EXHIBIT 2

CONTAINS CONFIDENTIAL INFORMATION
SUBJECT TO PROTECTIVE ORDER

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.: 05-12237 WGY

MAY 1, 2007 SUPPLEMENTAL EXPERT REPORT OF MICHAEL SOFOCLEOUS

I, MICHAEL SOFOCLEOUS, 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 Michael Sofocleous who submitted the April 6, 2007 Expert Report of Michael Sofocleous ("April 6, 2007 Exp. Rep."). My education and experience, compensation and prior testimony are set forth in my April 6 report, and a copy of my *curriculum vitae* is Exhibit A to that report. If called upon to do so, I will go through my *curriculum vitae* to discuss the contents, including my work as an Examiner, Patent Interference Examiner and Administrative Patent Judge (Examiner-in-Chief).

II. Materials Considered

2. In forming my opinions and preparing this report, I have considered the file histories of the patents-in-suit and related patents (*see, e.g.*, April 6, 2007 Exp. Rep. Section V) and the

materials cited and listed in this report, as well as the materials listed in attached Exhibit B-1. I have also relied on my many years of experience at the United States Patent and Trademark Office ("Patent Office" or "PTO") as an Examiner, Patent Interference Examiner and Administrative Patent Judge. Additionally, I have considered the Supplemental Expert Report of Bruce Spinowitz, M.D. and the Supplemental Expert Report of Richard A. Flavell, Ph.D.

III. Subject Matter About Which I Expect to Testify

3. As set forth in ¶14 of my April 6 report, I understand that this is a patent infringement action instituted by Amgen for infringement. I understand that each of the patents-in-suit shares a common specification with, and claims priority to, U.S. 4,703,008 ("the '008 patent") which expired in 2004. The '008 patent issued from a string of four continuation-in-part applications, with the earliest application filed on December 13, 1983. I understand that the continuation-in-part applications filed on February 21, 1984, September 28, 1984 and November 30, 1984 all added new information to the common specification.*

4. In addition to the subject matter and opinions set forth in my April 6, 2007 expert report, I presently also plan to testify and opine that Applicant violated the duty of candor and good faith owed the patent Examiner in prosecuting the '422 and '933 patents.

5. I may address other matters in response to reports or other evidence offered by Amgen. 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

* To be consistent with my April 6, 2007 report, when citing to information set forth in the common specification, I generally cite to the '868 patent.

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 C-1, and perhaps those that have not yet been prepared, but which are based on documents identified in this report, to illustrate my opinions.

IV. Violations of the Duty of Disclosure, Candor and Good Faith

A. Non-Disclosure of The Baron-Goldwasser Clinical Study And Other Prior Art

6. My April 6 expert report sets forth omissions regarding the Baron-Goldwasser Clinical Study and misrepresentations regarding prior art use of compositions of erythropoietin and human serum albumin. (*See* April 6, 2007 Exp. Rep. Section V.E and Section VI.J). As stated in ¶169 of my April 6 report, Applicant noted that the continuation application Ser. No. 07/609,741 was filed for the purpose of requesting an interference with claims 1-4 of U.S. Patent No. 4,879,272 (Shimoda, assigned to Chugai). (*See also* April 6, 2007 Exp. Rep. ¶¶170, 174-175; '741 File History, Paper 2, 11/6/90 Preliminary Amendment at 9-10; Paper 3 Examiner Interview Summary Record). More specifically, the purpose for filing the application was "to protect the current clinical formulation of Epogen(R), containing human serum albumin." (AM-ITC 00097004 - AM-ITC 00097018 at 005; also at AM-ITC 00097006 ("The current, clinical formulation of Epogen (R) contains HSA at a concentration of 0.25%.").

7. The proposed count for interference with the Shimoda '272 patent was: "An erythropoietin-containing, pharmaceutically-acceptable composition wherein human serum albumin is mixed with erythropoietin." (April 6, 2007 Exp. Rep. ¶¶170, 174-175; '741 File History, Paper 2, 11/6/90 Preliminary Amendment at 9-10; Paper 3 Examiner Interview Summary Record). Likewise, during the prosecution of the applications leading to the '422 patent,

Applicant also requested an interference with U.S. 4,806,524 (Kawaguchi *et al.*, assigned to Chugai) and proposed that the count be: "An erythropoietin preparation containing one or more selected from the group consisting of bovine serum albumin, human serum albumin and gelatin." (April 6, 2007 Exp. Rep. ¶¶184-187, 189; '197 File History, Paper 18, 12/20/93 Amendment at 2; Paper 17, Examiner Interview Summary Record; Paper 23, 12/1/94 Request for Reconsideration). Applicant requested that file claims 61-63 be designated as corresponding to the count, the same claims designated for interference with the Shimoda '272 patent. ('197 File History, Paper 18, 12/20/23 Amendment at 2; Paper 2, 11/6/90 Preliminary Amendment at 9).

