EXHIBIT UU

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LA ROCHE LTD, ROCHE DIAGNOSTICS GmbH, and HOFFMANN-LA ROCHE INC. Defendants.	Civil Action No. 05-12237 WGY

DECLARATION OF PATRICK P. DELUCA, Ph.D. IN SUPPORT OF DEFENDANTS' REPLY IN OPPOSITION TO AMGEN'S CLAIM CONSTRUCTION

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Counsel for Defendants,
F. HOFFMANN-LA ROCHE LTD,
ROCHE DIAGNOSTICS GmbH, and
HOFFMANN-LA ROCHE INC.

1. I, Patrick P. DeLuca, declare as follows:

2. I am a citizen of the United States residing at 3292 Nantucket Drive, Lexington, Kentucky 40502.

3. I make this declaration in connection with Defendants' Reply to Amgen, Inc.'s Claim Construction Brief.

I. EDUCATION AND QUALIFICATIONS

4. I am Professor of Pharmaceutical Sciences in the University of Kentucky College of Pharmacy in Lexington.

5. I received my B.S. and my M.S. in Pharmacy from Temple University in 1957 and 1960 respectively. I was awarded a Ph.D. in Pharmaceutical Sciences, also from Temple University, in 1963.

6. From 1957 - 1959, I was employed as an Analytical Chemist at Smith Kline & French Labs in Philadelphia. Upon completing my Ph.D. in 1963, I worked at CIBA Pharmaceutical Co. in Summit, New Jersey, where I held several positions in the company until 1969. Between 1969 to 1970, I was Plant Manager and Director of Development and Control at Cormedics Corporation in Somerville, New Jersey. I began my teaching career at the University of Kentucky College of Pharmacy in 1970 as an Associate Professor of Pharmacy. I was promoted to Professor in 1975, a position I still hold today. While at the College, I served as Assistant Dean and, subsequently, Associate Dean from 1971 - 1987 in the College of Pharmacy. I was the Acting Director for the Center for Pharmaceutical Science and Technology between 1987 - 1988. I served as Interim Chair for the Faculty of Pharmaceutical Sciences between 1998 - 2000.

7. My research has been directed towards the advancement of pharmaceutical technology in industry and the clinical setting. I have engaged in collaborative, interdisciplinary research associated with the preparation, administration and control of intravenously administered fluids. Currently, my research is focused on developing and evaluating

micro-particulate systems to target drugs and agents to specific organs and cells via parenteral and inhalation administration; formulation development of protein molecules and optimization of the freeze-drying process. I have taught courses in basic pharmaceutics; drug delivery systems and pharmaceutical technology. I have published over 200 research articles on lyophilization, photochemistry, stability testing, complexation, I.V. therapy, microsphere drug delivery, and particulate matter monitoring as well as several professional publications on pharmacy education. I have also authored chapters on "Sterile Products," "Kinetic Principles and Stability Testing," "Parenteral Drug Delivery Systems," "Formulation of Small Volume Parenterals," and "Particulate Matter" in pharmaceutical treatises and textbooks. I currently hold patents on drug delivery system related inventions.

8. I have consulted for the F.D.A. and many pharmaceutical companies including Amgen, Genetics Institute, Abbott Labs, Centocor, Wyeth, and Oakwood Labs, often concerning problems dealing with formulation research and development of proteins, peptides and small molecules.

