EXHIBIT 1

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

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

EXPERT REPORT OF HARVEY F. LODISH, Ph.D. REGARDING INFRINGEMENT

Contains Roche Restricted Access Confidential
BLA/IND Information Subject to Protective Order

specified the order of the amino acids in the protein. EPO is normally made with an N-terminal extension called a "signal peptide" or "leader sequence" as well as a C-terminal extension of one arginine residue, each of which is later removed to generate "mature" EPO having the 165-amino-acid sequence set forth in Figure 6 of Amgen's Patents. *See* Exhibit N (steps 4 and 5).

71. When the genetic construct was inserted into and expressed in CHO cells, Dr. Lin showed for the first time that these cells could appropriately glycosylate (add sugars to) the expressed EPO polypeptide, form the correct disulfide bonds, and secrete EPO that is functional in that it can stimulate the formation of red blood cells when administered to an animal.

72. Example 10 also taught how to increase EPO production levels by growing cells with amplified EPO DNA in culture. The cells secreted EPO protein that was correctly folded and glycosylated. The teaching of Example 10 and the rest of Amgen's Patents enabled others to purify and formulate the EPO protein into a pharmaceutical composition. *See* Exhibit N ("Process for EPO Production")

IV. ROCHE'S PEG-EPO AND MANUFACTURING PROCESS

73. Roche has referred to its peg-EPO product by a variety of names, including peg-EPO, CERA ("Continuous Erythropoietin Receptor Activator"), pegserepoetin alfa, RO0503821, Ro 50-3821, methoxy polyethylene glycol-epoetin beta, and MIRCERA™ For purposes of my report, I will refer to Roche's drug substance, the pegylated erythropoietin conjugate known by the Roche code name, RO0503821, as "peg-EPO." I will refer to the formulated pharmaceutical composition containing peg-EPO as MIRCERA™.

A. PRIOR EFFORTS BY ROCHE AND ITS PREDECESSORS TO MAKE, USE, AND SELL EPO IN THE UNITED STATES

74. Roche is currently seeking approval from the United States Food and Drug Administration ("FDA") to sell peg-EPO in the United States. Given Roche's relationship with

other companies who previously made or sold EPO, a short overview of those prior activities is warranted.

75. During the early 1980s, a U.S. company based in Massachusetts, Genetics Institute ("GI"), was in a race with Amgen to clone the human EPO gene, develop materials and techniques for producing therapeutically effective amounts of EPO, and obtain regulatory approval to sell EPO. GI's partner in Europe to develop and sell EPO was a German company called Boehringer Mannheim. GI's partner in Japan was a Japanese company called Chugai Pharmaceutical.[14] After a series of judicial proceedings in the courts and before the U.S. Patent and Trademark Office, it is my understanding that Amgen eventually was held to have won the race.[15]

76. It is my understanding that Genetics Institute stopped producing recombinant human EPO in the United States as a result of being found to have infringed Amgen's U.S. Patent No. 4,703,008. It is also my understanding that Genetics Institute did not attempt to sell any recombinant human EPO product in the United States after losing the lawsuit.

77. In 1985, GI created an EPO-producing cell line derived from Chinese Hamster Ovary cells called DN2-3α3. (Exh. 30 at ITC-R-BLA-00004723-24; Exh. 28 at ITC-R-BLA00005515). In 1988, as part of license agreement between GI and Boehringer Mannheim, GI transferred the DN2-3α3 cell line to Boehringer Mannheim's facility in Penzberg, Germany. (Exh. 28 at ITC-R-BLA00005515).[16]

---

[14] *See* Exh. 27 at AM-ITC-00166357 (AM-ITC-00166343-727); Exh. 26 at AM-ITC-00186908-7165 (AM-ITC-00186908-7243).

[15] *See Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1204 (Fed. Cir. 1991).

[16] GI also transferred the DN2-3α cell line to Chugai Pharmaceutical in Japan. (Exh. 26 at AM-ITC_00186934, 00186995, 00187011-12).

78. Boehringer Mannheim then used the DN2-3α3 cell line to make EPO in Germany for sale in Europe. Boehringer Mannheim referred to its EPO as Epoetin beta and sold it under the trade names Recormon and NeoRecormon.[17] (Exh. 28 at ITC-R-BLA-00005515). In 1997, Roche acquired Boehringer Mannheim. (*See* http://www.roche.com/media-news-1997-05-26-e.pdf).[18] As a result, Roche acquired the rights to use GI's DN2-3α3 cell line to make EPO. As discussed below, Roche uses the DN2-3α3 cell line – originally developed by GI and subject of the prior litigation between Amgen and GI – to make the Epoetin beta in its peg-EPO product. I have been informed that Roche sells NeoRecormon in Europe, but does not sell the product in the United States. In addition, I have been informed that Roche currently owns a controlling interest in Chugai Pharmaceuticals – GI's co-defendant in the Amgen lawsuit. A graphic depicting the relationship between GI, Boehringer Mannheim, Chugai, and Roche concerning the DN2-3α3 cell line is attached as Exhibit O.

