

**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

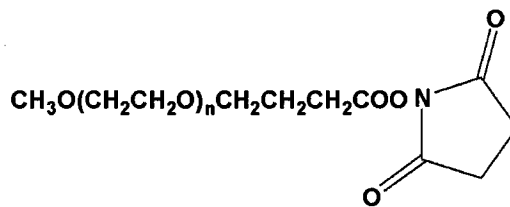
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pharmaceutical version of this recombinant human EPO glycoprotein outside the United States under the name NeoRecormon.

C. ROCHE'S PEG-EPO PRODUCT AND MANUFACTURING PROCESS

92. To make peg-EPO, Roche takes purified recombinant glycosylated human EPO polypeptide product (epoetin beta) from its already existing manufacturing process for NeoRecormon in Germany, subjects it to a pegylation reaction, purifies the peg-EPO, formulates it into a pharmaceutical composition by adding a diluent and carrier, and fills it into vials or syringes.

93. The PEG reagent used to make peg-EPO – methoxy-30 kDa PEG-SBA (“PEG-SBA”) – is a reagent commercially produced and supplied by a U.S.-based company, Nektar Therapeutics. (Exh. 41 at ITC-R-BLA-00004061 (ITC-R-BLA-00004031-4231)). According to Pascal Bailon, the named inventor of Roche's peg-EPO, this reagent was ordered from the catalog of Shearwater Polymer (now known as Nektar Therapeutics). (Exh. 25 at 53-54). PEG-SBA has the following chemical structure:



Wherein, $n = \sim 681$.

94. During the pegylation step, Roche attaches a PEG-SBA to the recombinant human EPO glycoprotein based on the reaction of the succinimidyl ester group of PEG-SBA with a free amino group of EPO forming a single amide bond connecting the two molecules. The resulting peg-EPO molecules have the following chemical structure:



Asserted Product Claims because the peg-EPO and MIRCERA™ contain EPO with the recited characteristics.

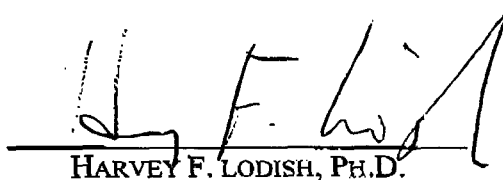
123. peg-EPO contains a non-naturally occurring glycoprotein product – a glycosylated recombinant human EPO polypeptide. As Dr. Haselbeck aptly described it, “EPO is one part of CERA.” (Exh. 55 at R004052565). Roche documents have characterized pegylated EPO molecules as “erythropoietin glycoprotein product.” (Exh. 64 at R000432918).

124. Roche’s EPO glycoprotein (Epoetin beta) is the product of the expression of an exogenous DNA sequence encoding human erythropoietin in a non-human mammalian cell – the DN2-3 α 3 CHO cell. The DN2-3 α 3 cells are grown in culture, and the human EPO is purified. The purified EPO has the amino acid sequence of human EPO isolated from human urine. The EPO produced – both before and after pegylation – has the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells. A therapeutically effective amount of peg-EPO is then formulated into the MIRCERA™ pharmaceutical composition with a pharmaceutically acceptable diluent – an aqueous solution containing sodium phosphate, sodium sulfate, mannitol, methionine, and poloxamer 188.

125. As Dr. Haselbeck, Roche’s 30(b)(6) designee on the manufacturing and characterization of peg-EPO, admitted, (a) Epoetin beta is “a recombinantly produced erythropoietin,” (b) Epoetin beta is a “glycosylated erythropoietin;” (c) Epoetin beta is “produced by Chinese hamster ovary cells that are grown in culture;” (d) CHO cells are “mammalian cells;” (e) Epoetin beta is the starting material used to make peg-EPO; (f) Roche 50-3821 (peg-EPO) is “a pegylated version of epoetin whereby one linear polyethylene glycol chain has been added to the recombinant erythropoietin molecule;” (g) Roche 50-3821 (peg-EPO) has “the biological property of causing bone marrow cells to increase production of

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.