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

DECLARATION OF VLADIMIR P. TORCHILIN, Ph.D., D.Sc.

I, Vladimir P. Torchilin, declare as follows: I am a citizen of the United States residing at 12 Shipway Place Charlestown, MA, 02129. 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. I am a Distinguished Professor of Pharmaceutical Sciences, Chairman of the Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, and Director of the Center for Pharmaceutical Biotechnology and Nanomedicine at Northeastern University. In 2006, the Department of Pharmaceutical Sciences at Northeastern University was ranked second in the country among private institutions in terms of the amount of research funding by the United States government. My current Curriculum Vitae, including a list of original publications, is attached to this declaration as Ex. A. I anticipate that I may testify in court further about the items listed on my Curriculum Vitae. Below follows a summary.

2. I obtained a Ph.D. in chemical kinetics and catalysis, from Moscow State University in 1971, and I obtained a D.Sc. in the chemistry of physiologically active compounds from Moscow State University in 1980. After obtaining my Ph.D., I was hired as a Junior Scientist at Moscow State University. As a Junior Scientist, I performed research on polymeric models of natural enzymes. In 1974, I was promoted to Senior Scientist of the Academy of Medical Sciences of the USSR. As a Senior Scientist I led a series of projects on polymeric modification of biologically active substances, including proteins. In 1985, I became a Professor of Biochemistry at the Academy of Medical Sciences.

3. In 1982, I was awarded the Lenin Prize of the USSR in Science and Technology for my work on protein – polymer conjugates, in particular, for a polymer – streptokinase conjugate developed by my laboratory and used in the treatment of heart attacks and eye injuries. In 1991, I became a full Member of the Russian Academy of Biotechnology. I served on the Board of Governors for the Controlled Release Society from 1995-1998. I also served as a Co-Chair for the 26th International Symposium on Controlled Release of Biologically Active Materials in 1999, and the Gordon Research Conference on Drug Carriers in Biology and

Medicine in 2002. As the Co-Chair of these conferences, I arranged and supervised the respective scientific programs.

4. In early 1991, my wife and I left the USSR and came to the United States. I was a visiting Professor at the University of Tennessee and at the University of California, San Diego, until the fall of 1991, when I became the Head of the Chemistry Program at the Center for Imaging and Pharmaceutical Research, Department of Radiology, Massachusetts General Hospital. In 1993, I became an Associate Professor of Radiology at Harvard Medical School. In 1998, I became a Professor of Pharmaceutical Sciences and Chairman of the Department of Pharmaceutical Sciences at Northeastern University, and in 2005 I became the Director of the Center for Pharmaceutical, Biotechnology and Nanomedicine at Northeastern University.

5. I am currently a member of the American Chemical Society, the Controlled Release Society, the American Association of Pharmaceutical Scientists, and the International Liposome Society.

6. I am a review editor for the Journal of Controlled Release, and I serve on the editorial boards of 15 other journals including the Journal of Drug Targeting, Bioconjugate Chemistry, Advanced Drug Delivery Reviews, the European Journal of Pharmaceutics and Biopharmaceutics, the Journal of Bioactive and Compatible Polymers, Molecular Pharmaceutics, Current Drug Delivery, Drug Discovery Today, and Current Protein and Peptide Science. As a review editor, I solicit, handle and review a variety of review papers in the broad area of drug delivery, drug targeting, long acting drugs, polymer-modified drugs, etc. As a member of these editorial boards, I am actively involved in the editorial process for many areas of the Pharmaceutical Sciences.

7. I have reviewed hundreds of articles for publication in these and other journals, and many of these articles have reported on protein-polymer conjugates, drug formulation and delivery of drugs in the body. In reviewing these articles, I must assess the strengths and merits of the described science. As a member of the editorial boards for these Journals, I and the other

editors must also decide whether the submitted articles are proper subject matter for and merit publication in the selected journal.

8. In 2002, I became a fellow of the American Institute for Medical and Biological Engineering, and a member of the European Academy of Sciences. The European Academy of Sciences is a member elected organization that establishes efficient collaboration among scientists, researchers, educators, engineers and public authorities world-wide. The European Academy of Sciences draws upon distinguished scientists to identify social, scientific, and technological trends and ideas that can be applied to solve current problems faced by today's society. I was elected to the European Academy of Sciences for my work in the area of Biomedical Sciences.

9. In 2003, I was Vice President of the Controlled Release Society, and was elected as a fellow to the American Association of Pharmaceutical Scientists. In 2005, I served as the President of the Controlled Release Society, I was a founding member of the American Academy of Nanomedicine, and I received a Research Achievement Award in Pharmaceutics and Drug Delivery from the American Association of Pharmaceutical Scientists for my work in Pharmaceutics and Drug Delivery. In 2007, I received a Research Achievement award from the Pharmaceutical Sciences World Congress for my contributions to the field of Pharmaceutics and Drug Delivery.

