EXHIBIT 30

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

SUPPLEMENTAL EXPERT REPORT OF BRUCE SPINOWITZ, M.D.

I, Bruce Spinowitz, M.D. submit this report pursuant to Fed. R. Civ. P. 26(a)(2)(B) on behalf of defendants, F. Hoffmann-La Roche Ltd, Roche Diagnostics GmbH and Hoffmann-La Roche Inc. (collectively "Roche") to set forth the opinions I have formed and may offer at trial of this action.

I. BACKGROUND

1. I am the same Bruce Spinowitz, M.D. who submitted the Expert Report of Bruce Spinowitz, M.D. on April 06, 2007 ("Spinowitz Report") on behalf of F. Hoffmann-La Roche, Ltd., Roche Diagnostics GmbH, and Hoffmann-La Roche, Inc. ("Roche") in the above referenced litigation. I incorporate my April 06, 2007 report by reference. My education and experience, compensation and prior testimony are set forth in my April 6 report, and a copy of my *curriculum vitae* is attached as Exhibit A to that report. If called upon to do so, I will go through my *curriculum vitae* to discuss the contents. I expect to testify at trial regarding the

matters set forth in this report, and in my previous reports, if asked about those matters by the Court or by the parties' attorneys.

2. I reserve the right to supplement or amend my opinions in response to opinions expressed by plaintiff's experts, or in light of any additional evidence, testimony, discovery or other information relating to the aforementioned issues that may be provided to me after the date of this report. I expressly reserve the right to supplement or amend my opinions as final transcripts of relevant testimony become available. In addition, I expect that I may be asked to consider and testify about issues that may be raised by defendant's experts in their reports or at trial. I reserve the right to rely on any documents that Amgen's experts use. In connection with my testimony, I may use certain graphic or demonstrative exhibits listed herein or attached hereto as Exhibit C1, and perhaps those that have not yet been prepared, but which are based on documents identified in this report, to illustrate my opinions.

3. I understand over 10,000 pages of documents were produced this week from the University of Chicago Hospital. I have not yet had an opportunity to review these documents and anticipate supplementing my report once I have had an opportunity to do so.

II. MY UNDERSTANDING OF THE LAW OF OBVIOUSNESS UNDER 35 U.S.C. § 103

4. I have been educated as to the law of obviousness. I now understand that subject matter when combined can render a patent claim invalid for obviousness. I understand that a patent claim may be invalid if the claimed subject matter would have been obvious from the prior art reference or references, taken either alone or in combination with other prior art to a person of ordinary skill in the art at the time the invention was made.

5. It is my understanding that in determining obviousness, in addition to any publication available to the public at the time of filing, among other things one can consider as prior art is

any earlier invention by another that an inventor has not either abandoned, suppressed or concealed, and for which from the time the inventor conceived it, the inventor was reasonably diligent in creating a working example. Such an invention can be combined with other prior art to render a claimed invention obvious. It is my understanding that among the factors to be considered in determining obviousness are included: (a) the scope and content of the prior art; (b) differences between the prior art and the claims at issue; (c) the level of ordinary skill in the field of the invention; and (d) certain other objective factors.

6. I have been informed that in determining obviousness, if a claimed invention was derived in part from information or material provided by someone who is not named as an inventor, such material or information is considered as having been available as prior art to the claimed invention. In my analysis, I therefore have considered whether the claims of Amgen's patents-in-suit would have been obvious assuming the skilled practitioner had available purified EPO protein in the quantity that Dr. Goldwasser provided to Amgen. In my opinion, with such material, it would have been obvious to use a pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin in humans in light of the testing done with the same and similar compositions in animals.

7. I also understand that on April 30, 2007, the Supreme Court issued a decision that has changed the standard to be used in deciding obviousness. I have not had time to review how the impact of this changed standard for obviousness on any of the opinions I expressed in my April 6, 2007 report or in this supplemental report. To the extent that any of the Supreme Court's decision is relevant, I intend to supplement my expert reports given time to consider the opinion and any impact it may have on my analyses and conclusions as to the obviousness of the asserted Lin patent claims.

III. SUMMARY OF MY OPINIONS

8. In addition to the opinions expressed in my April 6, 2007 report, it is my opinion that Claim 1 of the '422 patent and claims 9, 11, 12 and 14 of the '933 patent are invalid as obvious in light of the sheep study conducted by Dr. Eschbach ("Eschbach Sheep Study") which discloses the administration to sheep of a pharmaceutical composition, containing a therapeutically effective amount of EPO-rich plasma.

