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-CV-12237 WGY

SECOND DECLARATION OF DR. EDWARD EVERETT HARLOW, JR. IN SUPPORT OF DEFENDANTS' OPPOSITION TO AMGEN INC.'S MOTION FOR SUMMARY JUDGMENT OF NO OBVIOUSNESS-TYPE DOUBLE PATENTING

I, Dr. Edward Everett Harlow, Jr., declare under penalty of perjury that:

1. I am an expert for Defendants in the above-referenced case. I previously submitted a declaration in this case on June 12, 2007 in support of Defendant's Motion for Summary Judgment that the Claims of Patents-in-Suit are Invalid for Double Patenting over Amgen '016 Patent.

2. I make this declaration in support of the Defendants' Opposition to Amgen Inc.'s Motion for Summary Judgment of No Obviousness-Type Double Patenting. The patents-in-suit are U.S. Patent Nos. 5,441,868 ("the '868 patent"), 5,618,698 ("the '698 patent"), 5,756,349 ("the '349 patent"), 5,955,422 ("the '422 patent") and 5,547,933 ("the '933 patent"). The claims-in-suit are claims 1 and 2 of the '868 patent, claims 4-9 of the '698 patent, claim 7 of the '349 patent, claim 1 of the '422 patent, claims 3, 7-9, 11, 12 and 14 of the '933 patent. Prior to

obtaining the patents-in-suit, Amgen obtained the now expired U.S. Patent No. 4,667,016 ("the '016 patent"), which issued on May 19, 1987.

3. As I explained in my earlier declaration, a person of ordinary skill in the field reading the phrase "recombinant erythropoietin," especially as used in claim 10 of the '016 patent, would have well understood what the term "recombinant" meant when that term is used to described a protein; it meant that the protein was made using recombinant DNA techniques, which were well known by 1983 – and which are basically the techniques claimed in the patents-in-suit for making rEPO. Thus, this phrase, "recombinant erythropoietin," would have meant using a DNA sequence encoding human EPO and host cells transfected with such a DNA sequence. *See for example* my Declaration of June 12, 2007, ¶¶ 9-24, 32-35, 39-47, 87-95 and 104.

4. Based on my review of the patents-in-suit, the '016 patent, the Memorandum in Support of Amgen's Inc.'s Motion for Summary Judgment of No Obviousness-Type Double Patenting, the Declaration of Dr. Lodish in support of same, I do not see any way (and certainly not any practical or useful way) that the public can practice claim 10 of the '016 patent without facing infringement suits based on the patents-in-suit, despite the fact that the '016 patent expired over two years ago. In my earlier declaration, I said I thought that Amgen would argue that one could practice the subject matter of the '016 patent claim 10 with biologically inactive recombinant erythropoietin, and I said that I thought that this would be a disingenuous position. (*See* my Declaration of June 12, 2007, ¶ 103.) However, neither the Memorandum in Support of Amgen's Inc.'s Motion for Summary Judgment of No Obviousness-Type Double Patenting nor

the Declaration of Dr. Lodish in support of same describes any way that the public can practice claim 10 of the '016 patent without facing infringement suits based on the patents-in-suit.

5. The purification steps claimed in '016 claim 10 employ techniques that were well known to those in the art. The language of Claim 10 from the '016 patent reads as follows:

> A process for the efficient recovery of recombinant erythropoietin from a mammalian cell culture supernatant fluid, said process comprising the following steps in sequence:
>
> (1) subjecting the fluid to ion exchange chromatographic separation at about pH 7.9, thereby to selectively bind erythropoietin in said sample to a DEAE agarose cationic resin;
>
> (2) stabilizing materials bound to said resin against degradation by acid activated proteases through treatment with urea;
>
> (3) selectively eluting bound materials having a pKa greater than that of erythropoietin by treatment with aqueous acid at a pH of about 4.3.
>
> (4) selectively eluting erythropoietin by treatment with an aqueous salt at a pH of about 7.0;
>
> (5) subjecting erythropoietin-containing eluent fractions to reverse phase liquid chromatographic separation involving an immobilized C4 resin, thereby to selectively bind erythropoietin in said fluid to said resin;
>
> (6) selectively eluting bound erythropoietin from said resin with an aqueous ethanol solution of about 60 percent at a pH of about 7.0; and,
>
> (7) isolating erythropoietin-containing fractions of the eluent.