8. As set forth at ¶420 of my April 6 expert report, before initiating an interference with the Kawaguchi '524 patent, the Examiner rejected file claims 61-63 over the prior art. Specifically, Examiner Stanton argued that:

> Claims 61-63 are rejected under 35 U.S.C. § 103 as being unpatentable over any one of Miyake et al., 1977 (R), Takezawa et al., 1981 (B) or Takezawa et al., 1982 (C) in view of either applicant's admission on page 87, fines 29-31 or Bock et al. 1982 (D).
>
> The claims under instant consideration are drawn towards pharmaceutical compositions comprising erythropoietin in combination with human serum albumin.
>
> Miyake et al. disclose the purification of human erythropoietin derived from human urine (see e.g. Abstract, section entitled "Experimental Procedures" and Table V). Miyake et al. further disclose that "(e)rythropoietin is the substance that is responsible, in large part for the regulation of normal red blood cell differentiation. Because of this function and because it may have role in replacement therapy of some kinds of anemia, it is important to have pure erythropoietin in an amount sufficient for chemical characterization" (page 5555, first column, first paragraph, lines 7-10).
>
> Each of Takezawa et al. (B and C), disclose methods of purifying "erythropoietin (see e.g. Claims of each U.S. Patent and Example 3 of reference C). Note that Takezawa et al. (B) specifically state that "erythropoietin ... is a promising medicine for curing anemia" (Abstract at lines 2 and 3) and Takezawa et al. (C) states in column 1 at lines 21-23 that "erythropoietin is a promising therapeutic medicine in the clinic (sic) treatment of anemia or, in particular, renal anemia".
>
> None of Miyake et al. or Takezawa et al. (B or C) disclose a composition of erythropoietin comprising human serum albumin.

> Applicant admits on page 87 at lines 29-31 that "(s)tandard diluents such as human serum albumin" may be used in the claimed pharmaceutical compositions and therefore tacitly acknowledge that human serum albumin was a known and accepted pharmaceutical excipient.
>
> Bock et al., 1982 (D) teach that human serum albumin (HSA) was a known and recognized pharmaceutical carrier and that the carrier use of HSA was established as early as 1975 (see e.g. column 11 at lines 55-66).
>
> Since erythropoietin was a known compound with accepted therapeutic use, one of ordinary skill in the art at the time of the instant invention, would have been motivated to prepare pharmaceutical compositions comprising erythropoietin. Further, since HSA was a known and accepted pharmaceutically excipient, one would have used HSA in preparing any pharmaceutical composition. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have prepared the claimed pharmaceutical compositions comprising erythropoietin and HSA,

('197 File History, Paper 20, 6/1/94 Office Action (emphasis added); *see also* April 6 Exp. Rep. ¶¶187, 420). Thus, the Examiner made clear to Applicants that he did not discover a reference that expressly disclosed a composition of erythropoietin comprising human serum albumin during his search for prior art.

9. In response to the prior art rejections, Applicant argued that:

> The 35 USC §103 Rejections:
>
> The Examiner has cited three prior references showing various levels of purification of erythropoietin from urinary sources and combined those with Back and/or the present specification. First, it should be noted that none of these cited references (except the present specification) disclose or even suggest the claimed compositions. Bock relates to a totally different protein. The Examiner has in hindsight combined references disclosing urinary erythropoietin with references which suggest the use of HSA in general in pharmaceutical compositions. This is improper. From the disclosure of Miyake and the two Takezawa patents, there is no indication that a diluent such as human serum albumin would be required to prepare a pharmaceutical composition with erythropoietin.
>
> Second, the Patent Office has already determined that the claimed compositions are patentable in issuing not one but two patents encompassing the same subject matter as presently claimed. Both of these issued patents have priority dates well after the priority dates of the present invention. One of these issued patents, U.S. Patent No. 4,879,272 has already been disclaimed in view of an interference with the present application and the clear priority to the invention described and claimed in the present application. A second interference must now be declared with U.S.

> Patent No. 4,806,524. Applicant respectfully submits that the claimed invention is not obvious for the very same reasons that led to the issuance of '272 and '524 patents. For the Examiner to take a different position now with respect to the present invention which enjoys a much earlier filing date it simply not sustainable.
>
> Applicant therefor [sic] requests that the rejections be withdrawn and an interference be entered between this application and U.S. Patent No. 4,806,524.

('197 File History, Paper 23, 12/1/94 Request for Reconsideration at 2-3 (emphasis added); *see also* April 6 Exp. Rep. ¶¶189, 423). The §103 rejections were not maintained by the Examiner and, subsequently, the '422 patent issued (based on file claims 64-65) after the applicant argued that two Goldwasser references "do not disclose a pharmaceutically acceptable preparation, and there is no indication that BSA or other stabilizing additive would be necessary once the purified EPO was obtained." (April 6 Exp. Rep. ¶¶195-196, 424).

10. Despite the express arguments made by Applicant to the Examiner during the prosecution of the '422 patent, Applicant was aware of prior art that did disclose compositions with erythropoietin and human serum albumin (and erythropoietin and bovine serum albumin) because a search had been conducted and such prior art had been found. A November 1, 1990 memorandum to Steven Odre, Amgen's in-house patent counsel who bore primary responsibility for patent prosecution and to whom Stuart Watt reported (11/6/97 Watt Depo Tr. 6:10-6:24), as well as Jeffrey Browne, Joan Egrie and Thomas Strickland -- all of whom were intimately involved with the prosecution of the patents-in-suit (*see, e.g.*, April 6, 2007 Exp. Rep. ¶¶ 331, 430) reports that:

> In order to protect the clinical formulation and to support an interference filing against U.S. patent 4,879,272, a search for the prior art, including scientific literature, patents, and other documents, was conducted. 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 (emphasis added)). I understand that HSA is human serum albumin and BSA is bovine serum albumin.

11. The 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.")).

12. The memo also reported back to Mr. Odre that "many documents describe the use of HSA or BSA (bovine serum albumin) in combination with erythropoietin" (AM-ITC 00097005), and specifically acknowledged that the compositions of erythropoietin and HSA were disclosed in the "prior art":

> The use of HSA and BSA in erythropoietin preparations is also well documented in the prior art. A physician's IND for a clinical trial of human erythropoietin, dating no later than 1983, states that erythropoietin is diluted in HSA to stabilize the protein and permit an appropriate volume for administration. This document, which predates U.S. patent 4,879,272 (including the Japanese priority date) can be considered prior art that specifically teaches the use of HSA to stabilize erythropoietin in preparations intended for human administration. Additionally, a paper from 1971 reports administration of a solution of HSA and erythropoietin to animals ....