10. I have worked in the area of polymer-protein conjugates and drug formulation for over 30 years, and I have published over 300 papers, reviews and book chapters, and 15 books and special journal issues (as author and editor). Many of these publications are in the field of protein conjugation, pegylation, and Drug Formulation.

11. I was recently the Editor for a book published in 2006, entitled "Delivery of Protein and Peptide Drugs in Cancer." (Attached as Ex. B.) This book included chapters on basic strategies for making PEG protein conjugates and formulating proteins so they can be used in cancer treatment and immunotherapy. As the Editor for this book, I selected the topics,

solicited contributions for the various chapters, and reviewed and edited these chapters and the cited references. I also wrote certain chapters of the book myself.

12. In the past, I have not consulted with Amgen, Inc. or F. Hoffmann-La Roche Ltd, Roche Diagnostics GMBH, or Hoffmann La Roche Inc., and I do not currently consult with F. Hoffmann-La Roche Ltd, or Roche Diagnostics GMBH, or Hoffmann La Roche Inc.

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

14. I was retained on July 12, 2004, to act as an expert for this lawsuit. I am being compensated for my work on this case at an hourly rate of $400 per hour, which is my usual rate for consulting work. My fee is not contingent on the outcome of this case.

II. INFORMATION REVIEWED

15. In preparation for and in the drafting of my declaration, I reviewed:

- United States Patent No. 5,547,933 (attached as Ex. C.)
- United States Patent No. 5,955,422 (attached as Ex. D.)
- Poznansky, 21 PHARMAC. THER. 53-76 (1983) (attached as Ex. E.)
- August 16, 1994 office action '933 File History at 453-454 (attached as Ex. F.)

16. I reviewed the documents referred to herein and others listed above. As this case continues, I expect to review additional documents, which may include documents marked as exhibits by the parties for deposition or for the Claim Construction Hearing. I may rely on these additional documents to support my opinions at the Claim Construction Hearing. I reserve the right to supplement my opinions expressed herein in light of any additional materials, including opinions expressed by other witnesses retained by Defendants and/or other evidence that may be provided to me after submission of this Report.

III. TECHNICAL BACKGROUND

17. If I testify at the Claim Construction Hearing, I may present a tutorial on drug formulation and carriers.

A. DRUG FORMULATION AND DELIVERY

18. Formulation and delivery of drugs have been important to pharmaceuticals since the inception of drug treatment. In general, formulation of drugs involves the development of a prescribed recipe for reproducibly preparing a drug so that it may be safely and effectively administered to patients. The prescribed recipe should produce a drug composition that consistently delivers a known amount of drug and/or activity of the drug to patients. Ideally, this recipe should also produce a composition that delivers a known and consistent amount of drug to the target site for the drug within the patient's body.

19. Other goals of drug formulation and drug delivery include, for example, increasing the stability of the drug, increasing the longevity of the drug in the patient, improving the delivery of drug to the target site in the patient, increasing bioactivity in the patient while minimizing toxicity to the patient, and creating a composition of the drug that can be dispensed in reproducible quantities with reproducible amounts of activity.

20. For example, some drugs are rapidly removed from the body necessitating frequent administrations. Delivery of such drugs to their target sites in the body can be enhanced with sustained release formulations that maintain the concentration of drug in the body overtime so that more drug can reach its target site.

21. Another example of an enhanced delivery formulation arises with drugs administered through the intestines. Many such drugs can be destroyed by the harsh conditions in the stomach, but this destruction of the drug can be avoided with formulations that protect the drug and prevent release of the drug until the formulation reaches the intestines.

22. Stability of drugs can also be enhanced by, for example, buffers that control pH, or salts which complex with the drug to reduce electrostatic repulsion, or proteins that can interact with the drug to stabilize its structure and activity.

B. DILUENTS, ADJUVANTS, AND CARRIERS

23. The terms "diluent," "adjuvant," and "carrier" were coined to generally classify different types of molecules that can be used in drug formulation. These molecules can behave

independent of the drug, but most often interact with the drug through various bonds such as, covalent bonds, electrostatic bonds, hydrogen bonds, hydrophobic interactions and/or van der Waals interactions. These interactions between the drug and the diluent, adjuvant, or carrier may alter the uptake, stability, activity, half-life, and delivery of drugs in the body.

24. For example, diluents are a substance used to disperse a small amount of an active ingredient into a formulation. This is important for making a composition of drug that will reproducibly deliver the same weight and same activity of drug to the patient.

25. Adjuvants are molecules that, when added to a drug improve its action. Adjuvants can include other drugs that together with a primary drug promote more therapeutic activity in the patient than the primary drug alone.

