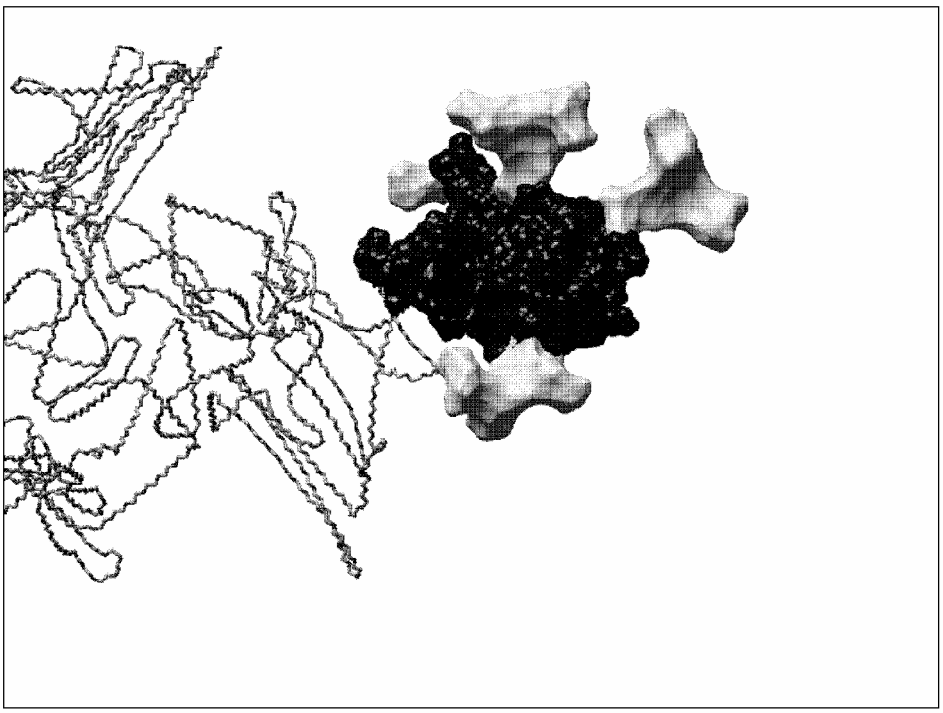
EXHIBIT A

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



100. In Roche's internal correspondence that I have reviewed, Roche scientists recognized that the EPO in peg-EPO is unchanged. In a 2004 email from Dr. Haselbeck, formerly the Preclinical Team Leader for Roche's peg-EPO project (Exh. 55 at R004052565), Dr. Haselbeck responded to a colleague's concern that an animated slide depicted both EPO and peg-EPO as having a "perfect fit" when binding to the EPO receptor:

> "I think the fit needs to be the same to emphasize that the binding region is still the same . . . . **I guess the only drawback in using this slide might be that one recognizes that EPO is one part of CERA**."

101. Similarly, the patent awarded to Roche relating to peg-EPO describes and claims Roche's conjugate of EPO and 30kDa methoxy-PEG-SBA (*i.e.*, Roche 503821), as comprising a conjugate of a PEG molecule and "the residue of a glycoprotein" that "is human erythropoietin" without "the free amino group which forms the amide linkage" and has the amino acid sequence

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supplement my report based upon my review of any additional documents and electronic files produced by Roche.

of human erythropoietin. (*See* Exh. 56 at Cols. 3-4, 6, 10-12, 17, and 19 (U.S. Patent No. 6,583,272)).

102. I have reviewed graphics and animations depicting computer-modeled representations of peg-EPO, which are attached as Exhibit S, that have been prepared in consultation with me. Based upon my review, I believe these graphics are fair and accurate attempts to represent the three-dimensional structure of peg-EPO based upon available scientific knowledge and are generally consistent with images from models previously generated by Roche.[25]

103. In these graphics, PEG is depicted as an inert and very flexible molecule that, in contrast to the glycosylated EPO polypeptide to which it is attached, has no fixed three-dimensional structure. In aqueous solutions such as blood or other body fluids, the linear PEG chain is constantly flexing and changing its three-dimensional structure.