9. It is my opinion that claim 1 of the '422 patent is anticipated and/or obvious in view of the hamster study conducted by Drs. Goldwasser and Baron ("Goldwasser and Baron Hamster Study"). Drs. Goldwasser and Baron administered to hamsters a therapeutically effective amount of human erythropoietin, with a diluent, adjuvant, or carrier. In my opinion the Goldwasser and Baron Hamster Study discloses every feature of claim 1 of the '422 patent rendering the claim invalid as anticipated. In the alternative, it is my opinion that the Goldwasser and Baron Hamster Study, which discloses a pharmaceutical composition suitable for administration to humans, would render claim 1 of the '422 patent invalid as obvious.

10. It is my opinion that claims 9, 11, 12 and 14 of the '933 patent are obvious in view of the Goldwasser and/ Baron Hamster Study and/or the Baron Clinical Study. Drs. Goldwasser and Baron administered to hamsters and humans a therapeutically effective amount of human erythropoietin, with a diluent, adjuvant, or carrier. In my opinion the Goldwasser and Baron Hamster Study and the Baron Clinical Study, which discloses a pharmaceutical composition suitable for administration to humans, would render claims 9, 11, 12 and 14 of the '933 patent invalid as obvious.

IV. CLAIM CONSTRUCTION

A. '422 Patent Claim 1

11. The only asserted '422 patent claim, independent claim 1 reads as follows:

> Claim 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.

12. I understand that this Court confirmed the use of the Federal Circuit construction of "therapeutically effective amount" as used in the '422 patent defined as an amount "that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals." (Claim Construction Hearing, April 17, 2007, pgs. 4:19-5:1) (*Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1303 (Fed. Cir. 2006) ("*Amgen VII*")).

13. I understand this Court construed the term "A pharmaceutical composition comprising...and a pharmaceutically acceptable diluent, adjuvant or carrier" to mean "a composition suitable for administration to humans containing a diluent, adjuvant or carrier." (Claim Construction Hearing, April 17, 2007, pgs. 76:24-77:4).

14. I understand this Court has also construed the term "human erythropoietin" to mean "a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine." (Claim Construction Hearing, April 17, 2007, pg 39:7-10).

15. As previously stated in paragraphs 91, 94 and 95, of my April 6, 2007 Report, I have been informed and understand that "wherein said erythropoietin is purified from mammalian cells grown in culture" is a source or process limitation that is irrelevant for determining whether a piece of prior art anticipates a patent claim. Nevertheless, Eschbach

discloses enriched plasma containing EPO that is ultimately derived from mammalian kidney cells.

B. '933 Patent Claims

16. Dependent claims 9, 11, 12 & 14 read as follows:

> 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.
>
> 11. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient.
>
> 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.
>
> 14. A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product.

17. As stated above, I understand this Court construed the term "A pharmaceutical composition comprising...and a pharmaceutically acceptable diluent, adjuvant or carrier" to mean "a composition suitable for administration to humans containing a diluent, adjuvant or carrier."

18. In addition, I understand that this Court construed "an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and" to mean an amount "that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit

levels in mammals." (Claim Construction Hearing, April 17, 2007, pg. 6:3-19) (*Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1303 (Fed. Cir. 2006) ("*Amgen VII*")).

V. Prior Art Administration of Pharmaceutical Compositions Comprising Erythropoietin

19. I have reviewed the literature and selected documents recently produced by Dr. Eschbach for evidence of the use of erythropoietin in mammals prior to the application dates of the Lin patents. (ESCH 0000001-67). These documents were produced on April 13, 2007, after the submission of my April 6, 2007 report. Therefore, I did not have an opportunity to opine on these documents. I found evidence of preparations of EPO-rich plasma that had been administered to sheep prior to Nov. 1983. In addition, I have supplemented portions of my report below in response to this Court's recent claim construction hearing.

A. Goldwasser and Baron Hamster Study Using Purified Human Urinary EPO in Hamsters disclosed in the IND 16,234 renders Claim 1 of '422 obvious and therefore invalid.

