EXHIBIT 3

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.: 1:05-cv-12237 WGY

FIRST EXPERT REPORT OF NANDINI KATRE, Ph.D.

CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

CONTAINS CONFIDENTIAL DISCOVERY MATERIAL

I, Nandini Katre, declare as follows:

I am a citizen of the United States residing at 343 Santa Helena, Solana Beach, California, 92075. I have knowledge of the following, and if called as a witness, could and would testify competently to this expert report's contents.

I. QUALIFICATIONS

1. A summary of my experience and qualifications is set forth in my Curriculum Vitae attached hereto as Exhibit 1. I anticipate that I may testify at trial further about the items listed on my Curriculum Vitae.

2. I am currently working as an independent consultant. In this capacity, I have worked with a number of different biotechnology and pharmaceutical companies in the areas of pegylation, drug delivery, and drug formulation technologies. I graduated from the University of Bombay, India in 1970 with a B.S. in Chemistry. Two years later, in 1972, I received my Masters Degree in Chemistry from the Indian Institute of Technology. I received my Ph.D. in Biochemistry in 1978 from the University of Pennsylvania. From 1979 to 1982, I received a post-doctoral fellowship from the University of California, San Francisco and in 1982 was hired as an Assistant Research Biochemist, a position I held until 1984.

3. From 1984 to 1990, I was a scientist at Cetus Corporation in Emeryville, California, where I was the project leader of polyethylene glycol (PEG)-protein development. My research focused on the conjugation of recombinant protein drugs with PEG to provide increased systemic exposure, increased potency, solubility and stability, and decreased immunogenicity. During that time, I participated in and/or supervised the synthesis of PEG conjugates of Interleukin-2 (IL-2), Interferon-ß (IFN-ß), Immunotoxins, Ricin toxin, Tumor Necrosis Factor (TNF), and Colony Stimulating Factor-1 (CSF-1) and supervised tissue distribution and pharmacokinetic studies of PEG-IL-2 and PEG-IFN- ß.

4. From 1990 to 1993, I was an independent consultant. In that capacity, I designed methods for the conjugation, purification and characterization of PEG-conjugated drugs for Amgen Corporation, Athena Neurosciences, Genentech Corporation, Miles Pharmaceuticals Inc.

and Synergen Inc. From 1994 to 2003, I directed the research and development of protein drug formulation and delivery at SkyePharma, Inc. in San Diego, California and in 1998 was promoted to the Director of Protein Development. Since 2003, I have been working as an independent scientific consultant for biotechnology and pharmaceutical companies.

5. I have over twenty years of experience in the research and development of proteins, including PEG-protein development. I have made PEG conjugates of a number of recombinant proteins, such as IL-2 and IFN- ß, as early as 1985. I was one of the first to attach water-soluble polymers to recombinant proteins to enhance their solubility and therapeutic potential, and demonstrate the relationship of *in vivo* clearance to the size of the conjugated protein. Further, I was one of the first to modify a recombinant protein by site-directed pegylation. I have published twenty-six peer-reviewed scientific papers, more than thirty conference abstracts, and was an invited speaker at twenty-two scientific conferences. I am a named inventor on thirteen patents.

6. In the past, I have not consulted with F. Hoffmann-La Roche Ltd, Roche Diagnostics GMBH, or Hoffmann La Roche Inc., (collectively "Roche") and I do not currently consult with F. Hoffmann-La Roche Ltd, or Roche Diagnostics GMBH, or Hoffmann La Roche Inc.

7. In the past four (4) years I have not testified at trial as an expert.

8. I was retained on June 23, 2004, to act as an expert for this lawsuit. I am being compensated for my work on this case at an hourly rate of $700 per hour, which is my usual rate for consulting work. My fee is not contingent on the outcome of this case.

II. INFORMATION REVIEWED

9. In addition to my general knowledge in the field based on over twenty years of experience, the materials I specifically reviewed in connection with the drafting of my First Expert Report are:

- Katre, *The conjugation of proteins with polyethylene glycol and other polymers*, 10 ADVANCED DRUG DELIVERY REVIEWS 91-114 (1993).

16. Many of the first proteins produced by recombinant DNA technology were interleukins, cytokines, and growth factors. A number of these proteins were pegylated between the mid 1980's and '90's, such as, Interleukin-2, Interferon-β, TNF, CSF-1, G-CSF, GM-CSF, hGH, Interferon-α, and EPO. (Exs. 2-4, Katre 1993; Delgado et al., 9 CRIT. REV. THERAPEUT. DRUG CARRIER SYS. 249 – 304 (1992); Bailon et al., 1 PHARMACEUT. SCI. TECHNOL. TODAY 352-356 (1998).) While at Cetus, my group pegylated Interleukin-2, Interferon-β, TNF, and CSF-1 using several different linking chemistries. In the context of pegylation, linking chemistry refers to the chemistry used to attach PEG to the protein.