This process requires two primary steps: (a) an ion-exchange chromatography step using DEAE agarose cationic resin (corresponding to claim elements (1) to (4)) and (b) a reverse-phase liquid-chromatography step (corresponding to claim elements (5) to (7)). Both of these steps were well known in 1983, and it was known to use them in combination to isolate and purify proteins. *See for example* Riendeau et al., "Purification of mouse interleukin 2 to apparent homogeneity," *The Journal of Biological Chemistry*, vol. 258, no. 20, pp. 12114-12117 (Oct. 1983), Ex. 34; Anzano

et al., "Sarcoma growth factor from conditioned medium of virally transformed cells is composed of both type alpha and type beta transforming growth factors," *The Proceedings of the National Academy of Sciences U.S.A.*, vol. 80, no. 20, pp. 6264-6268 (Oct. 1983), Ex. 35; and Green et al., "Identification and purification of a protein encoded by the human adenovirus type 2 transforming region," *The Journal of Virology*, vol. 41, no. 1, pp. 30-41 (Apr. 1982), Ex. 36. The remainder of the claim (e.g., urea treatment, the selection of eluting solutions, and the selection of pH levels) is directed to various parameters and techniques of implementing these two primary steps. The selection of these parameters and techniques were obvious design choices well within the ability of someone of ordinary skill in the field in 1983. The only thing potentially novel about claim 10 of the '016 patent was the starting material, recombinant erythropoietin; however, recombinant erythropoietin is the subject matter of the claims-in-suit. Therefore, it is my opinion that the process of claim 10 of the '016 patent would have been obvious in light of each of the claims-in-suit. *See also* Marquardt et al., "Transforming growth factors produced by retrovirus-transformed rodent fibroblasts and human melanoma cells: amino acid sequence homology with epidermal growth factor," *The Proceedings of the National Academy of Sciences U.S.A.*, vol. 80, no. 15, pp. 4684-4688 (Aug. 1983), Ex. 37; Carter et al., "The serine proteinase chain of human complement component C1s," *The Journal of Biological Chemistry*, vol. 215, pp. 565-571 (Aug. 1983), Ex. 38; Nicola et al., "Purification of a factor inducing differentiation in murine myelomonocytic leukemia cells. Identification as granulocyte colony-stimulating factor," *The Journal of Biological Chemistry*, vol. 258, no. 14, pp. 9017-9023 (July 1983), Ex. 39; Morel et al., "Evidence for a predominant form of Mr = 15,000 prosomatostatin in the mouse hypothalamus. Relationship with somatostatin-14 and -28," *The Journal of Biological Chemistry*, vol. 258, no. 13, pp. 8273-8276 (July 1983), Ex. 40; Birnbaum

et al., "Purification and amino acid sequence of a noncalcitonin secretory peptide derived from preprocalcitonin," *The Journal of Biological Chemistry*, vol. 258, no. 9, pp. 5463-5466 (May 1983), Ex. 41; Ronan et al., "Purification and characterization of apolipoprotein C-II from human plasma by high-pressure liquid chromatography," *Biochimica et Biophysica Acta*, vol. 713, no. 3, pp. 657-662 (Dec. 1982), Ex. 42; and Hammer et al., "Isolation of Human Intestinal Neurotensin," *The Journal of Biological Chemistry*, vol. 255, no. 6, pp. 2476-2480 (Mar. 1980), Ex. 43.

6. Although the process for purifying rEPO claimed in the '016 patent would have been obvious over the subject matter of the claims-in-suit, it should be noted that Amgen's "car wash" analogy is a gross over-simplification of the purification process. First of all, purification of a recombinant protein is necessary for its use as a pharmaceutical—whereas a car can be driven even though it is dirty. Secondly, a car wash can wash any kind of car—whereas the purification process must be adapted to the kind of protein to be purified. For example, the purification process developed for EPO will likely be different from the purification process required for other recombinant secreted proteins. Individual steps in any purification process will help with such issues as separation of the desired product from undesired molecules, the exchange of buffers, and adjusting the concentration of the desired product.

7. It remains my opinion that each of the claims-in-suit would have been obvious over the subject matter of claim 10 of the '016 patent. It would have been obvious to one of skill in the art in 1983 to use the mammalian cell culture from which to recover recombinant EPO (as

claimed in the ‘016 patent) so as to produce the glycosylated, biologically active rEPO protein of the claims-in-suit. *See for example* my Declaration of June 12, 2007, ¶¶ 9-124.

8. I declare that the foregoing is true and correct to the best of my knowledge and belief.

Executed this 29th day of June 2007 at Boston, Massachusetts.

/s/ Edward Everett Harlow, Jr.
Edward Everett Harlow, Jr.

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 the above date.

/s/ Julia Huston
Julia Huston

List of Exhibits

Exhibit 34 Riendeau et al., "Purification of mouse interleukin 2 to apparent homogeneity," *The Journal of Biological Chemistry*, vol. 258, no. 20, pp. 12114-12117 (Oct. 1983)

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