20. As stated in my April 6, 2007 report, Drs. Goldwasser and Baron conducted a toxicology study on test animals to measure the general effects of large doses of the pharmaceutical composition proposed in IND 16,234. This testing was conducted in 1978. As described in paragraphs 48 and 61 of my April 6, 2007 report, the erythropoietin that was administered to hamsters was the same pharmaceutical composition, comprising purified urinary EPO and human serum albumin (a pharmaceutically acceptable diluent - see '933 patent col. 33, ll. 61-64), as that administered to human patients during the Baron Clinical Study. Therefore, it is my opinion that the pharmaceutical composition administered to the hamsters was suitable for use in humans. This was confirmed in the Baron Clinical Study where the same pharmaceutical composition was administered to three humans. Additionally, Amgen admitted that HSA was suitable for administration to humans in a 1990 memorandum. (AM-ITC 00097006 "For

pharmaceutical purposes, the most desirable albumin is HSA, to minimize the problem of immunogenicity in human patients.").

21. As stated in paragraph 64 of my April 6, 2007 report, the results of the study demonstrated that administration of the pharmaceutical composition comprising purified human urinary EPO in two hamsters produced a significant increase in hematocrit. The average hematocrit of the hamsters receiving EPO was increased 40% compared to the average hematocrit of the control hamsters. It is my opinion that a 40% increase in hematocrit is significant. An increase in hematocrit observed by Drs. Baron and Goldwasser establish the therapeutic effectiveness of the human erythropoietin composition and is further support of the potency of this pharmaceutical composition in mammals. Therefore, it is my firm belief that the Goldwasser and Baron Hamster Study disclosed the use of a "therapeutically effective amount" of EPO as that term has been construed by the Federal Circuit.

22. Additionally, it is my opinion that based on the results of the Goldwasser and Baron Hamster Study, it would have been obvious to one skilled in the art prior to 1983 to use the pharmaceutical composition that was administered to the hamsters and administer it in humans.

B. The Eschbach Sheep Study Using EPO-rich Plasma In Sheep Renders Claim 1 of '422 obvious and therefore invalid.

23. Prior to April 1983, Dr. Eschbach and his team conducted sheep studies in which they administered EPO-rich plasma to uremic sheep. (ESCH 0000008; 0000060; 0000022-24 at 24). Dr. Eschbach states in his Biographical Summary attached to his Curriculum Vitae, that the sheep study using Epo-rich sheep plasma was conducted at the University of Washington from 1969-1980. (AM-ITC 00856495-504). These studies were specifically described in Eschbach et al., "The Anemia of Chronic Renal Failure in Sheep: The response to erythropoietin-rich plasma

in vivo", J. Clin. Invest., Vol. 74, (Aug. 1984), received for publication July 5, 1983. (ESCH 0000025-31). I understand that Dr. Eschbach is a nephrologist who has served as an expert consultant and witness for Amgen in this and previous litigations concerning the Lin patents.

24. In these studies Dr. Eschbach and his team developed a protocol to determine if erythropoietin is effective in sheep with chronic renal failure (CRF), maintained on dialysis, as compared to normal state sheep, and if the anemia of CRF sheep could be corrected by administration of erythropoietin. (ESCH 0000025-31 at 29). Dr. Eschbach and his team determined that anemia in uremic sheep was corrected by administering EPO-rich sheep plasma to the uremic sheep. (ESCH 0000008; 0000022-24 at 24). Based on the results of these studies, Dr. Eschbach "predicted that if and when human Epo became available in sufficient quantities it would correct the anemia...." (ESCH 0000022-24 at 24). In fact, Dr. Eschbach states that he later "confirmed the sheep study in a human by observing that Epo-rich plasma obtained by plasmapherisis from a patient with secondary polycythemia resulted in significant reticulocytosis and an increase in plasma iron turnover when infused into an ABO compatible dialysis patient." *Id.* As discussed in paragraphs 71-74 of my April 7, 2007 expert report, Dr. Eschbach's testimony in prior litigation confirmed that EPO-enriched plasma is a pharmaceutical composition comprising human erythropoietin as claimed in claim 1 of the '422 patent.