17. Many of the interleukins, cytokines and growth factors share structural motifs, such as, for example, a four helical bundle, and all are globular proteins that are soluble in the blood. Globular proteins are proteins that fold into a compact morphology typically having a hydrophobic core and hydrophilic surfaces. Thus, these proteins share structural similarities. When these proteins are expressed and purified from recombinant technology, they will adopt a similar structure to the native protein.

18. As a general rule, when the PEG is conjugated to the protein, these peg-proteins have greater *in vivo* half-lives than the unconjugated protein, and a greater therapeutic index than the unconjugated protein because of the increased systemic exposure. A greater therapeutic index means that for an equitoxic dose there is greater efficacy with the pegylated protein.

B. CHEMISTRY FOR ATTACHING PEG TO PROTEINS

19. Many different reactive groups have been used to conjugate PEG to proteins, such as carbonyl diimidazole, N-hydroxy succinimidyl esters, succinimidyl carbonate, hydroxyl nitrobenzene sulfonic acid, dithiocarbonate, chloroformate, and imidoesters. (Ex. 2, Katre 1993.) These reactive groups predominantly target the primary amino groups of the lysine amino acids in the polypeptide chain as well as the primary amino group at the protein's N-terminus.

20. Lysine is a good target for conjugation because most proteins, especially water-soluble proteins, have lysines on their surfaces. Lysines are usually accessible to conjugation because they are hydrophilic groups and found on the surface of the protein. The primary amino

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IV. INFRINGEMENT

22. I understand that Amgen is asserting the following claims against Roche: Claims 3, 7-9, 11-12, and 14 of United States Patent No. 5,547,933 ("the '933 Patent"), Claims 3-4 and 6 of United States Patent No. 5,621,080 ("the '080 Patent"), Claim 1 of United States Patent No. 5,955,422 ("the '422 Patent"), Claims 1 and 2 of the United States Patent No. 5,441,868 ("the '868 Patent"), Claims 4-9 of United States Patent No. 5,618,698 (the '698 Patent"), and Claim 7 of United States Patent No. 5,756,349 ("the '349 Patent"). (Exs. 5-10.)

23. I understand that the following are representative method claims from the asserted patents.

Claim 1 of the '868 Patent:

> 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.

Claim 6 of the '698 Patent:

> 6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property

26. I have been asked to assume that it is an act of infringement to import into the United States a product made by a method that infringes a United States method patent when the imported product has not been materially changed from the product made by the patented method, or become a trivial component of another product.

27. I understand that "materially changed" asks whether epoetin beta has been substantially changed by pegylation to make peg-epoetin beta. I understand that Amgen must prove that it is more likely than not that peg-epoetin beta is not materially changed from epoetin beta.

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29. I understand that Dr. Torchilin is examining other aspects of whether Roche's pegylation of epoetin beta (hereinafter "EPO") materially changed the structure and function of the Epo. I address the issue from the perspective of whether the linking chemistries that Roche used to pegylate EPO were known and routine and whether the use in the past of PEG with such linking chemistries demonstrated that a pegylated erythropoietin would maintain the biological activity of erythropoietin and have an increased half-life *in vivo*.

30. In my opinion, peg-EPO (Mircera, peg-epoetin beta) is not materially changed from Epo. Pegylation is a proven technology for delivering drugs to patients with improved pharmacokinetics, and many different commercial entities prior to Roche have used routine pegylation methods to make peg-erythropoietin that has bioactivity and improved pharmacokinetics.

31. Davis et al., Ortho Pharmaceutical Corporation, Enzon Incorporated, and Polymasc Pharamceuticals, PLC have published patents or patent applications that show how to make pegylated-EPO and all published by 1998. (Exs. 13-17, U.S. Patent No. 4,179,337; EP Patent Application 539,167 A2; WO 94/28024; WO 95/11924; WO 98/32466.)

36. A PCT application published in 1998 and assigned to Polymasc describes how to make peg-EPO using PEG activated with tresyl chloride. (Ex. 17, WO 98/32466.) The PEG was 5000 Da. This peg-EPO had bioactivity in an *in vitro* cell proliferation assay.

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39. This is the expected result based upon the experience with PEGylation of other cytokines, growth factors, and colony stimulating factors. When my group pegylated Interleukin-2, Interferon-β, TNF, and CSF-1 we found that the *in vitro* and *in vivo* bioactivities of these proteins were maintained following PEGylation and the *in vivo* half-life was increased. In

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addition, we used four different linking chemistries with Interleukin-2, three different linking chemistries with Interferon-β, and two different linking chemistries with CSF-1. All these peg-protein conjugates maintained the biological activity of the parent protein, and all had increased *in vivo* half-lives. Similarly, peg-EPO made by Ortho, Enzon, Polymasc and Roche/Shearwater with many different linking chemistries maintained EPO's *in vitro* and *in vivo* biological activities, and when measured, all had increased *in vivo* half-lives.

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I declare under penalty of perjury in accordance with the laws of the United States that the foregoing is true and correct and that this declaration and expert report was executed at Solana Beach, California, on April 6, 2007.

Nandini Katre