(AM-ITC 00097010-00097011 (emphasis added)).

13. Despite these findings, the '178 application was filed on November 6, 1990. In addition, despite these findings, based on my review of the certified file history, the Applicant waited nearly 8½ years before submitting an Information Disclosure Statement during prosecution of the '422 patent and did not list disclose the Baron-Goldwasser clinical study or the 1971 Garcia reference. ('197 File History, Paper 34, 4/28/99 IDS and PTO-1449). The IDS listed 1 article by Baron and 11 different articles by Goldwasser (including the 2 Goldwasser references discussed in my April 6, 2007 Exp. Rep. ¶¶424, 428) but not the Baron-Goldwasser clinical study. Likewise, Applicant disclosed 3 articles by Garcia, but not the 1971 article discovered by the literature search requested by Mr. Odre.

14. The face of the '422 patent also shows that neither the Baron-Goldwasser clinical study, including the 1979 IND in Amgen's possession, nor the 1971 Garcia article was cited during prosecution. ('422 patent, Cover page - 11). Likewise, the face of U.S. 4,879,272 and U.S. 4,806,524 -- the patents with which Applicant wanted to have an interference declared -- also do

not disclose either the Baron-Goldwasser study or the 1971 Garcia reference. ('272 patent, References Cited; '524, References Cited).

15. Other publications cited in the November 1, 1990 memorandum (*see* AM-ITC 0097012) were disclosed to the Patent Office but, as the memorandum states, only reported (1) HSA or BSA as a carrier for erythropoietin in RIA (radioimmunoassay),* (2) BSA as a carrier for extraction and characterization of erythropoietin,† and (3) BSA and erythropoietin for use in animals.‡ Given the description of the articles in the memorandum, none of the submitted articles disclosed use of erythropoietin and HSA in humans or other animals, and none disclosed use of erythropoietin and BSA in humans.

16. The failure to disclose the Baron-Goldwasser clinical study and the 1971 Garcia journal article is particularly egregious given the Examiner's rejections over the prior art and Applicant's response that: (1) the Examiner improperly "in hindsight combined references disclosing urinary erythropoietin with references which suggest the use of HSA in general in pharmaceutical" and (2) that the art of record did "not disclose a pharmaceutically acceptable preparation, and there is no indication that BSA or other stabilizing additive would be necessary once the purified EPO was obtained." (*See, e.g.*, April 6, 2007 Exp. Rep. ¶¶189, 420-424).

---

* Garcia (1979), Sherwood and Goldwasser (1979) and Garcia (1982). (*See also* AM-ITC 00097008 ("reporting the use of HSA as a carrier for erythropoietin in RIA procedures")).

† Yanagawa (1984), Dordal (1985) and Wang (1985). (*See also* AM-ITC 00097009 ("Three articles dating from 1984 and 1985 report the use of BSA as a carrier for erythropoietin during extraction, purification and characterization.")).

‡ Emmanoeul (1984). (*See also* AM-ITC 00097008 ("Emmanouel and coworkers published an article in which BSA is included in an erythropoietin preparation intended for administration to rats.")).

17. In addition to the information set forth in my April 6 expert report, the November 1, 1990 memorandum, shows that the Baron-Goldwasser clinical study would have been important to a reasonable examiner examining claims 1 and 2 of the '422 patent. But for the Applicant's failure to submit the information, the '422 patent would not have issued. Likewise, the 1971 Garcia journal article also would have been important to a reasonable examiner. As the prior art search conducted at Mr. Odre's behest reports, Garcia disclosed "HSA ... as an additive in erythropoietin preparations for parental administration to animals." (AM-ITC 00097007; *see also* AM-ITC 00097005 ("A 1971 journal article reports that human erythropoietin is diluted in HSA for administration to rats.")).

18. Because Applicant was interested in filing the application to protect the current clinical formulation of Epogen(R) containing human serum albumin by having an interference declared, he had everything to gain by withholding this information to gain patent protection. As discussed above, many individuals at Amgen involved with the prosecution of the patents-in-suit, including the legal department through Mr. Odre (*see also* April 6, 2007 Exp. Rep. ¶¶274, 428-433), knew of these references yet failed to disclose the information during the lengthy pendency of the '422 patent. Furthermore, by 1985, individuals at Amgen had concluded that a formulation with erythropoietin and HSA would be obvious and "not worth" a patent. (AM-ITC 00932278-285 at 279). Amgen had also determined that the use of HSA with erythropoietin was recommended by Dr. Strickland, not Dr. Lin, thus, raising inventorship issues as well. (*Id.*) This information apparently was not disclosed to the Examiner of the '422 patent either.

19. This prior art and inventorship information also would have been important to a reasonable examiner regarding the patentability of claims 9 and 12 of the '933 patent, which are

product-by-process claims. ('178 File History, Paper 11, 6/2/89 Amendment at 3; April 6, 2007 Exp. Rep.¶214). Claims 9 and 12 both depend from independent claim 3 (as well as others):

> 3. A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.
>
> 9. A pharmaceutical composition comprising an effective amount of 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.
>
> 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.

('933 patent (emphasis added)).

20. A product-by-process claim is a particular form of claim permitted by the Patent Office. A product-by-process claim allows an applicant to draft a product claim that defines the claimed product in terms of the process by which it is made. (MPEP §2173.05(p) (8th ed. Rev. 5, Aug. 2006); MPEP §706.03(e) (5th ed. Rev. 6, Oct. 1987)). If the product in the product-by-process claim is the same as or obvious from a product in the prior art, the claim is not patentable even though the prior product was made by a different process. (*Id.*). Thus, Applicant knew or should have known that the Baron-Goldwasser clinical study and 1971 Garcia article would have been important to a reasonable examiner because each reference discloses the administration of a composition of erythropoietin and HSA, which the common specification identifies as a diluent. (*See* AM-ITC 00097012 (Baron reference: comments-"stabilize for human administration"; Garcia reference: comments-"animal administration"; '868 patent, col. 35:24-27 ("Standard diluents such as human serum albumin are contemplated for pharmaceutical compositions of the invention ....")).