(i) Eschbach's Pharmaceutical Composition

25. Dr. Eschbach and his team induced the development of EPO-rich plasma in sheep which had been rendered anemic by virtue of a subcutaneous injection of phenylhydrazine, a substance which induces hemolysis, or disruption, of the red blood cells. These animals were maintained in an anemic state with regular phlebotomy, i.e. blood letting, in order to maintain the hematocrit level at an anemic level of 8-10%, as well as harvest the EPO-rich plasma for

subsequent infusion in the experimental uremic[1] sheep. After 2 to 3 weeks, the sheep were allowed to rebuild their red cell mass. This process was repeated until enough EPO-rich plasma was pooled for the sheep studies. (ESCH 0000022-24 at 24).

26. Dr. Eschbach infused the EPO-rich plasma into six uremic sheep and nine normal sheep. (ESCH 0000025-31 at 25). Three different EPO-rich infusion protocols were employed during the study. EPO was first given at a dosage of 10-27 U/kg, administered in two doses 24 hours apart. Twice the original dosage was given 3 weeks later, administered in two doses 24 hours apart. Three weeks later, one-half the original dose was given daily for 10 days. All dosages were infused as 500 ml of EPO-rich plasma over 20-30 minutes. (ESCH 0000025-31 at 26). The EPO-rich plasma dose ranged from 4 to 10 units/kg given daily or every other day for 1 to 54 days. (ESCH 0000044; ESCH 0000022-24 at 24).

(ii) The Erythropoietin Pharmaceutical Composition as Disclosed in the Eschbach Sheep Study Was Therapeutically Effective in Uremic Sheep

27. The erythropoietic response in sheep to the EPO-rich plasma infusions was measured by reticulocyte response, ferrokinetics (plasma iron turnover and marrow transit time) and by hemoglobin C synthesis. (ESCH 0000025-31 at 25 & 26). Reticulocytes were determined daily by standard techniques. *Id* at 26. Erythrocyte mass was determine by the injection of autologous erythrocytes labeled with 50 uCi of ^{51}Cr. *Id.* The plasma iron turnover, marrow

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[1] Uremia is a clinical condition consequent to failure of the excretory functions of the kidney, diagnosed by an increase in certain laboratory tests (blood urea nitrogen/creatinine), and the presence of an array of symptoms affecting virtually every body system, including, but not limited to lethargy, fatigue, itching, disordered taste, decreased appetite, altered mental function, nausea, vomiting, gastrointestinal bleeding, anemia, bone disease, and heart failure.

transit time, percentage erythrocyte utilization, plasma iron, and total iron binding capacity were also measured by standard techniques in Eschbach's laboratory. *Id.*

28. Drs. Eschbach observed that infusion of EPO-rich plasma resulted in increases in reticulocytes, plasma iron turnover, and erythrocyte mass changes. (ESCH 0000025-31 at 25). While Drs. Eschbach and Adamson did not infuse purified erythropoietin, they concluded that the erythropoietic response detected in sheep was due to erythropoietin because only "EP is known to produce all of the following: reticulocytosis, increased PIT, shortened MTT, HbC activation, and the production of polycythemia." (ESCH 0000025-31 at 29).

29. Additionally, Dr. Eschbach and his team concluded that they had demonstrated that administration of approximately 10 units/kg of EPO-rich sheep plasma given daily or every other day, corrected the anemia of uremic sheep. (ESCH 0000024; ESCH 0000025 ("The anemia was corrected in the uremic sheep after 15-40 daily infusions of Ep-rich plasma...")). Eschbach additionally concluded that "....anemia could be corrected completely by daily infusions of Ep-rich plasma" (ESCH 0000025-31 at 29; *see also* ESCH 0000042 ("When these animals were treated with EP-rich plasma, red cell production incresased, and anemia was corrected in all (Fig. 2).")). Dr. Eschbach's results also show a significant increase in the hematocrit of uremic sheep after continued infusions of EPO-rich plasma. (ESCH 0000042). I agree with Dr. Eschbach's conclusion.

30. These results demonstrate that Dr. Eschbach used a pharmaceutical composition containing amounts of erythropoietin sufficient to cause increases in reticulocyte count, plasma iron clearance rate (i.e., ferrokinetic effects), erythroid cells in the marrow, and red cell mass. Therefore, it is my firm belief that the Eschbach Sheep Study discloses the use of a "therapeutically effective amount" of EPO as that term has been construed by the Federal

Circuit. Moreover, these results indicate that an erythropoietic response had occurred in these mammals.

(iii) Based On The Results of His Sheep Study Dr. Eshbach Concluded EPO Administration to Humans Would Correct Anemia.