79. While Roche apparently considered but decided not to attempt to sell NeoRecormon in the United States, Roche (and its predecessor Boehringer Mannheim) developed a different method for making EPO in human cells using a technique called endogenous gene activation. (Exh. 36 at R000081242-265; Exh. 31 at R001517291-305; Exh. 32 at R001518321-335; Exh. 37 at R001517352-363; Exh. 34 at R001517232-236; Exh. 33 at R001516798-803; Exh. 35 (U.S. Patent No. 6,544,748)). Roche/Boehringer Mannheim told the U.S. F.D.A. that it was "currently developing EPO-EGA as a backup manufacturing process

---

[17] Recormon refers to Epoetin beta manufactured from the DN2-3α3 cell line using a serum-containing fermentation process, while NeoRecormon refers to Epoetin beta manufactured from the DN2-3α cell line using a serum-free fermentation process. (Exh. 28 at ITC-R-BLA-00005515).

[18] In 2002, Roche acquired ownership of the majority of shares in Chugai. *See* Exh. 29 (http://www.roche.com/media-news-2002-10-01-e.pdf).

since there may be less patent risk with that process compared to EPO-serumfree (EPO-SF)." (Exh. 33 at R001516799). The approach taken by Roche was very similar to the method used by Transkaryotic Therapies, Inc. to produce EPO in human cells that I am familiar with based upon my expert testimony in the *Amgen v. HMR/TKT* litigation. In a report dated August 17, 2001, however, Roche concluded that it would develop a peg-EPO product based upon EPO produced from CHO cells in serum-free conditions (*i.e.*, Epoetin beta) and not EPO produced in human cells using endogenous gene activation. (Exh. 38 at R001556170, R001556176-178 (R001556169-6191)).

B. ROCHE'S EPO MANUFACTURING PROCESS

80. Roche's peg-EPO comprises human EPO attached to a PEG molecule. Specifically, it is the reaction product of (a) human EPO and (b) methoxy-polyethylene glycol-succinimidyl butyric acid. The human EPO starting material used to make Roche's peg-EPO is Epoetin beta – the recombinant human EPO that is the active ingredient in Roche's Recormon and NeoRecormon products – and is produced from the DN2-3α3 cell line originally created by GI. The PEG that Roche attaches to the epoetin beta is a linear methoxy-polyethylene glycol molecule with an average molecular weight of around 30 kDa (30 kDa PEG-SBA).

81. Roche's manufacturing process for producing the recombinant EPO in peg-EPO closely tracks the teachings in Example 10 of Amgen's Patents. A series of graphics depicting GI/Roche's process for making EPO-producing cells and EPO are attached as Exhibit P.

82. Roche uses the same mammalian host cells (Chinese Hamster Ovary ("CHO") cells) described and claimed in Amgen's Patents to make the EPO in peg-EPO. (Exh. 39 at ITC-R-BLA-00004667 (ITC-R-BLA-00004662-4709)). The CHO host cells (CHO DHFR deficient DUKX-B11) were transformed with a plasmid vector (DN2-3) containing, among other things,

- DNA (specifically cDNA) encoding human EPO;

primary transcript encoding EPO is initiated from the adenovirus type 2 major late promoter. (Exh. 30 at ITC-R-BLA-00004854-855). The fact that a very small amount of RNA transcript could theoretically be initiated from the SV40 early promoter is inconsequential. (*Id.* at ITC-R-BLA-00004804 (stating that SV40 early promoter was "much less active in CHO cells than in AdVMLP"); Exh. 24 at 47-51).

148. The DN2-3α3 cells are also capable of secreting EPO into the culture medium at a rate exceeding 100 U, 500 U, and 1000 U of EPO per 10^6 cells per 48 hours as determined by radioimmunoassay (RIA).

149. While Roche itself has not produced data directly measuring EPO production of the DN2-3α3 cells using RIA, other data reported by Roche and its affiliate Chugai, indicate that such levels would be satisfied by Roche's DN2-3α3 cells.

