

EXHIBIT 4

**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*

62. The process of covalently linking an inert PEG polymer to a protein is called “pegylation.” Using well-understood techniques, PEG is covalently bonded¹³ at one or more locations to the protein. A number of recombinantly produced human proteins have been pegylated, including EPO, G-CSF, interferon- α 2b, interferon- γ , and IL-2. As early as 1977, publications described pegylated proteins as exhibiting extended half-life in the blood without triggering an immunogenic response (*i.e.*, formation of antibodies.). (See Exh. 21 (Abuchowski et al., “Effect of Covalent Attachment of Polyethylene Glycol on Immunogenicity and Circulating Life of Bovine Liver Catalase,” *J. Biol. Chem.*, (1977) 252:3582-3586). The longer *in vivo* half-life of pegylated proteins is believed to be the result of reduced clearance through non-specific routes of clearance such as the kidney or liver because of the larger size of the PEG-conjugate as well potential protection from enzymatic degradation.

63.

Redacted

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¹³ A “covalent bond” is a bond in which two atoms share a pair of electrons.

182.

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183.

184. Pegylation is a conventional technique for increasing the half-life of a therapeutic

protein. Like a chemical protective group, the peg molecule in peg-EPO helps protect the glycosylated EPO polypeptide against unwanted chemical reactions such as enzymatic degradation in the bloodstream or clearance by non-specific routes such as the liver or kidney. This is not a circumstance where pegylation has converted a therapeutically useless molecule into one having therapeutic utility. Rather, the PEG is utilized here to extend the half-life of a therapeutically effective molecule in hopes of offering longer intervals between doses.

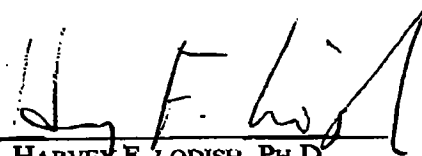
185.

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186.

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



HARVEY F. LODISH, Ph.D.