21. The November 1, 1990 memorandum, as well as the other information regarding the Baron-Goldwasser clinical study set forth in my April 6 report (April 6, 2007 Exp. Rep. Section VI.J), was known to the same individuals at the time the '933 patent claims were pending. Even after learning that the prior art disclosed compositions of erythropoietin and HSA, Applicant (including Mr. Odre) continued to pursue pharmaceutical composition claims in the application to issuance. (*See, e.g.*, '874 File History, Paper 37, 6/13/94 Preliminary Amendment at 2; Paper 39, 9/7/94 Examiner Interview Summary; Paper 42, 2/16/95 Amendment at 4).

22. As with the '422 patent, this information was not given to the Examiners of the '933 patent. The IDS statement submitted during the pendency of the patent application did not disclose any of the Baron-Goldwasser clinical study documents and did not disclose the 1971 Garcia article. (*See* '874 File History, Paper 36, 4/8/94 IDS and PTO-1449 Form). The face of the '933 patent also shows that neither the Baron-Goldwasser clinical study documents nor the 1971 Garcia article was cited during prosecution. ('933 patent, Cover page-10).

23. As stated at ¶¶431-433 of my April 6 expert report, I am aware that Amgen has relied upon the submission of Dr. Goldwasser's testimony before the United States International Trade Commission (Investigation No. 337-TA-281 before Judge Harris) to show that the clinical study was properly disclosed. *See e.g. Amgen v. HMR/TKT*, 126 F. Supp. 2d 69, 138 (D. Mass. 2001). For the reasons set forth in ¶¶ 28-33, 40, 200, and 431-433 of my April 6 report, however, such a submission is not disclosure to the Examiners of the '422 patent or the '933 patent, and does not comply with the duty of good faith and candor owed the Patent Office.

24. In addition, the selected portions of Dr. Goldwasser's testimony that were submitted to the Interference Board (AM-ITC 00900641 - AM-ITC 00900648 at 643 (Trial Ex. 102)(identifying only page 5, line 11 to page 44, line 18; page 59, line 17 to page 66, line 4; and

page 78, line 3 to page 86, line 18)) did not disclose what composition was used in the Baron-Goldwasser clinical study, i.e. human erythropoietin and human serum albumin. (*See, e.g.*, April 6, 2007 Exp. Rep. ¶¶425, 430, 432). The submitted testimony relating to the Baron-Goldwasser clinical study stated only:

> Q. Were there adequate amounts of EPO available for investigative or clinical research?
>
> A. Adequate, I would have to say no. When we finished the purification of the human urinary material, we had enough to do a very limited clinical trial on three patients. But the amount was too small to extend the trial long enough to see any result. So in essence, it was an abortive trial.
>
> Q. Did that limitation of the availability of material have a limiting factor on the research that could progress?
>
> A. Yes, it brought our clinical trial to a halt. We just could not do anymore.
>
> Q. Was there at that time in your judgment a need for larger amounts of erythropoietin?
>
> A. Absolutely. If its potential therapeutic effect were ever to be found out, it needed to have large enough amounts to use relatively large doses in the patient, and to use enough patients to get statistically significant results.

(AM-ITC 00177591-92 (page 22, line 22 to page 23, line 20)).

25. Furthermore, Dr. Goldwasser's conclusory testimony that insufficient amounts of erythropoietin were available to generate "any result" contradicts the statements made by Dr. Goldwasser and Dr. Baron to the U.S. Public Health Service (*e.g.* AM-ITC 00849306-341 at AM-ITC 00849307) and the FDA (AM-ITC 00245727-29 at AM-ITC 00245728), including the reported increase in reticulocyte number, increase in numbers of nucleated red cells/1000 bone marrow cells and the disappearance of radio-iron from plasma, of which Amgen was aware. (*Id.*; *see also* April 6, 2007 Exp. Rep. ¶¶421-422, 425-430).

26. I am also aware that Amgen has relied upon the reference to Dr. Goldwasser's testimony in Judge Harris' opinion that was submitted to Patent Office to demonstrate that the

information was disclosed. *See* 126 F. Supp. 2d at 138 (citing to Trial Ex. 101 at AM 17 027597 (*e.g.* AM-ITC 00900525 - AM-ITC00900640 at 534), Trial Ex.102 at AM 17 027580-81 (*e.g.* AM-ITC 00900641 - AM-ITC 00900648 at 641-642), Trial Ex. 109 at AM 27 015059 (*e.g.* AM-ITC 00900823 - AM-ITC 00900826 at 825) and Trial Ex. 2198 at 214-25 (*e.g.* AM-ITC 00997385-AM-ITC 00997392 at 390-391)). None of these documents, however, discloses the erythropoietin and human serum albumin composition used in the Baron-Goldwasser study or the patient data discussed above.