31. Based on the results of his sheep study, Dr. Eschbach repeatedly predicted the administration of EPO to humans would be effective in treating anemia. See, for example:

> Dr. Eschbach predicted "that if and when human EPO became available in sufficient quantities, it would correct the anemia...." (ESCH 0000022-24 at 24).
>
> "These results predict that Ep therapy should be effective in treating the anemia of CRF in humans." (ESCH 0000025-31 at 26).
>
> "These animal studies suggest that Ep therapy should correct the hypoproliferative anemia of CRF." (ESCH 0000025-31 at 30).
>
> "In addition, the experience with the sheep model suggested that Epo worked equally well in the uremic and normal condition, predicting that it would be effective in uremic humans." (ESCH 0000058).
>
> "...we speculated that Epo would be effective in human CRF if and when Epo became available." (ESCH 0000059).

I agree with Dr. Eschbach's conclusions.

32. Eschbach later confirmed the results of the sheep study in a human. Eschbach states that he observed that "Epo-rich plasma obtained by plasmapheresis from a patient with secondary polycythemia resulted in significant reticulocytosis and an increase in plasma iron turnover when infused into an ABO compatible dialysis patient." (ESCH 0000022-24 at 24) (see also, my April 6, 2007 report at paragraphs 71-74).

33. Dr. Eschbach also acknowledged that "erythropoiesis in the uremic sheep is similar to that in the human with CRF in that the anemia is hypoproliferative as quantified by ferrokinetic studies, and red cell survival is essentially normal." (AM-ITC 00065501) Further,

Eschbach stated- "[t]he data suggests that Ep if administered to patients with CRF, might be effective even if given infrequently and that its clearance would not be affected by the degree of renal function or the absence of renal tissue." (ESCH 0000043-47 at 46). I agree with Dr. Eschbach's conclusion.

34. Amgen confirmed the predictability of using an EPO pharmaceutical composition in humans, based on the results of Dr. Eschbach's Sheep Study by referring to the sheep study in its orphan drug application in 1986, stating "the sheep model of stable or progressive ESRD used in Eschbach's study mimics that seen in human disease." Further, Amgen stated in the same application "...Eschbach, et al., (1984) were able to demonstrate the efficacy of erythropoietin in uremic sheep." (AM-ITC 00081295)

C. Diluent's, Adjuvants & Carriers Were Well Known In The Art Before 1984.

35. As discussed in paragraphs 48, 61 and 67 of my April 6, 2007 report the use of a pharmaceutically acceptable diluent would have been well known at the time to a person skilled in the art before 1984. A pharmaceutically acceptable diluent (HSA) was used by Drs. Goldwasser and Baron in the studies they conducted in patients and in hamsters to determine the efficacy of EPO. Both studies produced clear evidence of erythropoiesis. It is therefore my opinion, that a pharmaceutical diluent meeting the limitation of claim1 was known and commonly used prior to 1983-84 and that the use of the pharmaceutical diluent by Drs. Goldwasser and Baron renders claim 1 of '422 patent invalid as anticipated. See also, for example, additional discussion in the April 6, 2007 Expert Report of Dr. Lowe at paragraph 165.

VI. The Baron, Goldwasser, Essers, and Eschbach Studies Render Claims 9, 11, 12, and 14 of the '933 Patent Obvious

36. In addition to invalidating claim 1 of the '422 patent, the foregoing clinical studies also render claims 9, 11, 12, and 14 of the '933 patent obvious. As demonstrated in the

April 6, 2007 Expert Reports of Dr. John Lowe and Dr. Rodney Kellems, one of skill in the art as of the time of the application of the patents-in-suit would have found it obvious to create a DNA clone encoding human erythropoietin and express such a cDNA in a mammalian host cell, such as a CHO cell. It is my opinion that once the skilled worker had recombinant human erythropoietin, it would have been obvious to develop a pharmaceutical compositions-with a therapeutically effective amount of erythropoietin and a "diluent, adjuvant, or carrier," as well as "treating a kidney dialysis patient...in an amount effective to increase the hematocrit level of said patient."