150. First, Roche's BLA reports that the DN2-3α3 cells are capable of producing at least 3.7 μg EPO/10^6 cells/day, which corresponds to 7.4 μg EPO/10^6 cells/48 hours. (Exh. 30 at ITC-R-BLA-00005073).[36] Roche's BLA also reports that the mean value of biological activity for the EPO produced by the DN2-3α3 cells was 207,700 IU/mg as measured with the normocythaemic mouse bioassay, which corresponds to 207.7 IU/ μg (Exh. 15 at ITC-R-BLA-00005581).[37] Thus, the DN2-3α3 cells are capable of producing at least 1536 IU/10^6 cells/48 hours, satisfying the claim limitation.

151. Second, while the above calculations were not measured using radioimmunoassay, Chugai, now owned by Roche and formerly a partner with GI to develop and sell EPO, previously submitted an Investigational New Drug Application with the FDA,

---

[36] EPO production amounts over time are also reported for manufacturing batches of EPO in Exh. 69 at ITC-R-BLA-00002375-378, which also support my opinion.

[37] "IU" refers to International Units. There are 1000 μg (micrograms) in every mg (milligram).

measuring the EPO produced by the DN2-3α3 cells using RIA.[38] Based upon its comparison of the results of in vivo mouse assays of EPO produced by DN2-3α3 cells with the International recombinant EPO reference standard, Chugai arrived at a conversion constant of 180,000 IU/mg or 180 IU/ μg that it used as a conversion constant to convert the weight of EPO as measured by RIA into a biological activity measurement expressed in International Units. (Exh. 26 at AM-ITC-00187104, Exh. 27 at A140563). Even if Chugai's conversion constant of 180 IU/ μg were applied to the EPO production levels that Roche reported for its DN2-3α3 cells, the values would be substantially higher than the levels required by the claims (7.4 x 180 = 1332 IU/10^6 cells/48 hours).

152. Third, Roche has produced manufacturing batch records showing EPO production levels from the DN2-3α3 cells as measured by enzyme-linked immunosorbent assay (ELISA) suggesting high levels of EPO production, and I would expect the values as measured by RIA to be similar. (Exh. 69 at ITC-R-BLA-00002369-2378).

153. Both ELISA and RIA assays are standard antibody-based tests for determining the concentration of a particular protein (the analyte, in this case EPO) in a sample. An RIA utilizes an antibody that binds to the analyte. Amgen's Patents describe a particular example of an RIA test to measure EPO in samples of cell culture medium (Exh. 104 at Col. 16:51-17:19). Like RIA, ELISA uses antibodies that bind to EPO to determine the concentration of EPO in a sample. If the same antibody were used in each test, I would expect the concentration of EPO determined by each test to be the same. This is because both assays determine the concentration of EPO in a sample by comparing the binding of the antibody to the EPO in that sample against a "standard curve" generated by binding the same antibody to known amounts of EPO. If different

---

[38] *Amgen v. Chugai* Trial Exhibits PX 809 (Exh. 26) (Chugai IND at A140432, A140345,

claims 9 and 12. In addition, the correction and treatment of anemia with MIRCERA™ would require MIRCERA™ to be able to raise the hematocrit level of patients, including patients on dialysis. Clinical trials cited in Roche's BLA demonstrate that MIRCERA™ is capable of increasing the hematocrit of kidney dialysis patients. (Exh. 46 at ITC-R-BLA-00000318-27).

166. While Roche employees may or may not directly perform this method, given that Roche is seeking regulatory approval to market MIRCERA™ for "treatment of anemia associated with chronic kidney disease including patients on dialysis," (*Id.* at ITC-R-BLA-00000217), I expect that Roche has either already encouraged or intends to encourage physicians to administer MIRCERA™ in a manner that would satisfy the limitations of '933 claims 11 and 14. For example, the proposed label for MIRCERA™ in Roche's BLA, states that "MIRCERA™ is indicated for the treatment of anemia associated with chronic kidney disease including patients on dialysis...." (*Id.* at ITC-R-BLA-00000217).

167. A detailed chart identifying evidentiary support for each of the limitations of the Asserted Method-of-Treatment Claims is attached as Exhibit W.

D. ROCHE'S PEG-EPO IS NOT MATERIALLY CHANGED FROM THE EPO PRODUCT OF THE ASSERTED PROCESS CLAIMS

168. I have been asked to assume that importation into the United States of a product which is made by a process patented in the United States is an act of infringement unless the product (a) is "materially changed by subsequent processes" or (b) "becomes a trivial and nonessential component of another product."