26. Carriers encompass many broad classes of molecules that can aid in the transport, diffusion or circulation of drugs in the body.

IV. CLAIM CONSTRUCTION

27. 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") (attached as Ex. 3), 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") (attached as Ex. 4), 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").

28. I understand that the following are claims from the asserted patents that recite the claim phrase "a pharmaceutical composition comprising . . . and a pharmaceutically acceptable diluent, adjuvant or carrier." Claim 9 of the '933 Patent:

> 9. A pharmaceutical composition comprising an effective amount a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Claim 12 of the '933 Patent:

> 12. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 7 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Claim 1 of the '422 Patent:

> 1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

A. A PHARMACEUTICAL COMPOSITION COMPRISING . . . AND A PHARMACEUTICALLY ACCEPTABLE DILUENT, ADJUVANT OR CARRIER

29. Summary Opinion: One of ordinary skill in the art as of the 1983/84 timeframe would understand the "a pharmaceutical composition comprising . . . and a pharmaceutically acceptable diluent, adjuvant or carrier" to mean a composition suitable for administration to humans containing at least a diluent, adjuvant or carrier. Such diluent, adjuvant or carrier may or may not be separate and distinct from the active ingredient.

30. I understand that Roche has defined this phrase to mean a ***mixture*** having in addition to the active ingredient (as defined in the claim), an ***additional distinct and separate ingredient*** that acts as a diluent, an adjuvant or a carrier. I do not agree that one of ordinary skill in the art in 1984 applying the ordinary meaning of the phrase in view of the claim language, the specification, and the prosecution history would read in a restriction that the diluent, adjuvant, or carrier must be separate and distinct from the active ingredient of the claim.

31. The specifications of the '933 and '422 Patents state the following about "a pharmaceutical composition comprising . . . and a pharmaceutically acceptable . . ."

> A focus of microbiological processing for the last decade has been the attempt to manufacture industrially and ***pharmaceutically*** significant substances using organisms which either do not initially have genetically coded information concerning the desired product included in their DNA, or (in the case of mammalian cells in culture) do not ordinarily express a chromosomal gene at appreciable levels.

(The '933 Patent at Col. 2:16-22) (emphasis added).

> Also comprehended by the invention are ***pharmaceutical compositions*** comprising ***effective amounts of polypeptide products of the invention together with suitable diluents, adjuvants and/or carriers*** which allow for provision of erythropoietin therapy, especially in the treatment of anemic disease states and most especially such anemic states as attend chronic renal failure.

(The '933 Patent at Col. 12:1-7) (emphasis added).

> A preferred method for administration of polypeptide products of the invention is by parenteral (e.g., IV, IM, SC, or IP) routes and the ***compositions*** administered ***would ordinarily include therapeutically effective amounts of product in combination with acceptable diluents, carriers and/or adjuvants***. Preliminary pharmacokinetic studies indicate a longer half-life in vivo for monkey EPO products when administered IM rather than IV. Effective dosages are expected to vary substantially depending upon the condition treated but therapeutic doses are presently expected to be in the range of 0.1 (.about.7 U) to 100 (.about.7000 U) g/kg body weight of the active material. Standard diluents such as human serum albumin are contemplated for ***pharmaceutical compositions*** of the invention, as are standard carriers such as saline.

(The '933 Patent at Col. 33:50-64) (emphasis added).

32. The specification of the '933 and '422 Patents state the following about pharmaceutically acceptable diluents, adjuvants or carriers.

> ***Standard diluents*** such as ***human serum albumin*** are contemplated for pharmaceutical compositions of the invention, as are ***standard carriers*** such as ***saline***.

(The '933 Patent at Col. 33:61-64) (emphasis added).

> ***Adjuvant*** materials suitable for use in compositions of the invention include compounds independently noted for erythropoietic stimulatory effects, such as testosterones, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin and triiodothyronine, as well as agents generally employed in treatment of aplastic anemia, such as methenolene, stanozolol and nandrolone [see, e.g., Resegotti, et al., Panminerva Medica, 23,, 243-248 (1981); McGonigle, et al., Kidney Int., 25(2), 437-444 (1984); Paviovic-Kantera, et al., Expt. Hematol., 8(Supp. 8), 283-291 (1980); and Kurtz, FEBS Letters, 14a(1), 105-108 (1982)]. Also contemplated as ***adjuvants*** are substances reported to enhance the effects of, or synergize,