9. Among my professional memberships, I am a member of the American Association of Pharmaceutical Sciences (AAPS); American Pharmaceutical Association; Academy of Pharmaceutical Sciences; Rho Chi Pharmaceutical Honor Society; and Sigma Xi. I served as the President of the American Pharmaceutical Association's Academy of Pharmaceutical Sciences in 1979. In 1995, I was the recipient of the William B. Sturgill Award at the University of Kentucky for outstanding contributions to graduate education and research and in 1998 received the First Research Achievement Award in Pharmaceutical Technologies from the AAPS. In 2000, I was recipient of the first AAPS Outstanding Educator Award in the Pharmaceutical Sciences and in 2001, was honored by the University of Kentucky as a Sullivan Medalist for my humanitarian efforts. In 2002, I was named Kentucky Pharmacist of the Year. I was the Swintosky Distinguished Lecturer at the University of Kentucky College of Pharmacy in 2003. I was awarded an Honorary Doctorate from the University of Perugia in Italy in 2006. Also in 2006, I received the AAPS Dale Wurster Research Achievement Award in Pharmaceutics. I have been the recipient of Outstanding Manuscript Awards in 1998, 2002, and 2006. I was Editor-in-Chief of the international journal, *Pharmaceutical Development and Technology* between 1995 -1999 and am now the Editor-in-Chief of AAPS online journal *PharmSciTech*. I am also on the editorial boards of several scientific

journals: *Pharmaceutical Technology, Journal of Pharmaceutical Sciences and Technology, STP Technology Pharm. Sciences and Microspheres, Microcapsules and Liposome.* I have served in review groups of the National Cancer Institute; National Institutes of Health; National Institute on Drug Abuse; Small Business Innovation Research; and F.D.A. Pharmaceutical Sciences Advisory Committee.

10. A copy of my Curriculum Vitae, including a list of my publications, is attached as Exhibit 1.

II. MATERIALS CONSIDERED

11. This declaration is provided to assist the Court in understanding the science and technology discussed in Defendants' [Proposed] Reply to Amgen, Inc.'s Claim Construction Brief and in answer to Dr. Torchilin's declaration submitted March 19, 2007.

12. In forming the opinions set forth in this expert declaration, I have considered U.S. Pat. No. 5,547,933 (Ex. B), U.S. Pat. No. 5,955,422 (Ex. F), Declaration of Vladimir P. Torchilin submitted March 19, 2007 and all exhibits therein (Pl. Resp.), Mark J. Poznansky, *Enzyme-Protein Conjugates: New Possibilities for Enzyme Therapy*, 21 PHARMAC. THER. 53 (1983) (Ex. E of Torchilin Declaration of Pl. Resp.), August 16, 1994, Office Action, 08/487,774-38 at 9-10 (Ex. 2), U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY: NONCLINICAL STUDIES FOR THE SAFETY EVALUATION OF PHARMACEUTICAL EXCIPIENTS at 1-9 (2005) (Ex. 3).

III. TECHNOLOGY OVERVIEW

A. DRUG FORMULATION AND DELIVERY

13. Pharmaceutical formulation is a process whereby different chemical substances are mixed with an active ingredient to produce a final drug product that can be used as a therapeutic. The final pharmaceutical composition should provide for consistent delivery of an active ingredient.

14. An active ingredient alone will not be typically delivered and absorbed effectively by the body. Agents are added to the drug formulation for a number of reasons, including to

provide for proper delivery of the drug and create a composition that can be dispensed in reproducible quantities and amounts of activity. Different excipients or inactive ingredients, such as diluents, adjuvants and carriers are added to the formulation to perform specific functions.[1]

B. DILUENTS, ADJUVANTS, AND CARRIERS

15. Diluents are diluting agents that act as vehicles or bulking agents aiding in the formulation, storage and delivery of the drug. Diluents have no therapeutic activity. After administration, diluents will separate from the pharmaceutical composition and be disposed of separately.

16. Adjuvants are molecules that separately and independently enhance the activity of other substances. In many instances, adjuvants synergistically improve the activity of the drug substance without modifying the active ingredient.

17. Carriers are inactive molecules that transport the active ingredient into the body. Once administered, the active ingredient and the carrier are free to separate from the formulation.