169. In order to determine whether the human EPO produced by Roche is "materially changed by subsequent processes" before importation into the United States, I have been asked to opine (a) whether the human EPO glycoprotein in Roche's peg-EPO product is significantly changed in structure and properties from Roche's human EPO glycoprotein starting material, (b)

175. It is also my opinion that human EPO glycoprotein and peg-EPO share the same basic utility. Both can produce an increase in red blood cells in humans and do so by binding to the EPO receptor in a manner that can stimulate production of reticulocytes and red blood cells. Both appear to have therapeutic utility for treating anemia. Notably, the Roche patent which claims to cover its peg-EPO product states,[42] "It has been found that the conjugates of this invention [*i.e.*, peg-EPO] can be used in the same manner as unmodified EPO." (Exh. 56 (U.S. Patent No. 6,583,272 at Col. 3:7-8)). Roche's patent also states, "The conjugates of this invention can be administered in a therapeutically effective amount to patients in the same way EPO is administered." (*Id.* at Col. 3:22-24). The fact that it may be possible to dose patients with peg-EPO less frequently than with recombinant human EPO may or may not be a convenience, but it does not change the basic utility of the product.

176. Roche's own documents confirm that Roche did not believe it was commercially viable to make EPO without practicing Amgen's patented processes. For example, Roche rejected alternative methods of producing EPO that Roche apparently believed at the time would not infringe Amgen's Patents, including chemical synthesis and endogenous gene activation because, among other reasons, these alternative methods were not commercially viable given the higher manufacturing costs as well as health and safety issues.[43] (Exh. 36 at R000081242-265; Exh. 63 at R001572657-680; Exh. 37 at R001517352-363).

177. For example, Roche, in conjunction with a company called Gryphon Therapuetics, developed a synthetic erythropoiesis product ("SEP") by chemically synthesizing peptides and linking them together. (Exh. 10 at 236-238); Exh. 63 at R001572657-680). The

---

[42] Exh. 25 at 25, 62 (Bailon Tr.).

[43] I note that given the result in *Amgen v. HMR/TKT*, Roche's "endogenous gene activation" method of making EPO in cultured human cells would likely have infringed Amgen's Patents.

molecule was an analog of human EPO in that the amino acid sequence was different from human EPO.[44] It was pegylated, but did not have attached carbohydrate structures. Roche believed that SEP would not infringe any of Amgen's EPO-related patents. (*Id.* at R001572667). However, during human clinical trial, patients developed antigenic responses that caused Roche to stop administering SEP to humans. (Exh. 76 at R000448078-104; Exh. 72 at R10-002323027-028; Exh. 73 at R000466990-991; Exh. 74 at R10-000176786-799). Roche developed peg-EPO to avoid amino acid substitutions that could give rise to immunogenic responses. (Exh. 62 at R10-000074715).

178. Given the value of the market for EPO in the United States and the fact that no competitor of Amgen, including Roche, has successfully developed an alternative method of producing human EPO glycoprotein in the United States that does not infringe Amgen's Patents provides further support that commercially viable, non-infringing alternative methods of manufacturing human EPO glycoprotein may not currently exist. (Exh. 75 at R001172303-354).

179. I do not view the fact that Roche was issued a patent covering its peg-EPO molecule as evidence that peg-EPO is materially changed from human EPO. It is my understanding that a patent grants a right to exclude others from practicing the patentee's invention, not grant a right to practice one's own invention. Thus, a patentee's manufacture, use, or sale of his invention might nevertheless infringe another's patent. For example, the inventor of an improved pencil with a new type of eraser might be awarded a patent for his improvement, but he still might need permission if a prior inventor received a patent on the pencil. The fact that Roche has a patent on a particular form of peg-EPO, which it claims is an "improvement" over EPO in some respect, does not grant Roche the right to make, use, or sell Amgen's patented

[44] The SEP product had an additional amino acid at position +166 as well as amino acid

products – activating EPO receptors to initiate the JAK2/STAT5 signaling pathway. Neither peg-EPO's increased half-life in the bloodstream nor its reduced binding affinity represent a significant difference or fundamental change in principle with respect to how peg-EPO functions. MIRCERA™ is also a pharmaceutical composition that is not changed in principle from, performs the same function as, and achieves the same result in substantially the same way as the pharmaceutical compositions claimed in the Amgen Patents, because it contains the glycosylated human EPO polypeptide that functions in the same way to achieve the same result as the human EPO claimed in the Amgen Patents.

Executed this 6th day of April, 2007 at Boston, Massachusetts.

HARVEY F. LODISH, PH.D.