> erythropoietin or asialo-EPO, such as the adrenergic agonists, thyroid hormones, androgens and BPA [see, Dunn, "Current Concepts in Erythropoiesis", John Wiley and Sons (Chichester, England, 1983); Weiland, et al., Blut, 44(3), 173-175 (1982); Kalmanti, Kidney Int., 22, 383-391 (1982); Shahidi, New. Eng. J. Med., 289, 72-80 (1973); Fisher, et al., Steroids, 30(6), 833-845 (1977); Urabe, et al., J. Exp. Med., 149, 1314-1325 (1979); and Billat, et al., Expt. Hematol., 10(1), 133-140 (1982)] as well as the classes of compounds designated "hepatic erythropoietic factors" [see, Naughton, et al., Acta. Haemat., 69, 171-179 (1983)] and "erythrotropins" [as described by Congote, et al. in Abstract 364, Proceedings 7th International Congress of Endocrinology (Quebec City, Quebec, Jul. 1-7, 1984); Congote, Biochem. Biophys. Res. Comm., 115(2), 447-483 (1983) and Congote, Anal. Biochem., 140, 428-433 (1984)] and "erythrogenins" [as described in Rothman, et al., J. Surg. Oncol., 20, 105-108 (1982)]. Preliminary screenings designed to measure erythropoietic responses of ex-hypoxic polycythemic mice pre-treated with either 5-α-dihydrotestosterone or nandrolone and then given erythropoietin of the present invention have generated equivocal results.

(The '933 Patent at Col. 33:65-34:31) (emphasis added). The '933 and '422 Patents also state that the above description of pharmaceutically acceptable diluents, adjuvants or carriers are exemplary of the diluents, adjuvants or carriers covered by the Patents.

> Viewed in this light, therefore, the specific disclosures of the illustrative examples are clearly not intended to be limiting upon the scope of the present invention and numerous modifications and variations are expected to occur to those skilled in the art.

(The '933 Patent at Col. 36:54-58.) None of these quotes state that the diluent, adjuvant or carrier must be separate and distinct from the EPO products.

33. Some of the standard diluents, adjuvants, and carriers identified in the specification can form a variety of bonds with drugs, and others do not. For example, saline can complex with protein drugs through the formation of electrostatic bonds. Albumin can be covalently attached to protein drugs (Poznansky, 21 PHARMAC. THER. 53-76 (1983), attached as Ex. E), or it and other proteins (*e.g.*, some of the listed adjuvants) can complex with protein drugs through electrostatic, hydrophobic, and van der Waals interactions. In contrast, some of

the adjuvants (*e.g.*, the small molecules) listed in the specification of the '933 and '422 Patents most likely will not form bonds with erythropoietin.

34. The prosecution history of the '933 and '422 Patents state the following about "a pharmaceutical composition comprising . . . and a pharmaceutically acceptable diluent, adjuvant or carrier."

> Claim 95 is rejected under 35 U.S.C. §103 as being unpatentable over either one of Sugimoto et al or Chiba et al as applied to claims 87-94 above, and further in view of applicant's admitted state of the prior art (page 87, line 29 through page 88, line 28). Applicant acknowledges ***pharmaceutically acceptable carriers, adjuvants, and diluents*** to be standard. It would be obvious for one of ordinary skill in the art to prepare a ***pharmaceutically acceptable*** composition containing the EPO of either one of the primary references ***in order to administer the EPO to an animal or human*** to effect a higher hematocrit.
>
> Claim 95 rejected under 35 U.S.C. §103 as being unpatentable over either one of Espada et al (Fed. Proc. 41: 1159 (1982)) or Miyake et al (J. Biol. Chem. 252: 5558 (1977)) as applied to claims 89-94 above, and further in view of applicant's admitted state of the prior art (page 87, line 29 through page 88, line 28). Applicant acknowledges ***pharmaceutically acceptable carriers, adjuvants, and diluents*** to be standard. It would be obvious for one of ordinary skill in the art to prepare a ***pharmaceutically acceptable*** composition containing the EPO of either one of the primary references ***in order to administer the EPO to an animal or human*** to effect a higher hematocrit.

(August 16, 1994 office action '933 File History at 453-454 (emphasis added), attached as Ex. F.)

35. Roche's definition requires that the recited erythropoietin and the diluent, adjuvant or carrier be distinct and separate. In my opinion, this definition is overly restrictive because it excludes diluents, adjuvants and carriers identified in the specification of the '933 and '422 Patents that complex with erythropoietin through covalent bonds, electrostatic bonds, hydrogen-bonds, hydrophobic interactions, and/or van der Waals interactions and is contrary to the understanding of one of ordinary skill in the art as of 1984. Thus, for example, Roche's definition would exclude saline (forms electrostatic bonds with protein), albumin (can be

covalently bound to protein, and can complex to protein through electrostatic, hydrophobic and van der Waal interactions) and adjuvant proteins (can complex to protein through electrostatic, hydrophobic and van der Waal interactions).

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 in Boston, Massachusetts, on March 19, 2007.

/s/Vladimir P. Torchilin
Vladimir P. Torchilin, Ph.D., D.Sc.