27. Furthermore, as explained in my April 6 report at ¶200, the '422 patent originated from a different line of continuation applications than the '933 and '080 patents. (*See also* AM-ITC 00906488). However, Applicant Lin submitted Judge Harris' opinion to Examiner Kushan in the file history leading to the '933 patent. (*See* '178 File History (of '933 patent), Paper 11, 6/2/89 Amendment at 6-7 (Trial Ex. 2198 at 214-215 (AM-ITC 00997385-AM-ITC 00997392 at 390-391)). The Examiners of the '422 patent would not have reviewed the file history of the co-pending '933 patent because it was not a parent application of the '422 patent. (MPEP §609.02 (8th ed. Rev. 5, Aug. 2006)("The examiner will consider information which has been considered by the Office in a parent application...")(emphasis added)). For the same reason, the Examiner of the '422 patent would not be in a position to give full faith and credit to the Examiner of the '933 and '080 patents. Therefore, the Examiner's notes in the file history of the '933 patent indicating that he reviewed the file from Interference 102,334, have no bearing on the '422 patent and do not indicate that the Baron-Goldwasser clinical study was disclosed during the prosecution of the '422 patent. (April 6, 2007 Exp. Rep. ¶¶234-235).

28. To the extent that the Initial Determination of the ITC was submitted in the file history that led to the '868 patent ('179 File History, Paper 19, 5/1/89 Request for Withdrawal of

Suspension), the Examiner of the application could not have substantively reviewed the submission until years later because (1) prosecution of the application for the '868 patent was suspended in 1988 ('179 File History, Paper 16, 12/9/88 Letter) and (2) only days after the ITC opinion was submitted, the application was forwarded to the Board of Patent Appeals and Interferences where it stayed until it was returned in early 1992 upon completion of Interference 102,097. ('179 File History, Paper 21, 5/6/89 Letter; Paper 22, Interference Digest; Paper 27, 2/2/93 Notice of Change of Address). However, the application of the '422 patent was filed on November 6, 1990 (splitting from the parent application Ser. No. 113,179), and from the portion of the Search Notes in the prosecution history of the '422 patent that are legibly copied, by December 1992, the Examiner only "consulted claims in App. No. 07/113,179". (*See, e.g.* Search Notes at AM-ITC 00899764; April 6, 2007 Exp. Rep. ¶200).

29. In submitting the Initial Determination of the ITC to the Interference Board, Applicant Lin designated only specific portions of the opinion and for the limited purpose of "identification", "patentability of the invention", "priority position" and "background information" and not for any discussion of the Baron-Goldwasser clinical study. (*See* AM-ITC 00900641-AM-ITC 00900643). Similarly, in submitting the opinion during the prosecution of the '933 patent, Applicant referred the Examiner only to pages 49-54 (AM-ITC00900550 - AM-ITC 00900555) and 153-160 (AM-ITC 00900629 - AM-ITC 00900636) of the decision. (*See* AM-ITC 00900641-AM-ITC 00900643). None of the referenced pages discloses the erythropoietin and HSA composition used or the results of the clinical study. Indeed, pages 153-160 of the opinion do not even mention Dr. Goldwasser or Dr. Baron. Finally, in submitting the opinion during the prosecution of the '868 patent, the Initial Determination was cited for no more than the fact that after the International Trade Commission reviewed the Initial Determination of the administrative

law judge, Amgen's ITC complaint was dismissed for subject matter jurisdiction. (AM-ITC 00900823 - AM-ITC 00900826 at 825).

30. Even if an examiner undertook to read the entirety of the opinion, which he would not do for the reasons set forth in my April 6 report (*see, e.g.*, April 6, 2007 Exp. Rep.¶¶ 28-33 and 39), the only information he would glean from the Initial Determination is that "there was simply not enough EPO available to perform any sort of clinical study" (AM-ITC 00900551 (emphasis added)) and that efforts to obtain purified EPO from urine resulted in "barely enough for investigative research and far too little for clinical research into the effectiveness as a treatment for anemia." (AM-ITC 00900552-553). Thus, a reviewing examiner would be left with an impression diametrically opposed to what happened in reality. The Initial Determination indicates that there was no clinical study of "any sort" when, in fact, Dr. Goldwasser and Dr. Baron did undertake a small clinical study in humans of which the U.S. Public Health Service, the FDA and Applicant were aware. The Examiners at the Patent Office, however, were not aware of the study, and any submission of the Initial Determination did not disclose that information which would have been important to a reasonable examiner, namely the composition used in the Goldwasser-Baron clinical study and the results.

B. Omissions and Misrepresentations Regarding Human EPO Fragments

31. Example 1 of the common specification sets forth information regarding human EPO fragment amino acid sequencing. ('868 patent, col. 16:7-17:25). In arguing for the patentability of file claims 64 and 65 (which eventually issued as claims 1 and 2 of the '422 patent), Applicant stated that:

> Human erythropoietin as recited in Claim 64 is disclosed in several examples of the application. Example 1 discloses the use of human erythropoietin isolated from the urine of patients afflicted with aplastic anemia ("urinary EPO") to produce tryptic fragments and the amino acid sequencing of those fragments. Examples 7 and 10 disclose the production of human erythropoietin in COS-1 and CHO cells,

> respectively. Thus, human erythropoietin is understood to include any polypeptide having the amino acid sequence of EPO isolated from human urine and may be produced in human cells or in other mammalian cells. The application further discloses that the glycosylation of human urinary erythropoietin may differ depending upon the host cell used for production. Claim 64, however, excludes EPO that is isolated from human urine by the phrase "purified from mammalian cells grown in culture."

('197 File History, Paper 33, 4/28/99 Amendment at 4-5 (emphasis added); see also April 6, 2007 Exp. Rep. ¶196). In the next office action, Examiner Martinell allowed the pending claims. ('197 File History, Paper 36, 5/28/99 Notice of Allowability; *see also* April 6, 2007 Exp. Rep. ¶200).

