such as other proteins made by the host cell).

123. The patents-in-suit have a single sentence that describes the purification process for the recombinant protein expressed in mammalian cells:

> Mammalian cell expression products may be readily recovered in substantially purified form from culture media using HPLC (C4) employing an ethanol gradient, preferably at pH7.

('422 patent, col. 28, lines 44-47.) If the levels of ordinary skill in the field were low – low enough that the differences between the claims-in-suit and the '016 claims or the '008 claims would not have been obvious – this one-sentence description of the purification process would not have provided enough detail to enable such a person to purify EPO from mammalian cells. At least the level of detail provided by the '016 patent for purifying the EPO from mammalian cells would be necessary to enable someone having the lower level of skill to purify the rEPO and thus provide a useful composition. Therefore, the patents-in-suit are not enabling for someone having this lower level of skill.

XII. OTHER TESTIMONY

124. If called upon, I may further testify as to facts, opinions and other matters relevant to this action. In this regard, I reserve the right to supplement my report as necessary to address any such additional matters.

125. I declare that the foregoing is true and correct to the best of my knowledge and belief.

Signed under the pains and penalties of perjury this 6th day of April, 2007

Edward Everett Harlow, Jr.

CERTIFICATE OF SERVICE

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

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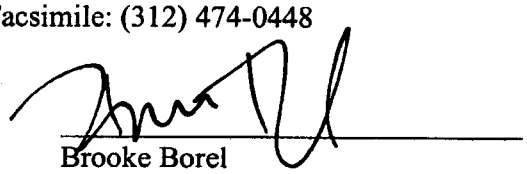

Brooke Borel
April 6, 2007