IV. CLAIM CONSTRUCTION

A. Claim 1 of the '422 patent and claims 9 and 12 of the '933 patent

18. Claim 1 of the '422 patent and claims 9 and 12 of the '933 patent are related to pharmaceutical compositions containing an active ingredient, and a pharmaceutically acceptable diluent, adjuvant or carrier. Claim 1 of the '422 patent reads,

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[1] The Food and Drug Administration ("FDA") defines excipients as "inactive ingredients that are intentionally added to therapeutic and diagnostic products, but that: (1) we believe are not intended to exert therapeutic effects at the intended dosage, although they may act to improve delivery (*e. g.*, enhance absorption or control release of the drug substance)..." (Ex. 3 at 1). The FDA treats excipients differently from active drug substances. If an applicant needs to add an excipient or replace an excipient in the formulation of a pending new drug application ("NDA"), the applicant does not need to file a different NDA, but simply supplement the pending NDA. On the other hand, if a molecule binds to or forms complexes with the active ingredient in a pending NDA, the FDA treats this new formed molecule as a new drug entity and the applicant must submit a NDA for the new product. (Ex. 3).

> 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.

Claim 9 of the '933 patent reads,

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

Claim 12 of the '933 patent reads,

> 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.

19. A person of ordinary skill in the art in 1983/1984 would have understood that the claims describe a pharmaceutical composition containing two separate and distinct ingredients, the active ingredient and either a pharmaceutically acceptable diluent, adjuvant or carrier.

20. A person of ordinary skill in the art applying the ordinary meaning of the terms diluent, adjuvant or carrier would interpret those terms to mean a formulation excipient used to act in a certain way. A diluent would be a substance that adds bulk and stability to the formulated pharmaceutical and is no longer mixed with the active ingredient after administration. An adjuvant would be a substance that separately and independently enhances the activity of other substances. A carrier would be a substance that carries the active ingredient but does not interact with it.

B. The Specification of the '422 patent[2]

21. The language in the specification of the '422 patent also suggests to a person of ordinary skill in the art that the active ingredient in the pharmaceutical composition is intended to be separate and distinct from the diluent, adjuvant or carrier. According to the specification,

[2] Because the specification for the '422 and the '933 patent are nearly identical, I will only refer to the specification of the '422 patent for simplicity.

the pharmaceutical composition contains the active ingredient and a second ingredient that allows for the provision of erythropoietin therapy. The specification states the following,

> 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***...

(Ex. F at col. 12, ll. 5-9) (emphasis added).

22. The specification also states that the "compositions administered would ordinarily include therapeutically effective amounts of product in combination with acceptable diluents, carriers and/or adjuvants." (Ex. F at col. 33, ll. 43-46). The patent lists common adjuvants that could be used in the pharmaceutical compositions and aid in delivery:

> 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)].

(Ex. F at col. 33, ll.56 - col. 34, ll.19) (emphasis added).

23. The patent clearly states that adjuvants are "independently noted for their erythropoietic stimulatory effects, " and would impart a synergistic effect to the active product's activity. It would be obvious to a person of ordinary skill in the art that adjuvants are not part of the active ingredient but mixed into the formulation separately.

24. Additionally, the specification gives only one example of a diluent and one example of a carrier. The specification states that "[s]tandard diluents such as human serum albumin are contemplated for pharmaceutical compositions of the invention, as are standard carriers such as saline." (Ex. F at col. 33, ll. 52-55).

25. Aside from the above discussion, the specification provides no additional disclosure or example regarding the diluent, adjuvant or carrier claimed and the only discussion in the patent indicates that a diluent, adjuvant and/or carrier is a separate ingredient from the active ingredient. There is no example of a pharmaceutical composition disclosed in the specification. One would assume the terms would be used in the ordinary way which is not chemically bonded to the active ingredient.

26. Dr. Torchilin indicates in paragraph 33 of his declaration that some of the standard diluents, adjuvants and carriers listed in the specification can interact or form a variety of bonds with the active ingredient. Dr. Torchilin relies on a reference by Poznansky. There is no mention of this article in the specification. Nor is it a well recognized reference in the art.

27. In paragraph 35 of his declaration, Dr. Torchilin states again that the diluent, adjuvant or carrier identified the specification can complex with the active ingredient through covalent bonds, hydrogen bonds, and electrostatic, hydrophobic and/or van der Waals interactions. One of ordinary skill in the art as of 1984 reading the patents would not have understood that is the case.