32. When amending a patent application to enter new claims, an applicant cannot include what is typically referred to as "new matter". (*See* MPEP §608.04, §2163 (8th ed. Rev. 5, Aug. 2006); MPEP §608.04 (5th ed. Rev. 8, May 1988)). The rule against adding new matter is to protect the public, especially competitors, from a patent applicant claiming subject matter that he did not invent or possess at the time of filing the application. An applicant is entitled to claim no more than he described in his patent application at the time of filing. In normal patent practice an applicant will point to the part of the original specification that shows he was in possession of the subject matter of a new or amended claim to obviate a new matter rejection by the Examiner.

33. In pointing the Examiner to Example 1 of the patent specification during the prosecution of the '422 patent, Amgen's attorney was affirmatively representing that Dr. Lin was in possession of correct, albeit partial, amino acid sequence information of human urinary EPO. If the patent specification had not disclosed the sequences in Table 1 of the patent specification a reasonable examiner would have rejected any claim, such as claims 64 and 65, that included an element covering the amino acid sequence of human urinary EPO for including new matter or subject matter that was not disclosed in the application at the time of filing.

34. I understand that the amino acid sequence information disclosed in Table 1 of Example 1 of the patent specification does not accurately reflect the amino acid sequence of human urinary

EPO. Fragment T28 disclosed in Table 1 of Example 1 indicates that within the sequence of human urinary EPO there is an amino acid sequence "E-A-I-S-P-P-D-A-A-M-A-A-P-L-R". ('868 patent, col. 16:33). It is my understanding that subsequent to filing the patent application, Amgen determined that human urinary erythropoietin does not contain such a sequence. For example, Amgen provided the amino acid sequence of human urinary EPO to the U.S. FDA in 1985 which does not include the sequence of amino acids shown in Fragment T28. (Figure 4B-7 at AM-ITC 00596041-42; *see also* AM-ITC 00595293 ("The complete amino acid sequence for human urinary-derived EPO protein in [sic] shown in Figure 4B-7")). In the sequence of human urinary erythropoietin provided to the FDA, it is my understanding that there is a glycosylated serine, "S" in place where one would expect an "M", methionine based on T28.

35. If Applicant had determined that the sequence for Fragment T28 did not accurately reflect the amino acid sequence information for human urinary EPO, the patent Examiner should have been told this by Amgen's attorneys at the time claims 64 and 65 were added to the application. A reasonable examiner would have found this to be important to the prosecution of the claims in determining whether there was adequate support in the original application. The duty of candor that Applicant owed to the Examiner required disclosure. If T28 contained a typographical error, it could not have been changed without introducing new matter unless it was an obvious error. (MPEP §608.04 (5th ed. Rev. 8, May 1988); MPEP § 1481 (5th ed. Rev. 3, May 1986) ("A mistake is not of minor character if the requested change would materially affect the scope of meaning of the patent.")); MPEP §608.04, §1481 (8th ed. Rev. 5, Aug. 2006)). However, this would not qualify as an obvious error because the patent specification states that the amino acid sequence of erythropoietin was not available to the public prior to the filing date of the application. ('868 patent, col. 9:5-7 (erythropoietin is "a substance for which no substantial amino

acid sequence information has been published."). Therefore, at the time of filing a person outside of Amgen could not have determined that T28 was an error. Moreover, documents from Amgen that I have considered indicate that the T28 fragment disclosed in the common specification was not a typographical error, but rather reflects the same sequence that Amgen laboratory records show. (AM-ITC 00415129).

36. If Applicant had determined that the sequence T28 was correct, but only that the human urinary EPO samples that he used to obtain the sequence information differed from other samples of human urinary EPO, that too should have been disclosed to the Examiner. First, a reasonable examiner would have limited the claims to the form of urinary EPO that the patent disclosed. Second, if Applicant knew that there were two different forms of urinary EPO, one with an "M" and one with a glycosylated "S", it would have been important to make that clear especially because Applicant (1) made several arguments during the prosecution that its invention differed in terms of glycosylation from urinary EPO (*see, e.g.*, '197 File History, Paper 23, 12/1/94 Request for Reconsideration at 3-4; Paper 33, 4/28/99 Amendment at 5) and (2) prosecuted claims with limitations including differences in glycosylation and carbohydrate content. (*See, e.g.*, April 6, 2007 Exp. Rep. Section V.F and Section VI.E-F). A reasonable examiner would have required evidence that products Amgen was claiming were different from both forms of human urinary EPO.

37. Examiners in the PTO are trained to make a record of the prosecution history because the prosecution file histories serve to inform the public about the scope of protection the U.S. Government is granting to a patentee. Likewise Courts rely on the prosecution file histories in defining the patented invention for litigation. I understand from counsel that Amgen has sought to define its invention only by the 165 amino acid sequence of human urinary EPO based on the

record it made in prosecuting the '422 patent and the fact that it pointed to Example 1 of the patent specification. This serves as a perfect illustration as to why the duty of candor is necessary. If Amgen withheld important information regarding the sequence of human urinary erythropoeitin which misled the patent Examiner, even if the claims would have issued, the public and the Court are deprived of full and complete prosecution history of the Government's position on the scope of the invention had the information been disclosed.

C. Additional Misrepresentations Regarding Sulfate Content of EPO

38. My April 6 report sets forth omissions and misrepresentations in the 1988 Declaration of Dr. Thomas Strickland, as well as the Examiner's reliance on that declaration in withdrawing his rejections during prosecution of the '933 patent. (*See, e.g.*, April 6, 2007 Exp. Rep. ¶¶ 209-212, 215, 217, 241, 340-348, 366 and 376). The 1988 Declaration cites a paper by Takeuchi et al. I understand that Dr. Strickland was in contact with Dr. Takeuchi at a time prior to signing his 1988 Declaration, but did not make that known to the PTO. (3/9/07 Strickland Depo. Tr. 299:7 – 300:14). The relationship with Dr. Takeuchi should have been disclosed to the PTO.