37. As stated in my April 6, 2007 expert report and above, the Goldwasser and Baron Hamster study, conducted in 1978, discloses a pharmaceutical composition comprising purified human urinary erythropoietin and human serum albumin, a commonly known diluent as described in the Lin patent. This study demonstrated an increase in hematocrit levels of up to 40% compared to control hamsters. Similarly, as stated in my April 6, 2007 expert report and above, Dr. Eschbach's Sheep Study, conducted prior to 1983, Dr. Eschbach's human study using EPO-rich plasma, conducted in 1984, and Dr. Essers' human study using EPO-rich plasma, conducted prior to 1983, all demonstrate the use of a pharmaceutical composition containing sufficient amounts of erythropoietin to cause increases in reticulocyte count, plasma iron clearance rate (i.e., ferrokinetic effects), erythroid cells in the marrow, and/or red cell mass.

38. Additionally, as stated in my April 6, 2007 expert report the Baron Clinical Study, conducted prior to 1983, discloses the use of a pharmaceutical composition comprising purified human urinary erythropoietin and human serum albumin, a commonly known diluent as described in the Lin patent. This study also demonstrated an increase in reticulocytes, an

increase in the number of nucleated red cells per 1,000 cells of the bone marrow, a shortened iron disappearance time and an increase in red cell mass.

39. Further, as stated above and as stated in my April 6, 2007 expert report, it is my opinion that it was understood by those skilled in the art that the administration of erythropoietin, whether recombinant or urinary, could be used to treat humans once enough erythropoietin was available. In attempting to discredit the results of the Baron Clinical Study, Amgen's expert, Dr. Eschbach, admits that the reason he believes Dr. Goldwasser and Baron had failed to see any therapeutic effect was because "their dosing regimen was insufficient. Dr. Baron administered doses that were too small and for too short an amount of time. He, however, had no choice as he administered all of the EPO that was available to them." (January 20, 2000 Expert Report of Dr. Eschbach at pgs. 20-21). Dr. Eschbach defines a therapeutic amount of EPO to be an amount that either corrects the anemia or maintains a predetermined near normal target hematocrit/hemoglobin. *Id.* at 15. This implies that had enough erythropoietin been available, the patients in the Baron Clinical Study would have had a "therapeutic effect" as defined by Dr. Eschbach, and therefore would have had an increase in hematocrit.

40. In fact, Dr. Lin testified in his deposition that once recombinant erythropoietin worked in mice, there would be a "reasonable expectation" that it would work in humans. For example, Dr. Lin testified as follows:

> THE WITNESS: By then, we already know the recombinant human erythropoietin is
> biologically active in vivo, which we would expect it would be pharmaceutical --
> therapeutically useful.
> BY MS. BEN-AMI:
> Q Now, when you say that at that point, you knew it was biologically active in vivo,
> under what system?
> A In the animal system

Lin Tr., dated 3/28/07, at 108-109,

> ...By November 30th, 1984, had you determined that if it worked in a mouse, the
> EPO would work in a human?
> [objection]
> THE WITNESS: I would think so.
> The reason is that -- one would probably worry it would not work in mice because there would be a difference between mice and human. If it work in mice, have a very good chance it would work in human.
> BY MS. BEN-AMI:
> Q So it was your understanding on November 30, 1984, that if EPO would work in
> mice, there would be a reasonable expectation it would work in humans?
> A That's correct.

Lin Tr., 3/29/97, at 375-377.

> Q When you were doing your work on EPO, when did you come to a complete understanding
> that you could make a pharmaceutically -- a pharmaceutical composition as is written out in
> claim 1 of the '422 patent?
> [objection]
> THE WITNESS: I'm not expert to --I'm not even qualified to explain the claim.
> But let me just put it this way: To say that after probably March, '84, once we have expressed erythropoietin gene that show that it have the in vivo activity, now we could expect that it could be -- would expect it would be useful for use in -- for use in patients which would require erythropoietin treatment such as patient under kidney dialysis, for example.
> Q Okay.
> So once you did what test?
> A After we have obtained the in vivo activity in the animal test.
> Q And all I'm asking you is what kind of test are you talking about?
> A The mouse test, yeah.
> At that time, was tested in mice.
> Q Okay.
> And once you did that, you conceived -- you had a fixed understanding that the EPO you were producing would be therapeutically effective in humans?

> [objection]
> THE WITNESS: We -- from those data, we would expect that it would work in the --the human -- the clinical setting

Lin Tr., 3/29/07, at 367-368.