104. I would expect the glycosylated EPO polypeptide in peg-EPO to maintain substantially the same shape and conformation as it has before pegylation, because of the intrinsic properties of the peg molecule and because the peg molecule is attached at only a single point to the EPO molecule. Roche's attachment of a peg molecule to EPO modifies only a single chemical bond – 1 out of more than 4000 – in the glycosylated human EPO polypeptide. Roche's experimental data demonstrating that peg-EPO maintains the specificity of the

[25] Because the BLA indicates that the N-terminus of EPO is the predominant site for pegylation in Roche's peg-EPO, the attached graphics and animations for peg-EPO show the PEG moiety attached to EPO at the N-terminus of the protein by an amide bond. (Exhs. 41-42 at ITC-R-BLA-00004030-4032). The PEG moiety is colored gray. The attached PEG moiety has not, and indeed cannot, be captured using techniques like x-ray crystallography. Moreover, a long, linear polymer like the attached PEG moiety in Roche's peg-EPO is a highly flexible molecule with no fixed structure that would be in constant motion. Thus, virtually any model consistent with known chemical constraints (bond lengths, angles, dihedrals, and atomic radii) is physically plausible. The attached graphics and animations, therefore, are an attempt to represent the PEG

glycosylated EPO polypeptide for binding with the EPO receptor to initiate erythropoiesis confirms that the glycosylated EPO polypeptide in peg-EPO maintains substantially the same shape and conformation as non-pegylated Epo. A series of computer-modeled animations depicting peg-EPO binding to the EPO receptor are attached as Exhibit T.[26]

105. In its BLA, Roche states that it was unsuccessful in isolating single positional pegylation isomers from each other. (Exh. 57 at ITC-R-BLA-00004319). Nevertheless, Roche states "experiments on the positional isomer distribution indicate that there are no significant differences in specific activity between the most prominent positional isomers," and that the "results reveal no evidence for a non active positional isomer." (*Id*. at ITC-R-BLA-00004330). Given the inability to isolate the positional isomers, I do not believe one can necessarily draw the conclusion that there are no non-active positional isomers. Isoforms with pegylation sites that are at or near Sites 1 or Sites 2 – the segments of the EPO polypeptide that bind to the EPO-R – may be unable or poorly able to bind to EPO receptors, since the presence of a PEG group could potentially interfere with the precise interactions of EPO with its receptor that are essential for binding. However, the primary pegylation sites for Roche's peg-EPO (the N-terminal Ala and Lys 52) are relatively distant from the known EPO/EPO receptor binding sites. (Exh. 4 (Syed et al., *Nature* (1998)). Positional isomers with pegylation near the EPO/EPO receptor binding sites are not found with any significant frequency (*e.g.*, Lys 97 or Lys 140).

106. Based upon the data reported in Roche's BLA, the addition of PEG to EPO does not prevent binding to the EPO receptor, nor does it prevent induction of the signaling pathways that ultimately leads to the stimulation of red blood cell production. In fact, according to Roche,

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moiety given the limits of our knowledge in order to illustrate or explain certain concepts.

[26] At trial, I may prepare and use a physical model based upon the graphics attached to my report that could be used to illustrate EPO, peg-EPO, and binding to the EPO receptor.

"The pharmacological action of Ro 50-3821 is identical to that of erythropoietin beta in binding to surface receptors of erythroid progenitor cells to trigger proliferation, maturation, and terminal differentiation of colony-forming units." (Exh. 58 at ITC-R-IND-00062646). As Dr. Haselbeck, Roche's Rule 30(b)(6) designee acknowledged, peg-EPO, like EPO, stimulates erythropoiesis, binds to the EPO receptors on the surface of erythroid progenitor cells, and has the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells. (Exh. 10 at 32-33).

107. Based upon my review of Roche's BLA, peg-EPO binds to the EPO receptors on erythroid progenitor cells, albeit with reduced affinity. (Exh. 60 at ITC-R-BLA-00006257-58). The binding of peg-EPO stimulates the same JAK2/STAT5 signaling pathway as does non-pegylated EPO. Experiments conducted at Roche's request revealed no significant differences in the signaling pathways activated by peg-EPO and EPO. (Exh. 10 at 129; Exh. 59 at R005310869-875).

108. Like non-pegylated human EPO glycoprotein, peg-EPO stimulates cultured cells expressing the EPO receptor to grow, and stimulates CD30 cells to differentiate. Roche's BLA also states that peg-EPO demonstrated a comparable therapeutic effect to non-pegylated EPO in correcting the anemia of chronic kidney disease patients. (Exh. 46 at ITC-R-BLA-00000326).

109. The ability to specifically bind with the EPO receptor, to stimulate the JAK2/STAT 5 and other signaling pathways, and to ultimately stimulate the production of red blood cell production in a manner that is therapeutically effective is solely attributable to the glycosylated human EPO polypeptide in peg-EPO. The amino acid sequence, glycosylation, and conformation of the glycosylated human EPO polypeptide in peg-EPO are necessary to achieve these biological and therapeutic effects. While the presence of the PEG molecule may increase

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.