39. In addition, Dr. Strickland's deposition testimony indicates that he had obtained information from his direct contact with Dr. Takeuchi that should have been disclosed to the PTO with the 1988 Declaration. (3/9/07 Strickland Depo. Tr. 305:14 – 309:10). In his declaration, Dr. Strickland concluded from his experiments that "u-EPO contains sialidase resistant negative charges not found in r-HuEPO". (*See* AM-ITC 00941134). However, Dr. Takeuchi reported to Amgen sometime earlier that some sialidase resistant negative charges suspected to be sulfuric acids could be removed from EPO "when more substrate and fresher enzyme were used." (AM-ITC 00067214 - 259 at 241). Dr. Strickland did not offer this alternative possible explanation of his results to the PTO Examiner.

40. While I offer no opinion on the relevant science, I do think a reasonable examiner would find the additional alternative explanation important to patentability. When a declaration is filed in support of patentability, as the Strickland 1988 Declaration was, the declarant has a duty to give a complete disclosure to the PTO Examiner. While examiners are technically trained to analyze data that is provided to them, they have no ability to run their own tests and obtain their own data. If a declarant is in possession of data that may possibly contradict a conclusion that is being drawn from his declaration, he has a duty to disclose it to the Examiner. Dr. Strickland's explanation for why he didn't provide all the information he had available to him to the Examiner seems to violate the duty of candor. (3/9/07 Strickland Depo. Tr. 307:2 – 311:3). A declarant who fulfills his duty of candor does not withhold information based on his own subjective view of the credibility of certain information. All of the information should be disclosed for the Examiner's review. Even if there is a belief that some information is not credible, that too can be brought to the Examiner's attention.

V. Errata

41. The following serves as to correct typos in my April 6, 2007 expert report:

- ¶23 -- "MPEP §706.03(d)(5th ed. Rev. 8, May 1988)" should read "MPEP §706.03(d) (5th ed. Rev. 6, Oct. 1987)"
- ¶74 -- Second full sentence should read "The '298 application is a continuation-in-part application of the '841 application, the '185 application and the '024 application, which added new matter to the specification."
- ¶107 -- The quote at the end of the full bullet point on page 42 should read "deals exclusively with non-glycosylated E. coli expression products". (The phrase "with non-glycosylated" was mistakenly written twice in my initial report.)
- ¶153 -- The last line on page 60 should read "that the files were not substantively considered during examination of the '698 patent."

- ¶165 -- The fourth line should read "that the files were not substantively considered during examination of the '349 patent."

- ¶166 -- Should read "On May 26, 1998, U.S. Patent No. 5,756,349 issued on the underlying '369 application. The '349 patent has no terminal disclaimer."

- ¶178 -- The second-to-last sentence should read "The Examiner also noted that the claim reads on naturally-occurring EPO present in blood."

- ¶181 -- The last sentence should read "This new application was assigned Serial No. 08/100,197 ("the '197 application")."

- ¶232 -- In the second bullet point on page 89, the quotation should read "[a]fter further consideration, Applicant's arguments presented in the § 116 amendment filed 11 January 1990 (Paper 19) are persuasive, and the obviousness-type double patenting rejection of claims 76-83 over Lai *et al.* is withdrawn."

- ¶250 -- The reference in the last line to "the '344 Interference" should read "the '334 Interference."

- ¶¶257-262 --Citations to the "'566 File History" should read "'556 File History."

- ¶268 -- "MPEP §2001.04 (5th ed. Rev. 14, 1992)" should read "MPEP §2001.04 (5th ed. Rev. 14, Nov. 1992)"

- ¶272 -- "MPEP §2002.03(b) (5th ed. Rev. 3, May 1986)" should read "MPEP §2002.03 (5th ed. Rev. 3, May 1986)"

- ¶296 -- Should read: "I have considered the expert reports of John Lowe, M.D. and Rodney E. Kellems, Ph.D regarding the state of the art with respect to recombinant processes for expressing proteins and glycoproteins."

- ¶332 -- "11/8/99 Borun Depo Tr. 325, 334-336" should read "11/10/99 Egrie Depo. Tr. at 325, 334-336"

- ¶448 -- References to claim 60 should be to claim 61.

- ¶455 -- The reference to the "'298 patent" should read "'298 application".

- ¶470 -- The first sentence should read: "This restriction requirement supersedes the earlier July 1986 restriction set forth in the '298 application for the applications leading to the '422 patent."

- ¶488 -- "until 4/22/1999" should read "until April 28, 1999".

"('197 File History, Paper 33, 4/28/99 Amendment at 4)" should read "('197 File History, Paper 35, 4/28/99 Amendment at 4)."

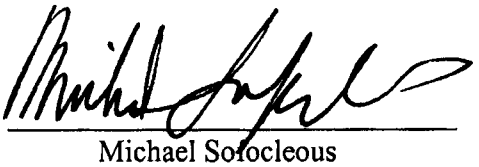
- ¶489-- The reference to "December 24, 1996" should be "December 20, 1996." Also, the cite to "('369 File History, 12/24/96 Second Preliminary Amendment at 9)" should read "('369 File History, Paper 8, 12/20/96 Second Preliminary Amendment at 9)".

- ¶496 -- The last sentence should read "until prosecution claim 98 was introduced on February 16, 1995. ('874 File History, 2/16/1995 Amendment after Final Office Action, at 5)."