41. In fact, Dr. Lin also testified that once the EPO gene was expressed in a mammalian host cell, he fully expected that it would have biological activity.

> Q My question was, whether you had the expectation when you had the genomic EPO gene
> that when put into a mammalian cell and expressed, that the resulting EPO would be
> biologically active?
> [objection]
> THE WITNESS: Of course, we would expect that it -- to be -- to have that activity -- in the biological activity.

Lin Tr., 3/29/07, at 367-368.

42. This is further supported by the fact that the specification contained no data on human clinical trials, but only a single mouse study involving 7 mice. See '868 patent, col. 29, ln. 49-62.

43. Thus, once it was obvious to make recombinant human erythropoietin in CHO cells (claims 3, 7, and 8), it is my opinion that these foregoing clinical studies also made it obvious for one of skill in the art to create pharmaceutical compositions with adjuvants, diluents, or carriers to treat kidney dialysis patients in an amounts effective to increase hematocrit levels, reticulocytes, and red blood cells (claims 9, 11, 12, and 14).

VII. Knowledge of The Baron Clinical Study Would Have Been Important to a Reasonable Examiner, Assuming The Examiner is to Consider the Science, Examining Claims 1 and 2 of the '422 patent and Claims 9 and 12 of the '933 Patent.

44. I have read the May 1, 2007 supplemental expert report of Michael Sofocleous ("May 1, 2007 Supplemental Exp. Rep."). I agree with the opinions of Mr. Sofocleous that knowledge of the Baron Clinical Study would have been important to a reasonable examiner,

assuming the examiner is to consider the science, examining claims 1 and 2 of the '422 patent and claims 9, 11, 12 and 14 of the '933 patent.

45. A November 1, 1990 memorandum to Steve Odre, Amgen's in-house patent counsel, and others ("the November 1990 memo") detailed a prior art search conducted at the request of Steve Odre:

> The search was directed toward the priorities outlined by S. Odre during the September 14, 1990. These priorities are listed in the order of importance:
>
> 1) Erythropoietin plus HSA for therapeutic administration
>
> 2) Erythropoietin plus HSA for other uses
>
> 3) Erythropoietin and BSA for therapeutic administration
>
> 4) Erythropoietin and BSA for other uses, and
>
> 5) Other therapeutic proteins plus HSA and/or BSA

(AM-ITC 00097004 - AM-ITC 00097018 at 006). I understand that HSA is human serum albumin and BSA is bovine serum albumin.

46. The November 1990 memo, which is entitled "Literature Search to Support an Interference Filing Against U.S. Patent 4,879,272," reports that four databases were searched for reports of combinations of erythropoietin plus albumins and that:

> Joan Egrie allowed us to search her files on erythropoietin and obtained a copy of the physician's IND for an early clinical trial of human erythropoietin.
>
> * * *
>
> Dr. J. Baron and coworkers initiated an early clinical trial of purified human erythropoietin. The physician's IND states that "the hormone [human erythropoietin] is diluted in Normal Serum Albumin (Human) (Albuspan (R), Parke Davis) (an injectible HSA preparation] at a concentration of 276 units/ml (80,000 units/mg H-EPO protein) to maintain stability and permit appropriate volume for adminstration" [Baron, J., D. Emmanouel, and E. Goldwasser].

> Since the study began in 1979 - 1980, the IND probably dates from those years. In any case, it cannot date later than 1983, since the clinical study concluded that year. The IND clearly teaches that HSA stabilizes erythropoietin and that preparations of erythropoietin with HSA are suitable for human administration. It also demonstrates that clinical use of erythropoietin and HSA, in combination, predates U.S. patent 4,879,272. In addition, HSA is disclosed as an additive in erythropoietin preparations for parenteral administration to animals in a 1971 journal article by J. F. Garcia and J. C. Schooley. The authors dilute purified, human erythropoietin in 5% HSA prior to subcutaneous administration to polycythemic mice.

(AM-ITC 00097007; see also AM-ITC 00097005 ("The physician's IND for any early clinical trial of human erythropoietin, dated no later than 1983, states that "the hormone [erythropoietin] is diluted in Normal Serum Albumin (Human) ... to maintain stability and permit appropriate volume for administration. A 1971 journal article reports that human erythropoietin is diluted in HSA for administration to rats.")). In addition, Amgen admits in the November 1990 memo that the physician's IND for the Baron Clinical Study is prior art. (AM-ITC 00097010).