28. Dr. Torchilin attempts to equate weak associations of molecules such as electrostatic, hydrophobic, and van der Waals interactions with true chemical bonds. Covalent bonds are stable, detectable, permanent attachments between two atoms as a result of sharing pairs of electrons, whereas the other interactions are weak and transient.

29. First, the patent does not teach or describe anywhere that the diluent, adjuvant or carrier used in the pharmaceutical composition can form a variety of bonds with the active ingredient. More specifically, nowhere in the patent is there an indication that saline, which is listed as a standard carrier can be complexed with the active ingredient through the formation of electrostatic bonds. Nor does the patent describe that albumin, a standard diluent, can be covalently attached to the active ingredient, or that the adjuvants listed can complex to the active ingredient through weak interactions.

30. Second, the patent does not teach that the diluent, adjuvant or carrier is chemically bonded to the active ingredient through a chemical reaction. The specification does not describe the pharmaceutical composition as being the product of the chemical reaction between the active ingredient and a diluent, adjuvant or carrier. Nor does the specification teach a person of ordinary skill in the art to chemically attach these substances to the active ingredient.

31. Moreover, when the patent describes a substance that is intended to be covalently bonded or chemically attached to the active ingredient, it explicitly states the fact. This is the case of detectable marker substances that form a covalent bond with the active product. "Polypeptide products of the invention may be "labelled" by covalent association with a detectable marker substance (e.g., radiolabelled with ^{125}I) to provide reagents useful in detection and quantification of erythropoietin in solid tissue and fluid samples such as blood or urine." (Ex. F at col. 12, ll. 12-16).

32. Third, the Poznansky reference describes enzyme conjugates and enzyme-albumin polymers as a means of prolonging the half-life of the enzyme in the circulation, and how albumin can be polymerized by cross-linking with glutaraldehyde. This is a complicated process as Poznansky explains. A similar chemical reaction would need to have been described in the patents for one to understand that albumin was intended to be used in this manner.

33. Covalent modification changes the nature, identity and properties of molecules, forming new compound. Simply adding albumin to a formulation would not be interpreted to mean that it is covalently bonded to the active ingredient. Albumin acts as a stabilizing agent by taking up space and minimizing intramolecular interactions of the active ingredient with itself

that could result in aggregation, precipitation and loss of activity. A person of ordinary skill in the art would have understood this to be the case.

34. The patents do not mention, let alone teach covalent bonding or other interactions between the active ingredient and the diluent, adjuvant or carrier listed in the claims. In the absence of any description or mention of bonding or interaction between the active ingredient and the excipient, a person of ordinary skill in the art would have understood that these substances were intended to be used as standard excipients which are mixed into the formulation to provide a specific function separate and distinct from the function of the active ingredient.

C. The Prosecution History

35. During prosecution of the '933 patent, the examiner stated that the applicant acknowledges that "pharmaceutically acceptable carriers, adjuvants, and diluents to be standard." (Ex. 2 at 9-10). Thus, the patent examiner and the inventor understood that the terms diluent, adjuvant or carrier meant standard excipients used in pharmaceutical compositions.

V. CONCLUSION

36. Having considered the above, it is my opinion that a person of ordinary skill in the art in 1983/1984 would have understood the terms diluent, adjuvant or carrier in claim 1 of the '422 patent and claims 9 and 12 of the 933 patent to mean an excipient that is separate and distinct from the active ingredient recited in the claims.

37. If requested by the Court I may provide oral testimony at a hearing or at trial consistent with the statements made in this declaration.

38. I reserve the right to supplement opinions rendered in this declaration as a result of the testimony and opinions of other witnesses or other information which might exist and which may be presented during the remainder of discovery or during trial of this matter, including graphic or demonstratives not yet prepared.

39. I declare under penalty of perjury that the foregoing opinion is true and correct to the best of my knowledge and belief.

Dated: March 27, 2007

/s/ Patrick DeLuca
Patrick DeLuca Ph.D.

CERTIFICATE OF SERVICE

I hereby certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on March 30, 2007.

/s/ Nicole A. Rizzo
Nicole A. Rizzo

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