42. Additionally, to correct and clarify information set forth in ¶497 of my April 6, 2007 report, I submit the following amended paragraph:

497. Similarly, in the prosecution of the '080 and '933 patents, the limitation directed to "non-naturally occurring" erythropoietin was not permanently introduced into the claims until 1995. ('556 File History, Paper 3, 12/20/95, Second Preliminary Amendment; '774 File History, Paper 45, 6/7/95 Amendment). "Non-naturally occurring" was initially introduced as a limitation during the prosecution of the '178 application ('178 File History, Paper 15, 7/11/89 Amendment), but this limitation was then removed during prosecution of the '874 application, the continuation of '178, only to be reinserted in 1995 in the '556 and '774 applications that issued as the '080 and '933 patents, respectively. Limitations specifying the in vivo biological activity of erythropoietin ("to increase production of reticulocytes and red blood cells") also were not introduced into any claim directed to a protein until December 1988, ('178 File History, Paper 6, 12/1/88 Amendment at 3). Since these amendments were made after the '016 Lai patent issued, the PTO could not have been solely responsible for the fact that the claims containing these limitations issued after the Lai '016 patent.

Dated: May 1, 2007



Michael Sofocleous

TABLE OF CONTENTS

Exhibit B-1: Documents Considered

U.S. 4,806,524

U.S. 4,879,272

U.S. 5,955,422

U.S. 5,547,933

AM-ITC 00415129

AM-ITC 00595293

AM-ITC 00596041-42

AM-ITC 00067214 - AM-ITC 00067259

AM-ITC 00177568 - AM-ITC 00177675 (June 17, 1988 Hearing Transcript, *In re: Certain Recombinant Erythropoietin*, Investigation No. 337-TA-281 (U.S. Int'l Tr. Comm'n))

AM-ITC 00898884-AM-ITC 00899768

AM-ITC 00900525-AM-ITC 00900640 (Initial Determination Opinion, *In re: Certain Recombinant Erythropoietin*, Investigation No. 337-TA-281 (U.S. Int'l Tr. Comm'n); *Amgen v. HMR/TKT* Trial Ex. 101)

AM-ITC 00900641 - AM-ITC 00900648 (Notice (III) By Lin Under 37 CFR 1.682(a); *Amgen v. HMR/TKT* Trial Ex. 102)

AM-ITC 00900823 - AM-ITC 00900823 (*Amgen v. HMR/TKT* Trial Ex. 109)

AM-ITC 00906488

AM-ITC 00932278 - AM-ITC 00932285

AM-ITC 00940928 - AM-ITC 00941763

AM-ITC 00097004 - AM-ITC 00097018 (11/1/1990 Memorandum)

AM-ITC 00997385 - AM-ITC 00997392 (*Amgen v. HMR/TKT* Trial Ex. 2198)

Garcia, JF, and JC Schooley, "Disassociation of Erythropoietin from Erythropoietin-Antierythropoietin Complex," *Proc. Soc. Biol. Med.* 138:213-215 (1971)

MPEP §608.04 (5th ed. Rev. 8, May 1988)

MPEP §608.04 (8th ed. Rev. 5, Aug. 2006)

MPEP §609.02 (8th ed. Rev. 5, Aug. 2006)

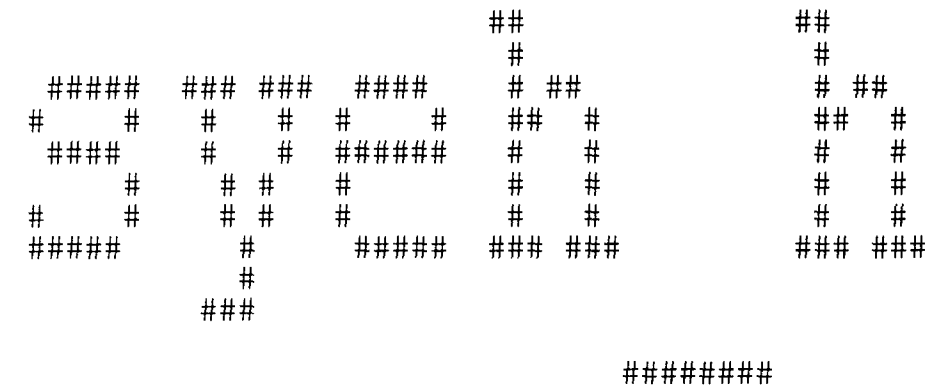
MPEP §706.03(e) (5th ed. Rev. 6, Oct. 1987)

MPEP § 1481 (5th ed. Rev. 3, May 1986)

MPEP §1481 (8th ed. Rev. 5, Aug. 2006)

MPEP §2163 (8th ed. Rev. 5, Aug. 2006)

MPEP §2173.05(p) (8th ed. Rev. 5, Aug. 2006)



Job : 59
Date: 5/1/2007
Time: 11:21:51 PM

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.

Lloyd R. Day, Jr. (*pro hac vice*)
David A. Madrid (*pro hac vice*)
Linda A. Sasaki-Baxley (*pro hac vice*)
DAY CASEBEER MADRID & BATCHELDER LLP
20300 Stevens Creek Boulevard, Suite 400
Cupertino, CA 95014
Telephone: (408) 873-0110
Facsimile: (408) 873-0220

D. Dennis Allegretti (BBO#545511)
Michael R. Gottfried (BBO#542156)
Patricia R. Rich (BBO# 640578)
DUANE MORRIS LLP
470 Atlantic Avenue, Suite 500
Boston, MA 02210
Telephone: (617) 289-9200
Facsimile: (617) 289-9201

William G. Gaede III (*pro hac vice*)
McDERMOTT WILL & EMERY
3150 Porter Drive
Palo Alto, CA 94304
Telephone: (650) 813-5000
Facsimile: (650) 813-5100

Kevin M. Flowers (*pro hac vice*)
Thomas I. Ross (*pro hac vice*)
MARSHALL, GERSTEIN & BORUN LLP
233 South Wacker Drive
6300 Sears Tower
Chicago IL 60606
Telephone: (312) 474-6300
Facsimile: (312) 474-0448

_____
Denise Lopez