47. I understand that the Baron Clinical Study was not cited during the prosecution of either the '422 patent or the '933 patent. (See April 6, 2007 Expert Report of Michael Sofocleous Paras. 426, 433 and May 1, 2007 Supp. Expert Report Paras. 13-14, 22).

48. As stated in paragraphs 38-58 and 91-92 of my April 6, 2007 report, it is my opinion that claim 1 of the '422 patent is anticipated by the Baron clinical study because the pharmaceutical composition discloses every relevant element of that claim. The Baron clinical study disclosed a "therapeutically effective amount of human erythropoietin" as that term has been construed by the Federal Circuit. Furthermore, Baron's IND discloses a "pharmaceutical composition" and a "pharmaceutically acceptable diluent, adjuvant, or carrier" stating:

> Human erythropoietin (H-EPO) has been prepared from the urine of patients with aplastic anemia....The hormone is diluted in Normal Serum Albumin (Human) USP (Albuspan®, Parke Davis) at a concentration of 276 units/ml (80,000 units/H-EPO protein) to

> maintain stability and permit appropriate volume for administration.

AM-ITC 01006660. Finally, I have been informed and understand that "wherein said erythropoietin is purified from mammalian cells grown in culture" is a source or process limitation that is irrelevant for validity purposes.

49. Because the Baron Clinical Study discloses every element of the claims of the '422 patent and therefore, anticipates the claims of the '422 patent, I believe the study would have been important to a reasonable examiner.

50. In addition, because it is my opinion that claims 9 and 12 of the '933 patent would have been obvious in light of the Baron Clinical Study, I believe the study would have been important to a reasonable examiner.

VIII. Opinions

51. It is my opinion that the Goldwasser and Baron Hamster Study conducted in 1978 disclosed a pharmaceutical composition suitable for administration in humans, containing a therapeutically effective amount of human erythropoietin, and a pharmaceutically acceptable diluent adjuvant or carrier. Therefore, it is my opinion that the Goldwasser and Baron Hamster Study disclosed every element of claim 1 of the '422 patent in 1978. It is also my opinion that based on the results of the Goldwasser and Baron Hamster Study, it would have been obvious to one skilled in the art in 1983 to a use a pharmaceutical composition in a human comprising a therapeutically effective amount of human or recombinant erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier.

52. It is my opinion that the Eschbach Sheep Study conducted prior to 1983, disclosed the use of a pharmaceutical composition in sheep containing a therapeutically effective amount of erythropoietin. It is my opinion that based on the results of his sheep study, it would have

been obvious to one skilled in the art that the administration of EPO to humans would be effective in treating anemia. It is also my opinion that the use of a pharmaceutically acceptable diluent would have been well known at the time to a person skilled in the art before 1983. Therefore, it is my opinion that based on the Eschbach Sheep Study it would have been obvious to one skilled in the art in 1983 to a use a pharmaceutical composition in a human comprising a therapeutically effective amount of human or recombinant erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier.

53. I understand that a patent claim may be invalid if the claimed subject matter would have been obvious from the prior art reference or references, taken either alone or in combination with other prior art to a person of ordinary skill in the art at the time the invention was made. It is therefore my opinion, that when taken together the results of Dr. Eschbach's sheep study, Dr. Baron's hamster study, Dr. Essers' & Dr. Eschbach's human plasma studies and the Baron Clinical Study strongly demonstrate that claim 1 of the '422 patent and claims 9, 11, 12 and 14 of the '933 patent are obvious and therefore, invalid.

Dated: May 1, 2007

/s/ Bruce Spinowitz
Bruce Spinowitz

Dated: May 1, 2007

Bruce Spinowitz

Exhibit B-1: Documents Considered

ESCH0000001-67

May 1, 2007 Supplemental Expert Report of Michael Sofocleous

Claim Construction Hearing, April 17, 2007 (Selected Portions)

AM-ITC 00097012

AM-ITC 00065501

AM-ITC 00097004-018

AM-ITC 00081295

AM-ITC 01006660

AM-ITC 00856495-504

Lin Transcript, March 28 - 29, 2007 (Selected Portions)

CERTIFICATE OF SERVICE

I hereby certify that a copy of this document was served upon the attorneys of record for the plaintiff (as listed below) by overnight mail on the above date.

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